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Aims and Scope

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E-mail: aslidonmez@hotmail.com
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Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Turkey
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
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Turk J Anaesthesiol Reanim 2023;51(3):157-169

Aspiration of Fractured Tracheostomy Tube in a Prone Positioned COVID-19 Patient: A Case Report and Review of the Literature

Büşra Tezcan[1], Asiye Yavuz[2], Bilge Taplamacı Ertuğrul[3], Abdulaziz Kaplan[3]

[1]Clinic of Intensive Care, University of Health Sciences Turkey, Etlik City Hospital, Ankara, Turkey
[2]Clinic of Intensive Care, Ankara City Hospital, Ankara, Turkey
[3]Clinic of Anaesthesiology and Reanimation, Ankara City Hospital, Ankara, Turkey

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Abstract

A 61-year-old male patient diagnosed with Coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome (ARDS) was managed with tracheostomy and intermittent prone positioning in the intensive care unit. After a sudden deterioration, examination of tracheostomy tube (TT) and X-ray of the chest revealed that he had aspirated the fractured TT. The fractured tube was removed through the tracheostomy stoma using a rigid ventilating bronchoscope and forceps. Prone positioning is a beneficial postural therapy capable of improving patient oxygenation. However, it has some complications, like unplanned extubation and facial tissue injury. Percutaneous tracheostomy is also a valuable and safe procedure and has been increasingly performed in critical care patients, including those who suffer from COVID-19 ARDS. Fractures and aspiration of a tracheostomy tube can occur anytime after tracheostomy. We think prone positioning may contribute to the rupture and aspiration of the tracheostomy tube in this study.

Keywords: Adverse events, critical care, mechanical complications, tracheostomy tube

Main Points

- Percutaneous tracheostomy is usually a beneficial and safe procedure.
- Fractures and aspiration of the tracheostomy tubes are rare but possible complications.
- Tubes can be manufactured as single rather than two connected pieces.
- Mechanical stress associated with prone positioning may have facilitated the fracture of tracheostomy tubes.

Introduction

Tracheostomy is a standard, reasonable surgical procedure for critically ill patients who require long-term mechanical ventilation.[1] Due to the increase in demand for critical care arising from the global Coronavirus disease 2019 (COVID-19) pandemic, the number of tracheostomized patients has also generally increased.[2]

Prone positioning is an adjuvant therapy for treating COVID-19-induced acute respiratory distress syndrome (ARDS).[3] Tracheostomy and prone positioning may reduce morbidity and mortality among mechanically ventilated patients by different mechanisms. Prone positioning relieves external compression forces, recruits the most atelectatic regions of the lungs, and thus recovers ventilation-perfusion ratio mismatching without subjecting the lungs to high airway pressures.[4] On the other side, tracheostomy improves patient comfort, safety, and communication ability. Better oral and airway care is possible with tracheostomy. At the same time, prone positioning has some airway complications like swelling of the tongue, accidental extubation, and obstruction of the ventilating tube by

Corresponding author: Büşra Tezcan, e-mail: busraytezcan@yahoo.com

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secretions.[5-8] Aspiration of a fractured tracheostomy tube is a rare complication, even in supine-positioned patients.

We present the case of a tracheostomized patient with COVID-19 whose fractured tracheostomy tube dislodged into the left main bronchus.

Case Presentation

A 61-year-old male patient with no comorbidities was referred to our emergency department for a persistent cough complaint for 6 days. He was positive for COVID-19 (diagnosed using polymerase chain reaction) and was admitted to the intensive care unit (ICU) because of respiratory failure. With worsening respiratory status, he was intubated on the third day of ICU admission without any complications. Due to persistent hypoxemia despite full ventilator support, he was prone at 16 h and supine for 8 h on the following 10 days. Percutaneous tracheostomy using the Griggs forceps-dilational technique was performed on the 14-day of ICU admission. The procedure was uneventful, and a tracheostomy tube (Easyflow; Boen Healthcare Co., Ltd, Jiangsu, China) was inserted easily. Intermittent prone positioning was carried out to optimize oxygenation. There were no acute complications following the procedure.

However, the patient deteriorated in the prone position five days after the tracheostomy. He developed sudden hypoxia and hypotension and was turned to the prone position. Examination of the tracheostomy tube showed that the flanges were securely tied around the neck while the stem was missing (Figure 1). The patient was orotracheally intubated, and a chest X-ray was performed. It revealed a foreign body in his left main bronchus (RMB) (Figure 2). He was transferred to the operating room for bronchoscopic removal under general anaesthesia. Using a rigid ventilating bronchoscope and forceps, the tube was removed through the tracheostomy stoma (Figure 3). After the procedure, with no complications, he was retransferred to the ICU as orotracheally intubated. The patient died on the 23rd hospital day of multiorgan failure related to septic shock.

Figure 1. The outer part of the tracheostomy tube.

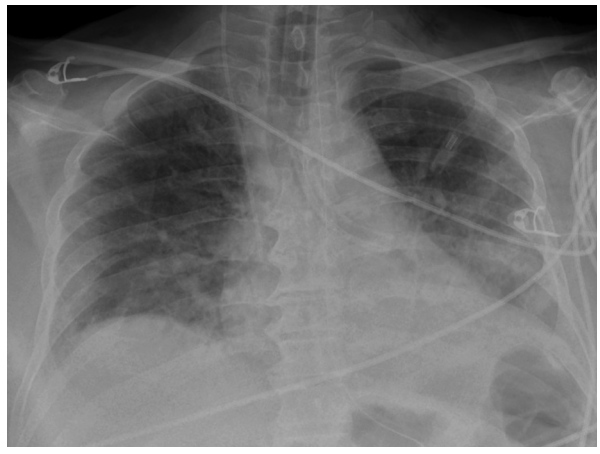

Figure 2. Chest radiograph showing the fractured tracheostomy tube in left main bronchus.

Figure 3. Inner part of the tracheostomy tube removed with bronchoscopy.

Discussion

Prone positioning of ventilated patients was first used in the 1970s and has been reported as a tool to improve respiratory function in patients with ARDS.[9] Increased incidence of pressure ulcers, obstruction of endotracheal or tracheostomy tubes, unplanned removals of arterial or venous catheters, unplanned extubation, accidental loss of thoracic or abdominal drains, facial edema, conjunctival hemorrhage, kinking of tubes and catheters, displacement of nasogastric tube and vomiting are some of the complications that have been associated with the use of prone positioning.[10]

Tracheostomy is another ICU practice used for patients requiring an extended mechanical ventilation period. Patients with tracheostomy can be managed in the prone position. Still, since the airway cannot be visualized in this position, the risk of displacement of the tracheostomy tube may be increased.[5,10] Fracture of the tracheostomy tube with migration into the tracheobronchial tree is a rare complication, even in supine-positioned patients. It is the first report of a fractured tracheostomy tube in a prone-positioned patient.

The first case report of a fractured tracheostomy tube was reported by Howarth[11] in 1913, although Bassoe and Boe[12] are known as the first. Since then, this complication has been published in the literature occasionally. Occasionally cases are reported in 65 articles after an extensive literature review.[11-75] Material and fracture sites of the tubes, possible causes and timing of the events, dislodgement sites, and treatment modalities are some of the topics worth discussing. The fracture of tracheostomy tube can occur from the first minutes of its placement and 22 years later.[53] Early breakage is usually considered a manufacturing defect.[14] Fractures after prolonged usage may be due to mechanical (repeated cleaning/boiling or sterilization, suctioning, removal, and reinsertion) or chemical (alkaline bronchial secretions, corrosive cleaning agents) stress.[14,26,28-30,35,36,42,56] Our review of 92 cases revealed that; 66 (71%) of fractures appeared to be associated with prolonged use (repeated boiling, corrosion, and cracking), 13 (14%) appeared to be associated with manufacturing defect and 2 (2%) were attributed to mechanical stress. There are no available data about the rest.

Tracheostomy tubes are made of metal, polyvinyl chloride (PVC), or silicone. Metallic tracheostomy tubes have two main types: Fuller and Jackson. Initially, metallic tubes were thought to allow for prolonged wear due to their physical properties. Silver, steel, copper, or zinc were the materials for manufacturing these tubes, all with poor corrosion resistance to alkaline pH. As a result, they have been corrodible by tracheal secretions and repeated boiling.[12,52,64] Fractures occur less frequently in PVC and silicone tubes than in metallic tubes.[48] In this study, the PVC tracheostomy tube was used only for five days before fracturing. Although it is plausible to consider a manufacturing defect that might have contributed to the fracture with its short time use, we believe that prone positioning might also contribute to the mechanical stress created by kinking of the tube. Therefore, this case appears to be an unusual complication of prone positioning.

Most fractures occur at the junction of the cannula and neck plates. As Table 1 reflects the author's own words, the term "flange" has been used instead of "neck plate" in some reports. On the other hand, the Fuller metallic tubes have flanges at the distal end of the main cannulas and sometimes get fractured at the junction of these flanges.[53] There are 31 reports about fractured PVC tubes in the literature; two have no data about the fracture sites, and only one siliconized PVC tube was fractured from the mid-shaft. In our case, the tracheostomy tube fracture occurred at the junction of the cannula and neck plate, similar to the other reported cases of fractured PVC tracheostomy tubes. The manufacturers of PVC tubes should be warned about strengthening the connection between the two components of the tubes. Li et al.[42] and friends mentioned that they filed a Medical Device Alert form, and the tube was returned to the supplier in their report. Hence, the supplier redesigned to incorporate a new shaft-to-head base assembly method to strengthen the connection.

RMB is more exposed to the lodgment of foreign bodies since it is mostly vertically positioned and has a larger diameter than the left main bronchus.[75] It was also the most common dislodgement site for fractured tubes (37 cases).

Clinical presentation depends on factors such as patient status, dislodgement style, and site of the fractured tube. Patients tracheostomized for chronic respiratory disorders can present with mild respiratory distress, cough, wheezing, recurrent pneumonia, and difficulty suctioning or reinserting the inner tube.[64,74] Some cases even remain asymptomatic in which the fractured part acts like a stent in the trachea or main bronchus.[36,62] Death may also occur, especially in pediatric patients, probably due to the small airway caliber.[28,54] Our patients suffered from acute and severe ARDS, and disconnection of the two parts of the tube resulted in inadequate mechanical ventilation. He needed urgent orotracheal intubation because of sudden hypoxia.

Large foreign bodies in the tracheobronchial tree are usually removed by rigid bronchoscopy. It is also recommended for the removal of fractured tracheostomy tubes in the literature. A bronchoscope is usually inserted through the tracheostomy stoma to avoid vocal cords and oral cavity from mechanical injury caused by a fractured tube during removal.[64] Flexible bronchoscopy, local exploration of the tracheostome, and removal with forceps, nasal endoscope, or Desjardin's forceps under C-arm guidance through the tracheostome, thoracotomy, and bronchotomy are some other treatment approaches.[33,40,61,63,65]

Conclusion

Fracture and aspiration of the tracheostomy tube is a rare complication that can occur anytime after tracheostomy. Regular care and replacement of worn-out tracheostomy tubes are essential to avoid this complication in patients with chronic tracheostomy. We also recommend checking

Table 1. Summary of the previous case reports

Year	Author (S)	Lodging site	Sex	Age	Possible cause	The duration of the wearing the same tracheostomy tube	Material	Fracture site	Treatment
1913	Howarth[11]	RMB	M	NAD	NAD	NAD	NAD	NAD	NAD
1960	Bassoe and Boe[12]	RMB	F	35 y	Prolonged use ("season cracking", long continued high internal stress in the surface)	6 m	Metallic (silver and nickel)	Distal end of cannula	Bronchoscopy
1972	Kemper et al.[13]	T and RMB	M	48 y	NAD	NAD	Metallic	Inner tracheostomy tube	NAD
1972	Kakar and Saharia[14]	T and LMB	M	40 y	Prolonged use	2 y	Metallic (copper and zinc)	Junction between tube and neck plate	Bronchoscopy
1973	Sood[15]	T	M	60 y	Prolonged use (repeated boiling)	5 y	PVC	Junction between tube and flange	NAD
1978	Maru et al.[16]	T and LMB (2 pieces)	M	50 y	Prolonged use	6 m	Metallic	Junction between tube and neck plate/midshaft	One of the pieces removed from widening tracheostome, other removed by bronchoscopy
1981	Gupta and Chhangani[17]	RMB	M	10 y	Prolonged use ("season cracking", long continued high internal stress in the surface)	4 y	Metal (silver and nickel)	Flange	Bronchoscopy
1981	Gupta and Chhangani[17]	LMB	M	15 y	Prolonged use ("season cracking", long continued high internal stress in the surface)	2 y	Metal (silver and nickel)	Flange	Bronchoscopy (through tracheostome)
1983	Okafor[19]	T and RMB	M	40 y	Prolonged use	8 y	Metal (silver and zinc)	Junction between tube and neck plate	Bronchoscopy (through the enlarged tracheostome)
1983	Bhalla et al.[18]	LMB	F	50 y	Prolonged use	2 y	NAD	Midshaft of outer tube	Bronchoscopy (through tracheostome)
1984	Myatt and Willatts[20]	T and RMB	M	76 y	Prolonged use	12 y	Metallic (silver)	Junction between tube and neck plates (Outer cannula)	Rigid bronchoscopy (through tracheostome)
1985	Bowdler and Emery[21]	T and RMB	M	3 y	Prolonged use	6 w	Metallic (silver)	Junction between tube and neck plates (outer cannula)	Bronchoscopy (through tracheostome)
1985	Bowdler and Emery[21]	C and RMB	M	76 y	Prolonged use	7 y	Metallic (silver)	Junction between tube and neck plates (outer cannula)	Bronchoscopy (through the enlarged tracheostome)
1985	Otto and Davis[22]	T and RMB	NAD	3 y	Manufacturing defect	6 m	Metallic (stainless steel)	Junction of the tube and flange	Bronchoscopy

Table 1. Continued

Year	Author (S)	Lodging site	Sex	Age	Possible cause	The duration of the wearing the same tracheostomy tube	Material	Fracture site	Treatment
1987	Gupta[23]	C	M	30-70 ys	Repeated boiling/Prolonged use/Erosion by secretions/Manufacturig defect (Reported with a "case series", no specific data)	NAD	Metallic (Fuller)	Flange	Bronchoscopy (through tracheostome)
1987	Gupta[23]	T	M	13 y	Repeated boiling/Prolonged use/Erosion by secretions/Manufacturig defect (Reported with a "case series", no specific data)	NAD	PVC	Junction	Bronchoscopy (through tracheostome)
1987	Gupta[23]	T	M	30-70 ys	Repeated boiling/Prolonged use/Erosion by secretions/Manufacturig defect (Reported with a "case series", no specific data)	NAD	PVC	Junction	Bronchoscopy (through tracheostome)
1987	Gupta[23]	RMB	M	30-70 ys	Repeated boiling/Prolonged use/Erosion by secretions/Manufacturig defect (Reported with a "case series", no specific data)	NAD	Metallic (Fuller)	Flange	Bronchoscopy (through tracheostome)
1987	Gupta[23]	RMB	M	30-70 ys	Repeated boiling/Prolonged use/Erosion by secretions/Manufacturig defect (Reported with a "case series", no specific data)	NAD	Metallic (Fuller)	Flange	Bronchoscopy (through tracheostome)
1987	Gupta[23]	RMB	M	30-70	Repeated boiling/Prolonged use/Erosion by secretions/Manufacturig defect (Reported with a "case series", no specific data)	NAD	Metallic (Fuller)	Flange	Bronchoscopy (through tracheostome)
1987	Gupta[23]	RMB	M	30-70	Repeated boiling/Prolonged use/Erosion by secretions/Manufacturig defect (Reported with a "case series", no specific data)	NAD	Metallic (Fuller)	Flange	Bronchoscopy (through tracheostome)
1987	Gupta[23]	LMB	M	30-70 ys	Repeated boiling/Prolonged use/Erosion by secretions/Manufacturig defect (Reported with a "case series", no specific data)	NAD	Metallic (Fuller)	Flange	Bronchoscopy (through tracheostome)
1987	Gupta[23]	LMB	M	30-70 ys	Repeated boiling/Prolonged use/Erosion by secretions/Manufacturig defect (Reported with a "case series", no specific data)	NAD	Metallic (Fuller)	Flange	Bronchoscopy (through tracheostome)

Table 1. Continued

Year	Author (S)	Lodging site	Sex	Age	Possible cause	The duration of the wearing the same tracheostomy tube	Material	Fracture site	Treatment
1987	Slotnick et al.[24]	RMB	M	67 y	Prolonged use	2 y	Metallic	The junction of the neck plate and tube (Inner cannula)	Bronchoscopy (through oral cavity, extraction through tracheostome)
1987	Slotnick et al.[24]	LMB	M	55 y	Prolonged use	7 y	Metallic	The junction of the neck plate and tube (Outer cannula)	Fiberoptic bronchoscope (through tracheostome)
1988	Jensen and Pedersen[25]	T	M	8 m	Mechanical stress	3 m	PVC	Junction of the tube and flange	Partly fractured cannula was changed using a suction catheter as a guide
1988	Jensen and Pedersen[25]	T	M	14 m	Mechanical stress	6 m	PVC	Junction of the tube and flange	Rigid bronchoscopy (through tracheostome)
1989	Ming and Ghani[27]	RMB	M	50 y	Manufacturing defect	3 d	Metallic (silver)	Junction between tube and (both inner and outer cannula)	Rigid bronchoscopy (through tracheostome)
1989	Majid[26]	LMB	F	63 y	Prolonged use	1 y	Metallic	Junction between tube and neck plates (outer cannula)	Rigid bronchoscopy (through tracheostome)
1987	Gupta[23]	RMB	M	7 y	Prolonged use	2 y	Metallic (Fuller)	Flange	Exitus
1991	Brockhurst and Feltoe[28]	NAD	F	16 m	Corrosion and cracking	NAD	Metallic(silver)	Junction between tube and neck plate (inner cannula)	Exitus
1992	Bhatia et al.[30]	NAD	M	68 y	Prolonged use	1,5 y	PVC	Junction of the tube and flange	NAD
1992	Bhatia et al.[30]	NAD	M	58 y	Prolonged use	6	PVC	Junction of the tube and flange	NAD
1992	Bhatia et al.[30]	NAD	M	63 y	Prolonged use	12	PVC	Junction of the tube and flange	NAD
1993	Rastogi et al.[31]	NAD	M	65 y	Repeated cleaning and boiling	24 d	PVC	Junction	NAD
1994	Bhattacharjee[32]	NAD	M	60 y	Repeated cleaning and boiling	3 m	PVC	Junction	NAD
1994	Bhattacharjee[32]	NAD	M	40 y	Repeated cleaning and boiling	2 m	PVC	Junction	NAD
1995	Kochhar et al.[33]	T	M	24 y	Manufacturing defect	Few m	PVC	Junction between tube and neck plate	Release with forceps through the tracheostome

Table 1. Continued

Year	Author (S)	Lodging site	Sex	Age	Possible cause	The duration of the wearing the same tracheostomy tube	Material	Fracture site	Treatment
1996	Gupta and Ahluwalia[34]	RMB and left posterior basal segment	M	10 y	Prolonged use	18 m	Metallic	Flange	Bronchoscopy (through tracheostome)
1999	Krempl and Otto[35]	T and RMB	M	48 y	NAD	NAD	NAD	Fenestra	NAD
2000	Gana and Takwoingi[36]	RMB and LMB	M	7 y	NAD	NAD	PVC	NAD	Bronchoscopy (through tracheostome)
2000	Yeh et al.[37]	LMB	M	77	Prolonged use, repeated cleaning and boiling	10 y	Metallic	Junction between tube and neck plate	The fiberoptic bronchoscope
2001	Poorey and Iyer[38]	LMB	M	28 y	Prolonged use	20 y	Metallic (Fuller)	Flange	Bronchoscopy
2003	Fraga et al.[39]	T	F	6 y	NAD	NAD	PVC	NAD	Bronchoscopy (through tracheostome)
2002	Ng et al.[40]	T and LMB	M	3 y	Prolonged use	21	Siliconized PVC	Junction	Flexible bronchoscopy (through tracheostome)
2003	Shivakumar et al.[41]	T	M	20 y	Prolonged use	5 y	Metallic (Fuller's tube)	Junction between tube and neck plates (Inner cannula)	Release through the tracheostomy after an incision
2005	Li et al.[42]	T	M	47 y	Manufacturing defect	28 d	PVC	Junction	Rigid bronchoscopy
2006	Qureshi et al.[43]	LMB	M	6 y	NAD	NAD	NAD	NAD	NAD
2007	Yoo et al.[44]	T	NAD	NAD	NAD	NAD	NAD	NAD	Flexible bronchoscopy
2007	Wu et al.[45]	T and LMB	F	14 m	Manufacturing defect	7 h	PVC	Junction between tube and neck plate	Bronchoscopy
2009	Radpey et al.[46]	LMB	M	41 y	Prolonged use	2 y	Metallic	Shaft	Rigid bronchoscopy (through tracheostome)
2009	Simtoco et al.[47]	The left upper quadrant of the abdomen	M	4 y	Prolonged use	40 m	PVC	Junction between tube and neck plate	Abdominal surgery
2010	Piromchai et al.[48]	RMB	M	14 y	Prolonged use	4 y	Metallic (stainless steel)	Junction between the inner tube and connector	Rigid bronchoscopy (through tracheostome)
2001	Srirompotong and Kraitrakul.[49]	LMB	M	7	NAD	NAD	NAD	Inner tracheostomy tube	Bronchoscopy (through tracheostome)

Table 1. Continued

Year	Author (S)	Lodging site	Sex	Age	Possible cause	The duration of the wearing the same tracheostomy tube	Material	Fracture site	Treatment
2010	Piromchai et al.[48]	LMB	F	5 y	NAD	NAD	NAD	NAD	Bronchoscopy
2011	Feng et al.[51]	RMB	M	81 y	NAD	NAD	NAD	NAD	NAD
2011	Feng et al.[51]	LMB	F	95 y	Prolonged time with improper care	NAD	NAD	Junction between tube and flange	NAD
2011	Herrag et al.[52]	LMB	M	52 y	Prolonged use	2 y	Metallic (Copper and zinc)	Junction between neck plate and tube	Flexible bronchoscopy (through tracheostome)
2011	Herrag et al.[52]	LMB	M	50 y	Prolonged use	5 y	Metallic (Copper and zinc)	Junction between neck plate and tube	Flexible bronchoscopy (through tracheostome)
2011	Agarwal and Agarwal[53]	LMB	F	35 y	Prolonged use	22 y	Metallic	Midshaft (a flange)	Rigid bronchoscopy (through tracheostome)
2012	Lynrah et al.[54]	T	F	5 y	Manufacturing defect	2 d	PVC	Junction between tube and flange	0^0 nasal endoscope (through tracheostome)
2012	Lynrah et al.[54]	RMB	M	7 y	Manufacturing defect	5 d	PVC	Junction between tube and flange	Bronchoscopy
2012	Lynrah et al.[54]	RMB	F	8 y	Manufacturing defect	NAD	PVC	Junction between tube and flange	Exitus
2014	Poduval et al.[55]	T	M	5 y	Prolonged use	3 y	Metallic	Junction between tube and neck plates (Outer cannula)	Rigid bronchoscopy (through tracheostome)
2014	Parida et al.[56]	T	M	1 y	Prolonged use	3 m	PVC	Junction between tube and neck plate	Local wound exploration and removal under direct vision
2014	Parida et al.[56]	T	F	11 y	Prolonged use	22 m	PVC	Junction between tube and neck plate	Bronchoscopy (through tracheostome)
2014	Parida et al.[56]	RMB	M	8 y	Prolonged use	25 m	Metallic (Jackson tube; copper, zinc, nickel)	Junction between tube and neck plates (inner cannula)	Bronchoscopy (through tracheostome)
2014	Parida et al.[56]	RMB	M	9 y	Prolonged use	2 y	Metallic (Jackson tube; copper, zinc, nickel)	Junction between tube and neck plate	Bronchoscopy (through tracheostome)

Table 1. Continued

Year	Author (S)	Lodging site	Sex	Age	Possible cause	The duration of the wearing the same tracheostomy tube	Material	Fracture site	Treatment
2014	Parida et al.[56]	RMB	F	13 y	Prolonged use	35 m	Metallic (Jackson tube; copper, zinc, nickel)	Junction between tube and neck plates (inner cannula)	Bronchoscopy (through tracheostome)
2014	Parida et al.[56]	RMB	F	15 y	Prolonged use	4 y	Metallic (Fuller tube; copper and zinc)	Junction between tube and flange	Bronchoscopy (through tracheostome)
2014	Parida et al.[56]	T and LMB	F	6 y	Prolonged use	30 m	Metallic (Jackson tube; copper, zinc, nickel)	Junction between tube and neck plates (inner cannula)	Bronchoscopy (through tracheostome)
2014	Parida et al.[56]	RMB	F	7 y	Prolonged use	10 m	PVC	Junction between tube and neck plate	Bronchoscopy (through tracheostome)
2014	Loh et al.[57]	RMB	F	70 y	Prolonged use	2 y	PVC	Midshaft	Flexible bronchoscopy (through tracheostome)
2015	Guggarigoudar[58]	RMB	F	11 y	Prolonged use	1 y	Metallic	Outer tube	Rigid bronchoscopy
2015	Kumar et al.[59]	RMB	M	24 y	Prolonged use	4 y	Metallic	flange	Bronchoscopy (through tracheostome)
2015	Al-Momani et al.[60]	LMB	F	4 y	Manufacturing defect	2 m	PVC	Junction between tube and neck plate	Rigid bronchoscopy (through oral cavity)
2016	Rana et al.[61]	RMB	M	67 y	Prolonged use	4 y	Metallic	Junction between tube and neck plate	Desjardin forceps (through tracheostomy under C-arm guidance)
2016	Viswanathan and Esakkimuthu[62]	RMB	M	4 y	Prolonged use	3 y	Metallic	Junction between tube and neck plate	Rigid bronchoscopy (through tracheostome)
2016	Ranjnan et al.[63]	T, RMB, and IM	M	65 y	Prolonged use	4 m	Synthetic	NAD	Thoracotomy and bronchotomy
2016	So-Ngern and Boonsarngsuk[64]	LMB	M	65 y	Prolonged use	18 m	Metallic	Midshaft of outer tube	Rigid and flexible bronchoscopy
2017	Moideen et al.[65]	LMB	M	42 y	Prolonged use	2 y	Metallic	Junction between neck plate and tube	The nasal endoscope (through tracheostome)
2018	Wongsa[66]	LMB	F	78 y	NAD	NAD	Metallic	Midshaft of inner tube	Rigid bronchoscopy

Table 1. Continued

Year	Author (S)	Lodging site	Sex	Age	Possible cause	The duration of the wearing the same tracheostomy tube	Material	Fracture site	Treatment
2020	Bd and Kothari[67]	T	M	50 y	Manufacturing defect	Few d	PVC	Junction between tube and flange	Holding with forceps through tracheostomy
2019	Akhter et al.[68]	C	F	3 y	Manufacturing defect	Few d	PVC	Junction between tube and neck plate	Rigid bronchoscopy (through tracheostome)
2019	Kumar et al.[69]	LMB	M	50 y	Prolonged use	2 y	Metallic	Junction between tube and neck plate	Rigid bronchoscopy (through tracheostome)
2020	Parida et al.[70]	C	M	14 y	Prolonged use	8 y	Metallic (Jackson's tube; copper, zinc, nickel)	Junction between inner tube and neck plates	Rigid bronchoscopy
2020	Parida et al.[70]	T	M	6 y	Prolonged use	63 m	PVC	Junction between inner tube and neck plates	Rigid bronchoscopy
2020	Parida et al.[70]	RMB	F	12 y	Prolonged use	4 y	Metallic (Fuller's tube; copper and zinc)	Just distal to the junction of two flanges	Rigid bronchoscopy
2020	Kashoob et al.[71]	RMB	M	29 y	Prolonged use	14 y	Metallic (Jackson)	Junction between neck plate and tube(inner parts)	Rigid bronchoscopy
2020	Mohammadi et al.[72]	RMB	M	58 y	Manufacturing defect	14 d	PVC	Junction between neck plate and tube	Rigid bronchoscopy
2021	Chehbouni and Benhoummad[73]	LMB	M	70 y	Prolonged use	3 y	Metallic	Tip of the inner cannula	Bronchoscopy (through tracheostome)
2022	Singhal et al.[74]	LMB	M	7 y	Manufacturing defect	1 d	PVC	Junction between the neck plate and tube	Rigid bronchoscopy (through tracheostome)

RMB, right main bronchus; LMB, left main bronchus; LPBS, left posterior basal segment; T, trachea; C, carina; NAD, no available data; PVC, polyvynylchloride; IM, intermediate bronchus; F, female; M, male; d, day (s); m, month (s); y, year (s); w, week (s) *"possible causes" are usually mentioned with the own words of the authors.

for manufacturing defects before insertion. Tubes can be manufactured as single rather than two connected pieces. On the other hand, we think that mechanical stress associated with prone positioning may have facilitated the fracture of the tracheostomy tube in this study. Tracheostomy tubes should be avoided kinking and mechanical stress during prone positioning.

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Management of Aneurysmal Subarachnoid Haemorrhage and its Complications: A Clinical Guide

Özlem Korkmaz Dilmen[1], Vincent Bonhomme[2]

[1]Department of Anaesthesiology and Reanimation, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey
[2]Department of Anaesthesia and Intensive Care Medicine, Liege University Hospital, Liege, Belgium and Anaesthesia and Perioperative Neuroscience Laboratory, GIGA-Consciousness Thematic Unit, GIGA-Research, Liege University, Liege, Belgium

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Abstract

Aneurysmal subarachnoid hemorrhage (aSAH) is an emergency that needs prompt diagnosis and treatment with endovascular coiling or surgical clipping of the aneurysm to prevent re-bleeding. In addition to neurologic manifestations, aSAH can cause respiratory and cardiovascular complications. The prevention of hypoxemia and hypercarbia, control of intracranial pressure, and restoration of cerebral perfusion pressure should be the primary aims of early management. Secondarily, the most important causes of persistent neurological deficits and physical dependence in aSAH are vasospasm and delayed ischemia following bleeding. During that period, a focus on the detection, prevention, and treatment of vasospasm should be the rule. Transcranial Doppler allows detection and follow-up of vasospasm, especially in severe cases. Nimodipine is the only drug that has proven efficacy for treating vasospasm. Balloon angioplasty is performed in cases of resistance to medical treatment. Along with angioplasty, intra-arterial vasodilators can be administered. New diagnostic and therapeutic advances will hopefully improve outcomes in the near future.

Keywords: Brain ischemia, intracranial aneurysm, pulmonary edema, subarachnoid hemorrhage, vasospasm

Main Points

- The ruptured aneurysms should be repaired as soon as possible to reduce the risk of re-bleeding by surgical clipping or endovascular coiling.
- Providing normoxemia and normocapnia, reduction of intracranial pressure should be the primary aims of early management.
- The monitoring, prevention and treatment of vasospasm and delayed ischemia following bleeding are essential.
- Pressure or oxygen reactivity index monitor provides determining optimal cerebral perfusion pressure (CPP).
- Keeping patient CPP in their optimum autoregulation range may improve long-term neurological outcomes.

Introduction and Epidemiology

Aneurysmal subarachnoid hemorrhage (aSAH) is mostly caused by the rupture of saccular aneurysms and its global incidence ranges between 2 and 16/100,000 persons a year.[1] SAH constitutes 2 to 5% of all strokes, and its mortality rate is estimated to range between 32 and 67%. Half of the survivors lives with varying degrees of physical dependence.[2] The main modifiable risk factors are smoking, high blood pressure, alcohol, and cocaine abuse. Other risk factors include Finnish or Japanese nationality, female sex, Ehlers-Danlos type IV syndrome, autosomal dominant polycystic kidney diseases, neurofibromatosis type I, Marfan syndrome, a family history of aneurysm, and aSAH.[3-6]

Corresponding author: Özlem Korkmaz Dilmen, e-mail: korkmazdilmen@gmail.com ozlem.dilmen@iuc.edu.tr
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Clinical Features

Most intracranial aneurysms remain asymptomatic until they rupture. Generally, at the time of rupture, patients suffer from the worst headache of their life. Other signs and symptoms include nausea, vomiting, stiff neck, photophobia, focal neurologic deficits including cranial nerve palsies, deterioration of consciousness, coma, and seizures. Some of them suffer from unusual headaches some days before the rupture due to episodes of minor bleeding.

Diagnosis

Patients with suggestive clinical presentation, especially when sudden onset neurological deficits and altered state of consciousness are noted, should benefit from a first intention radiological evaluation in the form of cranial computed tomography (CT) without contrast. The characteristic CT manifestations of SAH are hyperdensities in the subarachnoid spaces and cisterns. In case of equivocal CT, lumbar puncture is traditionally proposed as the next diagnostic approach, but nowadays CT or magnetic resonance angiography (CTA or MRA) are preferred. If SAH is detected on CT, digital subtraction angiography (DSA) is usually performed so that three-dimensional images can be reconstructed and the eventual aneurysm localized.

The severity of aSAH is categorized using the World Federation of Neurological Surgeons (WFNS) or Hunt and Hess Score grading systems (Table 1, 2).[7,8] The WFNS score is based on the Glasgow coma score and the presence or absence of motor deficits, while the Hunt and Hess score takes into account associated clinical signs and symptoms. The clinical grade correlates with the severity of the haemorrhage and the risk of subsequent morbidity and mortality. The Fisher grade scale is based on the aspect of blood deposition on CT (Table 3, Figure 1). Higher Fisher grades are associated with a higher incidence of vasospasm and delayed cerebral ischemia (DCI).

Early Management

Subarachnoid hemorrhage patients have better outcomes in centers treating a large number of them.

Table 1. World Federation of Neurological Surgeons Grading Scale

	Glasgow coma scale	Motor deficit
1	15	Absent
2	13-14	Absent
3	13-14	Present
4	7-12	Present or absent
5	2-6	Present or absent

Similar to the management of all brain-injured patients, the management of SAH patients should focus on maintaining brain homeostasis and avoid secondary brain injuries of systemic origin. Special attention should be paid to avoid prolonged episodes of anaemia, hypo-or hyperthermia, hypo-or hyperglycaemia, hypo- or hyperoxemia, hypo-hypertension, and hypo-or hypernatremia. Therefore, SAH patients should be monitored adequately and closely in these respects, and adequate measures should be promptly undertaken to correct any detected deviance. Both hypoxemia and hyperoxia have potential harmful effects following brain injury. Lower brain tissue oxygen tension and longer desaturation periods are associated with mortality after SAH.[9] Hyperoxemia-induced cerebral vasoconstriction, which may accelerate brain tissue ischemia, is well-known fact, but the actual cut off value for oxygen is not clear. Both hypercapnia and hypocapnia are associated with poor neurological outcomes. Hypercapnia elevates intracranial pressure (ICP) by inducing vasodilation and thus potentially impairs cerebral perfusion. Hypocapnia produces vasoconstriction and worsens cerebral vasospasm. However, short-term mild hyperventilation can sometimes be applied to decrease raised ICP, but only transiently. To ensure adequate gas exchange control, patients with a Glasgow coma score less than 9 should be intubated and beneficiated from mechanical ventilation using lung protective ventilation protocols described below in the section on neurogenic pulmonary oedema.

Management of Raised Intracranial Pressure and Restoration of Cerebral Perfusion

Acute elevation of ICP following aSAH causes acute neurologic deterioration in patients. Therefore, it is of utmost importance to detect it. Non-invasive optic nerve sheath diameter (ONSD) measurement by ultrasonography

Table 2. Hunt and Hess Grading Scale

0	Unruptured aneurysm
1	Minimal headache, slight nuchal rigidity
2	Moderate to severe headache, cranial nerve palsy, nuchal rigidity
3	Lethargy, confusion, mild focal deficit
4	Stuporous, hemiparetic, mild decerebrate posturing
5	Coma, decerebrate posturing

Table 3. Fisher Scale

1	No blood detected
2	Diffuse deposition or thin layer with all vertical layers of blood (<1 mm thick)
3	Localized clots and or vertical layers of blood ≥1 mm in thickness
4	Diffuse or no subarachnoid blood, but with intracerebral or intraventricular blood

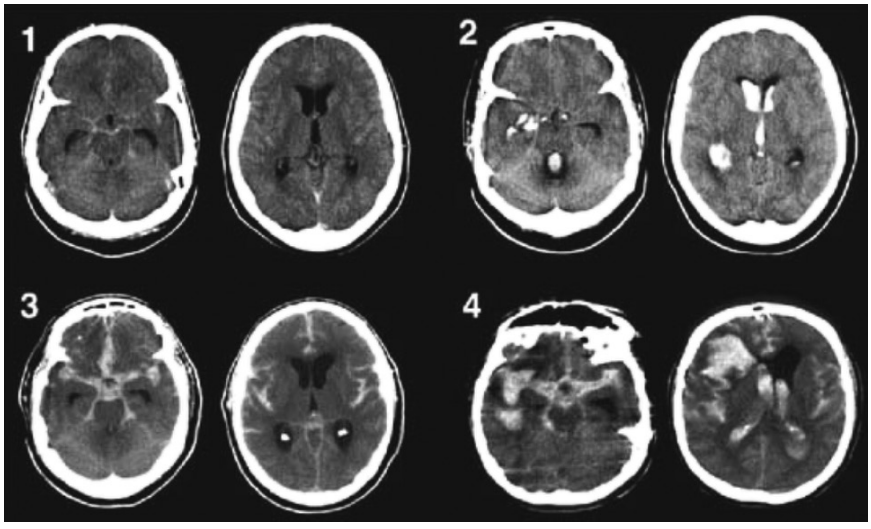

Figure 1. Fisher scale.

and transcranial Doppler (TCD) provide rapid diagnosis of raised ICP. More than 6 mm ONSD indicates elevated ICP (Figure 2). When a decreased diastolic flow velocity and increased pulsatility index above 2.13 are observed with TCD, a raised ICP should be suspected (Figure 3). The pulsatility index is a reflection of peripheral resistance, which is equal to the difference between the peak systolic velocity and end diastolic velocity divided by the mean velocity. A diastolic flow reversal indicates a severely elevated ICP.[10]

The early placement of an external ventricular drain (EVD) and cerebrospinal fluid (CSF) drainage reduces ICP and helps restore CPP. Noteworthy, excessive and rapid CSF drainage can cause an acute increase in the transmural pressure gradient at the level of the aneurysm wall and may favor re-bleeding if the aneurysm is not secured by coiling or clamping.[11]

There is no consensus regarding the duration and modalities of CSF drainage in aSAH. In a randomized, controlled study involving 60 patients and comparing intermittent and continuous drainage, EVD occlusion, bleeding, and infection were found to be more frequent in the continuous drainage group of patients. There was no difference between groups in terms of ICP control, occurrence of delayed ischemia, and quality of functional recovery.[12] CSF drainage by EVD or lumbar catheter reduces the risk of vasospasm, especially in aSAH cases with high Fisher grades.[13] Osmotic diuretics, mannitol, or hypertonic saline can be used in combination with CSF drainage to control ICP and CPP, as well as transient mild hyperventilation, as mentioned above.

The optimal CPP is unclear in different phases following SAH. The American Heart Association (AHA) guidelines recommend keeping systolic arterial pressure less than 160 mmHg by using nicardipine, labetalol, or esmolol to prevent re-bleeding until surgical clipping or endovascular

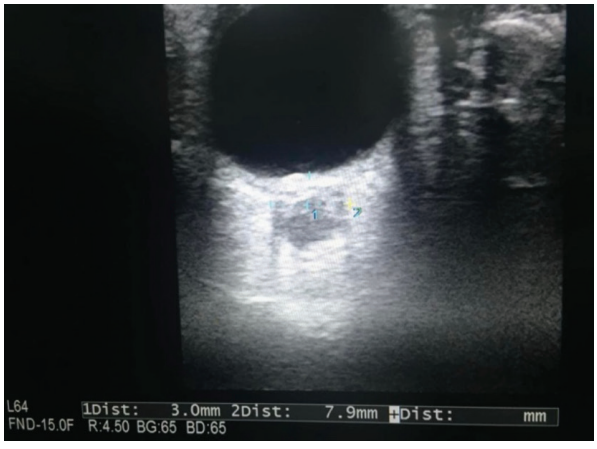

Figure 2. Measurement of optic nerve sheat diameter.

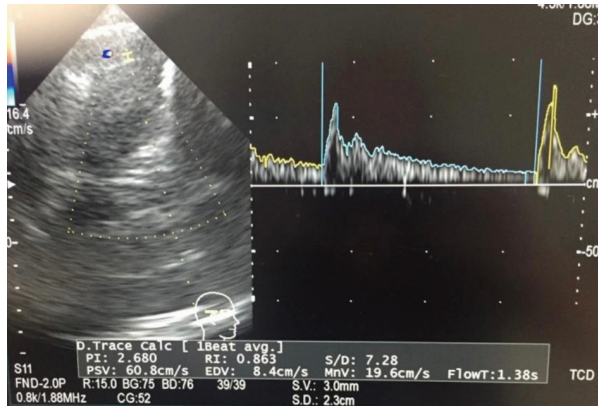

Figure 3. Transcranial Doppler in elevated intracranial pressure.

coiling are performed.[14] The aggressive management of blood pressure reduces the risk of re-bleeding, however, at the expense of an increased risk of secondary ischemia. In general, hypertension is advised following surgical clipping or endovascular coiling to prevent DCI, but the efficacy of induced hypertension has not been shown by randomized controlled studies.[15] There is an interindividual variability in cerebral autoregulation (CA). The continuous evaluation of CA has been developed by measuring the pressure reactivity index that calculates the Pearson correlation coefficient between the ICP and the mean arterial pressure. The oxygen reactivity index uses brain tissue oxygenation as a surrogate for cerebral blood flow. In addition, the measurement of cerebral oxygen saturation with near-infrared spectroscopy has been used as a continuous autoregulatory index. The cortical spreading depolarization (CSD) occurrence is correlated with impaired CA and may represent the pathological mechanism of DCI in patients with impaired CA. Keeping patients' cerebral perfusion pressures in their optimum CA range following aSAH may lead to a decreased incidence of CSD and improve long-term neurological outcomes.[16]

The occlusion of CSF passageways by blood or blood products and adhesions produces acute and chronic hydrocephalus. The patient's age (>65 years), the location of the aneurysm (anterior circulation), the Hunt and Hess IV and V class patients, and the amount of blood in the subarachnoid space and ventricles (Fisher III, IV class) are risk factors for developing shunt-dependent chronic hydrocephalus.[17]

The risk of developing hydrocephalus has been found to be higher after endovascular control of aneurysm compared with surgical clipping. Continuous CSF drainage using a lumbar catheter reduces the risk of hydrocephalus in patients whose aneurysm is excluded through an endovascular procedure.[18,19]

Prevention of Re-bleeding

Re-bleeding occurs in 4 to 13.6% of cases, and most frequently during the first 24 h after aSAH.[20-22] Early securing of the aneurysm by coiling or clipping is the treatment of choice to prevent re-bleeding. High grade on admission, maximal aneurysmal diameter, and hypertension increases the risk of re-bleeding. Hypertension should be treated until surgical clipping or endovascular coiling is performed. The aggressive management of blood pressure reduces the risk of re-bleeding, however, at the expense of an increased risk of secondary ischemia. The AHA guidelines recommend keeping systolic arterial pressure less than 160 mmHg by using nicardipine, labetalol, or esmolol until surgical clipping or endovascular coiling are performed.[14]

In patients chronically using anticoagulants, the treatment should be discontinued. The anticoagulant effects of warfarin or other anti-vitamin K agents should be reversed using prothrombin complex concentrates (50 U kg^{-1}) and vitamin K (10 mg IV) or fresh frozen plasma (10-15 mL kg^{-1} IV). Idarucizumab is used to antagonize dabigatran effects. There is no specific antidote for rivaroxaban, apixaban, and edoxaban, but prothrombin complex concentrates (50 U kg^{-1}) are recommended to partially antagonize their effects.[23]

The systematic intravenous administration of tranexamic acid (usual dose 10-15 mg kg^{-1} over 20 min) to reduce the risk of re-bleeding following aSAH should be considered. A meta-analysis examining the results of 8 studies investigating the use of tranexamic acid in SAH revealed that re-bleeding decreased in all study groups receiving the agent. One study found an increased risk of ischemia after tranexamic acid administration, while no difference was found in the other study. Tranexamic acid administration decreased mortality at a statistically insignificant level.[24] Therefore, tranexamic acid or aminocaproic acid administration is recommended, particularly in case of delayed surgery or endovascular intervention to exclude the aneurysm.

Aneurysm Repair

Ruptured aneurysms should be excluded from the cerebral circulation as soon as possible to reduce the risk of re-bleeding. This can be performed through surgical clipping or endovascular coiling.[14] Although some studies have shown that endovascular coiling reduces mortality and morbidity compared to surgical clipping, the choice of the aneurysm exclusion technique should not be done blindly. The size of an eventual hematoma and the location, size, and shape of the aneurysm should be taken into consideration.[25,26] For example, large neck aneurysms can sometimes not be approached through an endovascular technique. In addition, the experience of the team is essential for the decision.

The Treatment of aSAH-related Complications

Vasospasm and Delayed Ischemic Deficit

The most important cause of neurological deficit in aSAH is vasospasm in the cerebral arterial circulation and delayed ischemia. Vasospasm most commonly occurs as a result of segmental or diffuse macro and microspasms in the cerebral circulation between days 5 to 15 (may extend up to day 21) following bleeding. While the rate of vasospasm detected by angiography ranges between 70 and 90%, symptomatic vasospasm is seen only in one-third of cases.[27,28] Higher Fisher grades are associated with higher risk of vasospasm and DCI.

Pathophysiologically speaking, oxyhemoglobin, free oxygen radicals, and neuro-inflammation are held responsible for

an increased secretion of endothelin-1, which is a potent vasoconstrictor.[29]

Newly developed neurologic deficits should suggest vasospasm; clinical changes that may be due to other causes such as fever, leucocytosis, and hyponatremia should not preclude searching for a vasospasm, insofar as those events can also be seen during the vasospasm process.

The definitive diagnosis of vasospasm is performed by DSA; however, since TCD is non-invasive, and easily performed at the bedside, daily serial measurements using that technique are recommended to improve the detection of vasospasm before its clinical manifestations and to ensure its follow-up. It also helps determine the need for angioplasty and/or intra-arterial vasodilator application.

In high WFNS and high Fisher class patients, a progressive increase in the mean velocity rate within the middle cerebral artery (MCA) during the early stage of SAH indicates vasospasm. The normal MCA mean velocity rate was less than 80 cm s^{-1}. Mild vasospasm velocity rates are considered to range between 120 and 159 cm s^{-1}, moderate vasospasm between 160 and 199 cm s^{-1}, and severe vasospasm over 200 cm s^{-1}. Symptomatic vasospasm is often seen at mean velocities of 160 cm s^{-1}.[10]

The Lindegaard ratio corresponds to the ipsilateral MCA mean velocity divided by the ipsilateral extracranial internal carotid artery velocity. A Lindegaard ratio more than 3 indicates vasospasm, between 3 and 5 mild vasospasm, and more than 6 severe vasospasm.[30]

Nimodipine is the only drug that has been proven to be effective for treating vasospasm. Oral or enteral administration (4x60 mg a day) is more effective than intravenous administration. This calcium channel blocker dilates the arteries, reduces calcium-induced excitotoxicity, and decreases platelet aggregation. Nimodipine treatment should be started within 48 h after bleeding and continued for 21 days. If hypotension develops, vasopressor administration should be started without stopping nimodipine administration.[14]

Early targeted fluid therapy guided by preload and cardiac output monitoring in SAH patients with a high WFNS score reduces the risk of vasospasm and provides better functional outcomes.[31] Because a positive fluid balance adversely affects survival in SAH, the primary aim should be to provide euvolemia.[32]

The optimal hemoglobin (Hb) concentration in patients with SAH is debated. However, a Hb threshold of > 8-10 g dL^{-1} has been advocated in the latest recommendations.[33]

Cerebral microdialysis (CMD) is an invasive neuromonitoring bedside technique using a catheter with a semipermeable membrane probe placed in the brain parenchyma, lactate (L), pyruvate (P), and glucose to enter the perfusate and to be analyzed at hourly intervals. It would be used especially for poor-grade mechanically ventilated SAH patients. CMD can detect energy metabolic changes up to 16 h before DCI, potentially enabling the clinician to provide interventions.[34] When the LP ratio indicates ischemia, i.e., an increase in the LP ratio in the presence of low P, CPP augmentation is a therapeutic option. When the LP ratio is increased in the presence of low brain tissue oxygen, improving oxygen delivery via increasing the cerebral perfusion pressure, increasing inspired concentration of oxygen, and/or correcting anemia should be considered.[35]

Balloon angioplasty is performed in cases of vasospasm resistant to medical treatment. Along with angioplasty, intraarterial nimodipine, nicardipine, verapamil, and milrinone have also been used in cases of vasospasm. Among the aforementioned drugs, nimodipine is the most promising; however, further studies are needed.[36]

Historically, cerebral vasospasm has been advocated as the underlying mechanism of DCI, but studies targeting vasospasm have failed to reduce its incidence. This has driven a search for other involved mechanisms. The microcirculatory dysfunction in the cerebral parenchyma and coagulation alterations as well as fibrinolytic cascades alterations facilitate the development of microthrombosis that plays a role in the development of DCI after SAH. CSD can be observed and is thought to be related to arteriolar vasoconstriction and inverse neurovascular couplings. The high incidence of CSD following SAH increases the risk of DCI. Another process playing a significant role in the development of DCI is neuro-inflammation, which begins at the moment of arterial rupture and involves microglia. Several mechanisms have been investigated to better understand the pathophysiological pathways and find treatment options for DCI, but the complete picture is not yet clear.[37]

Seizures

Seizures develop at a rate of 10 to 20% in aSAH. They may further deteriorate the patient's clinical status. Therefore, anticonvulsant treatment is usually started early after aSAH. However, as the long-term use of anticonvulsants leads to cognitive dysfunction, their prophylactic use raises questions. Currently, it is recommended to initiate prophylactic anticonvulsant therapy in SAH cases where cerebral oedema, or intracerebral or subdural hematoma is evident on CT.[14,36]

Pulmonary Complications

Aneurysmal SAH may cause acute neurologic pulmonary oedema (NPE). The reported prevalence of NPE after SAH is highly variable in the literature and ranges between 27% and 40%.[38,39] Several pathophysiological mechanisms underlying the development of NPE have been described. SAH-induced elevated ICP is responsible for reduced CPP. The possible explanation for overactivation of the sympathetic nervous system because of elevated ICP is the stimulation of the hypothalamus and medulla oblongata. Sympathetic discharge increases the circulating catecholamine concentration and produces pulmonary and systemic vasoconstriction. Pulmonary vasoconstriction raises the pulmonary artery pressure, which in turn leads to an increase in pulmonary capillary permeability and ultimately to pulmonary oedema. Elevated ICP also triggers the release of cytokines, which worsens pulmonary capillary leakage.

NPE develops within minutes or hours in most cases, although a delayed presentation can be seen at 12 to 24 h following the central nervous system insult. The clinical manifestation consists of dyspnea, hypoxemia, tachypnea, rales, and excessive foamy secretions in the endotracheal tube. Symptoms generally resolve within 48 to 72 h following the initiation of the elevated ICP treatment and of the supportive treatment including diuretics and mechanical ventilation. Cardiogenic pulmonary oedema and aspiration pneumonia must be considered as differential diagnoses, especially during the acute phase.

As a rule, when mechanical ventilation is needed to prevent hypoxemia and hypercapnia, lung protective ventilation strategies should be used. They consist of protective tidal volumes (6 to 8 mL kg^{-1}) along with respiratory rate to avoid hypercapnia and its related increase in cerebral blood flow and ICP. Hypocapnia should also be avoided because of the associated risk of cerebral ischemia. Consequently, normocapnia ($PaCO_2$ between 35 and 40 mmHg) should be targeted. Hyperoxia has negative effects on survival after SAH. Hypoxemia (PaO_2 <60 mmHg and peripheral oxygen saturation <90%) can be prevented by optimizing the inspired oxygen fraction and positive end-expiratory pressure (PEEP). In normovolemic patients, if the patient's lung compliance is low, the application of PEEP up to 15 cm H_2O does not increase ICP. In the case of PEEP-induced low blood pressure, CPP may be impacted, and this should be prevented by fluid therapy and vasopressors.[40-42]

Fluid therapy can be guided with daily pulmonary ultrasonography evaluation, which can reveal B lines reflecting pulmonary oedema and interstitial fluid in patients with SAH.[43] Monitoring the cardiac output via transpulmonary thermodilution and pulmonary extravascular lung water (EVLW) can also be a guide for fluid therapy.[44] In lung oedema, EVLW increases either because of increased lung permeability or because of increased hydrostatic pressure in the pulmonary capillaries, or both. Transpulmonary thermodilution also provides the pulmonary vascular permeability index, which is an indirect reflection of the integrity of the alveolocapillary membrane. Fluid administration should be limited when EVLWI is already high.

Cardiovascular Complications

Electrocardiographic (ECG) changes such as ST-T wave changes, stress cardiomyopathy, and arrhythmias may develop due to the increase in sympathetic activity, especially in patients with high WFNS scores following aSAH. The incidence of ECG changes is 75% and the incidence of abnormal echocardiographic findings is 17% in patients with SAH. After the aneurysm is excluded, ECG changes often improve on the first following day, and ejection fraction and regional myocardial wall motion abnormalities improve on the second day.[45] Regional movement disorder in the myocardium and an increase in troponin I and brain natriuretic peptide are observed when stress cardiomyopathy is present (Takotsubo cardiomyopathy, neurogenic stunned myocardium). Supportive therapy with inotropes is the predominant treatment for stress cardiomyopathy.

Venous Thromboembolism

The incidence of venous thromboembolism is high in patients with aSAH and is an important cause of morbidity and mortality. The incidence of deep vein thrombosis (DVT) and pulmonary embolism is 3.4-24%.[46] Non-pharmacological prevention methods such as intermittent compression devices or compression stockings are usually applied during the early period, and pharmacological thromboembolism prophylaxis is delayed to prevent re-bleeding and allow surgery when needed. Note that pharmacological prophylaxis with low-molecular-weight heparin is recommended at the earliest 24 h after bleeding.[47]

High D-dimer levels, intraparenchymal hematoma, and motor deficits are important risk factors for DVT. The lower extremity venous Doppler should be performed early in patients with these criteria.

Neuroendocrine Disorders

The most common metabolic problem in aSAH is hyponatremia (<135 mmol L^{-1}) and the most common reason is cerebral salt wasting. The cerebral salt wasting syndrome is characterized by a hypovolemia and an increase in urine output and urinary sodium concentration (>50 mmol L^{-1}). This is due to an increase in brain natriuretic peptide secretion. The treatment of cerebral salt wasting

syndrome involves sodium and fluid replacement. In addition, fludrocortisone administration provides sodium reabsorption from the distal tubules. Inappropriate antidiuretic hormone secretion syndrome (SIADH) can also be seen in SAH cases in which the anterior cerebral circulation is involved. Hyponatremia is also evident in SIADH; however, urine output is not as high as in cerebral salt wasting. Fluid restriction is the mainstay of SIADH treatment.

Hypothalamo-pituitary ischemia and diabetes insipidus (DI) may develop due to decreased CPP and/or vasospasm in the anterior cerebral artery. DI results in hypernatremia (>145 mmol L^{-1}), increased urine output, and hypovolemia. The synthetic ADH analog desmopressin acetate and fluid replacement were used for its treatment. Hypernatremia is an indicator of the poor prognosis in SAH cases.[14]

The negative effects of hypo- and hyperglycemia on neurological recovery are known. It has been shown that blood glucose levels above 140 mg dL^{-1} increase the risk of adverse outcomes and mortality in SAH patients.

Central fever is a common complication of SAH. The causes of central fever are neuronal damage, presence of blood and blood products in the ventricles and subarachnoid space, vasospasm, and systemic inflammatory response. Fever has negative effects on cognitive recovery; therefore, normothermia should be sustained following aSAH.[48]

The Role of Neuroprotection after SAH

Neuroprotection might be an additional strategy to limit the extent of irreversible damage to neuronal cells after aSAH. Several drugs, potentially those blocking the excitatory cascade leading to secondary neuronal death, have been investigated to improve patient outcomes.[49] However, to date, none of them has proven to improve patient outcomes. Amantadine, an N-methyl-D-aspartate receptor antagonist, is widely studied in patients with traumatic brain injury. This substance is promising for the reduction of cognitive dysfunction following SAH.[50] However, further studies are needed to better understand its mechanism of action and better define the therapeutic window where it could be advantageous.

Conclusion

Despite improvements in the diagnosis and treatment facilities of aSAH, it is still an important reason for mortality and morbidity. Besides neurological manifestations, aSAH can cause respiratory and cardiovascular complications. The prevention of hypoxemia and hypercarbia, reduction of ICP, and the restoration of CPP should be the primary aims of early management. Rebleeding is the most common reason for mortality during the acute period. Therefore, ruptured aneurysms should be repaired as soon as possible to reduce the risk of rebleeding by surgical clipping or endovascular coiling. The most important cause of neurological deficit and physical dependence in aSAH is vasospasm between days 5 and 15 the following bleeding. We should focus on monitoring, prevention, and treatment of vasospasm during that period. Nimodipine is the only drug that has been proven to be effective for treating vasospasm. Balloon angioplasty is performed in cases of vasospasm resistant to medical treatment. Along with angioplasty, intra-arterial vasodilators can be administered. New diagnosis and management advances will hopefully improve outcomes in the near future.

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The Efficacy of Erector Spinae Plane Block for Patients Undergoing Percutaneous Nephrolithotomy

Mehmet Uğur Bilgin[1], Zeki Tuncel Tekgül[1], Tansu Değirmenci[2]

[1]Clinic of Anaesthesiology and Reanimation, University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital, İzmir, Turkey
[2]Clinic of Urology, University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital, İzmir, Turkey

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Abstract

Objective: Percutaneous nephrolithotomy (PCNL) is accompanied by somatic and visceral pain intraoperatively and postoperatively. However, pain management strategies lack a decisive consensus. Erector spinae plane block (ESPB) is a novel paraspinal fascial block that can be used in PCNL patients, and we aimed to investigate whether ESPB will reduce intraoperative and postoperative opioid consumption and postoperative pain scores in PCNL patients.

Methods: The study was randomized, controlled, and open-label. Two groups were formed as the control group (GCont) and block group (Gblock), and patients received total intravenous anaesthesia. GBlock received an ESPB catheter in addition in the prone position. Intraoperative parameters and infusion doses, postoperative rescue analgesic doses, and pain scores were recorded. The primary endpoint was intraoperative analgesic consumption, and the secondary endpoints were postoperative pain scores and analgesic consumption.

Results: Sixty-four patients were analyzed. Remifentanil consumption of GCont was found to be significantly higher (GBlock: 0.0865 ± 0.030 vs GCont: 0.1398 ± 0.034, μg kg^{-1} min^{-1}, $P < 0.001$). The control group reported higher pain scores between the 30th min and 24th hours and needed more analgesics between the 1st and 6th hours postoperatively. GBlock received local anaesthetics via ESPB catheter before nephrostomy tube removal and fewer patients needed analgesics [5 patients (15.6%) vs. 28 patients (87.5%), $P < 0.001$]. GCont consumed more tramadol postoperatively (262.5 mg vs. 75 mg, $P < 0.001$).

Conclusion: We found that ESPB reduced intraoperative opioid consumption. It also reduced the need for rescue analgesia and postoperative pain scores during nephrostomy tube removal. We concluded that the ESPB catheter may effectively be used in analgesia management during and after PCNL operations.

Keywords: Erector spinae plane block, nerve block, opioid, pain management, percutaneous nephrolithotomy, regional anaesthesia

Main Points

- Our results showed that erector spinae plane block (ESPB) reduces intraoperative and postoperative opioid consumption and postoperative pain scores.
- In addition, providing effective analgesia during nephrostomy catheter tube removal proves that ESP improves both visceral and somatic pain.
- Thus, we believe that the ESPB is a reliable analgesia option for percutaneous nephrolithotomy patients.

Introduction

Percutaneous nephrolithotomy (PCNL) may lead to severe postoperative pain. Acute pain may originate from the skin, muscles, renal capsule, renal parenchyma, and ureter. Nephrostomy tube removal and ambulation also cause visceral and somatic stimuli.[1] Visceral pain originating from the kidneys and ureters is transmitted via T10-L1 and T10-L2.[2] The cutaneous innervation of the incision site mainly originates from T10-T11 (T8-

Corresponding author: Mehmet Uğur Bilgin, e-mail: ugurbilginege@gmail.com

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T12). Systemic analgesics, regional anaesthesia, small diameter nephrostomy tube or tubeless surgery, and local analgesic infiltration techniques have been tried to improve postoperative pain management in PCNL patients.[3-8]

Erector spinae plane block (ESPB) was described by Forero et al.[9] in 2016 as an analgesic method for thoracic neuropathic pain. It provides unilateral analgesia of the anterior and posterior chest wall by craniocaudal spreading of the local anaesthetics (LA) applied below the fascia of the erector spinae muscle group (ESMG). By changing the injection site caudally, sensation in the abdomen and lumbar region can be blocked.[10]

We hypothesized that ESPB would be a safe and effective analgesia option for PCNL operations and designed our study to evaluate the effectiveness of ESPB for both intraoperative and postoperative analgesia.

We designated our primary goal as comparing the groups for intraoperative opioid consumption. Our secondary goals included comparing the pain scores and opioid consumption of the groups during nephrostomy tube removal, ambulation, and at certain postoperative hours.

Methods

The study was conducted as prospective, randomized, controlled, and open-label in a tertiary referral hospital. We followed the CONSORT 2010 guidelines and adhered to the Declaration of Helsinki. Ethics Committee for Clinical Studies of University of Health Sciences University Turkey, İzmir Bozyaka Training and Research Hospital approved the study with approval no: 5, date: 04.07.2018. Study design was also registered and approved in the ClinicalTrials.gov with the number NCT03652103. The eligible patients were informed about the study during the preoperative evaluation and their written consents were obtained.

A preliminary study was conducted for statistical power analysis based on the average intraoperative opioid consumption. The effect size was calculated as 0.936, with 95% statistical power and 5% type 1 error margin, and the sample size as at least 31 patients per group and 62 in total. 70 patients were enrolled, with the expectation of 62 patients in the end, estimating a drop-off rate of around 10-15%. The patients were assigned to either the Erector Spinae Plane Block Group (GBlock) or the Control Group (GCont) based on computer-generated randomisation.

Patient admission started on September 05, 2018 and ended on March 10, 2019. Patients older than 18 years with American Society of Anesthesiologists Physical Status I or II and 2-3 cm renal stones were included. Preoperative evaluation included coagulation profile, serum creatinine levels, urinalysis, urine culture, and computed tomography scan for urinary tract. Inclusion and exclusion criteria are further explained in the flowchart. After the excluded patients, the study was completed with 64 patients (Figure 1).

In the operating room, patients were monitored with electrocardiogram, blood pressure, pulse oximeter, and bispectral index (BIS). 4-electrode BIS Quatro® (Covidien IIc, USA) sensors were used for BIS monitoring. Induction was carried out with lidocaine 1.5 mg kg^{-1}, propofol 2 mg kg^{-1}, rocuronium 0.5 mg kg^{-1} and remifentanil 1 µg kg^{-1} IV. Total intravenous anaesthesia (TIVA) was commenced with propofol at a rate of 100 µg kg^{-1} min^{-1} and remifentanil at a rate of 0.07 µg kg^{-1} min^{-1} IV. For preventive analgesia, paracetamol 10 mg kg^{-1} IV was administered to all patients after the induction. The anaesthesia management of the patients was carried out by the primer anaesthesiologist of the room who was informed about the study. Hemodynamic and BIS parameters were recorded every five minutes, but the comparison of the groups for hemodynamic and BIS changes was limited to the shortest operation time to include all patients. The propofol infusion dose was titrated so that the BIS value of the patients was between 40 and 60[11]; the remifentanil infusion dose was titrated so that the heart rate and mean arterial pressure values remained within ± 20% of the patient's baseline.

After intubation, patients were positioned in the lithotomy position for ureteroscopy (URS). A ureteral catheter was placed. After retrograde pyelography was performed, patients were placed in the prone position for PCNL. All operations were performed by the same primary attending surgeon, who is also the co-author. Patients in the block group (GBlock) received the ESPB in the prone position after URS. ESPB catheter insertion sites were tailored to the location of the stone, thus surgical incision area, between T7-T10 vertebra levels. With these adjustments, we aimed to align the tip of the catheter with the mid-level of the kidney nerve roots and incision site in the medulla to standardize the LA injection site in all cases.

Following the marking of the thoracic vertebrae levels with a marker pen, the skin area was prepared with Povidone-iodine solution. The intervention was initiated when the transverse processes and the costotransverse joints on the relevant level were distinguished using a linear ultrasound probe. The catheter needle was inserted at a 30° angle to the skin in an in-plane and craniocaudal fashion. The tip of the needle was passed through the lower fascia of the ESMG and halted above the costotransverse joint. 5 mL normal saline (0.9%) was injected to confirm the localization of the needle tip and to aid catheter advance by hydrodissection. The catheter was advanced 2 to 4 cm inside to reach the designated level and reduce the risk of dislocation. Proper placement was confirmed with ultrasonography and then

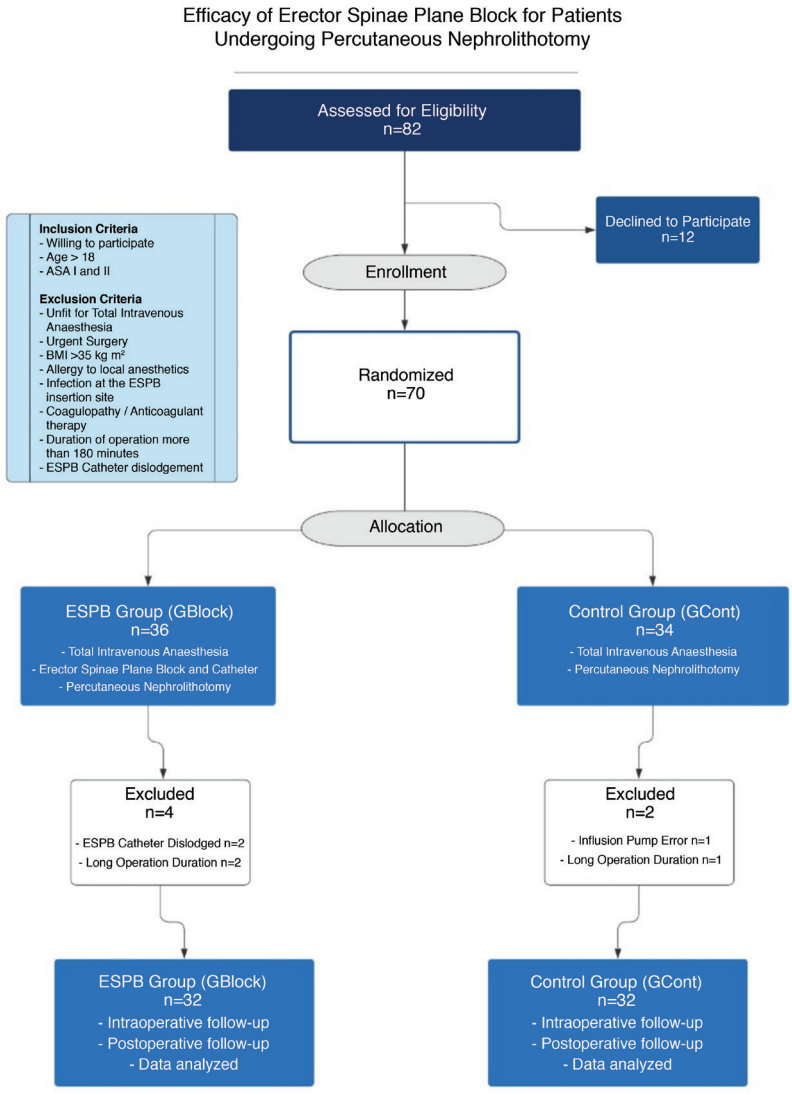

Figure 1. Flow chart.

ESPB, erector spinae plane block; BIS, bispectral index; GBlock, block group; GCont, control group.

20 mL of 0.25% bupivacaine solution was administered through the catheter for intraoperative and postoperative analgesia (Figure 2).

When the surgical procedure was completed, TIVA was stopped and sugammadex 4 mg kg^{-1} IV was administered to reverse the neuromuscular blockade. Patients were questioned for pain (with the Numerics Rating Scale - NRS) before leaving the operating room. This was recorded as 0^{th}-minute-NRS, and, if necessary, the rescue analgesics was administered. Rescue analgesia was planned to be tramadol 1 mg kg^{-1} IV (400 mg day^{-1} maximum) when patients' pain scores (NRS) were 3 or above. The patients were then transferred to the post-anaesthesia recovery unit (PACU).

Paracetamol 10 mg kg^{-1} IV was prescribed to every patient in the study every 8 h for postoperative analgesia. Patients' questionnaires for pain scores were scheduled at the end of the operation at the 30^{th} and 60^{th} minutes in the PACU and at the 2^{nd}, 6^{th}, 12^{th}, 24^{th}, and 48^{th} hours in the wards. In these questionnaires, rescue analgesic administrations were also recorded.

Patients were encouraged to ambulate on postoperative day (POD) 0, approximately 6 h after the operation. Patients in the GBlock group were administered 20 mL 0.25% bupivacaine solution via the ESPB catheter 30 min before ambulation. GCont patients did not receive any medications before ambulation with the motivation not to interfere with true analgesic consumption and to administer the same

postoperative systemic analgesia protocol for both groups. Pain scores of the patients during ambulation were recorded as NRS.

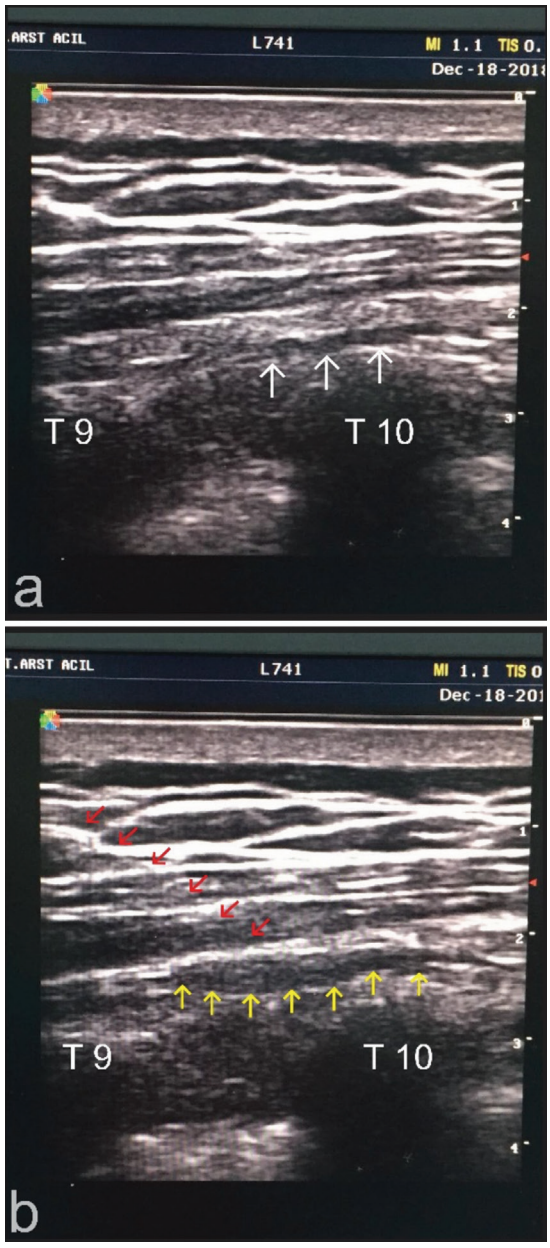

Figure 2. Ultrasound image of ESPB.

a. Before the application of local anaesthetic. b. After the application of local anaesthetic through the catheter.

T9: Costotransverse joint of T9 vertebrae, T10: Costotransverse joint of T10 vertebrae, white arrows: the lower fascia of erector spinae muscle group, red arrows: shadow of the erector spinae block catheter, yellow arrows: local anaesthetic filled area.

ESPB, erector spinae plane block.

On POD 1, GBlock received LA dose (20 mL 0.25% bupivacaine) twice at 12-h intervals. Both groups received rescue analgesics when their NRS scores exceeded 3 out of 10.

Nephrostomy tubes were removed at POD 2. Patients in the GBlock group received the same LA dose through the ESPB catheter 30 min in advance. For the same reasons as in ambulation, GCont did not receive any medication before tube removal. NRS scores of the patients during the removal of the nephrostomy tube were recorded.

ESPB- or LAs related complications (LA systemic toxicity, insertion site infection, muscle weakness, and pneumothorax) were monitored both intraoperatively and postoperatively.

Statistical Analysis

IBM Statistical Package for Social Sciences version 24 was used for statistical calculations. The compliance of the data to the normal distribution was determined by the single sample Kolmogorov-Smirnov test. Normally distributed quantitative data were compared with the independent sample *t*-test, and quantitative data that did not follow the normal distribution were compared with the Mann-Whitney U test. Chi-square test was used to compare qualitative data. Parametric test results were reported as mean and standard deviation and nonparametric test results as number and percentage or median and interquartile range.

The significance level was determined as $P < 0.05$ at the 95% confidence interval.

Results

The groups were similar in terms of age, height, weight and education level (Table 1).

The remifentanil consumption of the GCont was found to be significantly higher ($P < 0.001$). The groups were comparable in terms of other intraoperative data (Table 2).

GCont reported statistically significantly higher pain scores between the 30th minute and the 24th hour postoperatively ($P < 0.001$, P=0.002, $P < 0.001$, $P < 0.001$, $P < 0.001$, and P=0.015, respectively) (Table 3). However, rescue analgesic doses were found to be different only at the 60th minute, 2nd hour, and 6th hour (P=0.003, P=0.002, P=0.002, respectively). Comparison of pain scores and the number of patients who needed rescue analgesics during ambulation ($P < 0.001$ and $P < 0.001$, respectively) and removal of the nephrostomy tube ($P < 0.001$ and $P < 0.001$, respectively) showed significant differences between the groups. The median postoperative rescue analgesic dose was 75 mg [100, IQR] for GBlock and 262.5 mg [113, IQR] for GCont ($P < 0.001$) (Table 4).

Table 1. Demographics

	GBlock n = 32	GCont n = 32	*P* value
Age (years)	47.84 ± 14.67	49.34 ± 13.48	0.672
Weight (kg)	79.7 ± 14.42	77.5 ± 12.73	0.574
Height (cm)	172.88 ± 8.72	170.25 ± 8.17	0.219
Male / Female	22 (68.8%) / 10 (31.3%)	18 (56.3%) / 14 (43.8%)	0.302
Education*	0 (0%) / 4 (12.5%) / 12 (37.5%) / 16 (50%)	0 (0%) / 9 (28.1%) / 13 (40.6%) / 10 (31.5%)	0.188
ASA 1 / 2	7 (21.9%) / 25 (78.1%)	7 (21.9%) / 25 (78.1%)	-

Data represented as "Mean ± SD" or "n (%)".
*Illiterate / Literate or primary school graduate / Secondary or high school graduate / License degree or more.
SA, American Society of Anesthesiologists Physical Status Classification; SD, standard deviation; GBlock, block group; GCont, control group.

Table 2. Intraoperative Parameters

	GBlock n = 32	GCont n = 32	*P* value
Operation length (min)	129.84 ± 26.65	120.31 ± 22.6	0.128
ESP block duration (min)	10.63 ± 1.91	-	-
Propofol infusion rate (μg kg^{-1} min^{-1})	69.67 ± 21.50	76.50 ± 22.83	0.230
Remifentanil infusion rate* (μg kg^{-1} min^{-1})	0.0865 ± 0.030	0.1398 ± 0.034	<0.001
ESP block and catheter insertion levels	T7-8: 3 (9.37%) T8-9: 3 (9.37%) T9-10: 14 (43.75%) T10-11: 12 (37.5%)	-	-

Data represented as "Mean ± SD" or "n (%)".
*Denotes statistical significance ($P < 0.05$).
SD, standard deviation; GBlock, block group; GCont, control group.

Table 3. Postoperative Pain Scores

	GBlock n = 32	GCont n = 32	*P* value
Control NRS	0 [0]	0 [0]	-
0th min	0 [0]	0 [0]	0.371
30th min*	0 [2]	2 [2]	<0.001
60th min*	1 [2]	2 [2]	0.002
2nd hour*	1 [1]	3 [1]	<0.001
6th hour*	1 [1]	4 [3]	<0.001
12th hour*	1 [3]	3 [2]	<0.001
24th hour*	1 [2]	2 [2]	0.015
48th hour	1 [2]	1 [1]	0.142
During the nephrostomy tube removal*	2 [1]	5 [2]	<0.001
During the ambulation*	2 [2]	4 [2]	<0.001

Pain score was evaluated with "NRS".
Data represented as "Median [IQR]".
*Denotes statistical significance ($P < 0.05$).
GBlock, block group; GCont, control group, NRS, Numeric Rating Scale

Table 4. Rescue Analgesic Consumption			
	GBlock n = 32	**GCont n = 32**	***P* value**
At 0th min	0 (0%)	1 (3.1%)	0.313
At 30th min	4 (12.5%)	4 (12.5%)	-
At 60th min*	1 (3.1%)	10 (31.3%)	0.003
At 2nd hour*	2 (6.2%)	12 (37.5%)	0.002
At 6th hour*	5 (15.6%)	17 (53.1%)	0.002
At 12th hour	8 (25%)	12 (37.5%)	0.281
At 24th hour	2 (6.2%)	3 (9.4%)	0.641
At 48th hour	0 (0%)	0 (0%)	-
During nephrostomy tube removal *	5 (15.6%)	28 (87.5%)	<0.001
During ambulation*	1 (3.1%)	13 (40.6%)	<0.001
Total rescue analgesic consumption (mg)*	75 [100]	262.5 [113]	<0.001

Data represented as "n (%)" or "median [IQR]".
Results given in number and percentage represent the patients who requested rescue analgesic.
*Denotes statistical significance ($P < 0.05$).
GBlock, block group; GCont, control group; NRS, Numeric Rating Scale

Heart rate, mean arterial pressure, and BIS values were measured every 5 min during the surgery, and groups were comparable regarding changes in these parameters during the operation (Figure 3).

We did not detect any side effects or complications related to ESPB or LAs.

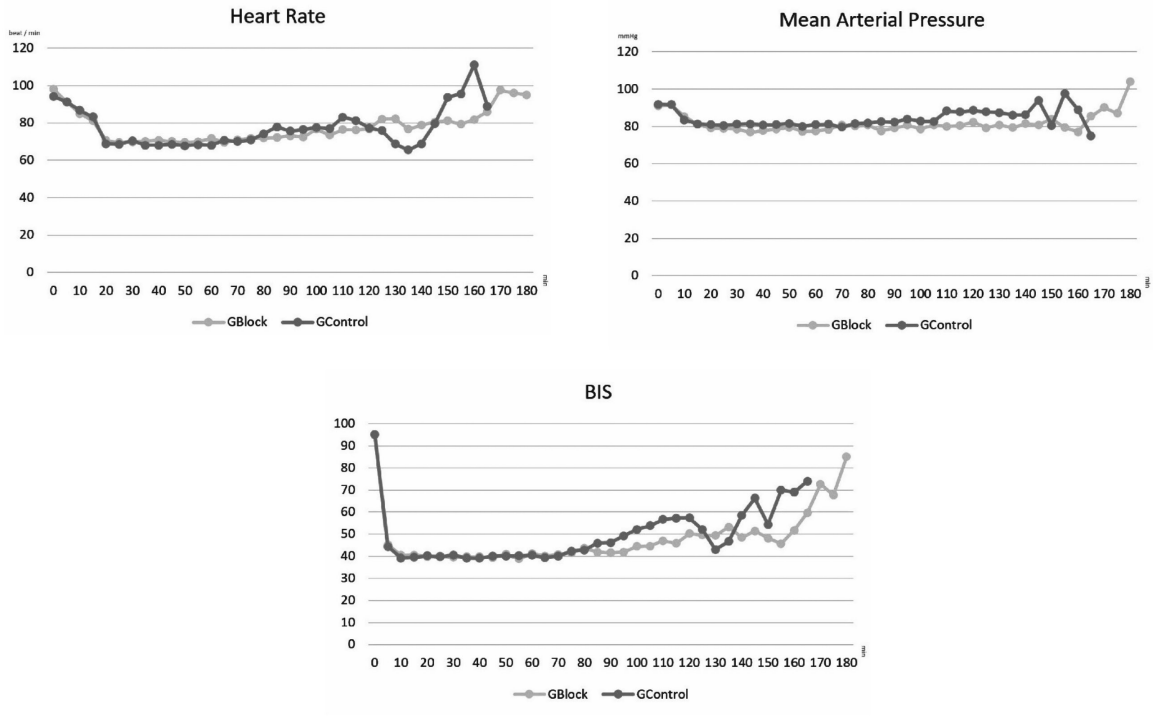

Figure 3. Intraoperative hemodynamic and BIS measurements.

BIS, bispectral index; GBlock, block group; GCont, control group.

Discussion

Efforts to provide a better understanding of the analgesic action mechanism of ESPB are on the rise. Even though it is not yet decisive, common opinion for the action of the mechanism is the LA effect at the ventral and dorsal rami of the spinal nerves. LA applied beneath the lowest fascia of ESMG spreads both craniocaudally and through the intertransverse space. This propagation provides analgesia and sympathetic blockage in a large area by interrupting the anterior, posterior, and communicating rami.[12,13]

ESPB was defined as a single shot injection block, but catheter placement for postoperative use has also been shown for various cases.[14] Single-shot ESPB studies show a pain ameliorate effect lasting up to 6-12 hours.[15,16] Even though there are case reports using LA infusions for ESPB catheters, bolus doses can be chosen, as in our study, due to the adequate duration and convenience of use. Oezel et al.[17] also marked that single-shot or catheter placement for ESPB has no superiority over one another.

ESPB is mentioned in many studies as a successful postoperative analgesia method. A study of 66 patients investigated whether ESPB provides benefits for pain in laparoscopic cholecystectomy. Authors marked that the postoperative NRS scores and opioid consumption in the ESPB group were lower.[18] Mostafa et al.[19] conducted a study investigating pain in laparoscopic bariatric surgery with a similar insertion site for ESPB as our study. They compared bilateral ESPB with a bilateral sham block at the T7 level and reported that ESPB provides "satisfactory postoperative analgesia with decreased analgesic consumption without significant difference in postoperative pulmonary functions." On the other hand, data regarding the intraoperative use of ESPB is in short supply and we aimed to fill this gap with our study.

ESPB has recently been shown to be effective for postoperative analgesia after PCNL operations.[20,21] To our knowledge we conducted the first randomized and controlled study to investigate the effectiveness of ESPB intraoperatively in PCNL patients. Our hypothesis regarding the use of ESPBs in PCNL operations is consistent with our results. Intraoperative TIVA infusion doses combined with similar BIS and hemodynamic changes in both groups, exhibited a valuable outcome. We found a statistically significant difference in remifentanil infusion doses between the groups (GBlock: 0.0865 μg kg^{-1} min^{-1} vs. GCont: 0.1398 μg kg^{-1} min^{-1}, $P < 0.001$). Painful stimuli during surgery cause stress response, which leads to hemodynamic changes (e.g. tachycardia and hypertension), increased catabolism, hyperglycemia, hypercoagulability, salt and water retention (hence edema), etc.[22] Lower doses of remifentanil infusion with similar hemodynamic readings between the groups clearly indicate that ESPB performed before surgery can reduce pain during surgery. Considering the unfavorable effects of surgical stress caused by noxious stimuli,[23] we can argue that the benefit of ESPB in PCNL patients may reach beyond just analgesia. This result successfully concludes our primary endpoint.

Our secondary outcomes are also promising. We detected that ESPB reduced postoperative pain in PCNL patients. GBlock described lower pain scores from the 30th minute to 24th hour postoperatively compared with GCont. But rescue analgesics were administered to GCont mostly from 60th minute to 12th hour. Both groups demanded very little opioids after 24th hour. We think that the difference in opioid use in the first 12 hour and the decrease of this difference in the following hour may point out that POD 0 is more significant for pain management in PCNL patients. In terms of postoperative total opioid consumption, patients in the block group received 75 [100] mg (median [IQR]) and the patients in the control group received 262.6 [113] mg (median [IQR]) tramadol IV ($P < 0.001$). These results reveal the success of ESPB in reducing postoperative pain and analgesic consumption in PCNL.

Nephrostomy tubes increase the acute pain after PCNL and patients mainly experience distress during the tube removal.[6,24] These tubes are in direct contact with the skin, kidney capsule, and kidney parenchyma and create noxious stimulation in these tissues during withdrawal. To alleviate nephrostomy tube removal pain, we would need to prevent both visceral and somatic stimuli at the relevant levels. The fact that we found a statistically and clinically significant difference in pain scores during removal of the nephrostomy tube stands out as an important finding in terms of the coverage of the ESPB. As for rescue analgesia, 28 (87.5%) patients in the control group and only 5 (15.6%) in the block group demanded rescue analgesia during nephrostomy tube removal. This result, along with the reduction of intraoperative opioid doses, can be interpreted as the two most striking clinical outcomes of this study.

Reducing pain during ambulation and thus facilitation of ambulation helps to avoid many postoperative complications such as ileus, edema, venous thromboembolism, et cetera.[25,26] We determined that the average NRS of GCont patients was 4 and GBlock patients was 2 during ambulation. Thirty-one patients (96.9%) in the control group requested rescue analgesic after ambulation. In the block group, the number was 19 (59.4%) ($P < 0.001$). Although a statistically significant difference was found, the fact that there was no clear difference as with nephrostomy tube removal suggests that visceral stimuli with a wider range of effects are at the forefront during ambulation. ESPB increased patient comfort during ambulation but could not provide sufficient analgesia alone.

Since its first publication, many studies have reported that ESPB has few or no complications and most of the known complications are due to LAs.[27,28] Consistent with these results, we detected no side effects or complications in any patient.

Our study has two main limitations: open-label design and the lack of a sham block group.

Open-label designs may put the integrity of studies into question. However, for our primary outcome, intraoperative dose titrations were strictly designated according to BIS and hemodynamic monitoring before the study, and we believe that the lack of physicians' blindness did not result in an increase in bias in intraoperative data.

The lack of a sham block group was intentionally decided to avoid unnecessary invasive intervention, considering that patients receive general anaesthesia for the procedure. We accept the criticism, particularly for postoperative pain follow-ups where evaluators (and patients) were aware of the questioned patient group.

The strength of our study comes from the strict, objective measurements of intraoperative data. Pain assessments are mainly subjective and may be affected by the perception of assessment scales, environment, and patient characteristics Postoperative pain assessments are valuable and may even be irreplaceable for pain investigation studies, considering that pain itself is subjective by definition.[29] However, we believe our result on intraoperative remifentanil consumption with hemodynamic consistency is a more reliable outcome for the success of ESPB compared with subjective postoperative pain assessments.

Conclusion

We concluded that with decreased opioid consumption both intraoperatively and postoperatively, analgesic efficiency, low profile of complications and side effects, and ease of application, the erector spinae plane block stands out as a useful technique for pain management in patients who will undergo PCNL operation.

Ethics Committee Approval: This study was approved by Ethics committee of Clinical Studies of University of Health Sciences University Turkey, İzmir Bozyaka Training and Research Hospital (approval no: 5, date: 04.07.2018).

Informed Consent: The eligible patients were informed about the study during the preoperative evaluation and their written consents were obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.U.B., Z.T.T.; Design - M.U.B., Z.T.T., T.D.; Supervision - Z.T.T., T.D.; Materials - M.U.B., Z.T.T., Z.D.; Data Collection and/or Processing - M.U.T., T.D.; Analysis and/or Interpretation - M.U.T., Z.T.T., T.D.; Literature Review - M.U.B., Z.T.T., T.D.; Writing - M.U.B.; Critical Review - M.U.B., Z.T.T., T.D.

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Combined Effects of Prone Positioning and Airway Pressure Release Ventilation on Oxygenation in Patients with COVID-19 ARDS

Bişar Ergün[1], Mehmet Nuri Yakar[2], Murat Küçük[1], Narmin Baghiyeva[2], Ahmet Naci Emecen[3], Erdem Yaka[4], Begüm Ergan[5], Ali Necati Gökmen[2]

[1]Department of Internal Medicine and Critical Care, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey
[2]Department of Anaesthesiology and Critical Care, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey
[3]Department of Public Health, Epidemiology Subsection, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey
[4]Department of Neurology and Critical Care, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey
[5]Department of Pulmonary and Critical Care, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

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Abstract

Objective: Coronavirus disease 2019 (COVID-19) can cause acute respiratory distress syndrome (ARDS). Invasive mechanical ventilation (IMV) support and prone positioning are essential treatments for severe COVID-19 ARDS. We aimed to determine the combined effect of prone position and airway pressure release ventilation (APRV) modes on oxygen improvement in mechanically-ventilated patients with COVID-19.

Methods: This prospective observational study included 40 eligible patients (13 female, 27 male). Of 40 patients, 23 (57.5%) were ventilated with APRV and 17 (42.5%) were ventilated with controlled modes. A prone position was applied when the PaO_2/FiO_2 ratio <150 mmHg despite IMV in COVID-19 ARDS. The numbers of patients who completed the first, second, and third prone were 40, 25, and 15, respectively. Incident barotrauma events were diagnosed by both clinical findings and radiological images.

Results: After the second prone, the PaO_2/FiO_2 ratio of the APRV group was higher compared to the PaO_2/FiO_2 ratio of the control group [189 (150-237)] vs. 127 (100-146) mmHg, respectively, (P=0.025). Similarly, after the third prone, the PaO_2/FiO_2 ratio of the APRV group was higher compared to the PaO_2/FiO_2 ratio of the control group [194 (132-263)] vs. 83 (71-136) mmHg, respectively, (P=0.021). Barotrauma events were detected in 13.0% of the patients in the APRV group and 11.8% of the patients in the control group (P=1000). The 28-day mortality was not different in the APRV group than in the control group (73.9% vs. 70.6%, respectively, P=1000).

Conclusion: Using the APRV mode during prone positioning improves oxygenation, especially in the second and third prone positions, without increasing the risk of barotrauma. However, no benefit on mortality was detected.

Keywords: Airway pressure-release ventilation, ARDS, intensive care units, mortality, SARS-CoV-2

Main Points

- When combining prone positioning with airway pressure release ventilation (APRV), improvement in oxygenation is better than controlled mode, especially in the second and third prone positions.
- APRV can be safely used in Coronavirus disease-2019 (COVID-19) acute respiratory distress syndrome (ARDS) as barotrauma events are similar in both groups.
- APRV did not reduce mortality more than controlled modes in COVID-19 ARDS patients.

Corresponding author: Begüm Ergan, e-mail: begumergan@hotmail.com

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Introduction

Coronavirus disease-2019 (COVID-19) is a pandemic caused by the severe acute respiratory syndrome. Coronavirus mainly affects the pulmonary system and can cause acute respiratory distress syndrome (ARDS).[1,2] The incidence of severe ARDS was 35% in mechanically ventilated intensive care unit (ICU) patients.[3] Mortality in COVID-19 patients with mild, moderate, and severe ARDS was 25, 33, and 41% respectively.[3] The survival advantage of prone position among patients with severe ARDS has been demonstrated in meta-analysis and randomized trials for a long-time.[4,5] In the supine position, since the dorsal trans-pulmonary pressure (airway opening pressure-pleural pressure) is higher than the ventral trans-pulmonary pressure, the ventral alveoli are prone to over-inflation and the dorsal alveoli are prone to atelectasis.[6] In the prone position, the difference between the dorsal and ventral trans-pulmonary pressure decreases and results in more homogeneous ventilation, lung aeration, and strain distribution than in the supine position.[7] Although ventilation distribution is affected by prone positioning, pulmonary perfusion is thought to be less affected by gravity.[8] Providing a better ventilation-perfusion match results in improved gas exchange, and a homogeneous distribution of ventilation results in a reduced risk of ventilator-induced lung injury.[7-9] Patients with COVID-19 ARDS have lung morphology and respiratory mechanics similar to patients with classical ARDS.[10] Mechanically ventilated COVID-19 patients with refractory hypoxemia were administered the prone position for rescue therapy,[3,11,12] resulting in improved oxygenation[3,11] and increased survival.[12]

Airway pressure-release ventilation (APRV) is an inverse ratio, pressure controlled, time-cycled, intermittent mandatory ventilation.[13] APRV delivers two levels of continuous positive airway pressure at which high pressure (P high) is delivered for a long duration (T high) and then falls to a lower pressure (P low) for a shorter duration (T low).[14] Maintaining a constant airway pressure (P high) for a long time (T high) ensures that multiple alveolar units are recruited, resulting in a greater surface area for gas exchange.[15] APRV permits spontaneous breaths at any time in the respiratory cycle.[13] Spontaneous breathing may improve the redistribution of ventilation to dependent lung areas, provide better ventilation/perfusion matching, improve venous return, and reduce the need for sedation and neuromuscular blockade.[16] APRV significantly increases the PaO_2/FiO_2 ratio and improves oxygenation in patients with ARDS compared with controlled methods.[17]

Overlapping physiological mechanisms that improve ventilation-perfusion mismatch in prone positioning and APRV may have potential synergistic effects on improving oxygenation in patients with COVID-19 ARDS. In this study, we evaluated the effects of combining APRV and prone positioning on gas exchange and mortality in patients with COVID-19 ARDS.

Methods

Study Population

After approval from the Local Ethics Committee of Dokuz Eylül University Non-Invasive Research Ethics Committee (date; 01.02.2021 and number; 2021/03-18) and the Turkish Ministry of Health, this prospective observational study was conducted in adult intensive care units of our center. All participants provided written informed consent. Between December 2020 and May 2021, all intubated patients (18 years and older) who met the Berlin criteria,[18] received both pronation and APRV or controlled mode interventions, and those diagnosed with COVID-19 were included in the study. SARS-CoV-2 infection was confirmed by either using a reverse transcriptase-polymerase chain reaction (RT-PCR) tested on respiratory samples or with clinical characteristics, laboratory, and computed tomography findings. Patients who did not meet the Berlin criteria and did not take the prone position after invasive mechanical ventilation (IMV) interventions were excluded from the study.

Definitions and Measurements

Our center uses APRV (Dräger Evita V300 and infinity V500, Lubeck, Germany) for patients with severe COVID-19-associated ARDS. APRV parameters were adjusted by an intensive care physician regarding previous guidelines.[15] It was aimed to maintain spontaneous breathing in the APRV group and was continuously monitored. Patients in the control group were ventilated according to the ARDSNet protocol. In our center, we applied the prone position when the PaO_2/FiO_2 ratio <150 mmHg despite IMV in COVID-19 ARDS. Prone positioning was performed in normal ICU beds. Patients with hemodynamic instability did not receive the prone position. Data on ICU-acquired infections included ventilator-associated pneumonia, bloodstream infections, and urinary tract infections. Incident barotrauma events, including new subcutaneous emphysema, pneumomediastinum, pneumopericardium, or pneumothorax were diagnosed by both clinical findings and radiological images. Sedation depth was assessed using the Richmond Agitation-Sedation Scale (RASS).[19] The sedation goal for most patients was a RASS score of -2 to +1.[19] For patients requiring deeper levels of sedation in the prone position, the most comfortable level that preserves spontaneous breaths was aimed for.

Variables

The demographic data (age, gender, smoking history, comorbidities), medical history, anthropometric measurements (Body Mass Index), Charlson Comorbidity Index (CCI), Acute Physiology and Chronic Health Evaluation (APACHE) II, and Sequential Organ Failure

Assessment (SOFA) scores were recorded. Blood pressure records were obtained from the first measurement of ICU admission. Disease characteristics for COVID-19 including RT-PCR results and blood tests were collected. The parameters of the mechanical ventilation and of the arterial blood gas analysis were recorded an hour before turning the patient to the prone position and within an hour following the prone episode. Sedative, analgesic, and muscle relaxant drugs were recorded in the prone periods. Complications such as emphysema, pneumothorax, hypotension, need for vasopressors, cardiac arrhythmia, vascular access removal, intubation tube removal, pressure ulcers, airway obstruction, corneal abrasion, oliguria, and anuria were recorded during prone position. Major events during ICU stay [presence of septic shock, ICU acquired infections, AKI, renal replacement therapy (RRT)] were recorded. Lengths of ICU and hospital stays, and mortality was recorded.

Outcomes

The primary outcome of the study was whether the combined use of APRV and prone positioning improves oxygenation in mechanically ventilated patients with severe COVID-19 ARDS. Secondary outcomes were the effects of the combined use of APRV and prone positioning on the length of stay and mortality.

Statistical Analysis

All categorical variables were expressed as numbers and percentages, and continuous variables were expressed as median and interquartile ranges. Categorical variables between groups were compared with the chi-square or Fisher's exact test, and continuous variables were compared with the Mann-Whitney U test. A two-tailed *P* value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences Version 24, IBM Corp., Armonk, N.Y., USA).

Results

General Characteristics

A total of 40 patients admitted to the ICU with COVID-19 were included in the study (Figure 1). All patients were mechanically ventilated and required at least one intervention of proning. The numbers of patients who completed the first, second, and third prone were 40, 25, and 15, respectively. Of the 40 patients, 27 (67.5%) were male and the median age of the study population was 65.0 (57.3-72.0 years; Table 1). A total of 23 patients were ventilated with APRV and 17 patients were ventilated with controlled modes. In the controlled mode group, 10 patients were ventilated in volume-controlled mode and 7 patients in pressure-controlled mode. Demographic factors, disease severity scores, and the PaO_2/FiO_2 ratio at admission and before intubation was similar in both groups. There was no difference between the groups in time from ICU admission to intubation and time from intubation to the onset of prone episodes. The time from ICU admission to intubation was 34.0 (6.0-99.0) hours. During this period before intubation, the most appropriate interventions including NIV, high-flow nasal oxygen, and awake-proning interventions were applied to the patients. After intubation, the duration of prone periods was similar between the two groups. D-dimer levels were lower in the APRV group than in the controlled mode group [1.37 (0.70-2.22)] vs. 3.60 (1.08-15.28) g mL^{-1}, respectively, P=0.042). Other laboratory parameters were similar between the two groups.

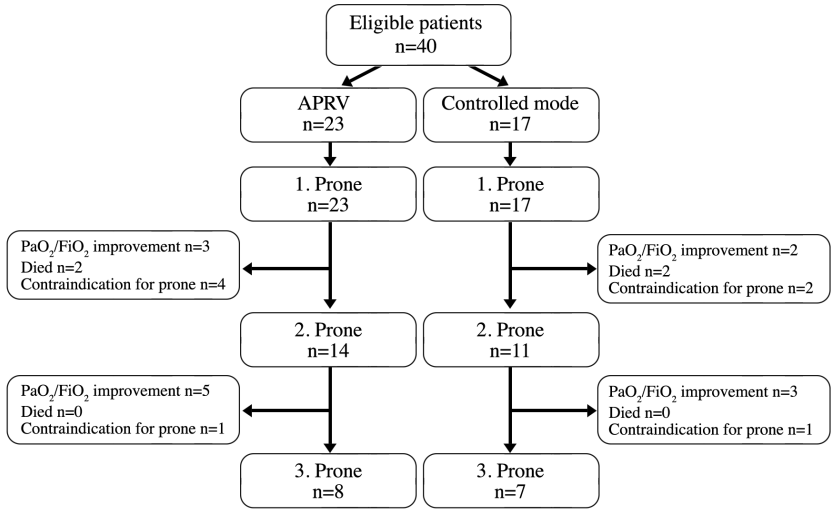

Figure 1. Flowchart of the study population.

APRV, airway pressure release ventilation.

Table 1. Demographic and Clinical Characteristics of Patients (Univariate Analysis)				
Characteristics	**All cases**	**APRV group**	**Controlled mode group**	***P* value**
	(n = 40)	(n = 23)	(n = 17)	
Age, years	65.0 (57.3-72.0)	61.0 (57.0-68.0)	68.0 (62.5-75.5)	0.075
Gender				
Female	13 (32.5)	7 (30.4)	6 (35.3)	1,000
Male	27 (67.5)	16 (69.6)	11 (64.7)	
Body mass index, kg m2^{-1}	27.0 (25.8-30.4)	26.6 (25.9-30.1)	27.0 (25.4-31.9)	0.315
Smoking history	6 (15.0)	2 (8.7)	4 (23.5)	0.373
Comorbidities				
Hypertension	20 (50.0)	11 (47.8)	9 (52.9)	1,000
Diabetes mellitus	13 (32.5)	6 (26.1)	7 (41.2)	0.496
Coronary artery disease	6 (15.0)	3 (13.0)	3 (17.6)	1,000
Congestive heart failure	2 (5.0)	1 (4.3)	1 (5.9)	1,000
Chronic kidney disease	4 (10.0)	2 (8.7)	2 (11.8)	1,000
Dementia	3 (7.5)	1 (4.3)	2 (11.8)	0.565
COPD	3 (7.5)	2 (8.7)	1 (5.9)	1,000
Malignancy	3 (7.5)	2 (8.7)	1 (5.9)	1,000
APACHE II	18.5 (12.3-24.0)	16.0 (13.0-23.0)	20.0 (11.5-25.5)	0.432
SOFA[1]	4.0 (3.0-6.8)	4.0 (3.0-7.0)	4.0 (3.0-6.0)	0.914
CCI	3.0 (1.0-4.8)	3.0 (1.0-5.0)	3.0 (2.0-4.5)	0.607
Laboratory values[2]				
Creatinine, mg dL^{-1}	0.95 (0.71-1.32)	0.91 (0.72-1.26)	0.99 (0.65-1.35)	0.957
Albumin, g dL^{-1}	3.02 (2.77-3.25)	3.04 (2.92-3.26)	2.88 (2.66-3.22)	0.095
ALT, U L^{-1}	61.0 (40.3-87.3)	30.0 (23.0-49.0)	37.0 (27.5-56.5)	0.432
LDH, U L^{-1}	715 (513-881)	533 (487-955)	736 (635-844)	0.290
Ferritin ng mL^{-1}	670 (368-1122)	705 (280-1182)	543 (378-986)	0.705
HS-Troponin I, ng L^{-1}	24.0 (13.4-83.0)	24.0 (11.8-53.8)	24.5 (14.0-491.0)	0.267
D-dimer, µg mL^{-1}	1.65 (0.99-5.45)	1.37 (0.70-2.22)	3.60 (1.08-15.28)	**0.042**
CRP, mg L^{-1}	168 (122-216)	166 (123-216)	184 (100-221)	0.914
Procalcitonin, ng mL^{-1}	0.33 (0.15-1.13)	0.60 (0.11-1.37)	0.28 (0.16-0.70)	0.626
WBC, x 10^{3} µL^{-1}	11.8 (8.3-16.5)	11.6 (8.1-15.8)	14.9 (8.4-18.1)	0.371
Lymphocyte, x 10^{3} µL^{-1}	0.5 (0.3-0.8)	0.4 (0.2-0.7)	0.5 (0.4-1.0)	0.201
Hemoglobin, g dL^{-1}	13.2 (12.1-14.3)	13.1 (12.0-14.8)	13.5 (12.6-14.2)	0.705
Arterial blood gas analysis (at the time of ICU admission)				
pH	7.45 (7.40-7.49)	7.45 (7.40-7.49)	7.45 (7.35-7.49)	0.516
PaO_2, mmHg	54.0 (46.3-69.8)	54.0 (43.0-70.0)	54.0 (48.0-66.2)	1,000
$PaCO_2$, mmHg	32.8 (28.0-37.0)	32.6 (28.0-37.0)	33.0 (28.7-41.5)	0.481
HCO_3, mmol L^{-1}	23.3 (21.0-26.0)	23.3 (21.0-26.0)	24.0 (18.9-26.0)	0.725
PaO_2/FiO_2, mmHg	90.0 (78.5-122.8)	90.0 (78.0-124.0)	90.0 (80.0-119.5)	0.902
Arterial blood gas analysis (before intubation)				
pH	7.38 (7.24-7.48)	7.43 (7.30-7.48)	7.33 (7.17-7.50)	0.386
PaO_2, mmHg	60.0 (51.0-67.5)	62.0 (51.0-70.0)	60.0 (51.5-61.5)	0.481
$PaCO_2$, mmHg	35.5 (32.7-48.8)	35.0 (32.6-40.5)	36.0 (30.5-54.0)	0.978
HCO_3, mmol L^{-1}	24.0 (19.0-27.0)	24.0 (21.0-26.7)	23.0 (16.5-28.4)	0.766
PaO_2/FiO_2, mmHg	96.5 (69.5-112.0)	95.0 (66.0-115.0)	98.0 (72.0-108.5)	0.880

Table 1. Continued

Characteristics	All cases	APRV group	Controlled mode group	*P* value
Prone characteristics				
Time from ICU admission to intubation, (h)	34.0 (6.0-99.0)	44.0 (6.0-95.0)	11.0 (5.0-110.0)	0.665
Time from intubation to APRV initation, (h)	2.0 (1.0-2.0)	2.0 (1.0-2.0)	N/A	N/A
Time from intubation to first prone, (h)	5.5 (3.0-24.0)	7.0 (3.0-32.0)	4.0 (2.0-18.5)	0.206
Time from intubation to second prone, (h)	34.0 (28.0-56.0)	44.0 (28.8-90.0)	31.0 (28.0-44.0)	0.153
Time from intubation to third prone, (h)	77.0 (52.0-96.0)	84.5 (52.8-150.0)	63.0 (51.0-86.0)	0.297
Duration of 1. prone, (h)	16.5 (14.3-18.0)	16.0 (14.0-18.0)	17.0 (14.5-19.0)	0.544
Duration of 2. prone, (h)	16.0 (15.0-17.0)	16.0 (14.8-16.3)	17.0 (15.0-19.0)	0.177
Duration of 3. prone, (h)	14.0 (8.0-17.0)	15.0 (12.3-17.0)	10.0 (6.0-16.0)	0.352

All values are expressed as numbers (percentages) or median (interquartile range). Statistically significant values are expressed in bold.

APACHE II, acute physiology and chronic health evaluation II; APRV, airway pressure release ventilation; ALT, alanine transaminase; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FiO_2, fraction of inspired oxygen; HS Troponin I, high-sensitive troponin I; ICU, intensive care unit; LDH, lactate dehydrogenase; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; SOFA score, the sequential organ failure assessment score; WBC, white blood cell count.

[1]Calculated on the day of ICU admission.

[2]Tested on the day of ICU admission.

Table 2. Characteristics Before and After 1. Prone Position

Characteristics	Before prone (within 1 h)			After prone (within 1 h)		
	APRV (n = 23)	Controlled mode (n = 17)	*P* value	APRV (n = 23)	Controlled mode (n = 17)	*P* value
Mechanical ventilation parameters						
P high (APRV)	25.0 (23.0-28.0)	N/A	N/A	25.0 (23.0-26.0)	N/A	N/A
P low (APRV)	3.0 (2.0-4.0)	N/A	N/A	3.0 (2.9-4.0)	N/A	N/A
PC/PS (controlled mode)	N/A	20.0 (12.0-20.5)	N/A	N/A	18.0 (16.0-24.0)	N/A
PEEP (controlled mode)	N/A	8.0 (6.0-11.0)	N/A	N/A	9.0 (6.0-10.0)	N/A
P peak	25.0 (24.0-29.0)	27.0 (23.0-31.0)	0.59	25.0 (24.0-29.0)	28.0 (25.5-31.5)	0.06
P mean	21.0 (19.0-24.0)	15.0 (12.0-16.0)	**<0.001**	20.0 (19.0-23.0)	15.0 (12.0-17.5)	**<0.001**
PEEP (controlled mode)	N/A	8.0 (6.0-11.0)	N/A	N/A	9.0 (6.0-10.0)	N/A
Minute ventilation	6.4 (5.6-8.0)	7.9 (6.4-9.6)	**0.014**	6.5 (5.7-8.6)	8.3 (7.5-9.0)	**0.002**
Cdyn	32.0 (23.0-38.1)	26.0 (18.9-40.5)	0.315	35.7 (23.0-43.0)	36.0 (20.5-42.0)	0.588
R	13.0 (9.8-16.7)	14.0 (11.3-16.0)	0.685	14.0 (12.0-15.0)	14.0 (11.3-18.0)	0.516
ETT diameter, mm	8.00 (8.00-8.00)	8.00 (7.75-8.00)	0.787	8.00 (8.00-8.00)	8.00 (7.75-8.00)	0.787
Arterial blood gas analysis						
pH	7.38 (7.29-7.44)	7.31 (7.23-7.38)	**0.010**	7.35 (7.28-7.41)	7.36 (7.29-7.38)	0.957
$PaCO_2$, mmHg	40.7 (37.2-53.0)	60.0 (42.0-64.0)	**0.015**	46.0 (41.0-55.4)	58.0 (44.5-62.5)	0.101
HCO_3, mmol L^{-1}	24.0 (22.0-26.6)	23.0 (20.4-27.9)	0.551	24.2 (20.7-27.5)	25.0 (20.5-29.1)	0.705
SaO_2, %	88 (80-92)	88 (84-93)	0.745	96 (93-97)	95 (90-96)	0.290
PaO_2, mmHg	57 (50-68)	61 (57-74)	0.173	87 (71-104)	76 (64-87)	0.201
PaO_2/FiO_2, mmHg	87 (73-113)	98 (82-119)	0.193	155 (125-185)	132 (110-150)	0.151

All values are expressed as numbers (percentages) or median (interquartile range). Statistically significant values are expressed in bold.

APRV, airway pressure release ventilation; Cdyn, dynamic compliance; ETT, endotracheal tube; FiO_2, raction of inspired oxygen; N/A, not applicable; P, pressure; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; PEEP, positive end-expiratory pressure; R, resistance; SO_2, arterial oxygen saturation.

The Characteristics of the 1. Prone

Of the 40 patients in the first prone position, 23 were ventilated with APRV and 17 were ventilated with a controlled mode (Table 2).

In patients ventilated with APRV, the median (interquartile range) of the PaO_2/FiO_2 ratio before the first prone was not different when compared with patients ventilated with controlled modes [87 (73-113)] vs. 98 (82-119)] mmHg, respectively, *P*=0.193). After the first prone, the PaO_2/FiO_2 ratio of the APRV group was higher compared to the PaO_2/FiO_2 ratio of the controlled mode group, but it was not statistically significant [155 (125-185)] vs. 132 (110-150) mmHg, respectively, *P*=0.151).

The Characteristics of the 2. Prone

Two patients in the APRV group and two patients in the controlled mode group died at follow-up after the first prone period. The physicians did not require the second prone position because the PaO_2/FiO_2 ratio improved for three patients in the APRV group and for two patients in the controlled mode group after the first prone. The second prone was not applied to four patients in the APRV group and to two patients in the controlled mode group because of hemodynamic instability. Of the 25 patients in the second prone position, 14 were ventilated with APRV and 11 were ventilated in the controlled mode.

Before the second prone, the PaO_2/FiO_2 ratio was 136 (96-171) mmHg in the APRV group and 123 (77-147) mmHg in the controlled mode group (*P*=0.149; Table 3). After the second prone, the PaO_2/FiO_2 ratio of the APRV group was higher compared to the PaO_2/FiO_2 ratio of the controlled mode group [189 (150-237)] vs. 127 (100-146) mmHg, respectively, *P*=0.025).

Characteristics of the Third Prone

The physicians did not require the third prone position because the PaO_2/FiO_2 ratio improved following the second prone position for five patients in the APRV group and for three patients in the controlled mode group. The third prone was not applied to one patient in the APRV group and one

Table 3. Characteristics Before and After 2. Prone Position

Characteristics	Before prone (within 1 h)			After prone (within 1 h)		
	APRV (n = 14)	Controlled mode (n = 11)	*P* value	APRV (n = 14)	Controlled mode (n = 11)	*P* value
Mechanical ventilation parameters						
P high (APRV)	22.5 (22.0-28.0)	N/A	N/A	22.5 (22.0-26.5)	N/A	N/A
P low (APRV)	3.0 (2.5-3.3)	N/A	N/A	3.2 (2.5-4.0)	N/A	N/A
PC/PS (controlled mode)	N/A	20.0 (14.0-22.0)	N/A	N/A	18.0 (14.0-23.0)	N/A
PEEP (controlled mode)	N/A	10.0 (7.0-12.0)	N/A	N/A	9.0 (6.0-10.0)	N/A
P peak	26.0 (22.0-28.0)	30.0 (24.0-33.0)	**0.03**	24.0 (22.0-26.5)	28.0 (24.0-35.0)	**0.04**
P mean	20.0 (18.7-25.0)	14.0 (11.0-17.0)	**<0.001**	20.0 (18.0-22.7)	16.0 (12.0-18.0)	**<0.001**
PEEP (controlled mode)	N/A	10.0 (7.0-12.0)	N/A	N/A	9.0 (6.0-10.0)	N/A
Minute ventilation	6.6 (5.7-8.3)	8.6 (7.3-9.8)	**0.021**	6.8 (5.8-9.7)	8.0 (6.9-8.5)	0.317
Cdyn	29.7 (19.5-40.8)	25.0 (16.9-45.0)	0.647	38.9 (25.9-54.5)	34.0 (30.0-48.0)	0.851
R	12.5 (10.8-15.3)	15.0 (12.0-17.2)	0.373	13.7 (9.9-16.2)	15.0 (14.0-17.3)	0.095
ETT diameter, mm	8.00 (7.50-8.00)	8.00 (8.00-8.00)	0.077	8.00 (7.50-8.00)	8.00 (8.00-8.00)	0.077
Arterial blood gas analysis						
pH	7.37 (7.30-7.41)	7.35 (7.31-7.38)	0.727	7.36 (7.32-7.44)	7.29 (7.22-7.38)	0.120
$PaCO_2$, mmHg	48.1 (41.0-55.0)	52.0 (46.0-63.0)	0.267	48.6 (43.2-52.1)	61.0 (44.0-95.0)	0.085
HCO_3, mmol L^{-1}	24.7 (22.0-30.5)	27.0 (24.0-28.0)	0.609	28.0 (23.0-32.3)	27.0 (24.0-33.0)	0.979
SaO_2, %	95 (93-96)	93 (84-97)	0.222	97 (96-97)	94 (90-97)	0.085
PaO_2, mmHg	79 (61-85)	72 (51-88)	0.434	96 (78-110)	70 (61-102)	0.107
PaO_2/FiO_2, mmHg	136 (96-171)	123 (77-147)	0.149	189 (150-237)	127 (100-146)	**0.025**

All values are expressed as numbers (percentages) or median (interquartile range). Statistically significant values are expressed in bold.

APRV, airway pressure release ventilation; Cdyn, dynamic compliance; ETT, endotracheal tube; FiO_2, fraction of inspired oxygen; N/A, not applicable; P, pressure; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; PEEP, positive end-expiratory pressure; R, resistance, SO_2, arterial oxygen saturation.

patient in the controlled mode group due to hemodynamic instability. Of the 15 patients in the second prone position, 8 were ventilated with APRV and 7 were ventilated with the controlled mode.

Before the third prone, the PaO_2/FiO_2 ratio was 132 (81-177) mmHg in the APRV group and 95 (57-102) mmHg in the controlled mode group (*P*=0.024; Table 4). After the third prone, the PaO_2/FiO_2 ratio of the APRV group was higher compared to the PaO_2/FiO_2 ratio of the controlled mode group [194 (132-263)] vs. 83 (71-136) mmHg, respectively, *P*=0.021). The change in the PaO_2/FiO_2 ratio over time is presented in Figure 2.

Major Events and Complications During the Prone Position and During ICU Stay

There was no difference between the two groups in major events or complications associated with prone positions (Table 5).

Spontaneous subcutaneous emphysema was detected in two patients in the pre-intubation follow-up. After intubation,

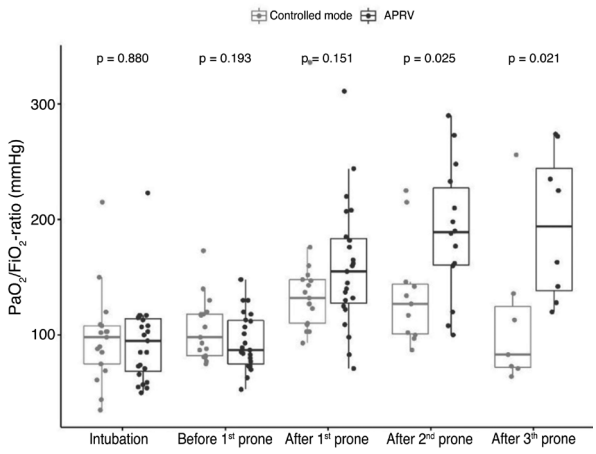

Figure 2. Median (interquartile range) of the PaO_2/FiO_2 ratio (mmHg) before the intubation and during the prone positioning in the study groups.

APRV, airway pressure release ventilation; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen.

Table 4. Characteristics Before and After 3. Prone Position

Characteristics	Before prone (within 1 h)			After prone (within 1 h)		
	APRV (n = 8)	Controlled mode (n = 7)	*P* value	APRV (n = 8)	Controlled mode (n = 7)	*P* value
Mechanical ventilation parameters						
P high (APRV)	26.0 (20.0-28.5)	N/A	N/A	26.0 (21.0-27.5)	N/A	N/A
P low (APRV)	3.1 (2.1-4.0)	N/A	N/A	3.6 (2.3-4.0)	N/A	N/A
PC/PS (controlled mode)	N/A	18.0 (14.0-25.0)	N/A	N/A	18.0 (14.0-24.0)	N/A
PEEP (controlled mode)	N/A	10.0 (9.0-10.0)	N/A	N/A	10.0 (8.0-11.0)	N/A
P peak	26.0 (22.0-29.8)	33.0 (24.0-39.0)	0.15	26.0 (21.3-27.8)	33.0 (25.0-35.0)	0.23
P mean	21.0 (17.2-23.8)	17.0 (14.0-18.0)	**0.04**	21.0 (18.0-23.5)	16.0 (15.0-18.0)	0.05
PEEP (controlled mode)	N/A	10.0 (9.0-10.0)	N/A	N/A	10.0 (8.0-11.0)	N/A
Minute ventilation	7.5 (5.6-11.6)	7.9 (7.1-9.5)	0.867	7.1 (5.7-9.5)	7.5 (5.9-8.1)	1,000
Cdyn	31.5 (24.5-39.7)	26.4 (17.0-54.0)	0.779	33.5 (22.2-47.4)	30.0 (18.0-72.0)	0.867
R	15.2 (7.1-20.7)	12.0 (9.6-15.9)	1.000	14.4 (9.5-16.6)	15.0 (12.9-19.8)	0.536
ETT diameter, mm	8.00 (7.50-8.00)	8.00 (8.00-8.00)	0.188	8.00 (7.50-8.00)	8.00 (8.00-8.00)	0.188
Arterial blood gas analysis						
pH	7.36 (7.29-7.44)	7.34 (7.23-7.41)	0.613	7.41 (7.24-7.47)	7.20 (6.9-7.4)	0.054
$PaCO_2$, mmHg	50.0 (43.0-66.8)	52.0 (46.0-62.0)	0.779	53.6 (44.5-57.2)	67.0 (55.0-104.0)	**0.029**
HCO_3, mmol L^{-1}	29.0 (24.3-33.1)	30.0 (20.0-35.4)	0.955	27.5 (21.2-32.5)	29.0 (13.7-31.0)	0.867
SaO_2, %	94 (87-98)	88 (75-92)	0.054	97 (92-98)	84 (82-92)	**0.040**
PaO_2, mmHg	66 (54-77)	51 (40-58)	0.094	92 (67-127)	51 (50-82)	0.054
PaO_2/FiO_2, mmHg	132 (81-177)	95 (57-102)	**0.024**	194 (132-263)	83 (71-136)	**0.021**

All values are expressed as numbers (percentages) or median (interquartile range). Statistically significant values are expressed in bold.

APRV, airway pressure release ventilation; Cdyn, dynamic compliance; ETT, endotracheal tube; FiO_2, fraction of inspired oxygen; N/A, not applicable; P, pressure; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; PEEP, positive end-expiratory pressure; R, resistance; SO_2, arterial oxygen saturation.

Table 5. Outcomes (Univariate Analysis)				
Characteristics	**All cases**	**APRV**	**Controlled mode**	***P* value**
	(n = 40)	**(n = 23)**	**(n = 17)**	
NMBA use during prone, n (%)				
First prone	4 (10.0)	0 (0)	4 (23.5)	**0.026**
Second prone	3 (7.5)	0 (0)	3 (27.3)	0.072
Third prone	2 (5.0)	1 (12.5)	1 (14.3)	1,000
Events/complications during prone positioning				
New-onset or increased need for vasopressors	10 (25.0)	4 (17.4)	6 (35.3)	0.274
Pressure ulcer	8 (20.0)	3 (13.0)	5 (29.4)	0.250
Oliguria/anuria	5 (12.5)	2 (8.7)	3 (17.6)	0.634
Arrhythmia	4 (10.0)	2 (8.7)	2 (11.8)	1,000
Catheter complications	1 (2.5)	0 (0)	1 (5.9)	0.425
Corneal abrasion	1 (2.5)	0 (0)	1 (5.9)	0.425
Events/therapies during ICU stay				
Need for any dose of vasopressors, n (%)	33 (82.5)	19 (82.6)	14 (82.4)	1,000
Number of vasopressor days	6.0 (2.0-8.0)	7.0 (2.0-9.0)	5.0 (1.5-8.0)	0.516
ICU-acquired infections	31 (77.5)	18 (78.3)	13 (76.5)	1,000
Acute kidney injury	22 (55.0)	12 (52.2)	10 (58.8)	0.755
Renal replacement therapy	14 (35.0)	9 (39.1)	5 (29.4)	0.739
Spontaneous subcutaneous emphysema/pneumomediastinum	2 (5.0)	1 (4.3)	1 (5.9)	1,000
Barotrauma events after IMV	5 (12.5)	3 (13.0)	2 (11.8)	1,000
Chest tube requirement	2 (5.0)	1 (4.3)	1 (5.9)	1,000
Treatment for COVID-19				
Favipiravir	40 (100.0)	23 (100.0)	17 (100.0)	N/A
LMWH	40 (100.0)	23 (100.0)	17 (100.0)	N/A
ASA	38 (95.0)	22 (95.7)	16 (94.1)	1,000
Dipyridamole	38 (95.0)	22 (95.7)	16 (94.1)	1,000
Corticosteroids	38 (95.0)	22 (95.7)	16 (94.1)	1,000
Pulse corticosteroid*	33 (82.5)	17 (73.9)	16 (94.1)	0.205
Tocilizumab	6 (15.0)	3 (13.0)	3 (17.6)	1,000
Duration of IMV (days)	10.0 (6.0-15.0)	11.0 (7.0-15.0)	7.0 (5.0-23.0)	0.411
Duration of APRV (days)	3.0 (0.0-7.0)	7.0 (3.0-10.0)	N/A	N/A
ICU length of stay (days)	14.0 (10.3-17.0)	14.0 (11.0-17.0)	13.0 (7.5-24.0)	0.467
ICU mortality	35 (87.5)	19 (82.6)	16 (94.1)	0.373
Hospital mortality	35 (87.5)	19 (82.6)	16 (94.1)	0.373
28-day mortality**	29 (72.5)	17 (73.9)	12 (70.6)	1,000

All values are expressed as numbers (percentages) or median (interquartile range). Statistically significant values are expressed in bold.

APRV, airway pressure release ventilation; ASA, acetylsalicylic acid; ICU, intensive care unit; IMV, invasive mechanical ventilation; LMWH, low molecular weight heparin; NMBA, neuromuscular blocking agents.

*Intravenous injection, 250 mg day for 3 days,

**Six patients died after the period of 28-day follow-up. These patients died because of secondary events. The median follow-up of these six patients was 35.5 (29.8-54.0) days.

one was ventilated with the controlled mode and the other with APRV. Emphysema did not worsen after IMV in both patients. Barotrauma events, including new subcutaneous emphysema, pneumomediastinum, pneumopericardium, or pneumothorax, were detected in 5 (12.5%) patients. One patient in the APRV group and one patient in the controlled mode group required a chest tube after barotrauma. The incidence of barotrauma events were not different in the APRV group and in the controlled mode group (13.0% vs. 11.8%, respectively; *P*=1000).

One of two patients with spontaneous subcutaneous emphysema survived. All 5 patients with barotrauma died.

ICU Length of Stay and 28-day Mortality

The length of stay in the ICU was similar in both groups. The 28-day mortality was 73.9% in the APRV group and 70.6% in the controlled mode group (*P*=1000).

Discussion

This prospective study addressed the possible combined effect of APRV and prone positioning on the improvement of oxygenation in patients with severe COVID-19, and obtained three important results. Firstly, when combining prone positioning with APRV, improvement in oxygenation was better than with the controlled mode, especially in the second and third prone positions. Secondly, APRV can be safely used in COVID-19 ARDS patients because barotrauma events are similar in both groups. Thirdly, APRV did not reduce mortality more than controlled modes in COVID-19 patients with ARDS.

To our knowledge, research on combined APRV and prone positioning is limited to one randomized clinical trial,[20] and a retrospective study of patients with severe 2009 pandemic influenza A (H1N1) pneumonia.[21] In the randomized controlled trial, 33 patients with acute lung injury who required the prone position were ventilated with either synchronized intermittant mandatory ventilation (SIMV) or APRV. They found that the PaO_2/FiO_2 ratio of the APRV group was greater than that of the SIMV group after the second prone [82 (37.0-141.0)] and 50 (24.0-68.0) mmHg, *P*=0.02, respectively. However, serious complications and 28-day mortality were similar in both groups in the randomized controlled trials.[20] In a retrospective study of patients with ARDS associated with 2009 pandemic influenza A (H1N1), 11 of 14 mechanically ventilated patients had refractory hypoxemia despite APRV administration. Maintenance of APRV and following proving improved hypoxemia in these patients.[21] Likewise, the positive effect of combined APRV ventilation and proning on the improvement of oxygenation have been demonstrated in a case series.[22] Our findings were similar to the literature. In this study, after the first prone period, the PaO_2/FiO_2 ratio was higher in the APRV group than in the controlled mode group but was not statistically significant. After the second prone period, the PaO_2/FiO_2 ratio was significantly higher in the APRV group than in the controlled mode group, and this significance was maintained after the third prone position.

In a historical-comparative study, barotrauma was detected in 15% (n = 89) of 601 COVID-ARDS patients, while barotrauma was detected in 10% (n = 28) of 285 patients with non-COVID-ARDS in the same center in previous years.[23] In another study of 20 mechanically ventilated patients with COVID-19, barotrauma events were detected in 8 (40%) patients.[24] Not only the result of barotrauma but also spontaneous subcutaneous emphysema or pneumomediastinum/pneumothorax was detected in COVID-19 patients.[25,26] High barotrauma events and cases of spontaneous pneumomediastinum/pneumothorax in COVID-19 patients raise questions about whether COVID-19 infection uniquely increases risk. In our study, we detected two patients with spontaneous subcutaneous emphysema at follow-up before IMV administration. Barotrauma events had a similar rate with literature in mechanically ventilated patients in our study. Barotrauma was an independent risk factor for death in mechanically ventilated COVID-19 patients.[23] Similarly, in this study, all five patients with barotrauma died.

In a meta-analysis, including 57,420 adult patients with COVID-19 who received IMV, the overall reported case fatality rate (CFR) was estimated as 45% [95% confidence interval (CI), 39-52%].[27] In this meta-analysis, among studies in which age-stratified CFR was available, pooled CFR estimates were 84.4% (95% CI, 83.3-85.4%) in patients with age above 80 years.[27] In previous studies, high mortality rates were reported in patients undergoing IMV.[28] Similarly, 28-day mortality was 72.5% (n = 29) in our specific study of patients with ARDS who underwent IMV and proning.

Limitations and Strengths of the Study

The limitations of the study are as follows: (1) Although care was taken to maintain spontaneous breathing in the APRV group, in rare cases, patients required temporary deep sedation due to prone position intolerance; (2) We did not correlate plateau pressures between groups during prone positioning because it was not possible to measure in APRV ventilation; (3) The sample size was small. On the other hand, our study had several strengths. This study was conducted on a homogenous population that included patients with ARDS. The factors affecting oxygenation were similar in both groups. This homogeneity can make comparisons between groups more clear.

Conclusion

Prone positioning and APRV ventilation have advantageous synergistic effects on oxygenation without increasing complications in patients with COVID-19 ARDS. This

combination can be considered rescue therapy in refractory hypoxemia in this group of patients. However, improvement in oxygenation did not benefit mortality. The effect of APRV ventilation and proning on mortality in COVID-19 ARDS need to be investigated in larger studies.

Ethics Committee Approval: This study was approved by of Dokuz Eylül University Non-Invasive Research Ethics Committee (approval no: 2021/03-18, date: 01.02.2021).

Informed Consent: The eligible patients were informed about the study during the preoperative evaluation and their written consents were obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.E., M.N.Y., M.K., E.Y., Be.E., A.N.G.; Design - B.E., M.N.Y., M.K., E.Y., Be.E., A.N.G.; Supervision - E.Y., Be.E., A.N.G.; Materials - B.E., M.N.Y., M.K., N.B., Be.E., A.N.G.; Data Collection and/or Processing - B.E., M.N.Y., M.K., N.B.; Analysis and/or Interpretation - B.E., M.N.Y., M.K., A.N.E., Be.E.; Literature Review - B.E., E.Y., Be.E., A.N.G.; Writing - B.E., M.N.Y., M.K., A.N.E., E.Y., Be.E., A.N.G.; Critical Review - E.Y., Be.E., A.N.G.

Declaration of Interests: The authors have no conflict of interest to declare.

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Paracetamol Versus Ondansetron for Prevention of Postoperative Shivering in Liposuction Surgeries Under Combined General Epidural Anaesthesia: A Randomized Controlled Trial

Amr Samir Wahdan[1,2], George Eshak Loza[1], Hussain Othman Alshehri[2], Ahmed Farag Shedid[1], Atef Kamel Salama[1], Wessam Samir Wahdan[3], Mennatallah Magdi Mohamed[1]

[1]Department of Anaesthesia, Surgical ICU and Pain Management, Cairo University Faculty of Medicine, Cairo, Egypt

[2]Department of Anaesthesia, Al-hada Armed Force Hospital, Taif, Saudi Arabia

[3]Department of Plastic and Reconstructive Surgery, Cairo University Faculty of Medicine, Cairo, Egypt

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Abstract

Objective: Postoperative shivering (POS) is considered one of the most common complications that is encountered by the anaesthetists worldwide. Despite using several treatment options, there has not been a clear consensus regarding this issue. This trial was conducted to investigate the efficacy and safety of paracetamol and ondansetron in preventing POS in patients undergoing liposuction procedures under combined general epidural anaesthesia.

Methods: One hundred twenty patients scheduled for liposuction were randomly allocated to one of three groups: group P (paracetamol group) which received 1 g paracetamol intravenously, group O (ondansetron group) which received 8 mg of ondansetron intravenously, and group S (saline group), which received 100 mL normal saline intravenously; all medications were given postoperatively. The primary outcome was the incidence of POS, and the secondary outcomes included shivering score, tympanic temperature, and the occurrence of side effects.

Results: The incidence of occurrence of POS was found to be lower in groups P and O compared to group S with values of 25% and 37.50% vs. 77.50%, respectively, with a *P* value <0.001. Additionally, the severity of POS was found to be lower in groups P and O compared to group S (*P* <0.001). Tympanic temperature and complications were comparable between the groups with no significant differences.

Conclusion: Prophylactic use of paracetamol or ondansetron at the end of the procedure was shown to be of great value in reducing the incidence and severity of POS, with no statistically significant difference between the paracetamol and ondansetron groups. Moreover, no significant drawbacks were reported as a result of using these medications.

Keywords: Lipectomy, ondansetron, paracetamol, postoperative complications, shivering

Main Points

- One of the most common postoperative complications is shivering in the recovery room. Many treatment options have been used in management of this adverse effect, but there is no consensus.
- Paracetamol is as effective as ondansetron when administrated at the end of surgery and can reduce the incidence and severity of post-operative shivering.

Corresponding author: Amr Samir Wahdan, e-mail: amrwahdan@kasralainy.edu.eg

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Introduction

Postoperative shivering (POS) is defined as detectable oscillations in skeletal muscle that are frequent, spontaneous, involuntary, and asynchronous, starting 5-30 min after induction of anaesthesia causing noticeable increase in the core temperature. It is mainly caused because of hypothermia that occurs following the use of general or regional anaesthesia techniques. However, POS was also detected in normothermic patients because of pyrogenic agent release postoperatively.[1,2]

POS is considered one of the commonest complications that occurs as a result of using general anaesthesia,[3] with an incidence varying between 5%-65% in patients who receive general anaesthesia and 30%-55% in those who receive regional anaesthesia. It is usually related to several risk factors including the patients' age, operating room temperature, gender and the operative time.[4] In addition to the discomfort caused by POS; it also causes an increase in both oxygen consumption and carbon dioxide production, thus resulting in hypoxemia and an increase in the lactic acid level. Moreover, it increases the sympathetic outflow because of catecholamine release, which can aggravate ischemic cardiac conditions in known cardiac patients as well as increase intracranial pressure and intraocular pressure.[5]

Therefore, preventing POS will not only reduce an unpleasant side effect of anaesthesia but also prevent postoperative complications.[6] To prevent POS, several techniques were used to prevent hypothermia, e.g., increasing the operating room temperature, using warm fluid infusion and forced air warmers, or administering pharmacological agents. It is always preferable to prevent post-anaesthesia shivering rather than to treat it once it develops.[7,8]

A wide diversity of pharmacological agents has been used to prevent or treat POS, including opioids (pethidine and tramadol) paracetamol, dexmedetomidine, ondansetron, ketamine, dexamethasone, and ephedrine. However, most of these pharmacological agents have undesirable side effects which render them unsuitable for use as anti-shivering agents.[9-12]

The goal of our trial was to measure the efficacy and safety of using paracetamol or ondansetron in reducing the incidence and severity of POS in patients undergoing mega liposuction procedures under a combined general epidural anaesthesia technique.

Methods

This prospective randomized controlled trial was conducted in general surgery operating rooms between January 2021 and January 2022. The approval of the Institute Ethical Committee was obtained [N-122-2020]. Informed written consent was signed by each participant before enrollment in this trial. One hundred twenty subjects aged between 18 and 40 years with an ASA physical score I-III, scheduled for elective liposuction surgery under combined epidural and general anaesthesia were enrolled in this study. Participants were excluded from this study if they refused to participate, had a body mass index >50 kg $m2^{-1}$ or ASA higher than III, had a history of any of the following co-morbidities: renal, hepatic, or thyroid disorders or seizures, allergy to the study drugs, and abnormal body temperature (less than or 36.5°C or more than 37.5°C). The same anaesthetic and surgery teams were involved in the procedure for all patients.

One day before the procedure, all participants were scheduled for preoperative evaluation in the form of medical history, physical examination, and routine laboratory values including complete blood count, coagulation profile, AST, ALT, urea, and creatinine. A full explanation of the study protocol was provided to the patients, including the drugs used and the anaesthesia technique. They were also informed that they could discontinue participation in the study whenever they desired.

Two anaesthesiologists were involved in the research, one who performed the randomization process and another who recorded the data. The study drug was transferred from its original vial to be prepared and labeled with the patient identification number in a specific Burette Set (Dosifix®, B. Braun). The study solution contained 1,000 mg of acetaminophen with a volume of 100 mL or 8 mg of ondansetron in 100 mL of normal saline or 100 mL of normal saline (for control group). A pharmacist not involved in conducting the trial; prepared the drug based on a randomization table, taking all precaution measures to guaranty the blinding of the anaesthesiologists and surgeons. Fortunately, both paracetamol and ondansetron are clear solutions, thus undistinguishable from the placebo saline solution.

On the day of the procedure, after confirming sufficient fasting time, the patients were taken to the preoperative-holding area. Demographic data were reported, an intravenous line was inserted using a 20-G intravenous (IV) cannula, and intravenous 0.01 mg kg^{-1} of midazolam, 0.15 mg kg^{-1} of metoclopramide, 8 mg of dexamethasone, and 40 mg of pantoprazole were. They were then transferred to the operating room; the operating room temperature was adjusted between 22°C-24°C.

Upon arrival to the OR, the standard routine monitors were attached to the patients, including non-invasive blood pressure, pulse oximetry (SpO_2) and electrocardiography, and baseline vital signs were obtained in addition to the tympanic membrane temperature: using a thermometer (FT 65 thermometer, Beurer®, Germany) pre-induction.

An epidural catheter (Perifix®, Braun, Germany) was inserted using complete aseptic technique through the midline approach and the loss of resistance was made using saline. Induction of general anaesthesia was accomplished using propofol (2 mg kg^{-1}), fentanyl (1.0-2.0 µg kg^{-1}), and rocuronium (0.6 mg kg^{-1}). Intraoperatively, maintenance of anaesthesia was done using sevoflurane 2-3% in oxygen (inspiratory fraction 0.5 at a flow rate of 2-3 L min^{-1}), and increments of rocuronium were administered. The patients were mechanically ventilated to keep end-tidal carbon dioxide between 30 and 35 mmHg. Through the epidural catheter, 20 mL of 0.125% levobupivacaine (Chirocaine®, Abbott) was injected followed by a continuous infusion of 0.125% levobupivacaine at 10 mL h^{-1}. Tumescent fluid for liposuction was injected using 2 mm entry sites using a blunt-tipped infiltration needle connected by a large bore tube to an air-compressed pump.

Intraoperative hypothermia was minimized by several techniques, including the use of a heat and moisture exchanging filter placed between the endotracheal tube and the breathing circuit, warming all infused fluids, and the operating room temperature was adjusted to 22°C-24°C.

At 30 min before the termination of the procedure, participants were randomly allocated to 3 groups regarding the study drugs: group P (paracetamol group) (n = 40) who received intravenously 1 gram of paracetamol (Perfalgan, Bristol-Myers Squibb, Italy), group O (ondansetron group) (n = 40) who received intravenously 8 mg of ondansetron (Zofran, GlaxoSmithKline, Italy) and finally group S (saline group) (n = 40) who received normal saline. All drugs were infused over 15 min and in 100 mL volume.

At the end of the surgery, the residual muscle relaxant was reversed using 0.02 mg kg^{-1} atropine mixed with 0.04 mg kg^{-1} neostigmine, followed by endotracheal tube removal in the semi-sitting position after regaining consciousness. The extubation time (which is defined as the time from discontinuing anaesthetics till endotracheal tube removal), room temperature, total amount of drug consumption in the epidural anaesthesia, amount of tumescent fluid, blood loss, and total fluid consumption were recorded.

Patients were transferred to the recovery room and covered with a cotton blanket. The temperature of the post-op anaesthesia care unit was kept the same as that of the operating room by adjusting the air conditioner settings.

The body core temperature was recorded every 15 min for 60 min. Any episode of POS was recorded using the shivering score (SS): No shivering was scored as 0, piloerection or peripheral vasoconstriction was given a score of 1, muscular activity in only one muscle group was scored as 2, muscular activity in more than one muscle group was scored as 3 and shivering affecting the whole body was scored as 4.[13] If POS grade was more than 3 for 15 min after administration of the test drug, meperidine 0.5 mg kg^{-1} was given intravenously as a rescue agent.

After 24 h of surgery, all patients were contacted to check their satisfaction with this technique, which was rated using 1-4 scales (1= poor; 2= fair; 3= good; 4= excellent).

The primary outcome was the incidence of POS in the first 60 min postoperatively as defined by a SS ≥3. The secondary outcome variables were to detect the time of the onset of POS by a SS of more than 3, in addition to comparing the score of the three groups and the total dose of meperidine administered.

Statistical Analysis

The sample size of this trial was based on a pilot study with 10 participants to determine the incidence of POS after liposuction. It was reported in 80% of all patients. At least a 50% reduction in the incidence of POS in the first postoperative hour was accepted as clinically significant. Assuming an α error=0.05 with a power of 0.9, at least 33 patients per group were considered. To allow for patient withdrawal from the study, we decided to include 40 patients in each group.

Statistical Package for the Social Sciences (SPSS) software version 25.0 (SPSS Inc., Chicago, IL, USA) was used to analyze data. The Kolmogorov-Smirnov test was used to determine the normal distribution. The data were presented as the mean and standard deviation, and categorical data were expressed as the number of patients and incidence. The chi-square test or Fisher's exact test were used to compare categorical variables between the three groups, while a one-way analysis of variance was used to analyze continuous parametric variables, followed by post-hoc analysis (Tukey's test) for intergroup comparisons. Moreover, the Kruskal-Wallis test was used to compare continuous non-parametric data variables, followed by post-hoc analysis (Mann-Whitney U test) for intergroup comparisons. $P < 0.05$ was considered statistically significant.

Results

One hundred and twenty-five patients were eligible for enrollment; however, data from 120 patients (40 in each group) were collected and analyzed (Figure 1).

There were no significant differences between the three groups regarding demographic, anaesthetic, and operative data (Tables 1, 2). There were no clinically significant differences between the three groups concerning the amount of meperidine required to treat shivering or the response rate with value (83.3% in the *P* group, 66.7% in the O group, and 47.8% in the S group) (Table 3).

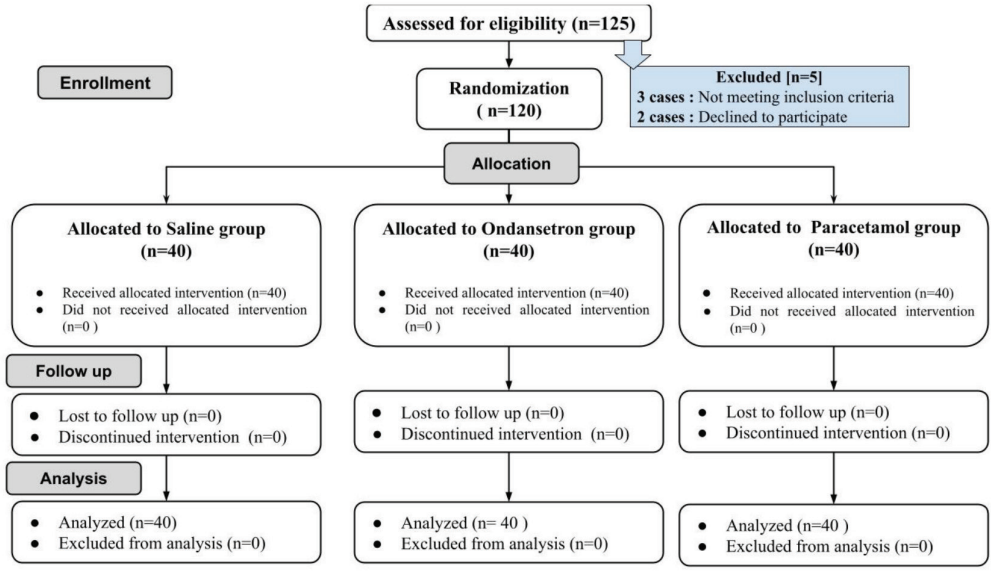

Figure 1. Consort flow diagram.

Table 1. Demographic Data of Study Groups

	Group S (n = 40)	Group O (n = 40)	Group P (n = 40)	*P* value
Age (years)	34.55 ± 7.70	33.83 ± 7.29	36.43 ± 7.93	0.296[a]
BMI (kg $m2^{-1}$)	37.13 ± 1.59	36.53 ± 2.39	36.08 ± 2.46	0.227[b]
Gender (M/F)	15/25	14/26	12/28	0.772[c]
ASA (I/II)	28/12	29/11	31/9	0.742[c]

Data represented as mean ± SD and [No (%)]. SD, standard deviation; [([a]ANOVA test); ([b]Kruskal-Wallis U test); ([c]Pearson's chi-squared test or Fisher's exact test (when n≤5)]; Group S, saline group; Group O, ondansetron group; Group P, paracetamol group.

Table 2. Anaesthetic and Operative Data of the Studied Groups

	Group S (n = 40)	Group O (n = 40)	Group P (n = 40)	*P* value
Duration of surgery (min)	230.25 ± 40.16	235.25 ± 36.30	241 ± 33.42	0.427[a]
Sevoflurane consumption (mL)	38.40 ± 6.25	40.90 ± 4.48	39.68 ± 5.04	0.114[a]
Amount of levobupivacaine (mL)	51 ± 5.68	52.68 ± 4.36	53.53 ± 5.46	0.092[a]
Total IV fluid used (L)	2.59 ± 0.50	2.73 ± 0.53	2.69 ± 0.52	0.472[a]
Amount of tumescent (L)	12.95 ± 1.15	12.68 ± 1.56	12.80 ± 1.84	0.728[a]
Amount of liposuction (L)	7.85 ± 1.14	7.40 ± 1.31	7.23 ± 1.29	0.075[a]
Total blood loss (mL)	586.25 ± 606.5	568.75 ± 660	570.75 ± 560.8	0.990[a]
No of patients with transfusion n (%)	6 (15%)	6 (15%)	5 (12.5%)	0.934[c]
Blood transfusion volume, (mL)	100 ± 258.20	112.5 ± 288.40	87.5 ± 250.32	0.916[a]
Total urine volume (mL)	1022.5 ± 454.31	1002.5 ± 337	1040 ± 359	0.910[a]
Extubation time (min)	20.8 ± 3.67	20.83 ± 3.80	19.13 ± 5	0.118[a]

Data represented as mean ± SD and [No (%)]. SD, standard deviation; [([a]ANOVA test); ([c]Pearson's chi-squared test or Fisher's exact test (when n ≤5)], Group S, saline group; Group O, ondansetron group; Group P, paracetamol group.

The incidence of POS (SS ≥3) was significantly lower in the P and O groups compared to the S group, with values 20% and 30% versus 65%, respectively ($P < 0.001$), while the onset of shivering was significantly later in the P and O groups compared to the S group with values of 24.38 ± 12.08 and 20.42 ± 10.33 versus 12.58 ± 6.83 respectively ($P < 0.001$). The need for additional antishivering treatment showed statistically significant differences between the studied groups, and was the most frequent in the S group when compared to the P and O groups with values 57.9% versus 15% and 22.5% respectively.

Furthermore, there was no significant difference in the frequency of postoperative complications recorded between the study groups (P=0.313) or postoperative patients' core temperatures (Table 4) (Figure 2). One day after surgery, all patients were asked about their satisfaction with the shivering relief by using the study drug. Most patients were satisfied with the use of paracetamol or ondansetron (P=0.002) (Table 4), with no statistically significant difference between both study groups.

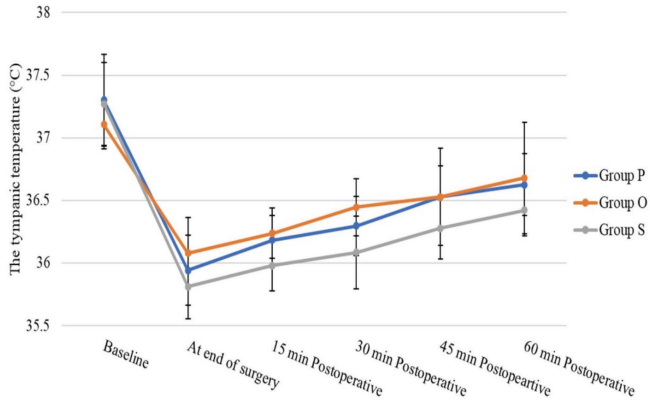

Figure 2. Patients' core temperatures.

Table 3. Incidence and Severity of Shivering

	Group S (n = 40)	Group O (n = 40)	Group P (n = 40)	*P* value
Incidence of shivering; n (%)	26 (65%)	12 (30%)*	8 (20%)*	0.000[c]
Onset of shivering (min)	12.58 ± 6.83	20.42 ± 10.33♦	24.38 ± 12.08♦	0.003[a]
Shivering score				
0	10 (25%)	20 (50%)♦	30 (75%)♦	0.000[c]
1	3 (7.5%)	3 (7.5%)	1 (2.5%)	0.545[c]
2	1 (2.5%)	5 (12.5%)	1 (2.5%)	0.088[c]
3	9 (22.5%)	5 (12.5%)	5 (12.5%)	0.368[c]
4	17 (42.5%)	7 (17.5%)*	3 (7.5%)*	0.001[c]
No of patient need anti-shivering treatment; n (%)	23 (57.9%)	9 (22.5%)*	6 (15%)*	0.000[c]
Shivering management by single dose of pethidine				
Good response	11 (47.8%)	6 (66.7%)	5 (83.3%)	0.243[c]
Incomplete response	12 (52.2%)	3 (33.3%)	1 (16.7%)	
Total pethidine used (mg)	52.39 ± 14.53	46.11 ± 10.54	42.50 ± 8.80	0.190[a]

Data represented as mean ± SD and [No (%)]. SD, standard deviation; [[a]ANOVA test followed by post-hoc analysis (Tukey's test)]; [[c]Pearson's chi-squared test or Fisher's exact test (when n ≤5)]; Group S, saline group; Group O, ondansetron group; Group P, paracetamol group; SS, shivering score. No shivering was scored as 0, piloerection or peripheral vasoconstriction, was given a score of 1, muscular activity in only one muscle group was scored as 2, muscular activity in more than one muscle group was scored as 3, and shivering affecting the whole body was scored as 4.

*Statistically significantly lower compared to the saline group ($P < 0.05$).

♦Significantly higher compared to the saline group ($P < 0.05$).

Table 4. Postoperative Complications and Patient Satisfaction

		Group S (n = 40)	Group O (n = 40)	Group P (n = 40)	*P* value
Duration in recovery room (min)		30.13 ± 5.89	31.33 ± 5.10	28.85 ± 5.57	0.139[a]
Postoperative complications	Hypotension	1 (2.5%)	2 (5%)	2 (5%)	0.313[c]
	Nausea	5 (12.5%)	1 (2.5%)	4 (10%)	
	Vomiting	4 (10%)	0 (0%)	3 (7.5%)	
	Pain	0 (0%)	1 (2.5%)	0 (0%)	
Patient satisfaction		2.50 ± 1.16	3.20 ± 0.88*	3.30 ± 0.94*	0.001[a]

Data represented as mean ± SD and [No (%)]. SD: Standard deviation, Group S: Saline group, Group O: Ondansetron group, Group P: Paracetamol group [[a]ANOVA test followed by post-hoc analysis (Tukey's test)], [[c]Pearson's chi-squared test or Fisher's exact test (when n ≤ 5)].
Patient satisfaction score (1: poor, 2: fair, 3: good and 4: excellent).
*Statistically significantly lower compared to the saline group ($P < 0.05$).

Discussion

The present study was conducted to investigate the effects of the prophylactic use of either ondansetron or paracetamol given intraoperatively on the incidence and severity of POS in patients who had undergone mega liposuction. It was found that shivering was markedly reduced in the paracetamol and ondansetron groups (with no difference amongst these groups) compared with the saline (control) group. Moreover, it was established that using the study agents improved patient satisfaction postoperatively without affecting the occurrence of complications.

Paracetamol is an effective, safe and widely used analgesic agent with antipyretic properties that inhibits prostaglandin synthesis to reduce the hypothalamic temperature set point. It has a rapid onset of action about 15-20 min after the injection and declines after 4 h. Unlike other antishivering drugs, paracetamol does not cause adverse effects such as sedation, respiratory depression, constipation, or vomiting.[9] Few studies have evaluated the feasibility of using paracetamol to treat postanaesthetic shivering.

The results of the current study agree with those of Kinjo et al.[14], who found that the perioperative use of paracetamol could prevent severe POS in subjects who had undergone gynecological laparotomy. However, the study was conducted on a few patients compared to ours, and paracetamol was given after induction of anaesthesia and 4 h after the start of the surgery if the duration of surgery exceeded this time.

Moreover, a study conducted by Gholami and Hadavi[15] also supports our study results, where prophylactic IV paracetamol was used during surgery on 110 pregnant women to prevent POS in cesarean delivery using general anaesthesia. The results showed a favorable response to prophylactic paracetamol regarding post-anaesthetic shivering; thus, it might replace opioids that have many side effects.

Data from 64 patients who underwent upper limb surgery under general anaesthesia in 2012 were collected by A. Khalili et al.[16] studied the effects of intravenous paracetamol on POS and core and peripheral body temperature. Patients were divided into two groups: one group received 15 mg kg^{-1} and up to 1 g acetaminophen before induction of general anaesthesia, and the control group received normal saline. These results go along with our study results although both studies were conducted differently.

The study participants who underwent general anaesthesia for gynecological cancer surgery between 2012 and 2019 were given paracetamol to prevent POS, as demonstrated by Shirozu et al.[17] in their retrospective study. These results are compatible with our study except that this study was retrospective, and the patients in each cohort were distributed unequally.[17]

Also, the results of the present study agree with those of Kashif et al.[18], who evaluated the effect of pre-emptive intravenous acetaminophen on preventing POS in patients undergoing elective septoplasty under general anaesthesia. This study showed that pre-emptive use of 1 g of acetaminophen 20 min before completion of surgery decreases the incidence of POS.

Ondansetron, a specific 5-HT3 antagonist, has generated much interest because of its excellent pharmacological profile. It has a wide therapeutic index. It is usually prescribed to prevent and manage nausea and/or vomiting during the perioperative period. Currently, it is recommended for the prevention of POS at a dose of 4-8 mg.[19]

The exact mechanism of 5-HT3 antagonists in preventing postanaesthetic shivering has not been clarified, but it might be related to the inhibition of serotonin reuptake in the hypothalamus. Serotonin receptors also affect heat production and heat loss pathways, as well.[20]

The results of the present study are similar to a trial carried out by Mahoori et al.[21], who had compared the efficacy of ondansetron and meperidine for treating shivering in 83 patients randomly divided into three groups: The first group was given 4 mg of IV ondansetron, the second group was given 8 mg of IV ondansetron, and the third group received 0.4 mg kg^{-1} of intravenous meperidine at the recovery room, and they found that 8 mg of IV ondansetron could control shivering and this is the dose of choice, especially in patients with POS in association of postoperative nausea and vomiting. These results were confirmed by Teymourian et al.[22], where ondansetron was administered 10 min before the end of surgery to 40 patients for the prevention of post-anaesthesia shivering after elective craniotomy, and they found that ondansetron was of great value in preventing POS.

Also, in a study carried out by Abdollahi et al.[23], who compared the efficacy of ondansetron and meperidine in preventing shivering after coronary artery bypass graft (CABG), they concluded that prophylactic administration of ondansetron 8 mg IV is equally effective as meperidine 0.4 mg kg^{-1} in the prevention of perioperative shivering in CABG patients.

An interesting meta-analysis of randomized controlled studies conducted by He et al.[20] investigated the effectiveness and safety of ondansetron in preventing POS and concluded that treatment with ondansetron is both effective and safe as well as reducing POS.

Our results showed a significant reduction in incidence and severity of POS, and these results were against the results of a randomized clinical trial carried out by Browning et al.[24] Who concluded that no significant difference between intravenous ondansetron 8 mg and placebo were given to parturient undergoing cesarean section under combined spinal-epidural anaesthesia. This may be explained by the criteria of these populations being all females, pregnant, and relatively young. There is evidence that POS in pregnancy and the peripartum period differs from thermoregulatory shivering seen in the non-pregnant population.[24]

Although Kelsaka et al.[25] used 8 mg intravenous ondansetron in their study, a slightly higher percentage of patients in the ondansetron group had shivering (8% compared to 5.9% in our study). This may be due to their lower operating room temperature (21-22°C). However, this has to be interpreted with caution since, contrary to expectation, a lower percentage of patients had to shiver in their control group compared to the control group in our trial (36% vs. 48.5%). The differences in the patient population in the two studies (non-obstetric versus obstetric patients) could also have accounted for the difference.

This study has some limitations. First, it was a single-center study, and the subjects were assessed for POS only for 60 min after the procedure. However, the incidence of POS can last up to 10 h.[4] Second, we did not measure the plasma levels of paracetamol or ondansetron; however, this may not be practical. Further trials are needed to evaluate the late effects of paracetamol and ondansetron on POS and determine the optimal timing of administration for maximum benefit. Future studies should clarify the mechanism and optimal dose of paracetamol and ondansetron and determine which patient populations would most benefit from its use.

Conclusion

In conclusion, in patients who have undergone liposuction under combined epidural and general anaesthesia, paracetamol is as effective as ondansetron when administrated at the end of surgery and can reduce the incidence and severity of POS.

Ethics Committee Approval: Institutional Research Ethics Committee of the Faculty of Medicine, Cairo University, approved the study (N-122-2020).

Informed Consent: The eligible patients were informed about the study during the preoperative evaluation and their written consents were obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.S.W., W.S.W.; Design - A.S.W.; Supervision - A.K.S., W.S.W.; Funding - W.S.W.; Data Collection and/or Processing - A.S.W., G.E.L.; Analysis and/or Interpretation - A.S.W.; Literature Review - G.E.L., A.K.S., W.S.W.; Writing - A.S.W., H.O.A., M.M.M., A.K.S.; Critical Review - A.S.W., G.E.L., M.M.M., A.K.S., A.F.S., W.S.W.

Declaration of Interests: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Original Article
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Pre-anaesthesia Telephone Consultation: A Safe Alternative for Anaesthesia Assessment in Case of Repeated Low or Intermediate Risk Surgeries: A Prospective Cohort Study

Charles-Herve Vacheron[1,2,3], Clemence Ferrier[4], Estelle Morau[5], Alexandre Theissen[6], Vincent Piriou[1], Pierre Yves Carry[1], Arnaud Friggeri[2,3,7]

[1]Department of Anaesthesia Resuscitation, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Lyon, France
[2]CIRI-International Center for Infectiology Research (Team PHE3ID), Univ Lyon, University Claude Bernard Lyon 1, Lyon, France
[3]Department of Anaesthesia Resuscitation, University Claude Bernard Lyon 1 Faculty of Medicine Lyon Sud, Lyon, France
[4]Department of Anaesthesia Resuscitation, Centre Hospitalier de Mayotte, Mamoudzou, France
[5]Department Anaesthesia Resuscitation, Douleur Urgence CHU Carémeau, Nîmes, France
[6]Department of Anaesthesia Resuscitation, Centre Hospitalier Princesse Grâce, Monaco, Monako
[7]Department of Anaesthesia Resuscitation, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite, France

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Abstract

Objective: Telemedicine has widely expanded during the coronavirus disease-2019 pandemic. Our objective was to evaluate the feasibility, safety, effectiveness, and satisfaction of pre-anaesthesia telephone consultation (PATC).

Methods: From December 2015 to October 2016, a prospective survey was administered to anaesthesiologists, nurse anaesthetists, and patients of the ambulatory and maxillofacial departments. Patients having a pre-anaesthesia consultation (PAC) within the previous year in the department, whose health state was considered stable, and for whom the surgical procedure was related to the previous one, were eligible for PATC. Three questionnaires concerning the pre- (Q1), per- (Q2), and postoperative (Q3) periods were answered by the patient, the anaesthesiologist, and the anaesthesiologist nurse to evaluate the feasibility and satisfaction of the PATC. We collected the cancelation rate and any incident occurring during the surgery.

Results: Over the study period, 210 patients were included. The response rate was 200/210 (95.2%) for Q1, 108/208 (51.9%) for Q2 and 146/208 (70.2%) for Q3. PATC was performed in a median (IQR) of 13 (7-20) days before the procedure. Patients answered directly in 73% of cases without the need for recall. During surgery, 4 incidents occurred and none were attributable to PATC. Patient satisfaction was 93.3% and 85.8% of them preferred PATC to conventional PAC. The kilometric saving was 74 (30-196) km per PATC.

Conclusion: Both patients and professionals were satisfied with PATC, which did not impact safety. On the selected patients, PATC brings many practical benefits and increases organizational flexibility.

Keywords: Anaesthesia, consultation, telemedicine

Main Points

- Pre-operative anaesthesia consultation allows a better patient safety.
- The pre-anaesthesia telephone consultation (PTAC) replacing physical consultation, allowed a good satisfaction both for healthcare professionals, and for the patient.
- The PTAC is a safe and reliable alternative in case of low or intermediate surgery.

Corresponding author: Charles-Herve Vacheron, e-mail: charles-herve.vacheron@chu-lyon.fr

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Introduction

Telemedicine combines the benefit of an equitable, affordable, and accessible way to healthcare resources.[1,2] While telemedicine has widely expanded during the coronavirus disease-2019 pandemic, it has currently been inadequately assessed concerning its safety and efficiency. Carrying out a pre-anaesthetic assessment optimizes the quality of perioperative care and anaesthetic safety while contributing to the economic efficiency at the hospital level.[3,4] In France, pre-anaesthesia consultation (PAC) has been legally mandatory since 1993 for every patient before anaesthesia, including isolated locoregional anaesthesia (LRA). The PAC aimed to evaluate the clinical condition of the patient, prepare the patient for surgery, and inform the patient about the modality of anaesthesia and analgesia in the perioperative period. In collaboration with the operator, the patient is able to give informed consent to the planned procedure and choose his modality of anaesthesia (LRA, general anaesthesia). Prior to each procedure, this consultation must be carried out by an anaesthesiologist, at least 48 hours before the intervention.[5]

Briefly, the PAC consists of a complete medical consultation: searches for medical, surgical, and anaesthetic history, current treatments, and history of allergy. The anaesthesiologist performs a physical examination, mainly to evaluate the predictable difficulty of ventilation or intubation. Moreover, the anaesthesiologist plans the potential discontinuation of medications interfering with anaesthesia and surgery, including antiplatelet, anticoagulant, or some antihypertensive drugs. Then, just before surgery, the anaesthesiologist performs a preoperative assessment based on this consultation.

Since 2014, pre-anaesthesia telephone consultation (PATC) has been performed as an innovative experiment in selected patients after governmental authorization. In 2017, the commission on risk assessment and risk management of the French society of anesthesiology [CAMR, Société Française d'Anaesthésie Réanimation, (SFAR)] defined the modalities for PATC, mainly to avoid patients' traveling in the case of repeated surgeries (surgical procedure related to the previous one).[6] However, there has been no evaluation of this practice in this situation in France.

We hypothesize that PTAC is a feasible and safe alternative to physical PAC. We therefore conducted this study to evaluate PATC as an alternative to traditional consultations for known patients in cases of low- or intermediate- risk surgeries following a previous surgical procedure with a previous pre-anaesthesia consultation. Our primary outcome was to estimate the surgery cancelation rate associated with PATC, and the secondary outcome included the evaluation of the quality, safety, feasibility, and satisfaction of PTAC.

Methods

Study Setting

A prospective single-center survey study was conducted between December 16th 2015 and October 16th 2016 (10 month). This survey focused on patients undergoing maxillofacial or outpatient surgery in a French University hospital. Consent was obtained from all participants. The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This study was approved by the Hospices Civiles de Lyon Committee (approval no: 19-139, date; 2015).

PATC Criteria

Inclusion criteria for the patient to be eligible for PATC were:

- ASA scores 1, 2 or 3.

- Stable health state.

- Previous physical PAC within the previous year for surgical or interventional procedure related to the consultation.

- No pre-operative blood testing needed.

- Agreements from the patients, surgeons, and anaesthesiologists.

The patients were informed that they could withdraw their consent anytime throughout the study period. The anaesthesiologist in charge could also decide to redirect during the PATC the patient to a conventional consultation.

Survey

Data were collected using 3 questionnaires drawn up by the anaesthesia team according to the 2013 guidelines of the French Health Authority.[7] They included closed dichotomous and multiple-choice questions, satisfaction or judgment scales, Likert scale-type or numeric and semantic closed-order scales, and additional open-ended questions (Appendix).

The first questionnaire (Q1 - supplementary data A) was divided into two parts. The first part was intended for the patient to assess his satisfaction. With 5 questions, it explored satisfaction regarding the technical modalities, quality and safety, and practical benefits provided by the PATC. The second part was responded to by the anaesthesiologist conducting the consultation. The physician answered eight questions concerning the patient's epidemiological data, information concerning PATC technical modalities (number of calls, consultation time frame, and connection quality), practical benefits of this type of consultation, and the anaesthesiologist's overall satisfaction.

The second questionnaire (Q2 - supplementary data B) was completed by the nurse anaesthetists. It aimed at collecting information during the perioperative period, with 11 questions regarding the efficiency, safety, and satisfaction regarding PATC. We also collected incidents such as intervention cancelation or postponement. Finally, in the third questionnaire (Q3 - supplementary data C) completed in the postoperative period, five questions were asked to the patient regarding his final satisfaction.

Objective

We estimated the surgery cancelation rate associated with PATC.

Secondary objectives were;

- The evaluation of the quality and safety of PATC, especially regarding the rate of incident attributable to PATC.

- The evaluation of the organizational and technical feasibility of the PATC.

- The evaluation of patient and anaesthesiologist satisfaction and benefit from the PATC.

Statistical Analysis

Descriptive statistics were expressed as the mean ± standard deviation or median (Q1-Q3) according to the normality of their distributions. Statistical analysis was performed using R software V 3.6.3.

Results

Over the study period, 210 patients were included (48% of the PATC performed in the different departments of the hospital during the study period). A total of 454 questionnaires was analysed. The response rate was 200/210 (95%) for Q1 (intended for anaesthesiologists and their patients after PATC), 108/208 (51%) for Q2 (intended for nurse anaesthetists on the day of the intervention) and 146/208 (70.2%) for Q3 (intended for patients in the postoperative period). Patients were 42 ± 21 years old, 198 (94%) were ASA 1 or 2, 172 (83%) had an outpatient surgery, 188 (90%) had a general anaesthesia (Tables 1, 2). PATC were performed in a median of 193 (84-313) days after the previous in-person PAC.

Among the 210 procedures planned after PATC, 2 (<1%) were cancelled because one for non-respect of fasting and the other for non-withdrawal of antithrombotic treatment, which was introduced after PATC. Apart from cancellations, 4 incidents were reported, 3 related to difficult airway predictors and 1 to unreported allergy. These incidents did not require a modification of the anaesthesia protocol.

Feasibility and Effectiveness

Median delay between PATC and surgical procedure was 13 (7-20) days, and the mean duration of PATC was 12 ± 4 minutes. The patient response was obtained upon first call in 75.0% of cases and a second call was necessary in 19% of cases. Anaesthesiologists considered the setting as optimal in 92.7% of PATC performed. Otherwise, the reasons given were poor technical conditions (n = 4), poor preparation of the patient for the consultation (n = 4), communication problems (n = 2), patient anxiety (n = 2), or patient incivility (n = 2).

Benefits and Satisfaction

The main advantage reported by patients was the possibility of performing the consultation outside the hospital,

Table 1. Patient Characteristics

	Patients (n = 210)
Age, years	42 ± 21
<18	21 (10%)
18-40	92 (44%)
41-64	61 (29%)
≥65	36 (17%)
Sex (Male)	96 (46%)
ASA score	
1	134 (64%)
2	64 (30%)
3	11 (5%)
4	1 (<1%)
Home to hospital distance, km	37 (15-98)

Table 2. Procedure Characteristics

Type of surgery	
Maxillofacial surgery	95 (46%)
Superficial cutaneous surgery	48 (23%)
Ear, nose and throat surgery	26 (12%)
Ophthalmic surgery	16 (8%)
Visceral surgery	11 (5%)
Digestive and urological endoscopies	7 (3%)
Other (diagnostic acts)	7 (3%)
Type of stay	
Ambulatory	172 (83%)
Hospitalisation	36 (17%)
Type of anaesthesia	
General anaesthesia	188 (90%)
Local and sedation	19 (9%)
Locoregional anaesthesia	1 (<1%)

thus avoiding the difficulties related to organization of professional activities.

The median distance between patients' home and hospital was 37 (15-98) km. Geographic distance was not the only concern raised by patients: traffic jams, parking problems, lack of vehicle, limited access to public transportation, need of a third party, or physical disability were also reported as advantages. The other benefits mentioned included the possibility of maintaining the surgery date despite the overloaded anaesthesia consultations and the time saved.

Among the anaesthesiologists, 87% were satisfied or very satisfied (Figure 1A) but 22% questioned the validity of PATC due to concerns regarding clinical examination (4%), patient reliability (2%), patient understanding (2%), or medical history (1%). According to 94% of the nurse anaesthetists, PATC did not alter management in the operating room. Exhaustivity of PATC was reported in 96% of cases, adequate patient information in 98%, and satisfaction from patients in 97% of cases.

Finally, patient satisfaction and safety scores were high (Figure 1B), with a 4-5 score in 93% and 92.3% respectively. Benefits provided by PATC were reported in 98% of cases and related to distance, occupation and childcare in 70%, 38% and 3% of cases, respectively.

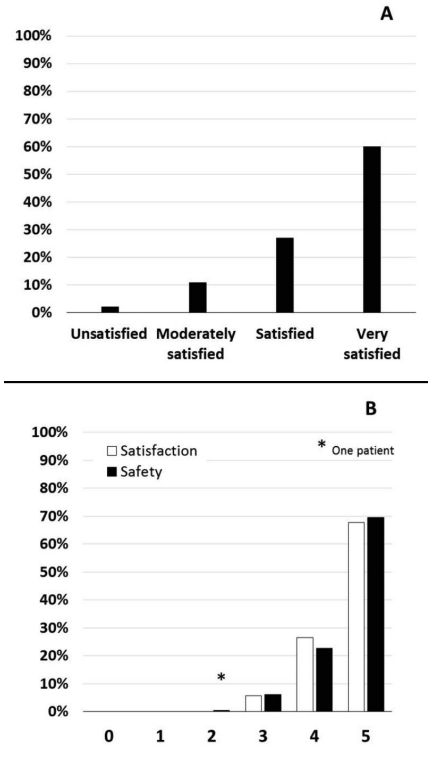

Figure 1. PATC satisfaction and safety evaluation by patients (A) and satisfaction evaluation by anaesthesiologists (B).

Following the intervention, 85% of patients felt safe using this type of consultation, 94% found PATC modalities effective, 96% reported practical benefits of PATC for which 76% was related to travel, 36% to occupation, and 6% to childcare, and 98% considered that all their questions were answered. Overall, 85.8% of the surveyed patients preferred PATC over conventional in-person consultation.

Discussion

PATC intends to assist and simplify consultation without degrading anaesthetic safety. In this study, the inclusion criteria entailed that PATC was performed in rather young and active patients with good medical conditions. In this context, the cancelation rate was low and not related to an error performed during the consultation. This is lower than the cancelation rates for elective surgery reported in the literature, ranging between 5% and 40%.[8-11]

Although several studies have evaluated pre-anaesthesia patient health status by telephone relying on a precise checklist, PATC herein consisted in a true consultation except for the lack of clinical examination.[9,11,12] In the French medical setting, in-person PAC is considered a legal gold standard, and any modification of the latter is a priori considered harmful for the patient and risky for the anaesthesiologist. Indeed, in France, the anaesthesiologist is in charge of all the medical and drug management related issues associated with surgery in the pre-, per-, and postoperative period. This explains the importance given to PAC by French anaesthesiologists. Importantly, the anaesthesiologist's professional satisfaction with PATC in this study seemed excellent. Following the severe acute respiratory syndrome coronavirus-2 outbreak, to avoid any contamination, telemedicine has spread widely in France, also in the preanaesthesia area.

PATC was performed in obstetrical setting and authors report a lack of information in 10% of cases and that this constituted a loss of opportunity in 1.5% of cases.[13] Our results indicated a lower rate, probably due to the prior evaluation of the patient and his medical records.

Others perform telehealth consultation that differs from PATC in that it uses a videoconference system. Telehealth consultation mimes face-to-face consultation in allowing physical examination (i.e., upper airway, venous access…) and improving patient-physician interaction.[14,15] Telehealth consultation is promising but was not available at the time of our study. In the future, our system could be improved by video conference tools.

Telemedicine for pre-anaesthesia assessment was also tested in Canada and USA, two very large countries with low medical density areas.[16,17] Teleconsultation facilitates care access in geographically remote areas or in those deficient

in care offer. It avoids patients traveling and thus reduces transport costs when the patient is distant from the care centre or in case of mobility impairment.[18,19] In previous studies, pre-anaesthesia teleconsultation was reported as safe and satisfying.[20,21]

Although the airway evaluation is a concern for anaesthesiologists, the observation of difficult airway predictors on the day of surgery was not associated with the procedure cancellation. Moreover, no serious adverse events were associated with the PATC procedure. Nevertheless, an ultimate check of the patients condition ("pre-anaesthesia visit") just before surgery is mandatory in France. During this visit, risk of difficult airway management can be assessed although, to date, airway evaluation scores have a low sensitivity.[22]

Regarding practical modalities, the results here showed that it is possible to perform PATC under good conditions within a reasonable time frame before surgery, highlighting more flexibility than conventional PAC for both patients and practitioners. This method can avoid the operative cancelation for patients who could not undergo PAC before the intervention due to lack of consultation availability. Moreover, teleconsultation could be implemented as a homeworking solution to save both the patient and anaesthesiologist a round trip to the hospital, thus improving their quality of life. Patient satisfaction was also excellent. From the patient perspective, PATC was considered effective and safe. The level of satisfaction observed here was comparable to those reported in the literature using telephone or video conference.[9,10,20,22,23]

In the case of communication impairment (deafness, tracheostomy, foreign language), the use of a third-party should help conduct PATC in good conditions. However, this raises the issue of patient confidentiality; the third-party role must be defined beforehand and should not be a hindrance to its realisation.

The most frequently highlighted benefits were travel and time savings. PATC brings a real benefit to people with limited autonomy and to the working population. Furthermore, the economic impact of PATC cannon be reduced solely by travel costs. Reduced costs concerning days off or childcare associated with increased flexibility in the management of medical time and surgery schedulings should also be considered.

Finally, the ecological benefit for the economy of road travel must be regarded in the global climatic crisis toward which we are going.

Study Limitation

The interpretation of our results needs to be considered regarding the usual precautions of a small, monocentric study. Indeed, the study is underpowered to detect a difference in very rare unusual events, and the PTAC might not fit in surgery requiring a lot of preoperative evaluation.

Conclusion

PATC may be an alternative to physical PAC in cases of repeated surgery and outpatient surgery. Despite being beneficial, PATC needs to be evaluated regarding the patient safety and cancelation rate of operations in severely ill patients and compared to a classical physical consultation.

Ethics Committee Approval: This study was approved by the Hospices Civiles de Lyon Committee (approval no: 19-139, date; 2015).

Informed Consent: The eligible patients were informed about the study during the preoperative evaluation and their written consents were obtained.

Peer-review: Externally and internally peer-reviewed.

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Original Article
Obstetric Anaesthesia

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Comparison of Prophylactic Infusion of Phenylephrine Versus Norepinephrine for the Prevention of Post Spinal Hypotension in Parturients Undergoing Elective Caesarean Section-a Randomized, Double-Blinded, Non-Inferiority Trial

Banupriya Ravichandrane[1], Rajeshwari Subramaniam[1], Thilaka Muthiah[1], Praveen Talawar[2], Rajasekar Ramadurai[3]

[1]Department of Anaesthesiology, All India Institute of Medical Sciences, Pain Medicine and Critical Care, New Delhi, India

[2]Department of Anaesthesiology, All India Institute of Medical Sciences, Rishikesh, India

[3]Department of Anaesthesiology & Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India

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Abstract

Objective: Postspinal hypotension occurs in nearly 50% of women undergoing cesarean section (CS). Although phenylephrine (PE) is currently the vasopressor of choice, severe maternal bradycardia may adversely affect the fetal status due to the reduction in the maternal cardiac output. Norepinephrine (NE) is not associated with bradycardia and is now being evaluated for the treatment of post-spinal hypotension in obstetric patients. The hypothesis of this study was that the prophylactic NE infusion was non-inferior to PE infusion when used for the prevention of postspinal hypotension.

Methods: This was a randomized, double-blinded controlled study conducted in 130 parturients scheduled for CS. The participants received either prophylactic NE (5 μg min^{-1}) or PE (25 μg min^{-1}) infusion beginning at the time of spinal injection. The primary outcome was the incidence of hypotension in both groups. Maternal bradycardia, reactive hypertension, nausea and vomiting, requirement of rescue boluses of vasopressor and/or atropine, and neonatal acid base status were also recorded.

Results: The incidence of hypotension was 33.80% (22 of 65) in Group PE and 26.10% (17 of 65) in Group NE (P=0.85). The absolute risk difference [90% confidence interval (CI)] in the incidence of hypotension between the groups was -7.7% (-20.9, 5.4). The upper limit of the CI was less than the non-inferiority margin of 20%, indicating that the NE infusion was non-inferior to PE.

Conclusion: Prophylactic infusion of NE is not inferior to prophylactic PE infusion in the prevention of postspinal hypotension in patients undergoing CS.

Keywords: Cesarean section, norepinephrine, obstetric anaesthesia, phenylephrine, postspinal hypotension

Main Points

- Hypotension is one of the most common consequences of spinal anaesthesia.
- Vasopressors like phenylephrine are the primary agents used for the management of post spinal hypotension.
- Phenylephrine-induced reflex bradycardia can be deleterious to the fetus.
- Norepinephrine was found to be equally effective in treating post spinal hypotension.

Corresponding author: Banupriya Ravichandrane, e-mail: banupriya147@gmail.com

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Introduction

Spinal anaesthesia is commonly preferred over general anaesthesia in parturients undergoing elective cesarean section (CS). Hypotension occurs in nearly 80% of the parturients due to the blockade of preganglionic sympathetic neurons and subsequent fall in systemic vascular resistance.[1]

Phenylephrine (PE), a pure alpha (α) agonist, has emerged as the vasopressor of choice for the management of post spinal hypotension since it has less propensity to depress fetal pH and base excess than ephedrine.[2,3] The associated bradycardia has a theoretical potential of causing a fall in maternal cardiac output and subsequent impact on the fetus. Hence the usage of norepinephrine (NE), an α1 adrenergic agonist with weak beta (β)1 adrenergic agonist activity, with minimal changes in maternal HR has been suggested recently.[4,5]

This randomized, prospective, double-blinded, controlled trial was designed to compare the efficacy of prophylactic intravenous (IV) infusion of PE and NE in the prevention of post spinal hypotension in parturients undergoing elective CS. The primary outcome measure was the incidence of hypotension between the groups. We hypothesized that NE is equally effective or not inferior to PE in the management of postspinal hypotension for elective CS. Secondary outcome measures included incidence of maternal bradycardia, nausea and vomiting, reactive hypertension, requirement of rescue boluses of vasopressor and/or atropine, and neonatal acid base status.

Methods

This prospective, randomized controlled double-blinded study was conducted after obtaining approval from the institute ethics committee. Written informed consent was obtained from all participants. The study was registered with Clinical Trials Registry of India at clinicaltrials.gov. The study was conducted over a period of 14 months (from August 2017 to October 2018). The manuscript has been prepared in accordance with the revised 2010 CONSORT guidelines, incorporating extra points from "Extension of CONSORT 2010 checklist when reporting a non-inferiority randomized trial".[6]

The American Society of Anesthesiologists grade II parturients with singleton term pregnancy scheduled for elective CS were included in the study. Patients with severe systemic illness (uncontrolled diabetes, hypertension, cardiac disease etc.), obstetric complications (pregnancy induced hypertension, abnormal placentation), and patients in active labor were excluded from the study.

Randomization was achieved using a computer-generated random sequence. Patient codes along with instructions to prepare the drug were placed into sequentially numbered sealed opaque envelopes. A resident anaesthesiologist who was not involved in patient management prepared the drugs. The patient and the attending anaesthesiologist conducting the CS were blinded to the study drug.

Anaesthesia Protocol: Patients were fasted overnight and were given IV metoclopramide 10 mg and ranitidine 50 mg. On arrival to the operating room (OR), electrocardiogram, non-invasive blood pressure (BP), and SpO_2 monitors were attached. Baseline heart rate (HR) and BP were noted by taking an average of three values recorded at an interval of 2 min in the OR with the patient in supine position with left lateral tilt. An 18G IV cannula was placed and coloading was achieved using 500 mL of lactated Ringer solution. Another wide-bore cannula was placed in the contralateral arm. Fetal HR was monitored by external cardicotocography until the commencement of surgery.

Subarachnoid block (SAB) was administered by an experienced anaesthesiologist (not necessarily the same person always) with 10 mg heavy bupivacaine and 150 µg of preservative free morphine in the L3-L4 interspace using a 25 G Quincke needle with the patient in the sitting position. After the block, patients were made supine with left lateral tilt, and vasopressor infusion was started at 15 mL h according to the group allocation:

Group 1 (later decoded as PE) patients received 25 µg min^{-1} of PE (diluted to reach a concentration of 100 µg mL).

Group 2 (later decoded as NE) patients received 5 µg min^{-1} of NE (diluted to reach a concentration of 20 µg mL).

There were no failed spinal blocks in either of the two randomized groups. The SAB was assessed until the loss of sensation for cold at the level of the T4-T5 dermatome and surgery was allowed to start. BP and HR values were recorded at intervals of every minute till the delivery of the baby and every 5 min till the end of surgery. Hypotension was defined as a decrease in systolic blood pressure (SBP) of >20% from baseline or the absolute value of SBP <100 mm of Hg, and was treated with a rescue bolus of PE 25 µg IV and repeated once more if there was no improvement in the SBP. In case of reactive hypertension, defined as an increase in SBP >20% from baseline, the study drug infusion was stopped. Patients with bradycardia (HR <50 beats min^{-1}) were treated with atropine (0.3 mg IV bolus) and repeated if necessary.

The oxytocin infusion (10 IU in 500 mL normal saline) was started for all parturients after the delivery of the neonate. The study drug was continued till uterine closure and the data was recorded at the end of surgery. Paracetamol 1 g IV and ondansetron 4 mg IV were administered before the transfer of the patient to the postoperative recovery area.

Data Collection: The primary outcome of our study was to compare the incidence of maternal hypotension after SAB. Secondary outcomes were to compare the incidence of maternal bradycardia, reactive hypertension, nausea, and vomiting, requirement of rescue boluses of vasopressor and/or atropine, and neonatal acid base status (umbilical cord blood gases). Apgar scores were also noted in 1 min and 5 min post delivery.

Statistical Analysis

The incidence of hypotension was reported as 30% in a previous study using the same dose of prophylactic PE infusion (25 µg min^{-1}).[7] For calculating a 90% confidence interval (CI) with a non-inferiority margin of 20%, a sample size of 65 patients was required per group, assuming a power of 80% and an alpha error of 0.05.

Statistical analysis was performed using Stata 12.0 (College Station, Texas, USA). Data were presented as mean ± standard deviations or number (percentage) or median (range) as appropriate. Continuous baseline characteristics were compared using an unpaired *t*-test (area under the curve for episodes of hypotension and neonatal APGAR scores and umbilical blood gas parameters) or Wilcoxon-rank-sum test (spinal induction to incision time and uterine incision to delivery time). The categorical variables were compared using the chi-square test or Fisher's exact test (parity, incidence of hypotension/bradycardia and requirement of rescue boluses) as appropriate. A *P* value of <0.05 was considered statistically significant. For the primary endpoint, the non-inferiority of prophylactic infusion of NE to PE was planned to be claimed if the difference (90% CI) in incidence of hypotension was less than the margin of 20%.

Results

One hundred and thirty patients consented and were randomly allocated to receive NE at 5 µg min (n = 65) or PE at 25 µg min (n = 65). All patients received the intended intervention and were available for final analysis (Figure 1). Patient demographics, as described in Table 1, were statistically non-significant between the groups.

Maternal outcomes are shown in Table 2. The difference in the incidence of hypotension with PE (22 out of 65, 33.8%) and NE (17 out of 65, 26.1%) was statistically non-significant [risk ratio: 1.29 (0.72, 2.29) *P* value-0.85. The difference (90% CI) in the incidence of hypotension between the groups was -7.7% (-20.9, 5.4) (Figure 2), which denote that NE was non-inferior to PE in preventing hypotension. The number of boluses of rescue vasopressor (*P*=0.48), pre-delivery HR (*P*=0.26), and post- delivery HR (*P*=0.74) were statistically non-significant between the groups.

The incidence of maternal bradycardia (HR <50 min) was 12.3% (8 out of 65) with PE and 10.7% (7 out of 65) with NE, which was statistically non-significant (*P*=0.46). The incidence of nausea was 9.2% (6 out of 65) with PE and 4.6% (3 out of 65) with NE, statistically non-significant (*P*=0.49) and was associated with hypotension in all patients; however, no patient had vomiting. Ventricular premature contractions (VPCs) occurred in 7 patients in the NE group as opposed to none in the PE group. Only 3 patients among 7 who had VPCs experienced reactive hypertension that required termination of infusion. None of these patients required further treatment.

Table 1. Patient Demographics and Operative Data

		PE group (n = 65)	NE group (n = 65)
Age (years)*		28.4 (4.4)	29 (4.8)
Weight (kg)*		66 (8.8)	65.7 (9.6)
Height (meters)*		1.57 (0.05)	1.58 (.05)
Block height+ (number of patients)	T4	33 (50.7%)	29 (44.6%)
	T5	32 (49.2%)	36 (55.3%)
Induction to incision time (seconds)‡		338 (80-980)	321.5 (120-689)
Incision to delivery time (seconds)‡		64.5 (25-213)	55.5 (20-133)

Data presented as, *mean (standard deviation); +number (%) and ‡median (interquartile range).
PE, phenylephrine; NE, Norepinephrine.

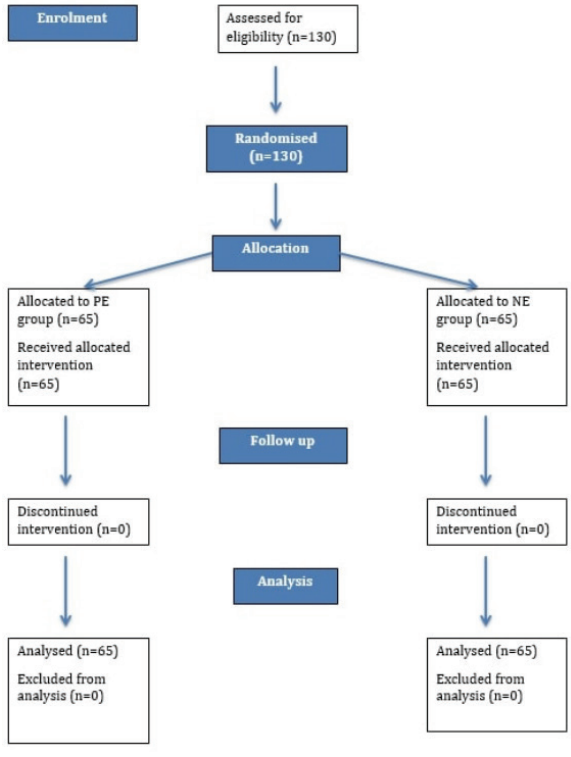

Figure 1. Consort flow diagram of the study.

The neonatal outcome was comparable between the groups (Table 3). The subgroup analysis in neonates born of patients with bradycardia in the PE group (n = 7) had lower umbilical cord pH compared to their counterparts in the NE group (n = 8), which approached significance (*P*=0.052).

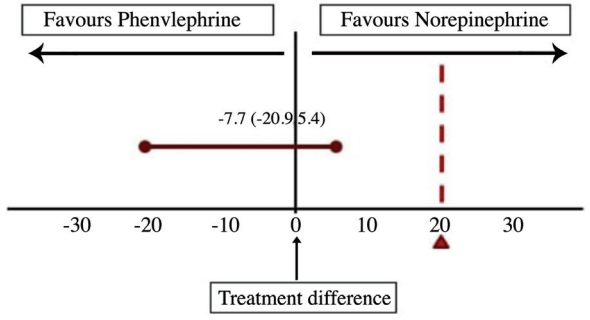

Figure 2. Figure showing the treatment difference between the groups. The upper limit of the 90% CI is less than the non-inferiority margin of 20%, which shows that prophylactic infusion of norepinephrine is non-inferior to the prophylactic infusion of phenylephrine in preventing post-spinal hypotension.

CI, confidence interval.

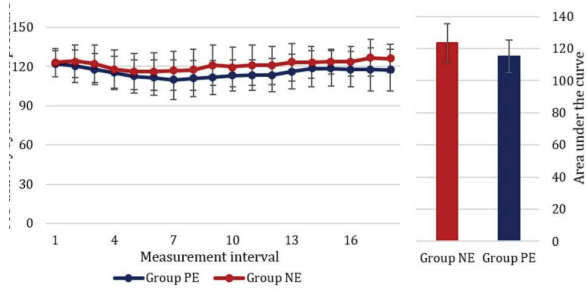

Figure 3. Figure showing trends of maternal pre-delivery systolic blood pressure.

PE, phenylephrine; NE, norepinephrine.

Table 2. Maternal Outcomes

	PE group (n = 65)	NE group (n = 65)	RR or Mean difference (95% CI)	*P* value
Incidence of hypotension	22 (33.80%)*	17 (26.10%)*	1.29 (0.76, 2.20)‡	0.85
Pre-delivery SBP (mmHg)	115.3 ± 10.2 †	123.4 ± 12.2†	-8.1 (-12.0, -4.19)§	0.04
Post-delivery SBP (mmHg)	113.3 ± 7.5†	115.7 ± 9.2†	-2.4 (-5.31, 0.51)§	0.19
No of rescue boluses required for hypotension	1 (1-6)||	1 (1-3)||	1 (0.06, 15.6)‡	0.48
Pre-delivery HR (beats min^{-1})	88.6 ± 15†	81.8 ± 15.7†	6.8 (1.47, 12.12)§	0.26
Post-delivery HR (beats min^{-1})	85.3 ± 13.8†	86.4 ± 18.1†	-1.1(-6.68, 0.48)§	0.74
Bradycardia	8 (12.30%)*	7 (10.7%)*	1.14 (0.44, 2.76)‡	0.46
Nausea	6 (9.2%)*	3 (4.6%)*	2 (0.52, 7.65)‡	0.49
Premature ventricular contractions	0	7	-	0.006
Reactive hypertension	0	3	-	0.08

Data presented as *number (%); †mean ± standard deviation; ‡Relative risk (95% confidence interval); §mean difference (95% confidence interval); ||median (range). SBP, systolic blood pressure; HR, heart rate; PE, phenylephrine; NE, norepinephrine.

Table 3. Neonatal Parameters

	Group PE (n = 65)	Group NE (n = 65)	*P* value
pH	7.29 ± 0.06	7.30 ± 0.05	0.211
PCO_2 (mmHg)	38.9 ± 6.1	38.5 ± 5.6	0.706
HCO_3 ($mEq\ L^{-1}$)	20.4 ± 2. 3	21.5 ± 2.9	0.022
Apgar score at 1 min	8.5 ± 1.01	8.7 ± 0.5	0.176
Apgar score at 5 min	9.7 ± 0.6	9.7 ± 0.5	0.608

Data presented as mean ± standard deviation.
PE, phenylephrine; NE, norepinephrine.

Discussion

The results of our study show that prophylactic infusion of NE is non-inferior to PE in maintaining maternal SBP after spinal anaesthesia. There was no statistical difference in the incidence of hypotension, maternal bradycardia, rescue bolus requirement of vasopressor, and neonatal effects between the groups. Post-spinal hypotension is common in parturients undergoing CS, with a decrease in systemic vascular resistance recognized as a significant contributor. Prophylactic administration of PE has been observed to be more effective than ephedrine in reducing the incidence of post spinal hypotension.[3] PE infusions at higher rates (75 μg min^{-1} and 100 μg min^{-1}) were associated with higher incidence of hypertension and bradycardia as compared to lower infusion rates (25 μg min^{-1} and 50 μg min^{-1}).[7,8] Hence we used the lowest effective dose (25 μg min^{-1}) of prophylactic PE infusion to maintain the SBP in our study.

Studies using bolus PE have reported significant maternal bradycardia compared to NE infusion or NE infusion and ephedrine boluses.[9,10] The reflex bradycardia associated with PE warranted the search for a new vasopressor; when NE (strong α-adrenergic with mild β-adrenergic action) was suggested as a reliable vasopressor for the management of post spinal hypotension.[4,11] Different NE dosing regimens have been evaluated for prevention of post spinal hypotension in the obstetric setting. Chen et al.[12] observed that NE at 5 and 10 μg kg^{-1} h^{-1} maintained BP with less episodes of reactive hypertension compared to 15 μg kg^{-1} h^{-1}. Since the relative potencies of NE and PE compared in previous studies ranged from 20:1 to 2:1, with no defined optimal potency ratio; we used infusions of NE at 5 μg min^{-1} and PE at 25 μg min^{-1}, the doses associated with minimal adverse effects.[5,11,13]

The incidence of hypotension observed in our study (33.8% with PE vs. 26.1% with NE) was similar between the groups and comparable to the previous works done with equivalent doses of vasopressors.[7,8,14] The predelivery SBP over time in the present study was significantly higher in the NE group (123.4 ± 12.2 mmHg) compared to the PE group (115.3 ± 10.2 mmHg) (P=0.04) (Figure 3) and the difference (90% CI) in incidence of hypotension between the groups was observed to be less than the margin of 20%, inferring that prophylactic infusion of NE is non-inferior (as effective as) to the prophylactic infusion of PE in preventing post-spinal hypotension. The requirement for rescue vasopressor was also similar between the groups. These findings are in agreement to the findings of Ngan et al.[5] and Vallejo et al.[11]

In the present study, the observed incidence of bradycardia (12.3% with PE and 10.7% with NE) was comparable with Allen et al.'s[7] (15% with 25 μg min^{-1} of PE) and Vallejo et al.'s[11] studies (23.7% with PE and 18.6% with NE). The reported higher incidence of bradycardia with PE compared to NE in previous studies could be due to the usage of relatively higher dose of PE compared to NE.[5] However, in this study, there was no significant difference in the incidence of bradycardia between the groups, likely due to the use of the lowest effective dosage. Chen et al.[15] also reported no significant difference in the incidence of bradycardia between prophylactic NE (3.2 μg min^{-1}) and PE (40 μg min^{-1}) infusion in twin pregnancy. Though the clinical importance of PE induced bradycardia remains uncertain in elective CS, it might have some possible adverse impact in the presence of pre-existing fetal compromise.[16]

There was no significant difference in neonatal Apgar scores and umbilical artery pH between the groups. However, a subgroup analysis of the umbilical artery pH of neonates born to mothers who developed bradycardia revealed that the PE group were more acidotic (7.26 ± 0.03) than the NE group (7.29 ± 0.06), P=0.05. This is in concordance with Ngan et al.[5], who also reported significantly lower umbilical venous pH in neonates born of mothers receiving PE. This subgroup analysis cannot be generalized since only a few mothers had bradycardia in our study. However, it is worth considering that bradycardia in mothers receiving PE could be a marker for reduced CO despite "normal" BP, which may further affect a compromised fetus. Similar to our findings, Ngan et al.[17] in his recent study, reported that NE was non-inferior to PE for neonatal outcome assessed by umbilical arterial pH.

The incidence of nausea and vomiting was found to be similar in both groups in this study. There was also a positive correlation between hypotension and nausea, which could be due to cerebral hypoperfusion. The incidence of reactive hypertension with NE infusion is a dose-dependent effect. The episodes of reactive hypertension with NE infusion, required cessation of infusion.[11,12] In this study, only 3 of 65 patients (4.6%) in the NE group had reactive hypertension, which is lower than the reported literature. In spite of the apparently "normal" dosing of NE in our study, seven patients had episodes of ventricular ectopics that resolved spontaneously. This could be directly attributed to NE because three of these patients also had a hypertension, necessitating the cessation of NE infusion.

The limitations of this study are as follows. Invasive BP measurement was not chosen for ethical reasons although the accuracy of BP measurements would have been enhanced. Administration of PE rescue bolus in both groups might have also affected the hemodynamics and could have biased the results. CO monitoring may have been more informative in this setting but was not used in our study due to non-availability. A control group could have widened the comparability and possibly explained the higher incidence of hypotension despite preloading and use of prophylactic inotropic infusions in both groups.

Conclusions

Prophylactic infusion of NE (5 μg min^{-1}) was observed to be equally effective (non-inferior) in the prevention of post-spinal hypotension in patients undergoing elective CS compared with PE infusion (25 μg min^{-1}). The neonatal effect of doses of PE resulting in maternal bradycardia must be further evaluated stringently. In case the significant fetal acidosis does occur, NE may emerge as the vasopressor of choice for the prevention and treatment of post-spinal hypotension in obstetrics.

Ethics Committee Approval: This study was approved by Institute Ethics Committee For Post Graduate Reserach All India Institute of Medical Sciences Ansari Nagar (approval no: IECPG-561, date: 01.02.2017).

Informed Consent: The eligible patients were informed about the study during the preoperative evaluation and their written consents were obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.R., R.S. P.T.; Design - B.R., R.S., P.T.; Supervision - R.S., T.M., P.T.; Materials - B.R., R.S., P.T.; Data Collection and/or Processing - B.R., R.S., T.M., P.T., R.R.; Analysis and/or Interpretation - B.R., R.S., T.M., R.R.; Literature Review - B.R., R.S., T.M., P.T., R.R.; Writing - B.R., R.S., T.M., R.R.; Critical Review - B.R., R.S., T.M., P.T., R.R.

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Original Article
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The Effect of Anaesthesia Management with Different Fresh Gas Flows on Cognitive Functions of Geriatric Patients: A Randomized Double-blind Study

Bilge Özge Kılıç[1], Meltem Savran Karadeniz[1], Emre Şentürk[1], Meltem Merve Güler[1], İbrahim Hakan Gürvit[2], Zerrin Sungur[1], Ebru Demirel[1], Kamil Mehmet Tuğrul[1]

[1]Department of Anaesthesiology and Reanimation, İstanbul University İstanbul Faculty of Medicine, İstanbul, Turkey
[2]Department of Neurology, İstanbul University, İstanbul Faculty of Medicine, İstanbul, Turkey

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Abstract

Objective: The present study aimed to compare the effects of two different fresh gas flows (FGFs) (0.5 L min^{-1} and 2 L min^{-1}) applied during maintenance of anaesthesia on recovery from anaesthesia and early cognitive functions in geriatric patients.

Methods: In this prospective, randomised, double-blind study, sixty patients were divided into two groups according to the amount of FGF. Minimal-flow anaesthesia (0.5 L min^{-1} FGF) was applied to group I and medium-flow anaesthesia (2 L min^{-1} FGF) was applied to group II during maintenance of anaesthesia. Following the termination of inhalation anaesthesia, recovery times were recorded. The evaluation of cognitive functions was performed using the Addenbrooke's Cognitive Examination (ACE-R).

Results: There was no significant difference between the two groups in terms of demographic characteristics and recovery ($P > 0.05$). There was no significant difference between the two groups in terms of the preoperative day, the first postoperative day, and the third postoperative day; ACE-R scores ($P > 0.05$). In group II, on the third postoperative day ACE-R scores were found to be significantly lower than the preoperative ACE-R scores ($P=0.04$). In group II, third postoperative day ACE-R memory sub-scores (14.53 ± 3.34) were found to be significantly lower than preoperative ACE-R memory sub-scores (15.03 ± 3.57) ($P=0.04$).

Conclusion: In geriatric patients, minimal-flow anaesthesia was not superior to medium-flow anaesthesia in terms of recovery properties and cognitive functions. Keeping in mind that hypoxaemia and changes in anaesthesia levels may occur with the reduction of FGF, both minimal- and medium-flow anaesthesia can be applied with appropriate monitoring without adverse effects on recovery and cognitive functions.

Keywords: Agitation, cognitive dysfunction, emergence, geriatric anaesthesia, low flow

Main Points

- With low-flow anaesthesia (LFA), personnel exposure, cost, and greenhouse gas effects are reduced; also, LFA contributes to respiratory physiology. Furthermore, LFA increases the quality of recovery, but if fresh gas flow (FGF) is not increased in the recovery phase, it may cause prolongation of such a phase.
- To avoid prolonged recovery times, closing the vaporiser by increasing the FGF to 6 L min^{-1} at the end of the operation can provide faster recovery without affecting the recovery quality and without facing the risk of awareness.
- There are not enough studies investigating the effect of different FGFs used in anaesthesia maintenance on early postoperative cognitive dysfunction. Neither minimal-flow anaesthesia nor medium-flow anaesthesia is superior to each other in terms of postoperative cognitive functions in geriatric patients. Both FGFs can be used in the maintenance of anaesthesia in geriatric patients without additional concern for cognitive dysfunction.

Corresponding author: Meltem Savran Karadeniz, e-mail: mskaradeniz@gmail.com

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Introduction

Environmental and economic advantages, as well as physiological ones (e.g., increasing the recovery quality, preserving the temperature and humidity of the inhaled gas mixture), have increased the popularity of low-flow anaesthesia (LFA) in recent years.[1] Modern anaesthesia machines, inspiratory air monitoring, and third-generation inhalation agents have made LFA possible with a fresh gas flow (FGF) of up to 250 mL min^{-1}.[2] Despite this trend, there are few studies examining the relationship between different FGFs and early postoperative cognitive dysfunction (POCD).[3]

Neurocognitive functions include components such as memory, attention and language, which are controlled by certain pathways and centres in the brain.[4] Since Bedford's 1955 article, it is well known that the perioperative process causes varying degrees of cognitive dysfunction in elderly patients.[4] Despite advances in perioperative medical knowledge and techniques, POCD is still associated with increased postoperative complications, prolonged hospitalisation, early retirement, increased cost, and mortality.[5]

Early POCD is seen in 26% of elderly patients in non-cardiac surgeries.[6] Neuroinflammation and inactivation of the cholinergic system play a key role in the pathophysiology of POCD.[7] Due to increased peripheral inflammatory responses and an impaired blood-brain barrier, major surgeries and advancing age are the most important risk factors for POCD. However, it has not been shown that any anaesthetic technique currently used is superior to the others.[4]

This study examined whether different FGFs (minimal or medium flows) influence recovery from anaesthesia and early postoperative cognitive functions in geriatric patients. Our primary hypothesis was that early postoperative cognitive function scores would be higher in minimal-flow anaesthesia than in traditional medium-flow anaesthesia. Therefore, our primary outcome was the change in postoperative cognition tests. Our secondary outcomes were eye opening, obeying verbal orders, first movement, extubation times, time to reach the Steward score, recovery agitation, awareness development, and hospital stay.

Methods

Study Group and Randomisation

This prospective randomised double-blind study was conducted between October 2017 and February 2018, following İstanbul University, İstanbul Faculty of Medicine Clinical Research Ethics Committee approval (27.10.2017/17) and patient consent. Patients aged ≥60 years scheduled to be operated on under general anaesthesia at the İstanbul University Urology Clinic, with American Society of Anesthesiologists classification I-II-III and an estimated operation time over 2 hours were included. Patients who refused to participate in the study, had neurological or psychiatric diagnoses, had hearing or vision problems, had language barriers, were followed up in the intensive care unit in the early postoperative period, could not perform at least one of the planned neuropsychological tests, or had a mini-mental test score of <26 were excluded from the study.

The participants were randomised and divided into two groups; 0.5 L min^{-1} FGF was applied to group I and 2 L min^{-1} FGF was applied to group II. The randomisation sequence of the study was obtained using a computer programme by a researcher blinded to the FGF level and the neuropsychological tests to be used on patients (https://www.graphpad.com/quickcalcs/randomise1/). The information concerning the group that the patients would be included in was placed in sealed, opaque envelopes. Each sealed envelope was opened just before the induction of anaesthesia. The patients and the clinician who performed the neuropsychological tests were blinded to the anaesthesia method.

Anaesthesia Management

Electrocardiography, pulse oximetry (SpO_2), arterial blood pressure oscillometric measurement, bispectral index (BIS), and end-tidal carbon dioxide ($EtCO_2$) monitoring were performed on all patients who were admitted to the operating room. The patients were warmed actively during the operation using a heating bed. Induction of anaesthesia was performed with 1 μg kg^{-1} fentanyl, 2 mg kg^{-1} propofol, and 0.6 mg kg^{-1} rocuronium. The age-related desflurane nomogram was used to determine the end-tidal desflurane concentration, which corresponds to the target minimum alveolar concentration (MAC) value of 1.2 after intubation.[8] The initial setting of the desflurane vaporiser was determined by adding 1% to the value measured on the nomogram. Ventilation parameters were adjusted so that FGF was 4 L min^{-1} with 60% O_2 and air mixtures. The tidal volume was 6-8 mL kg^{-1}. Respiratory frequency was 12-14, and positive end-expiratory pressure was 4-6 cm H_2O (Dräger Primus®). When the MAC reached 1.2, FGF was reduced to 0.5 L min^{-1} in group I and 2 L min^{-1} in group II. Intravenous remifentanil infusion (0.05-0.2 μg kg^{-1} min^{-1}) was administered to all patients throughout the operation to provide intraoperative analgesia. Remifentanil infusion was titrated with dose changes of 0.01-0.02 μg kg^{-1} min^{-1} so that BIS values were between 40 and 60. The inhalation of the hypoxic gas mixture and changes in anaesthesia levels were prevented by monitoring the inhaled O_2 concentrations (FiO_2) and MAC values throughout the operation. When FiO_2 dropped below 35%, O_2 flow increased by 10% of the total gas flow. When FGF was reduced to 0.5 L min^{-1} in group I, the desflurane vaporiser setting was increased by

1% of the FGF volume to prevent superficial anaesthesia levels. When FGF was reduced to 2 L min^{-1} in Group II, no change was made to the desflurane vaporiser setting. Up to 1% desflurane vaporiser setting change was allowed, keeping the MAC values at 1.2 in both groups.

At the end of the operation, FGF was adjusted to 6 L min^{-1} 100% O_2. 10 min after the end of the operation, 0.5 mg atropine and 1.5 mg neostigmine were administered to each patient. After the end-tidal desflurane concentration was 0% and the BIS value was >80, the patients who met the extubation criteria were extubated. The extubation criteria were as follows: the patient was cooperative, the tidal volume was >6 mL kg^{-1}, and the patient was able to raise his head for >5 s. Wake-up time was evaluated with the Steward recovery score (SRS).[9] Patients with SRS ≥4 were transported to the recovery room. The time it took patients to open their eyes, respond to verbal commands, be extubated, and be transported to the recovery room after the desflurane vaporiser shutdown was recorded.

Hypotension was defined as mean arterial pressure <65 mmHg and hypoxaemia as SpO_2 <90%. In the case of hypotension, 5 mg ephedrine IV was administered. Arterial blood samples were taken and analysed from all patients at 90-minute intervals, the first one being at the beginning of the operation. Erythrocyte suspension was administered to patients with haemoglobin <8 g dL^{-1}. The pre-operative and postoperative blood glucose and sodium values of all patients were recorded.

At the end of the operation, 1 g paracetamol IV and morphine 0.05 mg kg^{-1} IV were administered at 6-h intervals to each patient. 0.03 mg kg^{-1} morphine was administered as an additional analgesic to patients with visual analogue scale (VAS) ≥4.

The Richmond Agitation-Sedation Scale (RASS) was used to evaluate recovery agitation.[10] Recovery agitation was diagnosed in patients with RASS ≥2 in the recovery room follow-up. The cognitive functions of the patients were evaluated one day before the operation, on the first postoperative day, and on the third postoperative day using the Addenbrooke's Cognitive Examination (ACE-R). To prevent environmental conditions from affecting the neuropsychological test results, all tests were performed in a quiet room. To prevent the learning effect, three different forms of ACE-R adapted to Turkish society were applied.[11] Postoperative neuropsychological evaluations of all patients were performed when VAS <4. Awareness during general anaesthesia was questioned with the modified Brice scale on the days ACE-R was administered (Table 1).[12] According to this scale, patients who stated that they experienced awareness in questions 4 and 5 and those who answered "yes" to question 3 were diagnosed with intraoperative awareness.

Sample Size Calculation

The G-Power program (version 3.1.9.2, Kiel, Germany) was used to determine the sample size before the study. In the preliminary study, the effect size was determined as 0.7. In this study, which creates a sample at a ratio of 1:1 for both groups, α: 0.05. When 1-β: 0.80 and considering 25% data loss, the aim was to include forty patients for each group, or eighty patients.

Statistical Analysis

The SPSS 20.0 program (IBM, United States, 1963) was used for statistical analysis. The conformity of the data to the normal distribution was examined with the Kolmogorov-Smirnov test. Normally distributed data were expressed as the mean and standard deviation and compared with independent sample *t*-test. Nominal data were expressed as the number and percentage of cases and compared with the chi-square test (Pearson's chi-square test and Fisher's exact test). In-group changes were investigated in repeated measurements, and the single-factor ANOVA test was used. Statistical significance was accepted as $P < 0.05$.

Results

A total of eighty patients were included in the study. Seven patients who underwent preoperative ACE-R were excluded from the study because of the postponement of their operations. Six patients from group I and four patients from group II were excluded from the study because they did not accept the application of ACE-R on the first or third postoperative day. One patient from group I and two patients from group II was excluded from the study because they were followed up in the intensive care unit after the operation. The study was completed with thirty patients in both groups (Figure 1).

No significant difference was observed between the two groups in terms of gender, age, comorbid systemic diseases, education, occupation, smoking, multiple drug use, type of anaesthesia applied in previous surgeries, duration of operation, duration of anaesthesia and hospital stay ($P > 0.05$) (Table 2). There was no statistically significant difference between the two groups in terms of pre-operative and postoperative serum glucose and sodium values ($P > 0.05$) (Table 3).

Table 1. Modified Brice Questionnaire
1. What is the last thing you remember before your surgery?
2. What is the first thing you remember after waking up?
3. Can you recall anything between under anaesthesia and waking up?
4. Did you dream anything during surgery? If so, was it disturbing?
5. What did you find most unpleasant about the surgery?
6. Did you have problems going to sleep or waking up?

There was no statistically significant difference between the two groups in terms of intraoperative ephedrine requirement (33.3%; 26.6%) and intraoperative transfusion requirement (0%; 3.3%) ($P > 0.05$). The proportion of patients with FiO_2 <35% was found to be statistically significantly higher in group I (53.3%) than in group II (26.6%) (P=0.04) (Table 3). Hypoxaemia did not develop in any patients in the two groups.

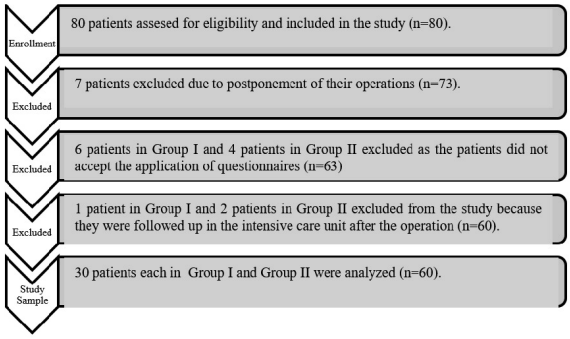

Figure 1. Flowchart of the study.

Table 2. Demographic and Operational Data of the Patients

	Group I (n = 30)	Group II (n = 30)	*P* value
Gender (female/male) (%)	13/17 (43.3%/56.7%)	8/22 (26.6%/73.4%)	0.18
Age (years)	66.6 ± 4.9	67.3 ± 5.1	0.60
ASA 1	6 (20%)	8 (26.6%)	0.50
ASA 2-3	24 (80%)	22 (73.3%)	
Radical prostatectomy	21 (70%)	18 (60%)	0.42
Radical-partial nephrectomy	9 (30%)	12 (40%)	
Education (≥8 years)	14 (46.6%)	8 (26.6%)	0.20
Occupation	16 (53.3%)	22 (73.3%)	0.24
Smoke	10 (33.3%)	13 (43.3%)	0.42
Multiple drug usage (3≥ drug)	22 (73.3%)	22 (73.3%)	1
History of general anaesthesia	22 (73.3%)	23 (76.6%)	0.67
History of spinal anaesthesia	3 (10%)	4 (13.3%)	0.52
Duration of anaesthesia (min)	187 ± 116.2	202 ± 100.5	0.62
Operation time (min)	169 ± 99.5	183 ± 90.5	0.50
Length of stay in hospital (hours)	52.6 ± 32	54.9 ± 34.9	0.79

Categorical data were expressed as the number and percentage of cases, and parametric data as mean ± standard deviation. ASA, American Society of Anesthesiologists Physical Status Classification System.

There was no statistically significant difference between the two groups in terms of eye opening, obeying verbal orders, first movement, extubation, and Steward score ≥4 ($P >$ 0.05) (Table 4). According to RASS, recovery agitation did not develop in any patients in the two groups. According to the modified Brice scale, awareness did not develop in any patients in the two groups. There was no significant difference between the two groups in terms of baseline, intraoperative 30th, 60th, 90th, and 120th min BIS values (P > 0.05) (Table 5).

The ACE-R scores and ACE-R subparameter scores of the patients in groups I and II are shown in Table 6. There was no statistical difference between the two groups in terms of ACE-R scores applied on the pre-operative day, the first postoperative day, and the third postoperative day ($P >$ 0.05). The ACE-R total scores of the patients in group I were found to be statistically similar on the pre-operative day,

Table 3. Perioperative Monitoring and Laboratory Data of the Patients

	Group I (n = 30)	Group II (n = 30)	*P* value
Preoperative sodium (mmol L^{-1})	141.6 ± 1.5	141.3 ± 2.7	0.19
Preoperative glucose (gr dL^{-1})	110.3 ± 28.3	114.1 ± 20.1	0.61
Postoperative sodium (mmol L^{-1})	141.2 ± 1.6	141.2 ± 2.1	0.15
Postoperative glucose (gr dL^{-1})	114.6 ± 22.6	118.5 ± 23.7	0.72
Hypotension	10 (33.3%)	8 (26.6%)	0.78
FiO_2 <35%	16 (53.3%)	8 (26.6%)	0.04
Transfusion	0 (0%)	1 (3.3%)	0.31

Parametric data are expressed as mean ± standard deviation. Categorical data were expressed as the number and percentage of cases. FiO_2 concentration of inspired O_2 in breath air.

Table 4. Comparison of Recovery Times of Patients

	Group I (n = 30)	Group II (n = 30)	*P* value
Eye opening time (min)	10.6 ± 5	10.1 ± 3.7	0.67
Verbal order obeying time (min)	11.4 ± 6	12.4 ± 6.1	0.57
Initial movement time (min)	7.9 ± 4.7	8.6 ± 4	0.79
Extubation time (min)	12.5 ± 6.4	12 ± 5.7	0.78
Steward score ≥4 (min)	16.1 ± 9.2	17.1 ± 9.5	0.71

Parametric data are expressed as mean ± standard deviation.

the first postoperative day, and the third postoperative day ($P > 0.05$). In group II, the third postoperative day total ACE-R scores (75.6 ± 7.3) were found to be statistically significantly lower than the pre-operative ACE-R scores (76.1 ± 10.04) (P=0.04). In group II, there was no statistically significant difference between the ACE-R scores obtained on the first postoperative day and the ACE-R scores obtained on the pre-operative day and the third postoperative day ($P > 0.05$). When the subsections of ACE-R were evaluated, there was no statistically significant difference between the two groups ($P > 0.05$). In group II, the third postoperative day memory scores (14.53 ± 3.3) were found to be statistically significantly lower than the pre-operative memory scores (15.03 ± 3.5) (P=0.04). No statistically significant difference was observed among other subsections of ACE-R administered at different times in group I ($P > 0.05$).

Table 5. Intraoperative BIS Values

	Group I	Group II	*P* value
BIS 0 min	97.97 ± 1.03	98.37 ± 1.16	0.16
BIS 30 min	56.23 ± 6.23	55.93 ± 7.05	0.86
BIS 60 min	56.07 ± 6.45	56.53 ± 7.85	0.80
BIS 90 min	54.43 ± 6.63	52.77 ± 6.90	0.34
BIS 120 min	50.80 ± 6.09	50.37 ± 7.03	0.80

Parametric data are expressed as mean ± standard deviation. BIS, bispectral index.

Table 6. Comparison of Preoperative, Postoperative 1st and 3rd Day ACE-R Total and Sub-Scores Between the Two Groups and Comparison of the Variation of ACE-R Total Scores Over Time within the Group

ACE-R Time	ACE-R subscores	Group I (n = 30)	Group II (n = 30)	*P* value
Preoperative	Attention/ Orientation	16.43 ± 1.59	15.90 ± 2.24	0.29
	Memory	15.63 ± 4.22	15.03 ± 3.57	0.55
	Fluency	9.27 ± 2.22	8.93 ± 2.63	0.59
	Language	22 ± 3.80	22.10 ± 3.6	0.91
	Visuospatial	13.80 ± 2.41	14.20 ± 1.86	0.47
	Total	77.1 ± 11.0	76.1 ± 10	0.71
Postoperative 1st day	Attention/ Orientation	16.43 ± 1.45	16.30 ± 1.82	0.75
	Memory	16.83 ± 3.70	15.73 ± 3.34	0.23
	Fluency	8.77 ± 2.32	8.67 ± 2.69	0.87
	Language	22.57 ± 2.12	22.10 ± 3.45	0.58
	Visuospatial	13.90 ± 2.13	13.57 ± 2.73	0.60
	Total	78.5 ± 8.6	76.3 ± 10	0.39
Postoperative 3rd day	Attention/ Orientation	16.83 ± 1.99	16.30 ±1.22	0.58
	Memory	16.76 ± 3.06	14.53 ± 3.34	0.26
	Fluency	8.77 ± 2.32	8.67 ± 2.69	0.36
	Language	22.17 ± 2.12	22.22 ± 3.56	0.49
	Visuospatial	14.01 ± 2.22	13.31 ± 2.22	0.31
	Total	80 ± 7.4	75.6 ± 7.3*	0.25
	p+	0.50	0.04	

The *t*-test was used for comparisons between the two groups and statistical significance was expressed as p. *In group changes, single factor ANOVA test was used for repeated measurements and statistical significance was expressed as p+. ACE-R, Addenbrooke's cognitive examination-revised.

Discussion

Our study showed that medium- and minimal-flow anaesthesia were not superior to each other in terms of recovery criteria and postoperative early cognitive functions among geriatric patients undergoing elective urological surgery. Furthermore, although it was not clinically significant in patients who underwent medium-flow anaesthesia, the general cognitive and memory scores on the third postoperative day decreased by about half a point compared to the pre-operative values.

Technological and pharmacological developments have made it possible to reduce the O_2 flow during the maintenance of anaesthesia to the basal metabolic needs of patients. The analysis of respiratory gases and the temporary increase of FGF has largely prevented the problems that may be encountered during LFA.[1] LFA reduces the consumption of inhalation anaesthetics, thus reducing cost, personnel exposure, and greenhouse effects. It also contributes to respiratory functions by preventing heat and moisture loss through respiratory gases during general anaesthesia.

A low FGF prevents rapid changes in brain and alveolar agent concentrations during the termination of anaesthesia, improving recovery quality but prolonging recovery time.[1,13] In the study of Jeong et al.[14], after desflurane anaesthesia was applied with different FG, recovery times were found to be longer in patients who were administered 2 L min^{-1} FGF (17.6 min) compared to 4-6 L min^{-1} FGF (9.9 min, 9.1 min, respectively). Recovery agitation or awareness did not develop in any of the patients in this study. It was concluded that if the desflurane vaporiser is turned off at the prescribed time according to the FGF applied before the end of the operation, it is possible to use LFA in the recovery phase without loss of time. However, 20% of awareness cases in anaesthesia occur during the recovery period.[15] In our study, the desflurane vaporiser was turned off after the operation was completed to avoid the risk of awareness in the last phase of the operation. The recovery times of our patients, whose FGF was increased to 6 L min^{-1} after the operation and whose time constant was

shortened, were consistent with those of Jeong et al.[14] 4-6 L min^{-1} FGF-applied patients, but they were faster than those in whom low flow was applied. Furthermore, none of our patients experienced awareness or recovery agitation. These data show that a quality recovery can be achieved without complications (e.g., awareness and agitation) with intraoperative depth of anaesthesia monitoring and closing of the vaporiser by increasing FGF up to 6 L min^{-1} after the operation is completed. Especially when monitoring methods such as BIS are not used, the vaporiser should not be turned off before the operation is completed.

In a randomised study, FGF was increased to 6 L min^{-1} during the recovery period of patients who underwent minimal-flow (0.5 L min^{-1}), low-flow (1 L min^{-1}) and medium-flow (2 L min^{-1}) anaesthesia, and no significant difference was found in terms of recovery duration among the groups.[16] These results show that recovery times are related to the adjusted FGF during the recovery period rather than the adjusted FGF during anaesthesia maintenance.

Early POCD is a serious complication associated with significant morbidity and mortality and it is seen in more than a quarter of post-operative geriatric patients. Geriatric surgery candidates constitute the riskiest patients in terms of postoperative cognitive dysfunction. Neuropsychological tests are essential to detect perioperative cognitive performance changes.[4] ACE-R, which was validated in our study, can be used to measure general cognitive performance and has different forms to prevent the learning effect.[11]

Chan et al.[17] showed that recovery from anaesthesia is faster and the incidence of early and late postoperative cognitive dysfunctions is reduced in patients with intraoperative BIS monitoring. However, a direct relationship between rapid and smooth recovery and POCD has not been demonstrated. In our study, we examined the relationship between minimal- and medium-flow anaesthesia methods and recovery and postoperative cognitive functions.

According to the results of our study, there was no difference in the ACE-R scores of patients who were administered medium- and minimal-flow anaesthesia at all times. Among the in-group ACE-R score changes according to time, we found that the general ACE-R and memory scores were lower on the third postoperative day compared with the pre-operative scores in only the medium-flow anaesthesia group. However, as in the criticism of Chandrasekhar et al.[18], we think that the 0.5-point difference, which was found to be statistically significant, is not clinically significant.[19] Our data show that the two different FGFs are not superior to each other in preventing POCD. As far as we know, there is only one study examining the relationship between different FGF currents and POCD. Muslu et al.[3] found no significant difference in POCD between the LFA method (1 L min^{-1} FGF) and the medium-flow anaesthesia method (4 L min^{-1} FGF) in laparoscopic cholecystectomy cases, where sevoflurane was used for anaesthesia maintenance. Since the neuropsychological tests were performed only on the first postoperative day and four times in total, a significant learning effect was experienced, similar to the patients in our study who underwent minimal-flow anaesthesia. Evaluation of tests at close intervals, patients' familiarity with the modified test format, and learning the answers to some questions may result in higher results in repeated tests in the postoperative period.

There is no significant difference between the two groups of our study in terms of demographic characteristics, medical history, surgical history, perioperative results and laboratory parameters, which have been shown in different studies to have an effect on advanced age and postoperative cognitive performance.[20]

During LFA, it is essential to monitor the concentrations of gases in the exhaled air to prevent the patient from inhaling a hypoxic gas mixture and to maintain adequate depth of anaesthesia. Hypoxaemia, insufficient anaesthesia, and deep anaesthesia levels are among the risk factors that have been shown to be associated with POCD.[17,21] In our study, standard anaesthesia management and monitoring were applied to prevent these factors from affecting the perioperative cognitive function scores. When the breathing air O_2 concentration in LFA falls below 30%, the FGF O_2 concentration should be increased by 10%.[22] Since hypoxaemia may develop, albeit rarely, when the intraoperative FiO_2 is ≤30, for ethical reasons, the intervention was performed on elderly patients who were more sensitive to the negative effects of anaesthesia and surgery when the FiO_2 was ≤35%.[23] According to the results of our study, the need to increase the O_2 concentration of FGF in the minimal-flow anaesthesia group was significantly higher than in the medium-flow anaesthesia group, but hypoxaemia did not develop in either group. As a result, with close follow-up and appropriate monitoring, LFA can be applied in elderly patients without adversely affecting oxygenation. Park et al.[24] showed that FiO_2 was lower in patients who underwent 0.5 L min^{-1} FGF in laparoscopic urological surgeries that were expected to last longer than 6 h, which confirms our results compared to patients who underwent 4 L min^{-1} FGF at every stage of the operation.

Despite a lack of evidence, it is thought that the risk of awareness is higher in LFA. Since MAC has an effect on the spinal cord rather than the brain and is completely independent from the effects of other intravenous agents, it is insufficient in patients with awareness risk.[25] In our study, certain inhalation anaesthesia protocols were applied to both groups, and the average BIS values were kept at around 50 in all patients. Awareness did not develop in any patient. In addition to the depth of intraoperative anaesthesia,

inadequate postoperative pain control is associated with postoperative cognitive dysfunction.[26] As carried out in our study, the application of standard analgesia protocols and the predetermination of the treatment to be applied when pain scores are high may be beneficial in preventing postoperative cognitive dysfunction.[6,27] In our study, all the neuropsychological tests were applied when the patient VAS was <4. However, a recent study found the threshold VAS value for POCD to be 2.6 with high specificity and sensitivity.[26]

Our study has several limitations. First, only the effects of LFA on early postoperative cognitive function were shown in our study, and long-term neuropsychological tests were not applied. Second, targeting lower VAS values could improve the standardisation of the two groups, since VAS =4, which we accepted as the threshold value at the time of our study, has been shown to be associated with early POCD recent studies. Third, although we have followed up on VAS in our patients, their VAS values and analgesic needs have not been recorded. Therefore, the sedation levels due to the use of additional morphine may have affected our results. Fourth, in the presence of a larger sample size, a significant difference could be revealed in terms of recovery times and perioperative cognitive dysfunctions, which were quite close to each other in our study. Fifth, the fact that neuromuscular monitoring and monitoring of inhalational anaesthetic agent consumption, which are additional monitoring methods, were not used constitutes another limitation of our study.

Conclusion

This study has shown that minimal- and medium-flow anaesthesia are not superior to each other in terms of recovery times and perioperative cognitive dysfunction in geriatric patients. Bearing in mind the complications (e.g., hypoxaemia and awareness) that may develop during the maintenance of anaesthesia in geriatric patients, both minimal- and medium-flow anaesthesia can be safely applied without adverse effects on recovery and perioperative cognitive functions, accompanied by monitoring of breathing air and depth of anaesthesia.

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Ethics Committee Approval: This study was approved by Ethics Committee of İstanbul University, İstanbul Faculty of Medicine Clinical Research (approval no: 17, date: 27.10.2017).

Informed Consent: The eligible patients were informed about the study during the preoperative evaluation and their written consents were obtained.

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The Relationship Between Decreased CD-8 T-Cells and Mortality in Patients with COVID-19 Pneumonia in the Intensive Care Unit, A Retrospective Study

Zeynep Tuğçe Sarıkaya[1,2], Bülent Güçyetmez[1,3], Ayşe Sesin Kocagöz[4], Lütfi Telci[3], İbrahim Özkan Akıncı[2], COVID-19 Study Group[2,3,5,6,7,8]

[1]Department of Anaesthesiology and Reanimation, Acıbadem Mehmet Ali Aydınlar University Faculty of Medicine, İstanbul, Turkey
[2]General Intensive Care Unit, Acıbadem Altunizade Hospital, İstanbul, Turkey
[3]General Intensive Care Unit, Acıbadem International Hospital, İstanbul, Turkey
[4]Department of Infectious Diseases and Clinical Microbiology, Acıbadem Mehmet Ali Aydınlar University Faculty of Medicine, İstanbul, Turkey
[5]General Intensive Care Unit, Acıbadem Maslak Hospital, İstanbul, Turkey
[6]General Intensive Care Unit, Acıbadem Taksim Hospital, İstanbul, Turkey
[7]Department of Infectious Diseases and Clinical Microbiology, Acıbadem Altunizade Hospital, İstanbul, Turkey
[8]Department of Infectious Diseases and Clinical Microbiology, Acıbadem International Hospital, İstanbul, Turkey

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Abstract

Objective: CD-8 T-cells are responsible for the clearance of virally infected cells. In patients with Coronavirus disease-2019 (COVID-19) pneumonia, there are quantitative reductions and functional impairments in T-cells. Low CD-8 T-cell levels cause worse clinical situations. In this study, the relationship between decreased CD-8 T-cells and mortality in patients with COVID-19 pneumonia in the intensive care unit (ICU) was investigated.

Methods: In this multicenter retrospective study, 277 patients were analyzed. Demographic data, ICU admission scores, blood gas levels, laboratory samples, and outcomes were recorded. Statistical Package for the Social Sciences version 28 was used for statistical analysis.

Results: Two hundred forty of 277 patients were included in the study. The mortality rate was 43.3%. In non-survivors, median values of age, Charlson comorbidity index, Acute Physiology and Chronic Health Evaluation II (APACHE-II), procalcitonin, leukocyte count, neutrophil count, neutrophil-lymphocyte count ratio, and duration of invasive mechanical ventilation were significantly higher, whereas median values of PaO_2-FiO_2 ratio, lymphocyte count, CD-4, and CD-8 T-cells were significantly lower than those in survivors. In the multivariate Cox regression model, the risk of mortality increased 1.04-fold (1.02-1.06) and 1.05-fold (1.01-10.8) by every one unit increase in age and APACHE-II, respectively, whereas it decreased 0.71-fold (0.58-0.87) by every hundred increase in CD-8 T-cells $P < 0.001$, $P=0.007$ and $P=0.001$ respectively.

Conclusion: According to our findings, age, APACHE-II, and CD-8 T-cell levels seem to be independent risk factors for mortality in patients with COVID-19 pneumonia in the ICU.

Keywords: CD-8, COVID-19, critical care, mortality, pneumonia, T-cell

Main Points

- SARS-CoV-2 infection can cause pneumonia, which can lead to life-threatening acute respiratory failure (ARF) and acute respiratory distress syndrome (ARDS).
- In patients with Coronavirus disease-2019 (COVID-19) pneumonia, T-cells may decrease or their function may be impaired.
- According to our findings, age, Acute Physiology and Chronic Health Evaluation-II (APACHE-II) and CD-8 T-cell level seem to be independent risk factors for mortality in patients with COVID-19 pneumonia in the intensive care unit (ICU).
- It should be kept in mind monitoring the CD-8 T-cell level could be a marker for subsequent infections and treatment modalities.

Corresponding author: Zeynep Tuğçe Sarıkaya, e-mail: tugcesrky@gmail.com

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Introduction

CD-8 T-cells play a crucial role in viral infection control in adaptive immunity by destroying virus-infected cells and generating effector cytokines.[1] Firstly, they are activated via their T-cell receptor by dendritic cells.[2] After this activation, naive T-cells are differentiated by [interleukin (IL)-12], IL-2 and type-1 interferon (INF) and they have effector functions as cytotoxic granules (perforin and granzymes), tumor necrosis factor-$_{\alpha}$, (TNF_{α}) (T-cell proliferation and target cell necrosis) and INF_{8} (IL-12 production, phagocytosis and increase in MHC-I and MHC-II).[3,4] Activated CD-8 T-cells are able to kill and eradicate infected cells and provide protection against infection.[2] During the Coronavirus disease-2019 (COVID-19) pandemic, it has been shown that there were quantitative reductions and functional impairments in T-cells in patients with COVID-19 pneumonia.[3] Moreover, it was demonstrated that hospitalized COVID-19 patients with low CD-8 T-cell levels had worsened clinical status and increased mechanical ventilation (MV) and intensive care unit (ICU) needs.[5] However, there are no specific data about the relationship between CD-8 T-cell levels and outcomes in patients with COVID-19 in the ICU. Therefore, we aimed to investigate the relationship between CD-8 T-cell levels and mortality in patients with COVID-19 pneumonia in the ICU.

Methods

Study Population

After approvals from the Scientific Committee of the Turkish Health Ministry (2020-08-21T18-17-45) and the Local Ethics Committee (ATADEK-2020/19), the study was retrospectively designed in 4 general tertiary ICUs between March 2020 and December 2020. Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board (ATADEK) (approval no: 2020-19/8, date: 03.09.2020). All data were fully anonymized without restriction after ethics committee approval, and the ethics committee waived the requirement for informed consent.

Two hundred seventy-seven patients with COVID-19 pneumonia were retrospectively evaluated. Patients whose T-lymphocyte subtypes were not studied, who were <18 and more than 90 years old or transferred to another center, who had human immunodeficiency virus (+) and who were administered immunosuppressive drugs were excluded from the study.

The patients were admitted to the ICU due to acute hypoxemic respiratory failure due to COVID-19 pneumonia resistant to conventional oxygen therapy and other accompanying organ failures. All patients were treated with antiviral drugs (favipiravir, hydroxychloroquine, azithromycin) and anticoagulant prophylaxis in accordance with the Turkish Health Minister's Algorithm for COVID-19. Since early pandemic patient data were collected, it was revealed that there were no patients receiving steroids.

Database

All data were collected from the Acıbadem Health Group Database. At the ICU admission, demographic data (age, body mass index, sex), charlson comorbidity index (CCI) and Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores, P_aO_2-FiO_2 ratio, C-reactive protein (mg dL^{-1}), and procalcitonin (µg L^{-1}) levels were collected; in the first week, maximum (max)-leukocyte count (leu_C) ($x10^3$ μL^{-1}), max-neutrophil count (neu_C) ($x10^3$ μL^{-1}), max-neutrophil-lymphocyte count ratio (NLCR), max-ferritin (ng mL^{-1}), max-D-dimer (mg L^{-1}), max-interleukin-6 (IL-6) (pg mL^{-1}) levels and minimum (min)-lymphocyte count (lym_C) ($x10^3$ μL^{-1}), min-CD-4 (μL^{-1}) and min-CD-8 (μL^{-1}) T-cells levels were collected. During the ICU period, culture results, the usage of IL-6 (tocilizumab, Actemra®, Switzerland) blocker, duration of invasive mechanical ventilation (IMV) (days), length of ICU stay (days), and mortality were also recorded. CD-4 and CD-8 T-cell levels were acquired using BD FACSCanto™ (Erembodegem, Belgium) device, which employs a flow cytometry system.

Statistical Analysis

Statistical Package for the Social Sciences version 28 was used for statistical analysis. The Kolmogorov-Smirnov test was used to detect normal distributions. Descriptive statistics were given as mean ± standard deviation, median (quartiles) and percentages. Student's *t*-test, Mann-Whitney U, and chi-square tests were used for group comparisons. For the risk of mortality, age, CCI, APACHE-II, P_aO_2-FiO_2 ratio, procalcitonin, max-leu_C, max-neu_C, max-NLCR, min-lym_C, min-CD-4, and min-CD-8 T-cells were added to the univariate Cox regression analysis. Significant variables in the univariate analysis were added to the multivariate Cox regression model and the forward stepwise (likelihood ratio) method was used in the model. ROC analysis was used to detect the cut-off value for CD-8 T-cells for mortality. Two groups were determined in accordance with the cut-off value of CD-8 T-cells. In both patients and the low CD-8 T-cell patient group, Kaplan-Meier analysis was used to show the effect of the use of IL blockers on survival. Relative risks were calculated to identify the impact of the administration of IL-blockers on secondary infections in the low CD-8 T-cell subgroup. A P value < 0.05 was considered statistically significant.

Results

Two hundred forty out of 277 patients were included in the study. In these patients, the mortality rate was 43.3% (Table 1). In nonsurvivors, age, CCI, APACHE-II, procalcitonin, max-leukocyte count, max-neutrophil count, max-NLCR

and duration of IMV were significantly higher, whereas median values of PaO_2-FiO_2 ratio, min-lymphocyte count, min-CD-4 and min-CD-8 T-cells were significantly lower than survivors (Table 2). For mortality, the cut-off value of min-CD-8 T-cell level was detected as ≤115 (μL^{-1}) ($P < 0.001$). In patients with CD-8 T-cell levels ≤115, age, CCI, APACHE-II, NLCR, CD-4/CD-8 ratio, mortality rate, min-lymphocyte counts, min-CD-4, and min-CD-8 T-cell levels were significantly different from those in patients with CD-8 T-cell >115 (Table 3).

Table 1. Demographic Data, Laboratories, Therapies and Outcomes

Patients, n	240
Age, years	63 (51-73)
Male, n (%)	178 (74.2)
BMI, (kg $m2^{-1}$)	27.6 (25.3-31.4)
CCI	3 (1-5)
APACHE-II	16 (13-21)
ICU admission	
PaO_2-FiO_2 ratio	100 (77-161)
CRP (mg dL^{-1})	10.6 (5.8-17.0)
Procalcitonin (μg L^{-1})	0.16 (0.06-0.56)
In the 1st week	
Max-leu_C, ($x10^3\mu L^{-1}$)	16.4 (12.8-20.2)
Max-neu_C, ($x10^3\mu L^{-1}$)	14.6 (11.3-18.5)
Min-lym_C, ($x10^3\mu L^{-1}$)	0.39 (0.28-0.58)
Max-NLCR	27.8 (17.6-41.0)
CD-8 T-cell, (μL^{-1})	118 (64-191)
CD-4 T-cell, (μL^{-1})	203 (120-336)
CD-4 / CD-8 ratio	1.8 (1.2-2.8)
Max-ferritin, (ng mL^{-1})	1361 (725-1896)
Max-D-dimer, (mg mL^{-1})	3.9 (1.8-7.9)
Max-IL-6, (pg mL^{-1})#(170)	41 (16-113)
The usage of IL-blockers, n (%)	69 (28.7)
Microorganisms, n (%)	
Gram (+) and Gram (-) and Fungi	66 (27.5)
Gram (+) and Gram (-)	41 (17.1)
Only Fungi	28 (11.7)
Gram (+) and Fungi	27 (11.3)
Only Gram (+)	21 (8.8)
Only Gram (-)	20 (8.3)
Gram (-) and Fungi	13 (5.4)
Duration of IMV, days	15 (10-28)
LOS-ICU, days	20 (13-30)
Mortality, n (%)	104 (43.3)

#: There were only 170 patients have IL-6 values.
APACHE, acute physiology and chronic health evaluation; BMI, body mass index; CCI, charlson comorbidity index; CRP, C-reactive protein; ICU, intensive care unit; IL, interleukin; IMV, invasive mechanical ventilation; LOS, length of stay.

In the univariate cox regression model, the risk of mortality was significantly increased 1.05-fold (1.03-1.06), 1.01-fold (1.00-1.01), 1.05-fold (1.02-1.08) and 1.20-fold (1.11-1.30) by one unit increase in the age, NLCR, APACHE-II and CCI respectively whereas it was significantly decreased 0.79-fold (0.66-0.95), 0.84-fold (0.75-0.95) and 0.85-fold (0.77-0.93) by every hundred increase in CD-8 T-cell, CD-4 T-cell and min-lym_C respectively ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P=0.011$, $P=0.007$ and $P < 0.001$ respectively) (Table 4). In the multivariate cox regression model, the risk of mortality was increased 1.04-fold (1.02-1.06) and 1.05-fold (1.01-1.08) by one unit increase in age and APACHE-II respectively whereas it was decreased 0.71-fold (0.58-0.87) by every hundred increase in CD-8 T-cell ($P < 0.001$, $P=0.007$ and $P=0.001$ respectively) (Table 4). In Kaplan-Meier survival analysis, there was no effect of the usage of IL blockers on survival in either all patients or the patients with CD-8 T-cell ≤115 ($P=0.541$ and $P=0.200$) (Figures 1 and 2). Furthermore, the relative risk of having more than one group of microorganisms throughout the ICU stay was 1.4-fold (1.1-1.8) greater in patients with CD-8 T-cell levels ≤115 and IL blockers (+) than in patients with CD-8 T-cell levels >115 and IL blockers (-) ($P=0.018$).

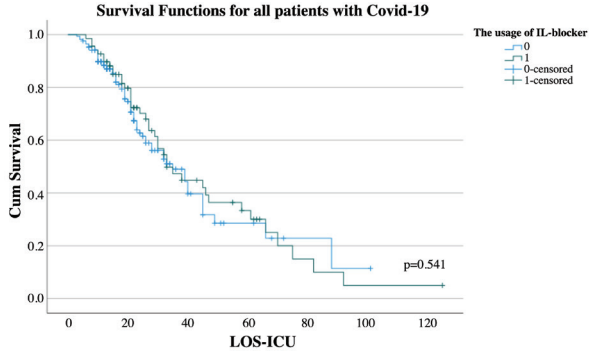

Figure 1. Survival functions for all patients with COVID-19.

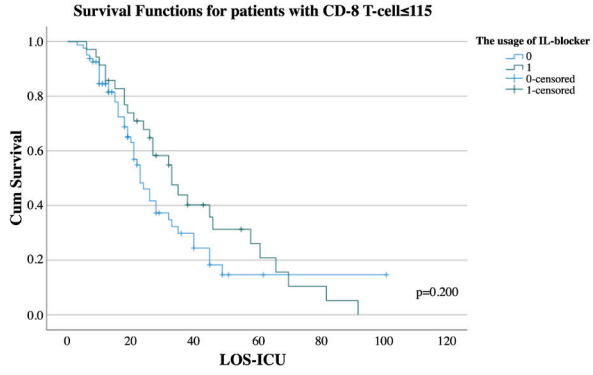

Figure 2. Survival functions for patients with CD-8 T-cell ≤115.

Table 2. Comparison Between Survivors and Non-survivors

	Survivors (n = 136)	Non-survivors (n = 104)	*P*
Age, years	56 (45-67)	71 (61-79)	***<0.001***
Male, n (%)	96 (70.6)	82 (78.8)	0.148
BMI, (kg $m2^{-1}$)	27.8 (25.5-32.5)	27.2 (24.7-29.8)	0.101
CCI	2 (1-4)	5 (2-6)	***<0.001***
APACHE-II	14 (11-18)	19 (15-24)	***<0.001***
ICU admission			
PaO_2-FiO_2 ratio	107 (81-133)	92 (74-116)	***0.011***
CRP (mg dL^{-1})	11.5 (6.4-17.9)	9.2 (5.1-15.8)	0.118
Procalcitonin (µg L^{-1})	0.15 (0.06-0.32)	0.21 (0.07-0.93)	***0.020***
In the 1st week			
Max-leu_C, ($x10^3 \mu L^{-1}$)	15.4 (12.0-19.8)	17.4 (13.9-20.6)	***0.024***
Max-neu_C, ($x10^3 \mu L^{-1}$)	13.3 (10.8-17.5)	15.7 (12.5-19.3)	***0.003***
Min-lym_C, ($x10^3 \mu L^{-1}$)	0.48 (0.33-0.64)	0.30 (0.19-0.44)	***<0.001***
Max-NLCR	21.8 (15.6-32.3)	36.8 (26.7-50.0)	***<0.001***
CD-8 T-cell, (μL^{-1})	155 (87-230)	78 (47-127)	***<0.001***
CD-4 T-cell, (μL^{-1})	214 (147-427)	159 (93-248)	***<0.001***
CD-4/CD-8 ratio	1.8 (1.1-2.6)	1.8 (1.2-2.9)	0.214
Max-ferritin, (ng mL^{-1})	1335 (720-1755)	1411 (750-2147)	0.334
Max-D-dimer, (mg mL^{-1})	3.8 (1.7-6.9)	4.1 (1.8-10.5)	0.321
Max-IL-6, (pg mL^{-1})#(170)	36 (13-98)(101)	45 (23-140)(69)	0.265
Microorganisms, n (%)			
Gram (+) and Gram (-) and Fungi	36 (26.5)	30 (28.8)	0.683
Gram (+) and Gram (-)	21 (15.4)	20 (19.2)	0.440
Only Fungi	15 (11.0)	13 (12.5)	0.725
Gram (+) and Fungi	11 (8.1)	16 (15.4)	0.076
Only Gram (+)	15 (11.0)	6 (5.8)	0.153
Only Gram (-)	9 (6.6)	11 (10.6)	0.271
Gram (-) and Fungi	8 (5.9)	5 (4.8)	0.715
Duration of MV, days	12 (8-22)	20 (12-32)	<0.001
LOS-ICU, days	19 (13-28)	21 (12-33)	0.470

#: There were only 170 patients have IL-6 values.

APACHE, acute physiology and chronic health evaluation; BMI, body mass index; CCI, Charlson comorbidity index; CRP, C-reactive protein; ICU, intensive care unit; IL, interleukin; MV, mechanical ventilation; LOS, length of stay.

Table 3. Comparison Between CD-8 T-cell Groups			
	CD-8 T-cell >115 (n = 124)	**CD-8 T-cell ≤115 (n = 116)**	***P***
Age, years	58 (45-69)	68 (57-78)	***<0.001***
Male, n (%)	89 (71.8)	89 (76.7)	0.381
BMI, kg $m2^{-1}$	27.8 (25.6-32.6)	27.2 (24.7-30.8)	0.092
CCI	2 (1-4)	4 (2-6)	***<0.001***
APACHE-II	15 (11-21)	17 (14-22)	***0.013***
ICU admission			
PaO_2-FiO_2 ratio	105 (80-132)	95 (74-117)	0.065
CRP (mg dL^{-1})	10.4 (5.9-17.6)	11.0 (5.6-16.6)	0.728
Procalcitonin (µg L^{-1})	0.15 (0.06-0.41)	0.19 (0.07-0.81)	0.209
In the 1st week			
Max-leu_C, ($x10^3 \mu L^{-1}$)	17.0 (12.3-20.9)	16.0 (12.9-19.5)	0.263
Max-neu_C, ($x10^3 \mu L^{-1}$)	14.9 (11.1-19.4)	14.1 (11.4-18.3)	0.472
Min-lym_C, ($x10^3 \mu L^{-1}$)	0.48 (0.31-0.66)	0.33 (0.21-0.44)	***<0.001***
Max-NLCR	21.8 (15.4-35.6)	34.4 (24.8-52.2)	***<0.001***
CD-8 T-cell, (μL^{-1})	187 (146-282)	63 (44-82)	***<0.001***
CD-4 T-cell, (μL^{-1})	300 (198-458)	130 (75-196)	***<0.001***
CD-4 / CD-8 ratio	1.6 (1.0-2.3)	2.1 (1.5-3.3)	***<0.001***
Max-ferritin, (ng mL^{-1})	1381 (725-1769)	1337 (722-2005)	0.684
Max-D-dimer, (mg mL^{-1})	4.0 (1.8-7.6)	3.7 (1.7-9.3)	0.861
Max-IL-6, (pg mL^{-1})#(170)	36 (14-99)(94)	49 (18-152)(76)	0.176
Administration of IL-blockers, n (%)	34 (27.4)	35 (30.2)	0.638
Microorganisms, n (%)			
Gram (+) and Gram (-) and Fungi	34 (27.4)	32 (27.6)	0.977
Gram (+) and Gram (-)	19 (15.3)	22 (19.0)	0.454
Only Fungi	13 (10.5)	15 (12.9)	0.555
Gram (+) and Fungi	14 (11.3)	13 (11.2)	0.984
Only Gram (+)	12 (9.7)	9 (7.8)	0.599
Only Gram (-)	12 (9.7)	8 (6.9)	0.436
Gram (-) and Fungi	10 (8.1)	3 (2.6)	0.054
Duration of MV, days	14 (9-25)	18 (10-32)	0.154
LOS-ICU, days	20 (13-30)	19 (12-33)	0.825
Mortality, n (%)	33 (26.6)	71 (61.2)	<0.001

#: There were only 170 patients have IL-6 values.
APACHE, acute physiology and chronic health evaluation; BMI, body mass index; CCI, Charlson comorbidity index; CRP, C-reactive protein; ICU, intensive care unit; IL, interleukin; MV, mechanical ventilation; LOS, length of stay.

Table 4. Cox Regression Analyses for the Risk of Mortality

	Univariate		Multivariate *Forward stepwise method Omnibus test significance P < 0.001*	
	HR (CI 95%)	**P**	**HR (CI 95%)**	**P**
Age, years	1.05 (1.03-1.06)	***<0.001***	1.04 (1.02-1.06)	***<0.001***
CD-8 T-cells (x10^2 μL^{-1})	0.79 (0.66-0.95)	***0.011***	0.71 (0.58-0.87)	***0.001***
APACHE-II	1.05 (1.02-1.08)	***<0.001***	1.05 (1.01-1.08)	***0.007***
CD-4 T-cells (μL^{-1})	0.84 (0.75-0.95)	***0.007***	0.92 (0.79-1.07)	0.096
NLCR	1.01 (1.00-1.01)	***<0.001***	0.96 (0.88-1.01)	0.195
Min-lym_C, (μL^{-1})	0.85 (0.77-0.93)	***<0.001***	0.84 (0.73-1.04)	0.291
CCI	1.20 (1.11-1.30)	***<0.001***	0.91 (0.77-1.25)	0.568
Procalcitonin, µg L^{-1}	1.03 (0.99-1.06)	0.084		
Max-neu_C, (x$10^3\mu L^{-1}$)	1.00 (0.98-1.04)	0.392		
PaO_2 /FiO_2 ratio	0.99 (0.98-1.00)	0.461		
Max-leu_C, (x$10^3\mu L^{-1}$)	1.01 (0.98-1.03)	0.710		

The forward stepwise (likelihood ratio) method was used in the multivariate Cox regression analysis by adding all significant variables in the univariate analysis.
APACHE, acute physiology and chronic health evaluation; CCI, Charlson comorbidity index; CI, confidence interval; HR, hazard ratio; leu_C, leukocyte count; lym_C, lymphocyte count; neu_C, neutrophil count; NLCR, neutrophil-lymphocyte count ratio.

Discussion

In this study, our findings strongly suggest that nonsurvivors are older, have more comorbidities, have the worst clinical status at ICU admission, have severe alveolar-capillary damage, and have poor immunity. However, only age, APACHE-II, and CD-8 T-cell level are independent risk factors for mortality in patients with COVID-19 pneumonia in the ICU.

Lymphopenia and its relationship with the worst outcome are known in patients with COVID-19.[6,7] There are two theories for this lymphopenia: the directly lethal effect of the virus on lymphocytes and the exhaustion of lymphocytes.[5,8] If there is a direct lethal effect, it can be expected that lymphocytes and their subgroups will be affected in the same way. Peng et al.[9] emphasized the importance of lymphocyte subgroup responses for recovery in patients with COVID-19. Iannetta et al.[10] also showed the relationship between T-cell subgroup levels and mortality in COVID-19 patients. However, Urra et al.[5] demonstrated that CD-8 T-cells were much more influenced than CD-4 T-cells. Interestingly, we observed lymphopenia (<1.3x10^3 μL^{-1}) in almost all patients (96.7%), whereas patients with low CD-8 (<200 μL^{-1}) and CD-4 T-cell levels (<300 μL^{-1}) accounted for only 75.8% and 70.4% of all patients, respectively. The reason for the difference in lymphocyte subgroups may be due to the more lethal effect on CD-8 T-cells only. This theory may explain why only the decrease in CD-8 T-cell levels was an independent predictor of mortality, although both CD-4 and CD-8 T-cell levels were significantly lower in nonsurvivors in our study. Regardless of the reason, we think that the level of CD-8 T-cells should be monitored at regular intervals in patients with COVID-19 in terms of prognosis. Moreover, treatments that could positively affect CD-8 T-cells should become a current issue, whereas others that could have adverse effects on CD-8 T-cells should be avoided.

The other crucial question is: can cytotoxic T-cell dysfunction be a reason for the ineffective immune response in COVID-19? Obviously, we did not examine any cytokines except for IL-6, which was similar in the CD-8 T-cell groups. Diao et al.[3] also found that IL-2, IL-4 and INF_8 were similar whereas TNF_α, IL-6 and IL-10 were significantly increased in patients with COVID-19. When considering the effect of these cytokines on T-lymphocytes,[4] these results actually show that T-lymphocytes have enough function. Moreover, it can be thought that excessive TNF_α and IL-10 may be the reason for T-cell exhaustion.

Naturally, the other theory that is more intriguing is CD-8 T-cell exhaustion. Wherry and Kurachi[11] defined three reasons for CD-8 T-cell exhaustion: persistent antigen exposure, activation of inhibitory receptors, and soluble mediators. The importance of exhaustion in CD-8 T-cells is that it results in the death of these cells, which may explain the decrease in their levels. Persistent antigen exposure and activation of inhibitory receptors on the surface of CD-8

T-cells can be accepted as two logical theories for this exhaustion. It is claimed that being in the chronic phase of viral infection is the main reason for the exhaustion in these two theories.[11-14] Thus, it is argued that if effective antiviral agents can be used in the early phase, they can prevent viral infection and CD-8 T-cell exhaustion.[11] Nevertheless, COVID-19 patients are still exposed to viral loads because there are no effective antiviral agents. The third reason is complicated; however, in our opinion, it is the most important event that should be discussed in patients with COVID-19. Implied soluble mediators are defined as immunosuppressive (IL-10 and TGFß) and inflammatory (IFNs and IL-6) cytokines.[11] It is clearly known that IL-10 causes exhaustion in CD-8 T-cells and that blockade of IL-10 prevents exhaustion.[15,16] On the other hand, IFNs are accused of exhaustion, especially in the chronic phase, whereas it is claimed that IL-6 may be required to control chronic viral infection and CD-8 T-cell exhaustion.[11] In contrast, Diao et al.[3] concluded that increased IL-6 reduced CD-8 T-cell levels based on a negative correlation between IL-6 levels and CD-8 T-cell levels. However, this negative correlation was quite weak.

Currently, IL-6 blockers are used to prevent the existence of cytokine release syndrome (CRS), which has been made responsible for the worst clinical status in patients with COVID-19.[17,18] However, the IL-6 level was a poor prognostic factor, and there was no threshold level for it.[19] In addition, it was demonstrated that there was no relationship between the usage of IL blockers and outcomes, and an increase in the rate of secondary infections could be observed after its administration.[19,20] In our study, IL-6 levels were similar in all groups. Moreover, in neither all patients nor patients with CD-8 T-cell levels ≤115, there was any effect of the usage of IL-6 blockers on survival. On the other hand, it can be seen that the percentage of the detected microorganism types was similar between the groups. We believe that more immunosuppressed patients could not handle secondary infections, except for COVID-19 infection. Additionally, we demonstrated that the relative risk of having more than one group of microorganisms throughout the ICU stay was greater in patients with CD-8 T-cell levels ≤115 and IL blockers (+).

Now we should ask ourselves this critical question: what is the real reason for the worst clinical status in COVID-19: increased IL-6 levels and CRS or decreased CD-8 T-cell levels and immunosuppression? If there are no effective antiviral agents and detected threshold values for IL-6 to define CRS or if there is a possibility of increased secondary infections caused by the usage of IL-6 blockers, we may contribute to the worst clinical status by ignoring all of them. For these reasons, we strongly believe that CD-8 T-cell levels should be checked especially before IL-6 blocker administration and routinely monitored in patients with COVID-19 to detect prognosis and regulation of treatments.

The most important limitation of this study is the small sample size. Conducting larger studies could make it possible to find thresholds for therapeutic and preventive approaches for this patient group and to be part of the ICU guideline. The lowest CD-8 T-cell level in the first week was included in the study. Repeated measurements may provide new data, especially in patients who require long stays in the ICU.

Age, APACHE-II, and CD-8 T-cell level are independent risk factors for mortality in patients with COVID-19 pneumonia in the ICU. These results bring along the necessity of monitoring CD-8 T-cells and checking their levels before IL blockers are administered. Additionally, in our opinion, monitoring CD-8 T-cells in patients with COVID-19 will ensure that secondary infections and treatments are monitored.

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Original Article

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Retrospective Analysis of Factors Affecting Chronic Postoperative Pain After Thoracotomy: Single Center Experience

Nurlan Israfilov, Çiğdem Yıldırım Güçlü, Süheyla Karadağ Erkoç, Güngör Enver Özgencil

Department of Anaesthesiology and Reanimation, Ankara University Faculty of Medicine, Ankara, Turkey

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Abstract

Objective: Despite various pain management methods, chronic pain is still a challenging issue after thoracotomy. This retrospective study was designed to determine the possible factors affecting the development of chronic pain following open thoracotomy.

Methods: The study included patients who underwent elective open thoracotomy at Ankara University İbni Sina Hospital, between 01.01.2016 and 31.12.2020. The medical files and electronic records of the patients were scanned from the system. Patient history, analgesic methods, and surgical details were recorded. The need for and usage analgesic drugs after the surgery were also recorded.

Results: A total of 229 patients who underwent thoracotomy were included in the study, and 83 (36.2%) patients had chronic pain. Duration of surgery, doses of remifentanil, fentanyl or NSAI drugs, duration or number of chest tubes (more than 4 days, or more than 2 tubes), diabetes, or PCEA usage were found as variables affecting pain. Logistic Regression, Multilayer Perceptron, Naive Bayes, AdaBoost, and Random Forest methods were used to evaluate the prediction performances. According to the model created with logistic regression, the rate of the correct classification was 90.8%. The duration of surgery, remifentanil administration, chest tube for more than 4 days, and diabetes were found to be risk factors for developing chronic pain. Fentanyl bolus, PCEA-bupivacaine, and NSAID bolus were determined as preventive factors.

Conclusion: A careful analysis of risk factors should be performed for each patient to prevent chronic pain after thoracotomy, and preemptive effective analgesia methods should be performed.

Keywords: Chronic pain, chronic pain risk factors, pain after thoracotomy, postoperative pain

Main Points

- Chronic pain after thoracotomy is not a rare complication
- Effective management of acute pain plays an important role in chronification of the pain
- Surgical duration plays an important role
- Intraoperative and postoperative continuous methods should be considered

Introduction

Chronic pain lasts longer than the course of the disease and may persist for 3 to 6 months after recovery. It can be nociceptive, neuropathic, or mixed.[1] Chronic pain following thoracotomy is not rare. The tissue around the surgical incision in thoracotomy is formed by musculoskeletal and nerve damage. It develops in two different periods: acute and chronic. If acute and severe pain that develops immediately after surgery is not adequately controlled or treated, the risk of developing chronic pain is high.[2]

Direct activation of nociceptors after surgery causes pain in and around the surgical site due to inflammation and nerve damage. Pain is associated with touch, movement, respiratory movements, or coughing. Additionally, it is

Corresponding author: Süheyla Karadağ Erkoç, e-mail: suheylakaradag@hotmail.com

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thought that neuropathic components due to nerve damage develop after surgery, and thus pain may develop even in the absence of inflammation or peripheral nociception. Symptoms related to nerve damage are seen. Chronic pain that develops after surgery limits the daily activities of patients and adversely affects their quality of life.[3]

This retrospective study was designed to determine the factors influencing the development of chronic pain in patients undergoing thoracotomy at our center.

Methods

This retrospective single-center study was conducted in Ankara University after ethical approval was obtained from the Human Research Ethics Committee of the Ankara University (Number: İ6-481-21). The clinical trial number for the study is NCT05501977. The study, initiated after the approval of the ethics committee dated 18.08.2021, was completed on 25.07.2022.

Patients with ASA I-III who were over 18 years of age and planned and scheduled for elective thoracotomy between 01.01.2016 and 31.12.2020 at Ankara University İbni Sina Hospital were included in the study. Patients with ASA IV and V, emergency or trauma thoracotomy, malignancy infiltrating the chest wall, more than one thoracotomy performed, cardiovascular, cerebrovascular, or musculoskeletal system affected at a level that would affect their daily activities after surgery, and patients with insufficient data for various reasons were excluded.

All patients' medical files and electronic records were obtained from the hospital medical record system. Patients who presented to the pain clinic and reported pain at 3 and 6 months in the thoracic surgery outpatient clinic controls were classified as chronic pain group. Patients without pain at 3 and 6 months were classified as the non-chronic pain group. Age, sex, weight, ASA score, smoking, comorbidities, intraoperative and postoperative analgesia method, duration of acute pain, type of surgery, duration of surgery, duration of anaesthesia, rib resection, number and duration of chest tubes, time to apply to the pain clinic, and the analgesic method applied were recorded.

Statistical Analysis

SPSS 11.5 was used in the analysis of retrospectively collected data. The mean ± standard deviation for quantitative variables and the number of patients (percentage) for qualitative variables were used as descriptors. To determine whether there is a difference between the categories of the qualitative variable with two categories in terms of quantitative variables, Student's *t*-test was used if normal distribution assumptions were met, and the Mann-Whitney U test was used if assumptions were not met. Chi-square and Fisher's exact tests were used to examine the relationship between two qualitative variables. Risk factors affecting pain were examined using univariate logistic regression analysis. The statistical significance level was taken as 0.05. Logistic Regression, Multilayer Perceptron, Naive Bayes, AdaBoost, and Random Forest techniques were used for the machine learning classification. The dataset was tested using 10-fold cross validation. Accuracy, F-measure, Matthews correlation coefficient (MCC), ROC curve, and precision recall curve (PRC) were used as performance criteria. All analysis were made using the R programming language, and the RWeka and e1071 packages in the language were used with this program.

Results

Between 01.01.2016 and 31.12.2020, a total of 326 patients who underwent thoracotomy at İbn-i Sina Hospital were initially examined. Of the patients examined, thirty-one patients were excluded because of missing data, nineteen patients due to ASA IV and V, seventeen patients due to death, twelve patients under the age of 18, and 8 patients due to emergency trauma surgery. A total of 229 patients who underwent thoracotomy was included in the study.

While 146 (63.8%) patients had no complaints of chronic pain, 83 (36.2%) patients had chronic pain. When examining whether there was a difference between chronic pain categories in terms of demographic and clinical data, a significant difference was found in terms of hypertension and diabetes; 45.8% of patients with hypertension and 59.6% of patients with diabetes had chronic pain (Table 1).

We examined whether there was a difference in the development of chronic pain in terms of the variables of the intraoperative and postoperative medical analgesia methods. While 64.6% of patients who were administered remifentanil had chronic pain, this rate was 21.3% of patients who received fentanyl. Chronic pain was present in 23.6% of patients who were administered lidocaine infusion. A total of 44.2% of the patients who underwent IV fentanyl-PCA had chronic pain, and it was determined that 29.5% of the patients who were treated with non-steroidal anti-inflammatory drugs (NSAIDs) had chronic pain. The patients (9.1%) who received epidural bupivacaine-PCA had chronic pain, while this rate was 44.8% in patients who did not receive epidural bupivacaine-PCA (Table 2).

The mean duration of surgery was significantly higher in patients with chronic pain. Rib resection is an important factor for chronic pain, 85.7% of patients with rib resection have chronic pain. Number of chest tube and chest tube duration time were found to be significantly higher in patients with chronic pain. The mean duration of acute pain was 4.29±1.60 days in patients with chronic pain and 3.71±1.34 days in patients without chronic pain (Table 3).

Table 1. Comparisons of Demographic and Clinical Characteristics for Chronic Pain After Thoracotomy				
Variables		**Chronic pain**		
		(-)	**(+)**	***P* value**
Sex, n (%)	Female	48 (57.1)	36 (42.9)	0.113[a]
	Male	98 (67.6)	47 (32.4)	
Age (years)	Mean ± SD	59.45 ± 11.58	61.19 ± 12.34	0.104[d]
BMI	Mean ± SD	26.52 ± 4.91	26.00 ± 4.64	0.436[c]
ASA, n (%)	I	68 (72.3)	26 (27.7)	0,077[a]
	II	72 (58.1)	52 (41.9)	
	III	6 (54.5)	5 (45.5)	
Smoking (pack/years)	Mean ± SD	26.06 ± 25.16	20.70 ± 19.86	0.248[d]
Hypertension, n (%)		45 (54.2)	38 (45.8)	0.024[a]
Diabetes, n (%)		19 (40.4)	28 (59.6)	<0.001[a]
ASHD, n (%)		28 (71.8)	11 (28.2)	0.252[a]
Asthma, n (%)		5 (62.5)	3 (37.5)	1,000[b]
COPD, n (%)		17 (68.0)	8 (32.0)	0.640[a]

ASHD, Atherosklerotik heart disease; COPD, Chronic obstructive pulmonary disease; SD, standard deviation; BMI, body mass index.
[a]Chi-square test, [b]Fisher-exact test, [c]Student-t test, [d]Mann-Whitney U test.

Table 2. Comparison of Variables of Intraoperative and Postoperative Analgesic Methods for Chronic Pain After Thoracotomy			
Variables	**Chronic pain**		
	(-)	**(+)**	***P* value**
Fentanyl, n (%)	118 (78.7)	32 (21.3)	<0.001[a]
Remifentanil, n (%)	28 (35.4)	51 (64. 6)	<0.001[a]
Lidocaine infusion, n (%)	42 (76.4)	13 (23.6)	0.026[a]
NSAID, n (%)	117 (70.5)	49 (29.5)	0.001[a]
Intercostal block, n (%)	53 (58.9)	37 (41.1)	0.218[a]
IV fentanyl-PCA, n (%)	72 (55.8)	57 (44.2)	0.005[a]
PCEA-bupivacaine, n (%)	50 (90.9)	5 (9.1)	<0.001[a]
Erector spinae plane block, n (%)	15 (62.5)	9 (37.5)	0.892[a]

NSAID, non-steroidal anti-inflammatory drug; IV, intravenous; PCEA, patient-controlled epidural analgesia, [a]Chi-square test.

Table 3. Conditions of Variables for Intraoperative and Postoperative Surgical Procedures for Chronic Pain After Thoracotomy				
Variables		**Chronic pain**		
		(-)	**(+)**	***P* value**
Number of chest tubes	Mean ± SD	1.05 ± 0.21	1.19 ± 0.40	<0.001[c]
Chest tube duration (day)	Mean ± SD	3.81 ± 1.93	7.37 ± 3.13	<0.001[c]
Surgery time (min)	Mean ± SD	213.49 ± 24.68	272.29 ± 35.22	<0.001[c]
Rib resesction, n (%)	Mean ± SD	1 (14.3)	6 (85.7)	0.010[b]
Acut pain duration (day)	Mean ± SD	3.71 ± 1.34	4.29 ± 1.60	0.008[c]

The risk factors affecting chronic pain were examined by logistic regression analysis, and hypertension and diabetes were found to be significant risk factors. The presence of hypertension increases the risk of chronic pain by 1.895 times, and the presence of diabetes increases the risk of chronic pain by 3.403 times.

The risk of chronic pain increases by 6,717 times in patients not using fentanyl. The risk of chronic pain increases by 2.175 times in patients who do not use lidocaine infusion. While the risk of chronic pain increases by 8.125 times in patients not using epidural bupivacaine-PCA. The use of NSAIDs also effects chronic pain. Increasing the duration of acute pain by one day increases the risk of chronic pain by 1,312 times, while increasing the duration of surgery by one minute increases the risk of chronic pain by 1,058 times. The presence of rib resection increases the risk of chronic pain by 11,299 times. Increasing the number of chest tubes by one increases the risk of pain by 4,742 times, and an increase in the duration of the chest tube by one day increases the risk of chronic pain by 1.747 times (Table 4).

As to decide the importance of the variable and the effect of the variables on pain were examined more tests performed (the gain ratio and information gain variable significance tests) (Figure 1). When the significance of the variable was evaluated according to the results of the tests and clinical significance, the model consisted of surgery duration, remifentanil IV bolus, fentanyl IV bolus, chest tube duration, PCA-bupivacaine, number of chest tubes, diabetes mellitus, NSAID IV bolus. As a result, 9 variables (8 independent, 1 dependent variable) were included in the study and machine learning analyzes were performed using these variables.

Logistic regression, multilayer perceptron, naive Bayes, AdaBoost and random forest methods were used to evaluate

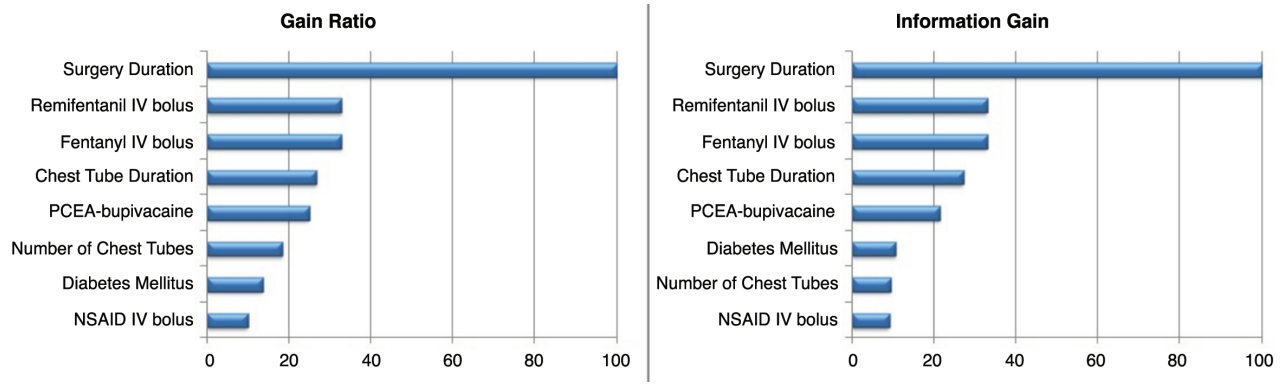

Figure 1. Variable Importances based on Gain Ratio and Information Gain Methods.

Table 4. Logistic Regression Analysis for Factors Affecting Chronic Pain After Thoracotomy

Variables (reference)		β	SE	*P* value	Odds ratio	Confidence interval
Hypertension (-)	(+)	0.639	0.284	0.024	1,895	1.0-3.3
Diabetes (-)	(+)	1.225	0.338	<0.001	3,403	1.7-6.6
Fentanyl (+)	(-)	1.905	0.308	<0.001	6,717	3.6-12.2
Remifentanil (-)	(+)	1.905	0.308	<0.001	6,717	3.6-12.2
Lidocaine infusion (+)	(-)	0.777	0.353	0.028	2,175	1.0-4.3
IV fentanyl-PCA (-)	(+)	0.812	0.289	0.005	2,253	1.2-3.9
PCEA-bupivacaine (+)	(-)	2.095	0.493	<0.001	8,125	3.0-21.3
NSAID (+)	(-)	1.029	0.305	0.001	2,799	1.5-5.0
Rib resection (-)	(+)	2.425	1,089	0.026	11,299	1.3-95.5
Number of chest tubes		1.556	0.477	0.001	4,742	1.8-12.0
Duration of chest tube (day)		0.558	0.075	<0.001	1,747	1.5-2.0
Surgery time (min)		0.056	0.007	<0.001	1,058	1.04-1.072
Acut pain duration (day)		0.272	0.097	0.005	1,312	1.0-1.5

β: coefficient for constant; SE, standard error; NSAID, non-streroidal anti-inflammatory drug; IV, intravenous; PCA, patient control analgesia.

the prediction performances, and the results of these methods are given in Table 1. Logistic Regression gave the best results according to the correct classification rate, F-criterion and MCC, which are among the most frequently used performance measures in the literature. This method was followed by AdaBoost, Naive Bayes, Multilayer Perceptron and Random Forest methods, respectively. The diagram of one of the trees created in Random Forest is given in Figure 2.

According to the model created with logistic regression, the rate of correct classification was 90.8%. With this model, when we made a general estimation of no/has pain for the patient, the accuracy rate of this estimation was 90.8%. In other words, with this model, the prediction result of about 90 out of 100 people was correct. In addition, the correct classification rate of the patients who said they had no pain in this model was 93.8%, and the rate of accurate classification of the patients who said they had pain was 85.5% (Table 5).

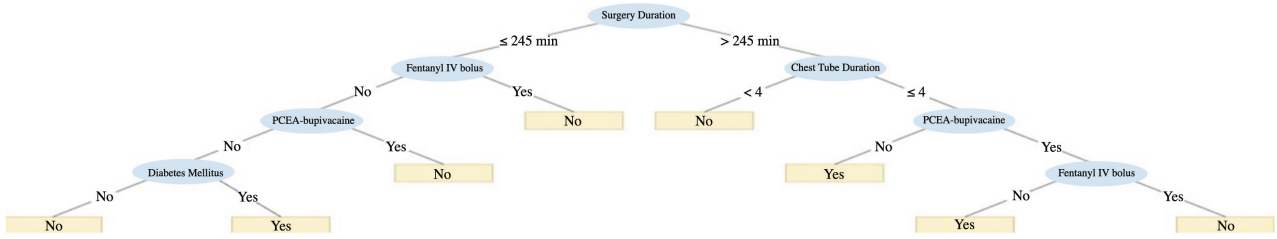

Figure 2. A Tree Diagram of the Random Forest Method.

Table 5. Performance Metrics of Machine Learning Models

Methods	Categories	Performance metrics				
		Accuracy	F-measure	MCC	PRC area	ROC area
Logistic regression	No	0.938	0.929	0.800	0.974	0.956
	Yes	0.855	0.871		0.929	
	Overall	0.908	0.908		0.958	
Multilayer perceptron	No	0.932	0.910	0.742	0.968	0.955
	Yes	0.795	0.830		0.934	
	Overall	0.882	0.881		0.956	
Naive bayes	No	0.904	0.913	0.766	0.976	0.955
	Yes	0.867	0.852		0.923	
	Overall	0.891	0.891		0.957	
AdaBoost	No	0.938	0.926	0.791	0.973	0.954
	Yes	0.843	0.864		0.928	
	Overall	0.904	0.903		0.956	
Random forest	No	0.932	0.910	0.742	0.967	0.950
	Yes	0.795	0.830		0.928	
	Overall	0.882	0.881		0.953	

MCC: Matthews correlation coefficient, PRC: Precision recall curve, ROC: Receiver operating characteristic.

Discussion

The incidence of CPAT is high. In different studies, the prevalence of chronic pain developing after thoracotomy varies between 25% and 68%.[4,5] In our study, the incidence of CPAT was 36.2%, which was consistent with the literature.

Advanced age is considered a risk factor for many diseases, but many studies have shown that patients who develop CPAT are at least 10 years younger than patients who do not develop pain and that the risk of developing pain is higher in patients under 60 years of age.[6] The higher risk in younger patients is thought to be due to stronger inflammatory and immune responses. In our study, age was not found to be one of the risk factors for CPAT because the majority of patients included in the study were elderly.

Different experimental studies have shown that there is a relationship between pain and hypertension. In studies, different mechanisms come into play to prevent and regulate blood pressure in hypertensive patients who develop pain. One of these mechanisms is the excessive release of endogenous opioids to control pain. Because endogenous opioid secretion is higher in hypertensive patients than in healthy individuals, tolerance develops after a certain period, and it is thought that an increase in pain sensitivity can be observed.[7] In our study, CPAT developed in 45.8% of patients with hypertension, and hypertension increased the risk of pain development by 1.9 times.

Polyneuropathy causing severe pain is seen in patients with diabetes. Complex mechanisms involving inflammation, microvascular, and immune responses contribute to the development of neuropathic pain in diabetic patients. Neuropathic pain developing before surgery is thought to trigger the development of chronic pain in the postoperative period together with surgical stress.[8] ASA I-IV patients over the age of eighteen who had undergone thoracotomy at Peking Union Medical College Hospital between 2009 and 2020 were examined. They found that the risk of developing chronic pain in patients with diabetes was significantly higher than that in patients without diabetes.[9] In our study, the results were similar, and the risk of developing CPAT was found to be 3,403 times higher in patients with diabetes.

It is thought that the use of intraoperative remifentanil causes the development of hyperalgesia in the postoperative period and pain that develops in the acute period affects the development of chronic pain. In this study, the effect of intraoperative remifentanil and fentanyl use on chronic pain after cardiac surgery was investigated. A randomized controlled study by de Hoogd et al.,[10] 126 patients were included, and the rate of chronic pain development at the third month after surgery was found to be significantly higher in the remifentanil group compared to the fentanyl group. In our study, chronic pain was observed in 21.3% of the patients who received fentanyl, whereas the rate was found to be 64.5% in patients who used remifentanil. Intraoperative use of remifentanil increased the risk of chronic pain by 6.7 times.

Lidocaine infusion, which is used in multimodal analgesia, prevents chronic pain that develops after surgery by different mechanisms. Its ability to prevent chronic pain is due to its sodium channel blockade in neurons, its ability to prevent inflammation, and its antihyperalgesic effects. In the study by Terkawi et al.,[11] which included sixty-one patients who underwent mastectomy, the patients were divided into two groups: placebo was administered to one group and intraoperative lidocaine infusion was administered to the other group. Because of the study, chronic pain developed in 30% of patients who received placebo at the 6th month after surgery, but this rate was found to be significantly lower in patients who received lidocaine infusion (12%).[11] Our results were similar; chronic pain developed in 23.6% of patients who received lidocaine infusion, but chronic pain developed in 40.3% of patients who did not receive lidocaine infusion.

Different treatment methods are used for pain control after thoracotomy. Among the multimodal treatment methods, intravenous and epidural patient-controlled analgesia methods are frequently and widely used. Li et al.[12] compared IV-PCA and epidural-PCA methods. Ninety-six patients who had undergone thoracotomy were included in the study, and the patients were divided into two groups: intravenous and continuous epidural analgesia. Because of the study, the rate of development of chronic pain in the third month was 55.2% in patients who received IV analgesia and 28.6% in patients who received continuous epidural analgesia.[12] In our study, it was determined that chronic pain developed in 44.2% of patients who received IV fentanyl-PCA chronic pain developed in 9.1% of patients who received epidural bupivacaine-PCA.

There are many studies on the relationship between acute postoperative pain and chronic postoperative pain. This relationship was shown in the study of Kalso et al.[13] in 1992 for the first time. The development of acute postoperative pain is a risk factor for postoperative chronic pain.[13] Wang et al.[9] investigated the risk factors affecting the development of chronic pain after thoracotomy. A total of 466 patients who underwent thoracotomy between 2009 and 2010 were included in the study, and it was found that each additional day of acute pain duration increased the risk of developing chronic pain by 1.2 times.[9] Similar results were obtained in our study. It was determined that increasing the duration of acute pain for one day increased the risk of chronic pain by 1,312 times, and more research is needed on this subject.

Neurological damage during surgery is thought to be the source of postoperative chronic pain. Rib resection and

suturing techniques increase the risk of nerve damage.[14] In the study of Maguire et al.,[15] it was determined that patients who did not undergo rib resection were exposed to more intercostal nerve damage during rib resection. Although the effect of rib resection on the development of postoperative chronic pain is controversial, there are studies with different results. In a study that retrospectively investigated the risk factors affecting the development of chronic pain after thoracotomy and included 208 patients, it was found that the risk of developing chronic pain increased by 9.8 times in patients who underwent rib resection.[16] In our study, rib resection increased the risk of chronic pain after surgery by 11.8 times.

The number of chest tubes placed after surgery is believed to influence the development of chronic pain. As the number of tissue damage increases, the risk of developing chronic pain after surgery also increases. In the study of Miyazaki et al.,[17] it was determined that intercostal nerve damage developed during chest tube insertion, with the risk increasing as the number of procedures increases. Mongardon et al.[6] included sixty-eight patients who underwent posterolateral thoracotomy between 2007 and 2008, in which 48% of the patients developed chronic pain. It was determined that the risk of developing chronic pain increased as the number of chest tubes increased.[6] The results of this study were similar, the risk of developing CPAT increased by 4.7 times in patients with two chest tubes compared with patients with one chest tube.

The risk of developing CPAT increases as the duration of the chest tube increases because of continuous exposure to tissue damage. In a retrospective study by Kar et al.[16] that included 208 patients in which the risk factors affecting the development of chronic pain after thoracotomy were investigated, it was found that the risk of developing CPAT increased as the duration of chest tube thrusting increased. In another study, risk factors affecting the development of chronic pain after thoracotomy was investigated. A total of 466 patients who had undergone thoracotomy between 2009 and 2010 were included in the study, and it was found that the risk of developing CPAT increased by 1.3 times as the duration of chest tube stay increased.[14] Similar results were obtained in our study, and it was determined that the risk of chronic pain increased by 1.747 times with each additional day of chest tube insertion.

After more detailed analysis of the statistics for related factors, the duration of surgery, remifentanil administration, chest tube existence for more than 4 days, and the presence of diabetes were found to be more related risk factors for the development of chronic pain than the others that were evaluated. The administration of a fentanyl bolus, PCEA-bupivacaine, and a NSAID bolus were determined as preventive factors.

The duration of surgery was found to be the most related factor to the development of chronic pain. Yoon et al.[18] evaluated 3200 patients after thoracic surgery, which covers a 10-year period. They concluded that the duration of surgery is a factor that relates to chronic pain, which is consistent with our results. The continuous and prolonged surgical impulses may explain these findings.[18]

Study Limitation

A limitation of the study is that as this is a retrospective study, it is not possible for us to form groups and compare methods. This study may guide us to establish a new prospective comparative study to determine an effective approach in the preventing of chronic pain in thoracotomy patients.

Conclusion

The development of chronic pain after thoracotomy is an important health problem influenced by multiple factors rather than a single cause. Because of our research, hypertension, diabetes, intraoperative intravenous remifentanil infusion, rib resection, prolongation of acute pain duration, number of chest tubes and prolonged chest tube duration were determined to be risk factors for the development of chronic pain after thoracotomy. Intraoperative fentanyl and lidocaine infusion, postoperative epidural bupivacaine-PCA, and NSAID uses have been found to significantly reduce the development of chronic pain after thoracotomy. Duration of surgery, remifentanil administration, chest tube existence for more than 4 days, and diabetes were found to be more related to chronic pain after thoracotomy. By identifying these factors, we applied the necessary treatments to prevent the development of chronic pain and improve patient outcomes.

Ethics Committee Approval: This study was approved by the Human Research Ethics Committee of the Ankara University (Number: İ6-481-21, date: 18.08.2021).

Informed Consent: Informed consent for this study was not taken because retrospective study.

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Original Article

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Effect of Educational Tools on the use of Patient-Controlled Analgesia Devices

Olcayto Uysal[1], Serkan Karaman[2], Tuğba Karaman[2]

[1]Clinic of Anaesthesiology and Reanimation, Tokat State Hospital, Tokat, Turkey

[2]Department of Anaesthesiology and Reanimation, Tokat Gaziosmanpaşa University Medical School Hospital, Tokat, Turkey

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Abstract

Objective: In the literature, there are confusing data about educational tools and device use. Therefore, it is not clear which method is superior to the other. The aim of this study was to evaluate the effects of educational tools on patient-controlled analgesia (PCA) usage in patients undergoing hysterectomy.

Methods: Ninety-six patients undergoing hysterectomy were enrolled in the study. Patients were randomly assigned to a group (verbal, brochure, or video) consisting of 32 patients each using the closed envelope method. After operations, all patients were sent to the ward and evaluated with numerical rating scale score for pain at 15th min., 2nd, 4th, 6th, 12th, 18th, 2nd, 4th, 6th, 12th, 18th, 24th hours. Given dose, the number of button presses, presence of nausea and vomiting, and static and dynamic pain scores were recorded. During visits, patients who had a pain score ≥4 were administered paracetamol 1 g IV. Ondansetron 8 mg IV was injected into patients who had nausea and vomiting.

Results: No significant differences were determined in resting and dynamic pain scores, number of button presses, and given doses between groups at 15th min., 2nd, 4th, 6th, 12th, 18th, 24th hours.

Conclusion: In this study, education type did not affect PCA device use. We believe that whatever method the infrastructure of hospitals is suitable for, should be used for PCA device education.

Keywords: General anaesthesia, hysterectomy, pain management, patient controlled analgesia, patient education, postoperative pain

Main Points

- Patient Controlled Analgesia devices play an important role in the management of postoperative analgesia. It is not known which method is superior among others in PCA device training. Each health center can provide device training in accordance with its own physical conditions.

Introduction

Postoperative pain is known to be the cause of complications such as atelectasis, cardiopulmonary complications, and prolonged hospital stay, which impair the patient's quality of life. Even acute pain can transform into chronic pain when treated improperly. Therefore, postoperative pain management is one of the cornerstones of the perioperative period.

Patient controlled analgesia (PCA) is widely used for postoperative pain management, and PCA devices allow patients to self-administer medications to relieve pain and are an effective method of postoperative pain control.[1] It provides simple, fast and adequate pain relief without the need for a specialized anaesthesiologist.[2] The intravenous (IV) method is commonly used, but some devices administer analgesics via oral, subcutaneous, epidural, or intrathecal ways.[1,3] However, in order for this method works optimally, the device must be understood and used properly by the patient. For this reason, the patient should also consider how to use the device appropriately. However, surgical stress and postoperative pain can make the process of learning to use the device difficult.[4] In

Corresponding author: Olcayto Uysal, e-mail: uolcayto@gmail.com

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some patients, the learning period may be time consuming.[4] Disruptions related to this process may also lead to problems in postoperative pain control.

The education process can be performed verbally, using written sources such as brochures, or using visual education tools such as videos. There has been some disagreement about which educational tool is most effective in educating patients on the proper usage of PCA devices. Therefore, this study determines the effect of verbal, brochure, or video education on the use of PCA devices in patients undergoing a hysterectomy.

Methods

After obtaining approval from the Tokat Gaziosmanpaşa University Clinical Research Ethical Board (17-KAEK-101) and registration to Clinical Trials (NCT03807960), this prospective randomized study was conducted with 96 [American Society of Anesthesiologists (ASA) I-II-III] patients scheduled for elective abdominal hysterectomy at Tokat Gaziosmanpaşa University Medical School Hospital between January 2018 and June 2019. The inclusion criteria of the patients were being aged 18-65 years, having ASA status of I-II-III, and being literate. None of the patients had PCA usage experience. Patients completed informed consent forms before participating.

Patients were randomly assigned to either the verbal group, brochure group, or the video group, each comprising 32 patients. For the patients participating in the verbal group, face-to-face meetings was performed on the day before surgery. The meetings were 15 min long and were carried out in quiet places to ensure an effective dialog between the educator and the patients. Patients were informed about how to use the PCA device (CADD-Legacy Smiths Medical Model 6300, St Paul, MN), and the educator addressed concerns such as overdose and fear of addiction. Patients in the brochure group were given an informative leaflet about how to use the PCA device, possible side effects, and concerns about overdose and fear of addiction on the day before the operation, which the patients were able to read until the time of operation. A short video consisting of general information written in the leaflet and on device usage was made for the video group, which patients watched for over and over one hour on a day before the surgery.

Patients in all three groups were instructed on the use of the 11-point numerical rating scale (NRS) system (0=no pain, 10=intolerable pain) for postoperative pain assessment at pre-operative visits. Patients were also informed of our aim to control postoperative pain using PCA devices; however, it was emphasized that pain may not completely disappear.

On the day of surgery, patients were monitored with electrocardiogram, non-invasive blood pressure, and pulse oximetry (SpO_2). Anaesthesia was induced with fentanyl 1 μg kg^{-1} IV, propofol 2 mg kg^{-1} IV, and rocuronium 0.6 mg kg^{-1} IV. After denitrogenation with 60-80% O_2 and 4 L min^{-1} fresh air supply, patients were intubated. Anaesthesia maintenance consisted of sevoflurane targeting mean alveolary concentration 1, along with an oxygen flow (50-50%), at a total gas flow of 4 liters. Before incision, morphine 0.1 mg kg^{-1} IV was administered (max. dose 8 mg) and 20 min before the end of the surgery paracetamol 1 g IV was administered. After extubation, PCA devices were implemented in the patients and the patients were taken to the recovery room where their follow-ups started. The timing of anaesthesia and surgery was also noted.

The drug solution was prepared by mixing 144 mL saline (0.09%) and 300 mg tramadol, giving a tramadol ratio of 2 mg mL^{-1}. The device was programmed to inject tramadol 20 mg with lock-out interval of 10 min (max. 60 mg h^{-1}) and maximum of three button presses per hour. The continuous infusion was not permitted. The first follow-up of the patients was performed at the 15th minute in the recovery room. Patients were sent to the gynecology ward when the Aldrete score reached 10 points and were assessed at postoperative 2nd, 4th, 6th, 12th, 18th and 24th hours. Patients were asked whether they had pain, and pain scores at rest and during coughing were noted. Nausea and vomiting were also evaluated. Doses given, the number of button presses, and the presence of nausea and vomiting was recorded. Patient satisfaction with PCA education was evaluated with 10 point NRS (0: unsatisfied, 10: very satisfied) assessments were performed by anaesthesiologists.

During visits, patients who had a pain score ≥4 were administered paracetamol 1 g IV and patients with nausea and vomiting were administered ondansetron 8 mg IV. At the last visit, patients were asked whether they were satisfied with the PCA device, and discharge times were noted.

Statistical Analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) 20.0 (SPSS Inc. Chicago, IL). Qualitative data were given as frequencies and percentages, whereas quantitative data were given as means and standard deviations. The Kolmogorov-Smirnov test was used to examine the data distributions, the Pearson chi-square test was performed to compare descriptive statistics, and the Kruskal-Wallis and Mood's Median tests were used to compare groups that had non-normal distributions. Tukey's HSD test was performed for post-hoc analysis; $P < 0.05$ was considered statistically significant.

Gülhaş et al.[5] found a mean Visual Analog Scale (VAS) value of 3.9 ± 1.3 in cases in which PCA was used after hysterectomy. In our study, we predicted that education would improve the adaptation to the use of PCA and reduce

the VAS value by 25%, and the sample size was calculated as 27 patients per group when the bilateral type I error was accepted as 0.05 and the power value was 0.80. Considering possible exclusions, at least 30 patients per group (total 90) were planned to be included in the study.

Results

This study enrolled 96 patients who underwent hysterectomy. Patients were divided into three groups: verbal, brochure, and video, consisting of 32 patients each.

Table 1 shows the demographics of the patients. No significant differences were determined in the resting and dynamic pain scores between the groups at the 15th min and at the 2nd, 4th, 6th, 12th, 18th and 24th hours ($P > 0.05$, $P > 0.05$ respectively). Table 2 shows the mean NRS scores of the patients with resting pain.

Figures 1 and 2 show the number of button presses and given doses of the groups at the 24th hour ($P > 0.05$, $P > 0.05$, respectively).

The number of patients requiring additional analgesics was 25 in verbal group, 19 in brochure group, and 15 in the video group. The presence of nausea was detected in 22 patients in the verbal group, 24 in the brochure group, and 19 in the video group. No significant difference was found among the groups in terms of the additional dose of analgesics and the presence of nausea (P=0.061, P=0.40, respectively).

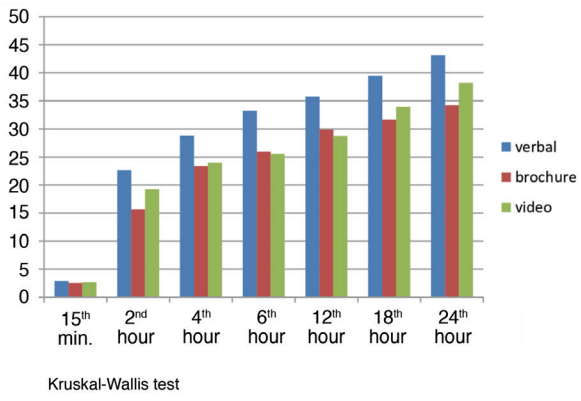

Figure 1. Number of Button Presses.

PCA, patient-controlled analgesia.

Table 1. Patients Demographics

	Verbal (Mean ± SD)	Brochure (Mean ± SD)	Video (Mean ± SD)	*P* values
Age (years)	47.69 ± 5.99	46.66 ± 5.24	47.87±6.46	0.773
ASA				
I	4	9	4	0.158
II	26	22	20	
III	2	1	8	
Education status				
Primary education	26	27	30	0.360
Middle school	2	1	0	
High school	4	1	2	
University	0	3	0	
Duration of anaesthesia (min.)	133.91 ± 52.15	137.19 ± 55.19	150 ± 52.11	0.245
Duration of surgery (min.)	111.56 ± 48.63	115.63 ± 52.66	125.78 ± 49.79	0.317
Discharge time (day)	3.5 ± 1.24	4.16 ± 5.03	3.91 ± 2.11	0.757

Kruskal-Wallis test, Tukey's HSD test.
ASA, American Society of Anesthesiologists; min., minute.

Table 2. Mean Values of Pain Scores at First 24 Hour

	15th min	2nd hour	4th hour	6th hour	12th hour	18th hour	24th hour
Verbal (NRS)	5.56	3.97	2.78	2.38	2.00	1.97	1.63
Brochure (NRS)	5.13	3.72	2.72	1.91	1.63	1.66	1.63
Video (NRS)	5.00	4.41	2.94	2.56	2.00	2.22	2.16

NRS, numerical rating scale; min, minute.

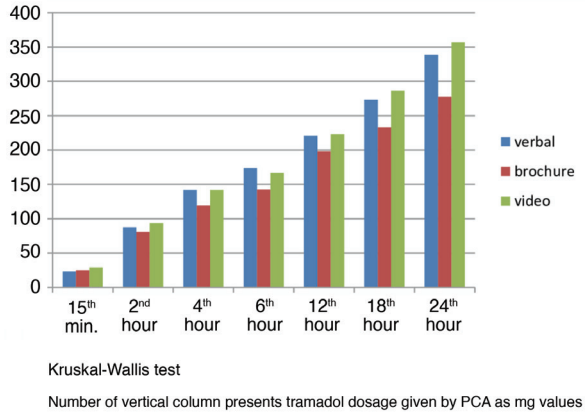

Figure 2. Given Doses by PCA.

Patients were asked whether they were satisfied with PCA education types. Mean values of verbal, brochure, and video groups were 9.28, 8.66, and 9.38, respectively (verbal min: 7 max: 10; brochure min: 4 max: 10; video min: 7 max: 10; assessed with 10 point NRS). Groups were compared for patient satisfaction, and no significant differences were found between the groups (P=0.175).

Discussion

The findings of our study showed that no significant differences existed between the three education methods for PCA device use based on the patients' resting and dynamic pain, number of button presses, and doses given. Additionally, no significant differences were found between the patient satisfaction scores.

PCA devices are widely used in postoperative settings, and it has been shown that these devices ensure a reliable way to achieve effective analgesia.[6] However, as users need to be trained on how to use the device correctly, it is important to determine which type of training is most effective. Highly educated users will use the device more appropriately. This study determined the best education type for the correct use of a PCA device.

Patient education has developed considerably in recent years and can be performed in several ways, such as verbally, using written materials such as brochures, and using multimedia tools such as videos.[7] Verbal education is one of the most commonly used methods in pre-operative education. Dealing with the patient directly and answering the patients questions make this method an effective educational tool. However, problems such as cultural differences between the patient and the educator and the time constraints of the healthcare professional providing the education should be considered.[8] Written educational materials, such as brochures or leaflets, may solve the time constraints because the patient can read them at any time. Such materials should be written with short sentences and avoid technical or medical language; adding explanatory pictures to these materials increases intelligibility.[9] Nevertheless, some patients may not understand these forms or may not even read them.[10] Thus, video-assisted educational systems may be preferable because videos can be made more entertaining using animation. Videos are easy for patients watch and can be watched many times, as with brochures or leaflets. Additionally, the patient learning curve time may be decreased due to the live action style of content in videos. Nonetheless, these types of systems requires sophisticated equipment. All three methods can be used for patient education during the pre-operative period. Ascertaining the treatment steps, sharing treatment decisions with healthcare professionals, and enhancing recovery during the postoperative period are some well-known benefits of pre-operative education.[11] Our study compared these three methods to determine which is most beneficial for PCA device usage.

The impact of education on PCA device usage is a challenging issue that has been investigated by many researchers. Although many studies claim that the type of education does not impact PCA usage, other studies show the superiority of certain methods. For instance, Chumbley et al.[12] investigated parameters such as VAS scores, symptoms such as nausea and vomiting, and itching at the postoperative period to compare verbal and brochure methods on PCA device use. The findings revealed no significant difference between the methods. The results of their study are compatible with our results.

Some existing research also underlines the positive effect of structured education, which is formed by combining different types of education on PCA device usage. A study from South Korea performed with gynecological surgery patients gave videos and brochures about PCA device usage to the patients the day before surgery and compared the outcomes with patients receiving "in person" education. The findings showed that the structured education group was significantly more successful at pain control and experienced fewer side effects.[13] Another study of orthopaedic patients showed that the structured education group used PCA devices more effectively than the routine education group; thus, their pain scores were significantly lower. The findings of this study underlined that when patients received only verbal education, they could misunderstand the knowledge, and when only written education was given, patients did not have the opportunity to ask questions. Researchers have emphasized that using both written and verbal methods together is the most effective way to perform patient education.[14] Further, a study of cancer patients by Lovell et al.[15] showed that using both videos and brochures was significantly more effective for patients compared to using

these methods separately, as both methods reinforce the information given to the patient. Although we did not use any method in combination, analgesia and patient satisfaction in our groups met the desired level.

The impact of preoperative education on PCA device use has not only been researched among adult patients. In their study, Kotzer et al.[16] questioned the effect of PCA device education in children. The patients were divided into two groups. The experimental group watched an eight-minute video about the purposes of pain treatment, drugs used in PCA devices, side effects of the drugs, etc., and the patients practiced using the device, had their questions answered, and were given a brochure. The routine education group was educated by different nurses each time. Instead of a standard verbal education, the nurses were free to elucidate their opinions about PCA device use, and patients were not allowed to practice using the PCA device; instead, the nurses explained how to use the device verbally. At the end of the study, the researchers determined that the total number of PCA demands and given doses in experimental and routine education groups were not significantly different.[16] Furthermore, no statistically significant difference was found in the satisfaction of the patients' families. The results of their study are consistent with our results. The researchers underlined that there was no statistically significant difference between the groups clinically, but it is important to inform the patients and caregivers about possible side effects, the drugs used in the device, and addiction development.[16]

Besides the pain parameters, no significant difference was observed between the scores recorded for nausea and vomiting. One of the well-known side effects of opioids is nausea and vomiting. In the literature, several articles have shown a relationship between tramadol usage and a high nausea and vomiting.[17,18] In contrast, a study conducted by Ozalevli et al.[19] in children undergoing tonsillectomy revealed that the tramadol-using group had a lower incidence of nausea and vomiting than the morphine-using group. None of our patients had treatment-resistant nausea or vomiting.

Respiratory depression, itching, and sedation are other side effects of using opioid-derived drugs with PCA devices. However, no studies have shown the superiority of one analgesic drug over another in terms of itching profile.[20] Neither itching nor respiratory depression was seen in our patients. Furthermore, the basal infusion dose was not used in our study. Along with infusion doses making no contribution to pain management, increasing side effect incidence is a well-known impact of background infusion usage.[21] Further, tramadol usage may cause less sedation compared to other opioids.[22]

Our study has several limitations. First, we did not evaluate the anxiety levels of patients. It is thought that preoperative education reduces patients' anxiety levels.[9,23] Second, no tests were performed to determine patients' knowledge of the education materials. Instead of tests, we considered that the number of times the button was pressed would indicate the patient is to use the PCA device. Third, while the questions of patients in the verbal group were answered, patients in the brochure and video groups had no question-and-answer sessions.

The findings of our study showed that education type did not affect PCA device use. To provide adequate analgesia and ensure patient satisfaction with the PCA device, any method of education can be used according to the personnel and technical possibilities of hospitals.

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Evaluation of Peripheral Versus Central Route of Ondansetron as Pretreatment to Prevent Pain on the Injection of Propofol: A Randomized Controlled Study

Deepak Kumar[1], Prakash K. Dubey[1], Kunal Singh[2]

[1]Department of Anaesthesiology and Critical Care Medicine, Indira Gandhi Institute of Medical Sciences, Patna, India
[2]Department of Anaesthesiology and Critical Care Medicine, All India Institute of Medical Sciences, Patna, India

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Abstract

Objective: We evaluated whether systemic ondansetron was also useful in the attenuation of propofol injection pain similar to ondansetron pretreatment.

Methods: Eighty patients were enrolled. Patients in group S received ondansetron 4 mg in saline in the right hand followed 30 min later by 5 mL saline in the left hand along with venous occlusion. Group L patients received 4 mL of saline in the right hand followed by 5 mL 4 mg ondansetron in the left hand after 30 min. Two minutes later the occlusion was released. Patients received one-fourth of the calculated total dose of propofol, and their level of pain was graded on a scale of 0 to 3, with 0 denoting no discomfort. Mean blood pressure and heart rates were also recorded. Continuous variables were checked for normality using Shapiro-Wilks test. Normal continuous variables were expressed as mean standard deviation and non-normal continuous variables were expressed as median interquartile range. *T*-test for the difference in the mean and paired test were used for normally distributed continuous variable whereas Mann-Whitney U test-Wilcoxon test and sign test were used for non-normally distributed variables. Repeated measure analysis of variance was used for a variable measured over different periods of time to control for the baseline effect on subsequent measures.

Results: Our results demonstrated that both systemic administration 30 min before and local venous pretreatment with ondansetron were equally beneficial in reducing pain during propofol injection.

Conclusion: A systemic administration of ondansetron may play a role in the attenuation of propofol injection pain.

Keywords: Central analgesia, injection pain, local anaesthesia, ondansetron, propofol

Main Points

- Lignocaine and ondansetron pretreatment have been found to be effective in the alleviation of propofol injection pain.
- Systemic administration of ondansetron was compared with ondansetron pretreatment in this study.
- Systemic administration of ondansetron may play a role in alleviating propofol injection pain.

Introduction

Given its rapid onset and short duration of action, ease of titration, and benign side effect profile, propofol 2,6-di-isopropyl phenol is an extremely popular medication for inducing anaesthesia worldwide.[1] Propofol injections, however, cause discomfort in roughly three out of five individuals, with a third of these patients report severe pain. According to several of these patients, the most unpleasant phase of the perioperative period was anaesthesia's induction. To alleviate this pain from propofol injection, many therapies have been researched. According to a

Corresponding author: Prakash K. Dubey, e-mail: pkdubey@hotmail.com

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2000 comprehensive review, the most efficient technique was venous occlusion followed by lidocaine pretreatment.[2] However, due to the time required to apply the tourniquet, this approach is not very popular. The discomfort brought on by the injection of propofol continues to be a matter of concern and more than 100 new researches have looked into additional and alternative methods. These include novel propofol emulsions,[3,4] modified emulsions, and microemulsion formulations,[5-7] part from other drugs and interventions.

The 5-hydroxytryptamine (5-HT) antagonist ondansetron blocks sodium channels in rat brain neurons and is 15 times more potent than lidocaine on subcutaneous injection.[8] Ondansetron is a useful alternative for the alleviation of propofol injection pain.[9,10]

Intravenous ondansetron has also been found to be an effective treatment for neuropathic pain.[11] However, there are conflicting reports about this role of ondansetron. The local anaesthetic lidocaine has been found to alleviate the pain of propofol injection by both local anaesthetic and central analgesic effects.[12] We designed our study to determine if systemic ondansetron was also effective in attenuating pain on propofol injection similar to ondansetron pretreatment. Our hypothesis was based on the premise that propofol injection pain is systemically induced, as suggested by Nakane and Iwama.[13]

Methods

This double-blind randomized controlled trial was conducted after obtaining ethical approval from the Institute Ethics Committee, Indira Gandhi Institute of Medical Sciences: Sheikhpura: Patna-14 Office of the (approval no: 1077/IEC/IGIMS/2019, date: 03.10.2019). The trial was registered prospectively with the national trial registry. Before enrolment, written informed consent was obtained from all patients. This manuscript adhere to the applicable CONSORT guidelines. The study was conducted at a university hospital between February 2020 and March 2021 and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013).

We included 80 patients aged 18-60 years of either gender and American Society of Anesthesiologists (ASA) class I to II scheduled for elective surgery. Exclusion criteria included patient sensitivity to ondansetron and those on concomitant analgesics, sedatives, or antiepileptic medications. Patients were randomly allocated into two groups with 40 patients in each group using a computer-generated randomization list. Sequentially numbered, opaque sealed envelopes were used to conceal the randomization sequence. The investigator and the patient were unaware of the group allocation. An independent clinician prepared the study medication.

The previous evening, all patients were orally provided alprazolam 0.5 mg and ranitidine 150 mg. On the day of surgery, no premedication was administered. A 20-gauge intravenous cannula was placed in the dorsum of both hands as soon as the patient entered the operating room, following the application of ECG, non-invasive blood pressure, and pulse oximeter monitoring. No analgesics were administered before induction. On the left upper arm, a pneumatic tourniquet was applied, and the pressure was raised to 70 mmHg to cause venous occlusion.

Patients in group S received ondansetron 4 mg (2 mL) (Ondem, Alkem Laboratoris Ltd, Mumbai, India) in saline (2 mL) intravenously over 10 s in the right hand. They were given 5 mL of the pretreatment solution (saline) intravenously 30 min later over the course of 10 s, while the venous drainage was restricted by applying a pneumatic tourniquet to the upper arm at a pressure of 70 mmHg. The occlusion was released after 2 min. Group L patients received 4 mL saline intravenously over 10 s in the right hand. After thirty minutes, patients received a 5 mL pretreatment solution (4 mg ondansetron in saline) intravenously in the left hand over a period of 10 s,[14] while a pneumatic tourniquet (pressure raised to 70 mmHg) was applied to the upper arm to occlude venous drainage. The occlusion was released after 2 min. Thereafter, one fourth of the total calculated dose of propofol (Propofol-Lipuro, B Braun Ltd, Melsungen, Germany) stored at room temperature was administered for a period of 5 s and patients were assessed by an independent clinician for pain intensity. We questioned each patient if they found the injection to be comfortable. The verbal response was observed along with behavioral cues such as tears, facial grimacing, or arm withdrawal.[15] The pain was graded on a scale of 0 to 3, with 0 indicating no pain, mild pain, moderate pain, and severe pain, respectively. Mean blood pressure (MAP) and heart rate (HR) were recorded immediately before the interventions and before and after propofol administration. Rescue medications in the form of atropine for bradycardia less than 50 bpm and mephenteramine for hypotension less than 20% of the baseline value were administered. After giving fentanyl, the remaining amount of propofol was used to continue the anaesthetic induction. Vecuronium was used to assist tracheal intubation, while isoflurane, nitrous oxide in oxygen, and intermittent positive pressure breathing was used to maintain anaesthesia.

Statistical Analysis

The primary objective of this study was to determine the incidence and severity of pain on propofol injection following local or systemic administration of ondansetron. In one study, the incidence of propofol pain was 46% when patients were administered 4 mL of saline intravenously

over 10 s.[15] Another study showed a 25% incidence of pain among patients who received ondansetron 4 mg in 2 mL saline intravenously over 10 s.[9]

Based on these informations, the sample size, at 5% level of significance and 80% power to detect the difference in incidence rate between the two groups, was approximately 80, i.e., 40 in each group.

Analyses were performed using Stata version 10 (Stata Corp, College Street, Houston, Texas) and IBM SPSS 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Continuous variables were checked for normality assumptions using Shapiro-Wilks test. The statistical significance level was determined as $P<0.05$. Normally distributed variables were given as mean, standard deviation, and non-normal distributed variables were expressed as median and interquartile range. Independent samples *t*-test was used for normally distributed data comparing two groups, whereas the Mann-Whitney U test was used for non-normally distributed variables. Paired sample *t*-test was used, and Wilcoxon signed-ranked tests were used to compare dependent samples. Repeated measure analysis of variance was used for variables measured over different periods.

Mauchly's test of sphericity was used for checking the sphericity assumptions. In the case of significant violation of the sphericity assumption, Greenhouse-Geisser corrections were applied for adjusting the degree of freedom. Post-hoc comparisons between different pairs of time were done after Bonferroni corrections.

Results

A total of 80 patients were included in the study and there was no dropouts (Figure 1). Table 1 displays the demographic details of the study groups. When age, gender, weight, and ASA class were compared between the groups, there was no significant difference between them. Table 2 presents the pain score measured for the patients in both groups and was found to be non-significant ($P=0.793$).

A repeated measures ANOVA was applied to test the equality of mean HR across three time points, as shown in Table 3. Mauchly's test of sphericity indicated that the assumption of sphericity had been violated significantly (chi-square at 2 df: 136.618, $P=0.0001$). Hence Greenhouse-Geisser corrections were applied for adjusting the degree of freedom. The mean HR was significantly different across the three time points [F (1.093, 77)=25.305, $P=0.0001$)]. A post-hoc pairwise comparison using the Bonferroni correction showed a minimum change in HR between the baseline assessment and before pre-treatment assessment (mean difference =-0.138), but this was not statistically significant ($P=1.00$). However, a decrease in HR reached

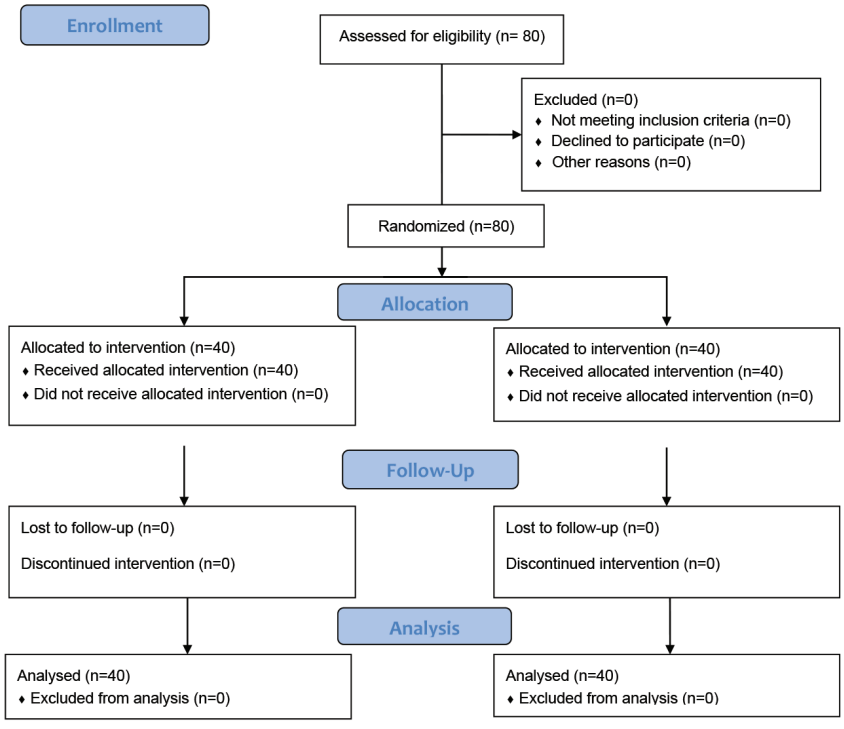

Figure 1. Consolidated standards of reporting trials flow diagram of participants through the study.

significance when comparing the initial assessment to post-treatment assessment (mean difference =-5.688, *P*=0.0001) and also between pre- and post-treatment assessments (mean difference =-0.5825, *P*=0.0001), respectively. Therefore, we can conclude that the results of ANOVA indicate a significant difference in HR between the two groups at various time intervals.

Repeated-measures ANOVA was applied to test the equality of mean MAP across three time points, as shown in Table 4. Mauchly's test of sphericity indicated that the assumption of sphericity had been violated significantly (chi-square at 2 df: 98.02, *P*=0.0001). Hence Greenhouse-Geisser corrections were applied for adjusting the degree of freedom. The mean MAP was significantly different across the three time points [F (1.163, 77) =94.604, *P*=0.0001)]. A post-hoc pairwise comparison using the Bonferroni correction showed a minimum change of MAP between the baseline assessment and before pre-treatment assessment (mean difference =-0.438), but this was not statistically significant (*P*=0.706). However, a decrease in MAP reached significance when comparing the initial assessment to post-treatment assessment (mean difference =-11.40, *P*=0.0001) and also between pre- and post-treatment assessment (mean difference =-10.96, *P*=0.0001), respectively. Therefore, we can conclude that the results of ANOVA indicate a significant difference in MAP between the two groups at various time intervals.

Table 1. Comparison of Demographic Profile

Characteristics	Group S (n = 40)	Group L (n = 40)	*P* value
Gender			
Male	19 (47.5%)	13 (32.5%)	0.171[a]
Female	21 (52.5%)	27 (67.5%)	
Age in years			
Mean ± SD	34.35 ± 11.51	37.37 ± 12.10	0.2557[b]
(95% CI)	(30.67-38.03)	(33.50-41.24)	
ASA physical status			
I	36 (90%)	32 (80%)	0.348[c]
II	4 (10%)	8 (20%)	

*CI, confidence interval; †ASA, American Society of Anesthesiologists; [a]chi-square test; [b]Student's *t*-test; [c]Fisher's exact test.

Table 2. Comparison of Pain Scores Between the Groups

Pain score	Group S	Group L	Total
0	17 (42.5%)	20 (50.0%)	37
1	12 (30.0%)	13 (32.5%)	25
2	8 (20.0%)	5 (12.5%)	13
3	3 (7.5%)	2 (5.0%)	5
Total	40	40	

Pearson chi-square at 3 df: 1,1756 Fisher's exact *P* value =0.793.

Table 3. Repeated Measure ANOVA of Heart Rate Over Time

Sources	Partial SS	df	Mean SS	F-stat	*P* value
Model	1841.5	5	368.3	2.21	0.053
Between-subject effects group	41.66	1	41.66	0.097	0.756
Within-subjects effects time	1767,72	1,093*	1617.997	25.305	0.0001
Group*time	31.90	1,093*	29.202	0.457	0.518

SS, sum of square; *df, degree of freedom adjusted using Greenhouse-Geisser correction for violation of Sphericity assumption (Mauchley's test for Sphericity chi-square =136,618 at df: 1, *P* value =0.0001); Greenhouse-Geisser epsilon (ε)=0.546. Post-hoc comparison, Baseline vs pre-treatment (mean difference =-0.138, *P*=1.00); Baseline vs. post-treatment (mean difference =5,688, *P*=0.0001); pre-treatment vs post-treatment (mean difference =5,825, *P*=0.0001), Boneferroni corrections applied for type I error.

Table 4. Repeated Measure ANOVA of MAP Over Time					
Sources	**Partial SS**	**df**	**Mean SS**	**F-stat**	***P* value**
Model	68886,48	5	1377,29	9.07	0.001
Between-subjects effect group	205,35	1	205,35	0.534	0.467
Within-subjects effect time	6675,41	1,163	5740,895	94,609	0.0001
Group*Time	5,725	1,163	5,924	0.081	0.922
SS, sum of square; *df, degree of freedom adjusted using Greenhouse-Geisser correction for violation of Sphericity assumption (Mauchley's test for Sphericity chi-square =98.02 at df: 2, *P* value =0.0001); Greenhouse-Geisser Epsilon (ε) =0.582 Post-hoc comparison, Baseline vs pre-treatment (mean difference =0.438, *P*=0.706); Baseline vs. post-treatment (mean difference =11.40, *P*=0.0001); pre-treatment vs. post-treatment (mean difference =10,963, *P*=0.0001), Boneferroni corrections applied for type I error.					

Discussion

Our results suggest that both systemic administration and local venous pretreatment with ondansetron were equally effective in alleviating pain on propofol injection.

Intravenous pretreatment with ondansetron has been successful in attenuating pain on the injection of propofol.[9] A single intravenous dose of ondansetron was found to act as an analgesic for neuropathic pain, suggesting its systemic action.[11] We planned our study to find out if systemic ondansetron was also effective in alleviating propofol injection pain similar to local ondansetron pretreatment.

Ondansetron is routinely used at our centre for the prevention of postoperative nausea and vomiting, usually in a dose of 4 mg. Based on an animal experiment, it was felt that 30 min was appropriate for ondansetron to reach the cerebrospinal fluid and exert its systemic action.[14]

In our study, 42.5% of the patients who received systemic ondansetron reported no pain on injection compared with 50% of those administered local pretreatment. Also, the incidence of moderate pain (20% versus 12.5%) and severe pain (7.5% versus 5%) was higher in the patients who were administered systemic ondansetron compared with the local ondansetron pretreatment group. However, none of these were statistically significant (*P*=0.793).

The baseline hemodynamic profile was not different in both groups and so were the hemodynamic changes following propofol administration. Patients in both groups saw a significant drop in HR and MAP as compared to their baseline values, which is a reflection of the normal effect of propofol administration.

5-HT3 receptors have been found to play a role in spinal pain transmission and endogenous pain suppression. They are expressed in the monoaminergic descending inhibitory system, certain brain regions, autonomic afferents, peripheral nerve terminals, and other tissues. When spinal 5-HT3 receptors in the dorsal horn are stimulated, they produce an antinociceptive response probably due to the release of GABA and subsequent activation of the descending inhibitory system.[16] The 5-HT3 receptor antagonists interrupt this antinociceptive effect.

Skin, mucous membrane, and venous intima get irritated by propofol, which is chemically phenol. A high aqueous free propofol concentration has been implicated in causing injection pain.[17] Nakane and Iwama,[13] proposed a systemic mechanism for this pain, whereas the dissociation of propofol activates the plasma kallikrein-kinin system, releasing bradykinin and causing pain. This was substantiated when it was observed that centrally acting analgesics like tramadol, ketamine and non-steroidal anti-inflammatory drugs like flurbiprofen also alleviated this pain.[12] Non-selective ligand-gated cation channels such as transient receptor potential (TRP), ankyrin 1, and TRP vanilloid 1 have been found to mediate release of neuropeptides and produce propofol-induced pain.[18]

We used a propofol formulation containing medium chain triglyceride because it has a reduced concentration of free propofol in the aqueous phase and is known to cause lesser pain on injection.[19]

In animal models of nerve damage, it has been hypothesized that intrathecal injection of 5HT-3 receptor antagonists such as ondansetron reduces mechanical and thermal hypersensitivity.[20,21] Serotonin plays a crucial role in the endogenous analgesia process. Serotonergic neural regulation that descends to the spinal cord from the rostral ventromedial medulla reduces neuronal activity and hypersensitivity and aids in analgesia.[22] This has been linked to the serotonin activity on the G-protein coupled 5HT-1 and 5HT-7 subtypes of serotonin receptors.[23] G-protein coupled receptors also play some role in the attenuation of propofol-induced pain.[9] However, there are certain limitations to our study. Due to ethical concerns, a placebo group was not included in our study. Estimation of cerebrospinal fluid and serum levels of ondansetron could not be performed for logistic reasons.

Conclusion

The findings that systemic administration of ondansetron may play a role in alleviating propofol injection pain can be

a basis for further research into its use as an analgesic in pain models other than neuropathic.

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Trial registration: Clinical Trial Registry India (www.ctri.nic.in) vide registration number CTRI/2019/12/022386.

Ethics Committee Approval: This study was approved by Institute Ethics Committee, Indira Gandhi Institute of Medical Sciences: Sheikhpura: Patna-14 Office of the Ethics Committee (approval no: 1077/IEC/IGIMS/2019, date: 03.10.2019).

Informed Consent: The eligible patients were informed about the study during the preoperative evaluation and their written consents were obtained.

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Is Laryngeal Mask a Good Alternative in Children Undergoing Laparoscopic Inguinal Hernia Repair with Percutaneous Internal Ring Suturing Under and Over Two Years Old?

Damla Uysal[1], Sanem Çakar Turhan[1], Ergun Ergün[2], Özlem Selvi Can[1]

[1]Department of Anaesthesiology and Reanimation, Ankara University Faculty of Medicine, Ankara, Turkey
[2]Department of Pediatric Surgery, Ankara University Faculty of Medicine, Ankara, Turkey

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Abstract

Objective: This study aimed to evaluate respiratory parameters during percutaneous internal ring suturing (PIRS) for inguinal hernia repair in two different-aged pediatric patients in whom the airway is provided with a laryngeal mask or endotracheal tube for general anaesthesia.

Methods: After local ethics committee and parental consent, 180 ASAI-II children were randomly allocated to 4 groups; according to their age (0-24 months / 25-144 months) and airway device laryngeal mask (LMA) / endotracheal tube (ETT) used for general anaesthesia (45 children each) for laparoscopic inguinal hernia repair. Standard anaesthesia induction was done with lidocaine, propofol, and fentanyl, and 0.6 mg kg^{-1} rocuronium was added to the ETT groups. Sevoflurane is used for maintenance. Hemodynamic parameters, peak airway pressure, end-tidal carbon dioxide ($EtCO_2$), and peripheric oxygen saturation (SpO_2) values were recorded after induction, before, and during pneumoperitoneum. The duration of anaesthesia, surgery, recovery time, and surgical satisfaction was recorded. Airway complications (cough, laryngospasm, bronchospasm, desaturation, and aspiration) were recorded.

Results: Hundred and eighty patients (45 in each group) were analyzed. Duration of surgery and surgical satisfaction were similar in all groups. Duration of anaesthesia and recovery times were significantly shorter in the LMA groups. Peak airway pressure and $EtCO_2$ levels were significantly lower in the LMA groups. Rare airway complications were observed without significance.

Conclusion: In laparoscopic inguinal hernia repair with the PIRS technique, LMA offered comparable operating conditions and surgical satisfaction.

Keywords: Airway management, outpatient anaesthesia, pediatric anaesthesia, perioperative care, pharmacology

Main Points

- Inguinal hernia repair is one of the pediatric patients' most frequently applied surgical procedures.
- Open standard herniorrhaphy is a classical technique, but the frequency of laparoscopic techniques is increasing. Percutaneous internal ring suturing (PIRS) for laparoscopic herniorrhaphy in pediatrics enabled the completion of surgery in a relatively short time by using only one umbilical port and needle puncture point.
- The most common technique for airway management during laparoscopy is endotracheal intubation with neuromuscular blocker agent.
- The results of this study revealed that in children aged 0-24 months and 25-144 months, laparoscopic inguinal hernia surgery with PIRS technique can be performed safely with Classic LMA without using muscle relaxants. This way, complications related to muscle relaxants and intubation could be avoided while providing similar surgical conditions and ventilation parameters.

Corresponding author: Sanem Çakar Turhan, e-mail: sanemcakar@yahoo.com

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Introduction

An inguinal hernia is a protrusion of the peritoneum and viscera that needs to be surgically repaired. In pediatric patients, inguinal hernia repair is one of the most frequently applied surgical procedures. While indirect hernia comprises more than 99% of all cases, direct inguinal hernia is rare.[1,2] Open standard herniorrhaphy is a classical technique, but in recent years there has been an increased use of laparoscopic techniques. Patkowski et al.[3] described percutaneous internal ring suturing (PIRS) for laparoscopic herniorrhaphy in pediatric surgery, which enabled using only one umbilical port and needle puncture point. It involves the closure of the internal ring extraperitoneal by a needle under laparoscopic guidance. The method is favorable because of the very low risk of recurrence and excellent cosmetic results with a very short surgery with less inflammatory stress (Figure 1).[3-7] Laparoscopic surgery has another advantage additionally as it gives a chance to diagnose contralateral indirect hernia in the same session.

Laparoscopic surgery has various advantages, including reduced postoperative pain and fewer wound-related complications. The most common technique for airway management during laparoscopy is using a cuffed endotracheal tube (ETT) with a neuromuscular blocker agent and positive pressure ventilation.[8] With this approach, the risk of aspiration is reduced while providing effective ventilation. Laryngeal mask airway (LMA) is generally used without neuromuscular blocker agent to provide the airway during general anaesthesia. Therefore, in appropriate cases, it can prevent side effects due to muscle relaxants and intubation. Recently, LMA has been used in some laparoscopic surgeries in adults; however, its use in pediatric patients is limited in laparoscopic surgeries.[9-17] Small working spaces in children may even become smaller due to gastrointestinal distention because LMA ventilation may be the major limitation of its use. To the best of our knowledge, the effect of LMA on laparoscopic surgery in different ages of pediatric patients is not compared with ETT. In this prospective randomized controlled trial, children scheduled for single-sided inguinal hernia repair with the PIRS technique were randomized according to their age (0-24 months or 25-144 months) and airway equipment used for airway management (classic LMA and ETT) to analyze respiratory parameters and operating conditions.

Methods

This randomized controlled study was conducted prospectively after ethical approval (Ankara University Clinical Research Ethics Committee; 17.06.2021 / I6-402-21) between August 2021 and July 2022 in the operating rooms of Ankara University İbni Sina Hospital. One hundred eighty ASA I-II children aged 0-144 months who were scheduled for operation due to single-sided inguinal hernia with PIRS technique were included in the study after parents signed informed consent. After the patient was taken into the age-appropriate group, laryngeal mask

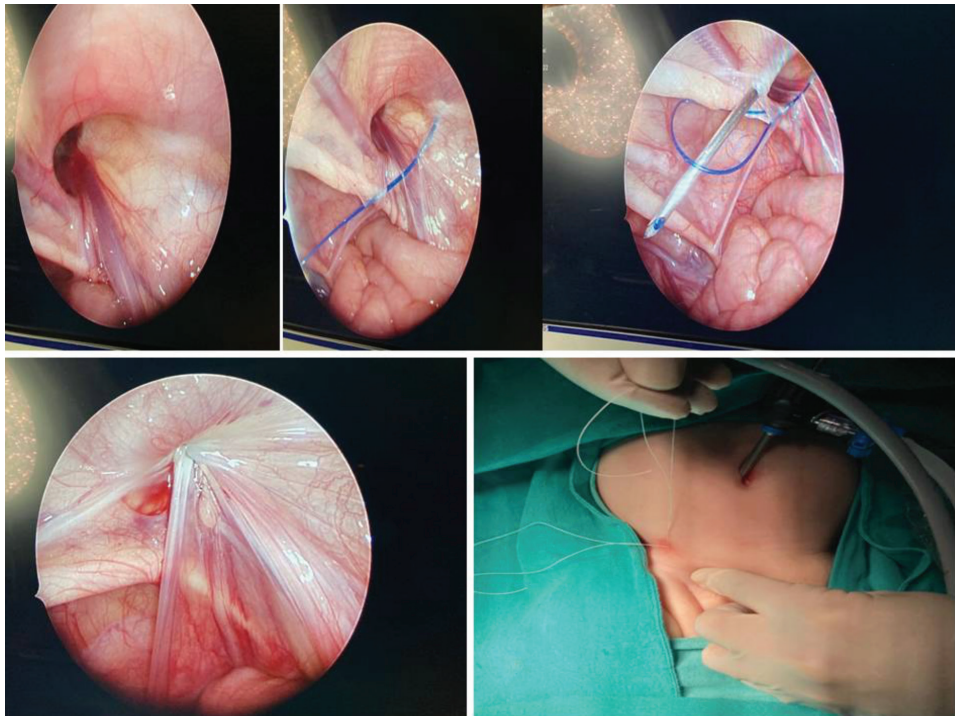

Figure 1. Percutaneous internal ring suturing (PIRS) for laparoscopic herniorrhaphy.

or ETT usage was decided using a computer-generated allocation system, and patients were randomly divided into four groups, 45 patients in each group according to their age and airway management equipment:

Group Y-LMA (Younger LMA group; 0-24 months)

Group O-LMA (Older LMA group; 25-144 months)

Group Y-ETT (Younger ETT group; 0-24 months)

Group O-ETT (Older ETT group; 25-144 months).

Patients who needed emergency surgery for strangulated or incarcerated inguinal hernia, patients with an anticipated difficult airway, cardiovascular or pulmonary disease, ASA physical status ≥ III, allergy to study drugs, and those who underwent different surgery in addition to hernia repair were excluded from the study. Standard American Society of Anaesthesiology recommendations for perioperative fasting were used.

All patients underwent routine ASA monitoring, and anaesthesia induction was achieved with a face mask with 8% sevoflurane in O_2 after transferring to the operating room. "Gentle mask ventilation was performed in all patients to prevent gastric and bowel insufflation." Following losing consciousness, an intravenous (IV) line was inserted. In all patients, IV lidocaine 1 mg kg^{-1} + propofol 2-3 mg kg^{-1} and fentanyl 1 µg kg^{-1} were administered. In ETT groups, rocuronium bromide 0.6 mg kg^{-1}) was added. Before placing LMA or ETT, an appropriate nasogastric (NG) tube was inserted to relieve gas and fluid in the stomach. Proper localization of the NG tube was confirmed by auscultation of the epigastrium and gastric aspiration performed before airway intervention, and the NG tube was secured until the end of surgery.

Appropriate cuffed ETT was inserted, inflating the cuff until minimal leakage with 15-20 cm H_2O and confirming the correct position of the ETT with capnography and auscultation of the chest. ETT selection was made as follows: For children, 2 years of age and older, 3.5 + (age in years / 4) formula was used. For children 1 to <2 years of age, a 3.5 mm internal diameter cuffed endotracheal tube and a 3.0 mm internal diameter cuffed endotracheal tube were used for children <1 year of age. Additional tubes one size larger or smaller than calculated should also be available.

LMA Classic™ (LMA North America, Inc., San Diego, CA, USA) (C-LMA) is used in all LMA groups. The appropriate size of C-LMA was chosen according to the patient's weight, and proper positioning of LMA was confirmed by adequate chest rising with no audible leak.

After airway device placement, anaesthesia was maintained with 1-1.5 MAC sevoflurane in O_2 40%. Ventilatory settings were initially done with a tidal volume (TV) of 6-8 mL kg^{-1} in 4 L min^{-1} of fresh gas flow, $EtCO_2$ levels were closely monitored throughout the entire process, and the respiratory rate was adjusted to keep $EtCO_2$ levels in the range of 35-40 mmHg during surgery. Peritoneal insufflation pressure was preset and maintained between 6 and 10 and mm high CO_2 during surgery. Intraabdominal pressure is also recorded during surgery.

Demographic variables, heart rate (HR), mean arterial blood pressure, peripheric oxygen saturation (SpO_2), peak airway pressure (P peak), and $EtCO_2$ levels were recorded before and after airway device placement, each 5 min intervals after pneumoperitoneum and 1 min after desufflation.

Anaesthesia time (from putting a face mask on the patient's face until stopping sevoflurane), surgical time (after finishing local anaesthetic infiltration before inserting umbilical port to last skin suturing), recovery time (after completing surgery and stopping sevoflurane inhalation to discharging from the operating room to post-anaesthesia care unit). The surgical team was blinded to airway device selection and neuromuscular blocker agent usage. Surgeons' evaluation of the surgical field and conditions with a 5-point Likert scale (1: very poor, 2: poor, 3: fair, 4: good, 5: excellent) was questioned at the end of surgery and recorded.

At the end of the operation, IV paracetamol 6-15 mg kg^{-1} was administered according to the patient's age. In the ETT groups, neuromuscular block was reversed with neostigmine 50-70 µg kg^{-1} + atropine 10 µg kg^{-1}. Patients who achieved adequate spontaneous ventilation and reflexes were extubated. In the LMA groups, LMA was removed when the patient achieved adequate ventilation. Laryngospasm, bronchospasm, coughing, breath holding, and desaturation (SpO_2 <90%) during the recovery period were recorded. Patients who achieved a Modified Aldrete score >9 were discharged to the clinical ward from PACU. Sore throat, nausea, and vomiting were evaluated at the postoperative 2nd hour in children who could communicate and answer questions; in the rest, only vomiting was recorded.

Statistical Analysis

Data analysis was done in the SPSS for Windows 11.5 (SPSS Inc, Chicago, IL, USA) package program. Descriptive statistics are shown as mean ± standard deviation for variables with normal distribution, median (minimum-maximum) for variables with non-normal distribution, and number of subjects (n) and (%) for nominal variables.

Our primary outcome was the presence of differences between groups in terms of recovery time. A preliminary estimate of a sample size of 45 patients per group of 180 patients was determined with an effect size of 0.25, a power of 0.80, and a margin of error 0.05. The sample size calculation was done with the G*Power 3.1.9.7 program.

The significance of the difference between quantitative variables of groups in the study was investigated using the Student-t test/Mann-Whitney U test. Nominal variables were evaluated using the Pearson chi-square/Fisher's exact test. Mixed Design ANOVA was used to determine whether there was a difference between the groups in terms of P peak, intra-abdominal pressure, SpO_2, and blood pressure values taken from individuals at 5 different time points. $P < 0.05$ was considered statistically significant.

Results

Initially, 200 patients were studied for inclusion in the study. After the patients were randomized into groups, 17 patients were excluded because of contralateral inguinal hernia diagnosis and repair, and three patients were excluded because of improper placement of the LMA. The results of 180 patients, 45 in each of the four groups, were analyzed (Figure 2).

When the results of all 180 patients included in the study were analyzed, 42 were girls (23.3%), and 138 (76.7%) were boys. The mean age of all patients was 39 ± 23.72 months. One hundred and seventy-six patients (97.8%) were ASA I; four (2.2%) were ASA II. The surgical procedure was completed laparoscopically in all patients. The mean duration of anaesthesia for all patients was 43.54 ± 9.01 minutes, the mean operation time was 33.59 ± 9.67 minutes, and the mean recovery time was 9.54 ± 3.17 minutes.

There was no difference in gender, age, weight, height, and ASA physical status between the 0-24 months-old Y-LMA and O-ETT groups. However, the duration of surgery was similar between groups, and anaesthesia and recovery times were significantly higher in the intubated group ($P < 0.001$) (Table 1).

Also, there was no significant difference in gender, age, weight, height, and ASA physical status between the 25-144-month-old Y-LMA and O-ETT groups. Similarly, with younger groups, anaesthesia and recovery times were significantly higher in the intubated group ($P < 0.001$), and the duration of surgery was almost the same (Table 2).

Peak airway pressure difference was significant between the patients in Y-LMA and Y-ETT at all time intervals ($P < 0.001$). At all times, patients in Y-LMA had an average of 3.639 cm H_2O lower peak airway pressure values than patients aged Y-ETT ($P < 0.001$). In addition, patients in the Y-LMA group had an average of 0.876 mmHg lower $EtCO_2$ when compared with patients in the Y-ETT group at all times ($P < 0.001$) (Table 3).

Desaturation was not observed in group Y-LMA and group Y-ETT patients at all time intervals, and there was no significant difference between the groups regarding saturation values. For mean blood pressure, there was a significant difference between the group-independent times and between the groups ($P < 0.001$, and P=0.003, respectively). The patients in Group Y-LMA had an average

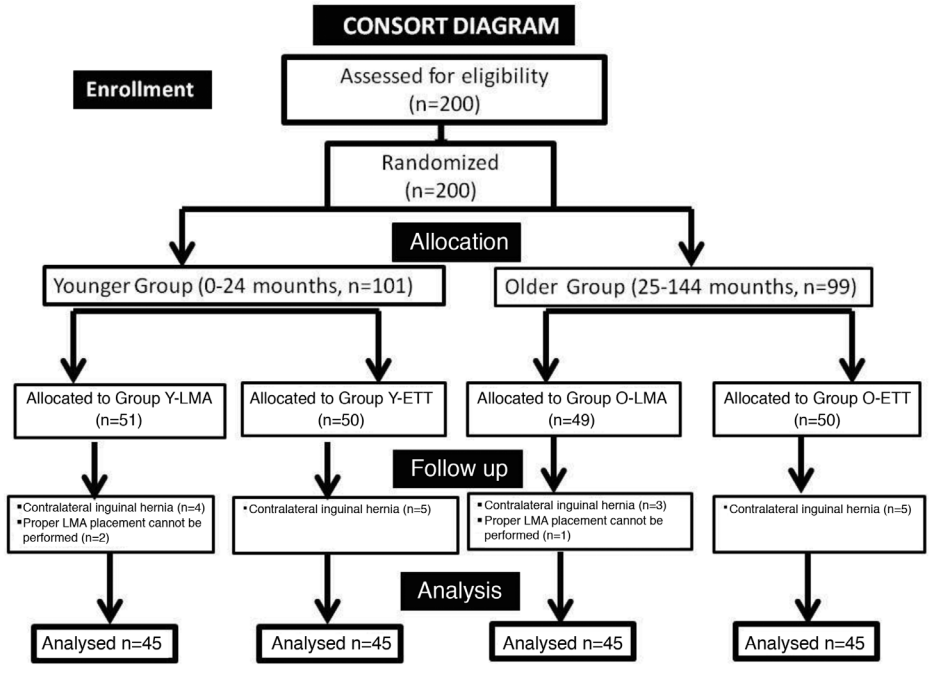

Figure 2. CONSORT flow diagram of patient distribution.

of 2.814 mmHg higher mean blood pressure than patients in Group Y-ETT at all times (P=0.026). There was also a significant difference between groups-independent times for the HR and between groups Y-LMA and Y-ETT (P=0.002 and P=0.003, respectively). Patients in Group Y-LMA had an average of 3.153 units higher HR each time than those in Group Y-ETT. Also, patients in Group Y-LMA had a significant increase in HR in the 1st minute after airway intervention compared with those in Group Y-ETT (P=0.018).

Table 4 presents peak airway pressure and $EtCO_2$ levels between the groups 25-144 months of age who underwent LMA or ETT. For peak airway pressure, significant differences were found between group-independent times and between groups ($P < 0.001$, and $P < 0.001$, respectively). Patients in Group O-LMA had an average of 2.161 cm H_2O lower P peak values each time than O-ETT. Also, Group O-LMA had an average of 0.292 mmHg lower $EtCO_2$ than patients who underwent ETT at all times ($P < 0.001$) (Table 4). There was no significant difference between the groups regarding SpO_2 at any time interval.

Desaturation was not observed in Groups O-LMA and O-ETT at all time intervals. For mean blood pressure, patients in O-LMA had an average of 0.550 mmHg higher mean blood pressure than patients in O-ETT at all times, but this difference was not significant (P=0.105). There was no significant difference between groups and independent times for the HR between the O-LMA and O-ETT groups (P=0.165, and P=0.593, respectively).

In the postoperative period, cough was observed in 13 (7.2%) patients during recovery; 4 (2.2%) patients in group Y-LMA,

Table 1. General Descriptors of Patients Aged 0-24 Months in whom LMA or ETT was Used

		Group Y-LMA	Group Y-ETT	*P* value
Age (month)	Mean ± SD	10.49 ± 5.87	10.67 ± 6.71	0.881[b]
Gender, n (%)	Girl	8 (17.8)	12 (26.7)	0.310[c]
	Boy	37 (82.2)	33 (73.3)	
Weight (kg)	Mean ± SD	9.18 ± 2.46	9.38 ± 2.69	0.714[a]
Height (cm)	Mean ± SD	72.42 ± 8.53	72.58 ± 9.97	0.937[a]
ASA, n (%)	1	41 (91.1)	45 (100.0)	0.117[d]
	2	4 (8.9)	0 (0.0)	
Anaesthesia duration (min)	Median (min-max)	36.00 (30.00-75.00)	51.00 (37.00-70.00)	<0.001[b]
Operation time (min)	Median (min-max)	35.00 (26.00-44.00)	39.00 (28.00-40.00)	0.607[b]
Recovery time (min)	Median (min-max)	6.00 (4.00-10.00)	14.00 (10.00-20.00)	<0.001[b]

Y- LMA / Y-ETT: The younger laryngeal mask group / Younger endotracheal tube group.
[a]Student-t test; [b]Mann-Whitney U test; [c]chi-square test; [d]Fisher's exact test; SD, standard deviation; min, minimum; max, maximum; $P < 0.05$ is taken as statistically significant.

Table 2. General Descriptors of Patients Aged 25-144 Months in whom LMA or ETT was Used

		Group O-LMA	Group O-ETT	*P* value
Age (month)	Mean ± SD	70.18 ± 32.59	66.20 ± 32.14	0.480[b]
Gender, n (%)	Girl	15 (33.3)	7 (15.6)	0.050[c]
	Male	30 (66.7)	38 (84.4)	
Weight (kg)	Mean ± SD	23.73 ± 12.12	23.31 ± 10.07	0.762[a]
Height (cm)	Mean ± SD	109.27 ± 23.39	112.22 ± 18.62	0.509[a]
ASA, n (%)	1	45 (100.0)	45 (100.0)	-
	2	0	0	
Anaesthesia duration (min)	Median (min-max)	36.00 (32.00-45.00)	49.00 (30.00-60.00)	<0.001[b]
Operation time (min)	Median (min-max)	34.00 (26.00-40.00)	32.00 (28.00-36.00)	0.516[b]
Recovery time (min)	Median (min-max)	8.00 (6.00-12.00)	10.00 (7.00-16.00)	<0.001[b]

O-LMA / O-ETT: the older laryngeal mask group / older endotracheal tube group, [a]Student-t test; [b]Mann-Whitney U test; [c]chi-square test; SD, standard deviation; min, minimum; max, maximum.
$P < 0.05$ is taken as statistically significant.

2 (1.1%) patients in group O-LMA, and group Y-ETT was observed in 3 patients (1.7%), and 4 (2.2%) patients in group O-ETT. During recovery in group Y-LMA, only one patient developed bronchospasm, and one developed desaturation. Two patients in group O-ETT developed laryngospasm, and no blood contamination on the airway device or aspiration was observed in any patients. Nausea and vomiting were not observed in any patient, and sore throat was observed in 5 patients at the second postoperative hour in group O-ETT. The age of the patients or maintaining the airway with LMA or ETT was not found to affect the development of cough, laryngospasm, bronchospasm, or desaturation.

Surgeons' evaluation of surgical field and conditions using a 5-point Likert scale was 4 points in 6 patients. All the remaining patients were given a score of 5 points, and there was no significant difference in this parameter between general anaesthesia with LMA or ETT in both age groups.

Table 3. Ventilation Parameters of 0-24 Months Patient Groups During Surgery

Ventilation parameter	Time interval	Y-LMA (n = 45)	Y- ETT (n = 45)	*P* value
P peak (cm H_2O)	1 min after airway device placement	13.36 ± 1.45	18.56 ± 1.98	$P < 0.001^{a,b}$
	Before peritoneal insufflation	13.62 ± 1.85	19.02 ± 1.98	
	During peritoneal insufflation	17.02 ± 2.05	19.51 ± 1.79	
	1 min after peritoneal desufflation	13.58 ± 1.52	18.20 ± 1.53	
$EtCO_2$ (mmHg)	1 min after airway device placement	36.64 ± 1.57	38.29 ± 0.79	$P < 0.001^{a,b}$
	Before peritoneal insufflation	36.87 ± 1.62	38.73 ± 1.03	
	During peritoneal insufflation	39.27 ± 1.60	39.53 ± 1.10	
	1 min after peritoneal desufflation	37.07 ± 1.56	39.18 ± 0.98	

P peak: Peak airway pressure.
$EtCO_2$: End-tide carbon dioxide.
Y-LMA / Y-ETT: The younger laryngeal mask group / younger endotracheal tube group.
Values are presented as mean ± standard deviation.
[a] and [b]: Mixed-design analysis of variance test. Differences between group-independent times and between groups.
$P < 0.05$ is taken as statistically significant.

Table 4. Ventilation Parameters of 25-144 Months Patient Groups During Surgery

Ventilation parameter	Time interval	O-LMA (n = 45)	O-ETT (n = 45)	*P* value
P peak (cm H_2O)	1 min after airway device placement	11.58 ± 2.35	13.96 ± 1.35	$P < 0.001^{a,b}$
	Before peritoneal insufflation	11.62 ± 1.85	15.11 ± 1.73	
	During peritoneal insufflation	13.96 ± 2.57	15.31 ± 1.76	
	1 min after peritoneal desufflation	11.76 ± 2.07	14.22 ± 1.36	
$EtCO_2$ (mmHg)	1 min after airway device placement	37.47 ± 1.01	38.07 ± 0.99	$P < 0.001^{a,b}$
	Before peritoneal insufflation	37.62 ± 1.15	38.73 ± 1.03	
	During peritoneal insufflation	39.38 ± 1.30	39.53 ± 1.10	
	1 min after peritoneal desufflation	38.44 ± 1.56	38.47 ± 0.94	

P peak: Peak airway pressure.
$EtCO_2$: End-tide carbon dioxide.
O-LMA / O-ETT: the Older laryngeal mask group / older endotracheal tube group.
Values are presented as mean ± standard deviation.
[a] and [b]: Mixed-design analysis of variance test. Differences between group-independent times and between groups.
$P < 0.05$ is taken as statistically significant.

Discussion

This study showed that using C-LMA in laparoscopic inguinal hernia repair with the PIRS technique in two groups of pediatric patients (0-24 months and 25-144 months) provides similar intraoperative respiratory parameters and surgical conditions with the use of ETT and muscle relaxants. In the LMA groups, surgery times were similar to those in the ETT groups in both ages, but anaesthesia and recovery times were significantly shorter.

In laparoscopic surgeries, intra-abdominal pressure increases due to pneumoperitoneum. Muscle relaxants given during surgery reduce intra-abdominal pressure and help obtain a comfortable working space. Also, increased intra-abdominal pressure decreases lung compliance and may cause increased P peak values.[18] Our results showed that if the airway is provided with LMA, regardless of age, peak airway pressure was lower in LMA groups compared with ETT groups in both age groups (3.639 and 2.436 cm H_2O in younger and older groups, respectively). Also, no difference was found between the LMA (without muscle relaxants) and ETT (with muscle relaxants) groups regarding intra-abdominal pressure and $ETCO_2$ values in both age groups.

The surgeons may experience difficulties during the procedure due to the lack of muscle relaxation regarding the smaller working area. In this study, the surgical team was blinded to the airway device. Their evaluation and satisfaction were similar between the LMA and ETT groups, and the surgery duration was consistent, indicating that lack of muscle relaxants did not affect the surgical conditions in laparoscopic PIRS surgery. Also, peak airway pressures were below 20 cm H_2O in all groups, and $EtCO_2$ levels could be kept below 40 mmHg during the whole procedure, indicating that LMA without muscle relaxants can be used as an alternative in the younger age group in short-term laparoscopic inguinal hernia operations.

Ozbilgin et al.[12] conducted a study on adult patients. They placed LMA without muscle relaxants, and ETT was applied using muscle relaxants in laparoscopic gynecological surgeries. In patients who underwent ETT, P peak values were significantly higher at the 2nd minute after intubation and just before extubation. Similar to their results in both age groups, we observed significantly lower airway pressures in the LMA groups. The endotracheal tube, which is preferred for the airway, may have caused an increase in pressure due to the slightly narrowing diameter of the airway compared to supraglottic placed LMA. It may indicate that intubation affecting the infraglottic airway causes more airway reaction than methods affecting the supraglottic airways, such as LMA.

LMA is frequently used in short procedures where general anaesthesia is applied due to its ease of insertion and use without muscle relaxants, less hemodynamic instability during insertion, less metabolic stress response, and a lower risk of tracheal trauma.[9-11] Despite all these, a laryngeal mask is not always suitable for all laparoscopic surgeries, but it can be a good alternative to ETT for short procedures. In appropriate patients and surgical procedures, LMA prevents intubation risks and the adverse effects of residual block due to muscle relaxants. This study achieved good anaesthesia and surgical conditions with LMA for laparoscopic inguinal hernia repair in pediatric patients aged 0-144 months and weighing between 4 and 70 kg. We observed significantly shorter anaesthesia and recovery times in the LMA group in younger patients. Moreover, these results were similar in older patients.

The most important reasons for refraining from using LMA in laparoscopic procedures are the risk of aspiration and inadequate ventilation. We did not observe the aspiration in any group. We believe this is because all interventions were elective, and appropriate fasting periods were achieved. Effective gastric drainage was provided with a nasogastric tube before the airway device was placed in all patients, and there was no need for exaggerated Trendelenburg in the PIRS technique. Ozdamar et al.[19] compared LMA and ETT on ventilation and gastric pressure in pediatric laparoscopic surgeries, and similar to our results, the nasogastric tube allowed gastric drainage, reduced gastric inflation, and did not affect ventilation. Our study did not use second or third-generation LMAs with gastric drainage channels. This is because the classical LMA is used more frequently than the new generation LMAs in our clinic and general practice for different reasons (such as inaccessibility and lack of appropriate pediatric dimensions). In addition, the gastric drainage tube cannon always be placed correctly and easily through the gastric drainage canal with second or third-generation LMAs, especially in small numbers.[20]

In this study, in all age groups using both ETT and LMA, very few airway complications (cough, laryngospasm, bronchospasm, desaturation) were observed, that did not cause any significant difference between the groups. Common airway complications were observed less in using LMA.[11,17,21-24] A laryngeal mask may also provide an advantage in patients with an upper respiratory tract infection (URTI) and who require emergency surgery because of an incarcerated or strangulated inguinal hernia. Also, some children have a frequency of URTI of 6-8 episodes per year, so it may be challenging to schedule the child during a symptom-free interval for elective surgery; LMA will be a better alternative for appropriate surgical procedures in children at high risk of airway complications.[25]

McHoney et al.[26] has shown that on laparoscopic surgeries, a negative correlation was found between $EtCO_2$ value and age, and it was shown that carbon dioxide elimination was higher in young children compared to older age. We did not have any difficulties in any group to keep the target values with close follow-up of $EtCO_2$ and ventilation monitoring during laparoscopy.

Study Limitations

This study has limitations; PIRS is a relatively short surgery and can be performed in a supine or minimal Trendelenburg position. The surgeon's experience is very influential; if the surgery is prolonged or excessive, Trendelenburg is required, and LMA may not be an appropriate option. Therefore, the results of this study can not be generalized to all laparoscopic surgeries in pediatrics.

Conclusion

In conclusion, in children aged 0-144 months, laparoscopic inguinal hernia surgery with the PIRS technique can be performed safely with a C-LMA without using muscle relaxants. This way, muscle relaxants, and intubation-related complications can be avoided while providing similar surgical conditions and ventilation parameters.

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Original Article

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Awareness of Postdural Puncture Headache Among Specialists who Perform Lumbar Punctures and/or Monitor Patients Following the Procedure

Mesut Bakır[1], Şebnem Rumeli[2], Ümit Durmuşoğlu[3], Erman Balıkçı[3]

[1]Clinic of Anaesthesiology and Reanimation, Mersin City Training and Research Hospital, Division of Algology, Mersin, Turkey

[2]Department of Anaesthesiology and Reanimation, Mersin University Faculty of Medicine, Division of Algology, Mersin, Turkey

[3]Department of Anaesthesiology and Reanimation, Mersin University Faculty of Medicine, Mersin, Turkey

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Abstract

Objective: Lumbar puncture (LP) is performed by specialists in different branches of medicine, complications may be encountered in various settings. In our study, we evaluated the awareness and knowledge of the diagnosis and treatment of post-dural puncture headache (PDPH) among specialists who performed LP and/or encountered complications.

Methods: This was a prospective questionnaire/scale study of 253 physicians: LP performers (anaesthesiologists, Group A; others, Group B) and those who worked in departments that did not perform LP but frequently encountered complications following LP (Group C). The questionnaire assessed specialization, frequency of LPs utilization, needle types used, positions employed, awareness of LP complications, diagnosis, management, and risk factors for PDPH.

Results: Group A had the highest percentage of physicians who stated they had knowledge about PDPH (Group A: 96.4%, Group B: 77.3%, Group C: 39.4%; *P*=0.000). Group C was found to be statistically less informed than the other two groups (*P*=0.000). It was determined that only one (1%) physician from Group C correctly answered the question about the diagnostic criteria for PDPH.

Conclusion: To our knowledge this is the first study in which the awareness of PDPH has been compared according to physicians' fields of specialisation. We believe that post-specialty training programs should be organized for physicians who will either perform LP or monitor patients who have undergone LP, and the curriculum content in relevant specialties should be reviewed.

Keywords: Adult anaesthesia, education and training, pain management, postdural puncture headache, regional anaesthesia

Main Points

- The most frequent complication of lumbar puncture (LP) used for diagnosis or therapy is post-dural puncture headache (PDPH), which has a higher risk of morbidity and mortality if left untreated.
- If physicians recognize and treat PDPH at an early stage, this will significantly reduce the development of morbidity associated with this complication.
- Post-specialty training programs should be organized to better train physicians who will either perform LP or monitor patients who have undergone LP.

Corresponding author: Mesut Bakır, e-mail: mesutbakir@gmail.com

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Introduction

Postdural puncture headache (PDPH) is one of the most common complications of lumbar puncture (LP).[1] Early diagnosis and treatment of PDPH are essential to prevent significant morbidity and mortality.[2]

LP is often performed by anaesthesiologists, paediatricians, neurologists, infectious disease, and emergency medicine specialists. Among other groups of physicians who must be aware of PDPH, one of the complications of the procedure, are physicians who do not perform this procedure but who frequently encounter these patients and are responsible for their follow-up and treatment, for instance, surgical department specialists. It has been reported in the literature that if anaesthesiologists and other physicians recognize and treat PDPH at an early stage, this will significantly reduce the development of morbidity associated with this complication.[3,4]

The factors that increase the risk of developing PDPH following LP are well defined in the literature. Among the patient groups at a high risk of developing PDPH are young people and women, particularly those who are pregnant.[5,6] The needle size and type are also two important factors that increase the risk.[7,8] The American Academy of Neurology recommends the use of small-scale atraumatic needles and placing the stylet into the needle in retries to reduce the risk of PDPH.[9] Physicians should be fully aware of these factors that increase the risk of PDPH before performing LP.

The symptoms of certain diseases with high mortality, such as meningitis, intracranial hemorrhage, and sinus vein thrombosis, may be similar to the symptoms of PDPH. Physicians should have sufficient knowledge to make a differential diagnosis in patients suspected of having PDPH.

In our study, we aimed to evaluate the awareness of PDPH and the knowledge of its diagnosis and treatment among specialists who applied LP and/or encountered LP complications.

Methods

A prospective questionnaire/scale study was conducted between 01.03.2020 and 15.03.2020. With ethics committee approval (date: 19.02.20, issue no.: 2020/184), a total of 255 local physicians were enrolled, consisting of LP performers (anaesthesiologists, Group A; others, Group B) and those working in departments that do not perform LP but may frequently encounter patients experiencing LP complications (Group C; Table 1). Non-active physicians and general practitioners were not included in the study.

The questionnaire consisted of 17 open-ended and multiple-choice questions for which many had answers ordered within a specific system. The principles of objectivity and avoidance of leading the participant to certain answers were employed when setting the question options. Participants were not asked for private information such as their name or the institution they worked for; we merely collected basic demographic data using simple closed questions. An information letter for the participants on the purpose and nature of the questionnaire was given in its introduction. There was no time restriction for filling out the survey. The questionnaire covered covered topics such as the residency program attended, number of LPs performed, types of needles used, positions applied, awareness of LP complications, knowledge of PDPH diagnosis, treatment approaches, and risk factors.

Physicians were enrolled in the study by emailing them the questionnaire. Support was received from the national anaesthesia association and physician communication networks in the relevant specialties in our province to obtain email contact information for the physicians. Only two questionnaires with incomplete answers were excluded from the study, resulting in a total of 253 sets of data available for analysis.

When reviewing the curricula for specialty education in our country, we found that course contents on intervention, diagnosis, and treatment of PDPH were available for anaesthesiologists and specialty physicians performing LP (Table 2).

Statistical Analysis

Data for statistical evaluation were entered into the Statistical Package for Social Sciences version 24 (SPSS v.24) program. The E-PICOS program was also used to make calculations in line with the MedicReS Good Biostatistical Practice principles. Descriptive statistics were employed for categorical variables, and frequency calculations were expressed in percentage terms. The chi-square test was applied for cross-comparison tables. Independent- and dependent-group *t*-tests were performed for comparison of the mean values. A P value <0.05 was considered statistically significant.

Results

The study included a total of 253 physicians, with 110 (43.5%) in Group A, 110 (43.5%) in Group B, and 33 (13.0%) in Group C.

Table 1. Groups of Physicians According to their Specialty

Group A	Group B	Group C
Anaesthesiology and Reanimation	Neurology	Orthopaedics
	Infectious diseases	General surgery
	Emergency medicine	Urology
	Neurosurgery	Obstetrics and gynaecology
	Paediatrics	
	Internal medicine	Plastic reconstructive and aesthetic surgery

Among the participants, 197 physicians reported performing LP (Group A, n = 104, 52.8%; Group B, n = 93, 47.2%). The rate of those with 50 or more LPs performed was found to be 53.8% (n = 136; Figure 1). More specifically, the rates were 86.4% (n = 95) in Group A and 37.3% (n = 41) in Group B. One physician did not specify the number of procedures performed.

The rates of physicians who stated they had knowledge about PDPH in the questionnaire were 96.4% in group A (n = 106), 77.3% in group B (n = 85), and 39.4% in group C (n = 13). It was determined that the awareness of group A was statistically higher than that of the other two groups (*P*=0.000). Group C was found to be statistically less informed compared to the other two groups (*P*=0.000). A total of 49 physicians (19.4%) stated that they did not have any information on PDPH.

Most (69.6%, n = 16) of the 23 physicians who had not encountered PDPH before were in Group B (p = 0.029; Figure 2). Among the other complications of lumbar puncture that were noted besides PDPH, 47.4% (n = 120) of the physicians reported having encountered lower back pain and 3.95% (n = 10) meningitis.

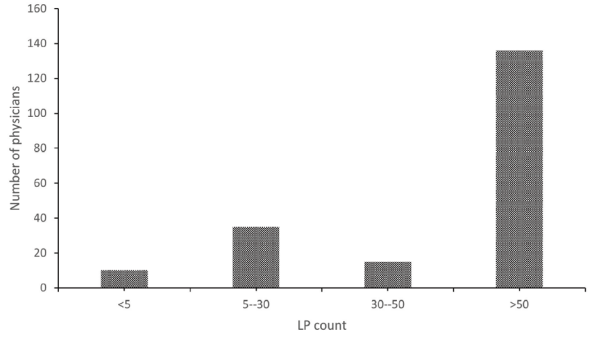

Figure 1. Number of LPs performed by physicians. LP, lumbar puncture.

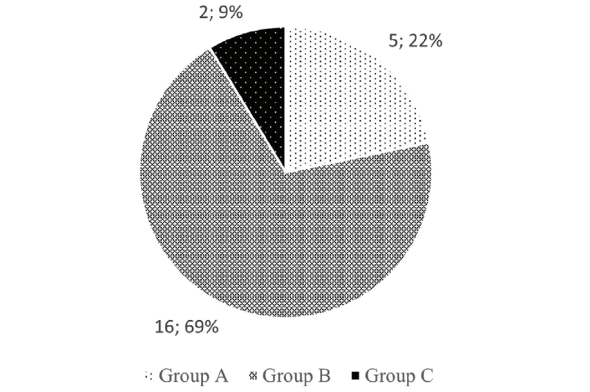

Figure 2. The ratio of those who did not encounter PDPH according to the physician groups. PDPH, post-dural puncture headache. n; %

The physicians were found to use a 25-gauge (G) needle (n = 90, 45.7%) most frequently for LP. Almost all (95.2%, n = 40) of the 42 physicians using a 20-G needle were in group B (Table 3).

Of the 155 physicians who stated their needle type preferences, 74.2% (n = 115) preferred Quincke, 32.2% (n = 50) atraumatic, and 6.46% (n = 10) preferred both. More specifically, 75.5% (n = 83) of those in group A stated that they preferred Quincke and 26.4% (n = 29) atraumatic. The rate of those without any idea about the needle type was 21.3% (n = 42), and all of them were in group B.

Among those who stated that they used only the lateral position for patients during the LP procedure, 7.1% (n =

Table 2. Subject headings and specified competency levels that may be associated with lumbar puncture attempts in the training curricula of the specialties

Specialty	Subject	ICL
Anaesthesiology and Reanimation	Spinal anaesthesia	4
Neurology		4
Pediatrics	Lumbar puncture	4
Infectious diseases	Lumbar puncture	4
Emergency medicine	Lumbar puncture	3
Internal medicine	Lumbar puncture	1
Orthopaedics and traumatology*	Local and regional anaesthesia	1
Urology	-	-
General surgery*	Regional and spinal anaesthesia to be familiar with regional anaesthesia complications	1
Obstetrics and gynaecology*	Regional anaesthesia	-
Plastic reconstructive and aesthetic surgery*	Local and regional anaesthesia complications	-
Neurosurgery*^	General and local anaesthesia applications Approach to the patient with headache	1 1

ICL, Interventional competency levels.
Interventional Competency Levels
1: It refers to the level of having knowledge about how the intervention is performed and making explanations when necessary.
2: It refers to the level of being able to perform this intervention in an emergency situation, in the presence of guidance or instruction or under supervision and control.
3: Refers to the level of being able to perform the intervention in typical, uncomplicated cases.
4: Refers to the level of performing the intervention in all kinds of cases, whether complex or not.
External rotation targets *Anaesthesia rotation, ^Neurology rotation.

5) were in group A, while this rate was 92.9% (n = 66) in group B.

The rate of those who marked the three patient groups at a high risk of PDPH as pregnant, female, and young was 39.1% (n = 99). More specifically, 63.6% (n = 63) of those were in Group A, 30.3% (n = 30) in Group B, and 6.1% (n = 6) in Group C. Group A had a significantly better understanding of the risk groups compared to the other groups (*P*=0.000).

Only one physician (1%) from Group C correctly listed the diagnostic criteria for PDPH determined by the International Headache Society (*P*=0.001; Figure 3).

The only statistically significant difference between the groups was that fewer physicians in group C knew that tinnitus was a supporting criterion compared with the other groups (*P*=0.000) Figure 4.

The knowledge about drugs and methods used in PDPH treatment varied among the groups (Table 4), with epidural blood patch (EBP) being the least known method.

In the differential diagnosis, meningitis was the most considered disease by physicians in all groups (Table 5).

Table 3. Distribution of Gauges of the Preferred Needles for Lumbar Puncture

Gauge	Group A n (%)	Group B n (%)	Total n
26	19 (100)	0	19
25	83 (92.2)	7 (7.8)	90
24	4 (57.1)	3 (42.9)	7
22	28 (46.7)	32 (53.3)	60
20	2 (4.8)	40 (95.2)	42

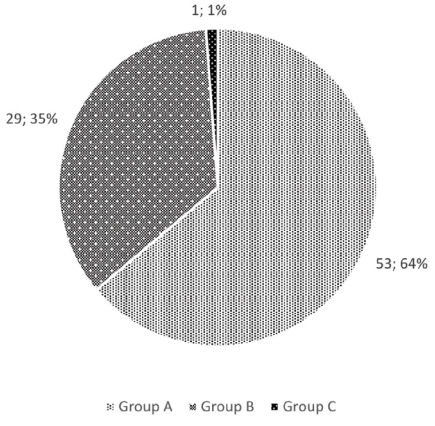

Figure 3. Distribution of those who correctly identified the diagnostic criteria by groups. n; %

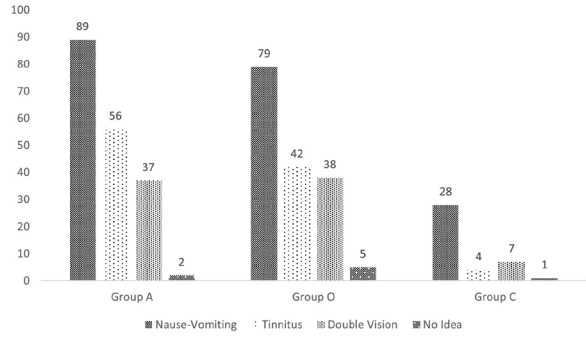

Figure 4. The distribution of those who knew the findings supporting the diagnosis of PDPH by groups. PDPH, postdural puncture headache.

Table 4. Distribution of Those Who Have No Idea About the Drugs and Methods Used in PDPH Treatments, by Groups

	Group A n (%)	Group B* n (%)	Group C n (%)	Total n
Resting	1 (6.6)	7 (46.7)	7 (46.7)	15
NSAID	3 (13.1)	11 (47.8)	9 (39.1)	23
Caffeine	-	6 (50.0)	6 (50.0)	12
Theophylline	10 (18.9)	29 (54.7)	14 (26.4)	53
EBP	5 (8.2)	39 (63.9)	17 (27.9)	61

**P*=0.000, there were more people who did not know in group B compared to group A. EBP, epidural blood patch; NSAID, non-steroidal anti-inflammatory drug.

Table 5. Distribution of Diseases Considered in Differential Diagnosis by Groups n (%)

	Group A n (%)	Group B n (%)	Group C n (%)	Total n
Meningitis	44 (60.3)	21 (28.8)	8 (10.9)	73
Intracranial haemorrhage	17 (56.7)	11 (36.7)	2 (6.6)	30
Hypotension	1 (25)	2 (50)	1 (25)	4
Chronic headache	10 (55.6)	6 (33.3)	2 (11.1)	18
rICP syndrome	3 (37.5)	4 (50)	1 (12.5)	8
Sinus vein thrombosis		10 (100)		10
Spinal abscess		1 (100)		1

rICP, raised intracranial pressure.

Discussion

To our knowledge, this study is the first to compare the awareness levels of PDPH held by different specialist groups. Among the specialist physicians who performed LP or encountered patients experiencing LP complications, it

was found that anaesthesiologists had greater awareness of the risk groups, diagnostic criteria, differential diagnosis, and treatment compared with other groups. However, anaesthesiologists preferred the seated position more than other specialists, although it is among the factors that increase the risk of PDPH. Meanwhile, although other specialist groups frequently performed LP with the patient positioned lying down, they preferred large needle diameters for the intervention, which also increase the risk of PDPH. In addition, it was found that physicians in all specialties had insufficient information about the supporting findings in the diagnosis of PDPH.

It has been reported that the incidence of PDPH varies between 6 and 36% after LP.[10] In our study, the rate of physicians who stated that they had knowledge about PDPH was statistically significantly higher in group A compared with the other groups. We propose that the reason we found a difference in knowledge about PDPH was that anaesthesiologists performed LP more frequently after their residency compared to other groups and therefore were more likely to encounter PDPH at a time when they could apply learnings recently gained through specialty education, thus retaining such knowledge. Additionally, the knowledge of group C was significantly lower. It is obvious that the awareness of group C should be increased in their practice.

The literature contains few studies on the awareness of physicians regarding PDPH. In a survey conducted by Salzer et al.[11], it was reported that only one in eight Swedish neurologists followed the algorithms recommended during LP to prevent PDPH, and two-thirds of the participants were found never to have used atraumatic needles before, a finding similar to that in our study concerning the use of atraumatic needles. Davis et al.[12], meanwhile, showed that the use of atraumatic needles decreases the incidence of PDPH.

Many studies in the literature have stated that large-diameter needles are a risk factor. In one study, 22% of patients were found to develop PDPH with small- and 30.2% with large-diameter needles.[13] In our study, it was found that physicians other than anaesthesiologists preferred large needle diameters. It is possible that these groups of physicians prefer a larger diameter because it enables them to collect more CSF, which supports them with the differential diagnosis of patients, or perhaps they can apply drugs more easily during intrathecal treatment with large needle diameters. As a next step, to refresh the knowledge of these physician groups on the relationship between needle diameter and PDPH, we believe that specialty education institutions should intervene to increase their awareness by creating tailored "recap" training materials.

In another area of research, previous studies investigated the patient position during LP and the development of PDPH. In one study, 125 patients who underwent LP were divided according to the procedure position into lateral and seated positions, and the incidence of PDPH was found to be significantly lower in lateral-position LPs.[14] It was notable that most of the physicians who preferred the lateral position in our study were in group B. However, the same group chose a larger needle diameter, thus increasing the risk of the intervention, which poses a question whether they prefer the position in terms of low risk, ease of application or for another reason. We think that the real reason can be revealed through future studies.

While physicians' experience increases as the number of procedures performed increases, their experience of encountering complications may not increase. In a study by Flaatten et al.[15], clinicians were divided into five groups according to their degree of experience. The researchers then examined the PDPH complications patients developed in a follow-up of 100 LPs they performed, and no significant difference was found between the groups.[16] In our study, it was found that the anaesthesiologists had both better knowledge of PDPH and a higher average count of LPs performed compared to the other groups. However, we cannon comment on whether their LP accordingly resulted in fewer complications because the PDPH frequency was not assessed in our study. Low awareness of PDPH in group C, where physicians never performed LP but monitored patients at risk of LP complications, suggests a serious knowledge deficiency for this group in terms of the condition diagnosis and treatment, which should be overcome through training programs organized by specialist associations.

It has been previously shown that young, female and pregnant patients are in the PDPH risk group.[17] In a study by Khlebtovsky et al.[18] conducted on 144 patients, PDPH risk factors were investigated and the risks for females and young people were found to be statistically significantly higher than those for other groups. In our study, the anaesthesiologists who had the highest knowledge about PDPH were the physicians who knew the risk groups best. Because group C included gynecologists and obstetricians, we thought we would find the best knowledge of high-risk groups among its physicians. However, the findings showed that the level of awareness was the lowest in this group, potentially because physicians in group C do not feel responsible for PDPH treatment.

Evaluation of additional symptoms in the differential diagnosis is important for early diagnosis. Ignoring additional symptoms may delay the diagnosis, result in extra interventional treatment steps, and increase the risk of morbidity. Turnbull et al.[19] reported that symptoms such as nausea/vomiting, tinnitus, and double vision accompanies

PDPH. Of the physicians participating in our study, 22.5% knew these were additional symptoms of PDPH, which indicates that physicians are not sufficiently aware of the additional criteria for the condition.

The most important diseases to be considered when making a differential diagnosis of PDPH are intracranial bleeding and meningitis. Meningitis was identified by 73% of the physicians in this study, while the identification rate of intracranial bleeding was 30%. In the future, we believe that both physicians who perform LP and those who monitor patients who have undergone LP should be made aware of intracranial haemorrhages, which may result in mortality if not diagnosed immediately and treated appropriately.

When non-invasive methods fail in PDPH treatment, the gold standard treatment is the epidural blood patch (EPB).[20] Again, in this study, the majority (63.9%) of individuals who were unaware that EPB is included in the PDPH treatment algorithm belonged to Group B. This finding suggests that awareness that PDPH should be particularly increased in this group. A timely applied EPB prevents morbidity associated with PDPH, and therefore, we believe that its inclusion in the treatment algorithm should be commonly known among physicians.

Study Limitations

The data included in the study were merely self-reported by those who participated in the survey. Furthermore, we surveyed only specialists in a single city, and we could not reach the sample size required to represent each specialty groups nationwide. In a further limitation, the core training objectives for specialization branches in our country have been shaped in the last 10 years; yet, in this study, no grouping was made according to the time when specialty education was completed. Therefore, unfortunately, any difference in knowledge between those educated before and after the curriculum restructuring could not be assessed.

Conclusion

In conclusion, PDPH, the most common complication that follows LP performed for diagnosis or treatment, is a condition with increased morbidity and mortality risk when it goes untreated. In our study, although the rate of PDPH diagnosis was found to be quite high among the physicians who performed LP, the awareness about its differential diagnosis and treatment steps was found to be quite low. We propose that post-specialty training programs should be organized to better educate physicians who will either perform LP or monitor patients who have undergone LP, and the curriculum content in relevant specialties should be reviewed.

Ethics Committee Approval: A prospective questionnaire/scale study was conducted between 01.03.2020 and 15.03.2020. With Mersin University Ethics Committee approval (date: 19.02.20, issue no: 2020/184).

Informed Consent: The eligible patients were informed about the study during the preoperative evaluation and their written consents were obtained.

Peer-review: Externally peer-reviewed.

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Case Report

Cardiovascular and Thoracic Anaesthesia

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Positive Bubble Study But No Evidence of Interatrial Defect in a Patient with Recurrent Cryptogenic Stroke

Nika Samadzadeh Tabrizi[1], Perry A. Stout[1], Joseph Cahill[2], Imran Ramzan Sunesara[3], Patrick Chan[2], Chanderdeep Singh[2], Thomas Fabian[2], Alexander D. Shapeton[4], Sridhar Reddy Musuku[5]

[1]Albany Medical College, New York, United States

[2]Department of Cardiothoracic Surgery, Albany Medical Center, New York, United States

[3]Houston Methodist Debakey Heart & Vascular Center, Houston Methodist Hospital, Houston, United States

[4]Department of Anaesthesia, Critical Care and Pain Medicine, Tufts University Faculty of Medicine, Boston, United States

[5]Department of Anaesthesiology and Perioperative Medicine, Albany Medical Center, New York, United States

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Abstract

Pulmonary arteriovenous malformations (PAVMs) can be asymptomatic or result in a range of complications such as brain abscesses or cryptogenic emboli, which can contribute to morbidity and mortality if not diagnosed and treated in a timely manner. To date, there have been several reports of delayed diagnosis of PAVMs, which have been largely attributed to the misconception that PAVMs are too rare to be of clinical significance. Furthermore, because intracardiac shunting secondary to a patent foramen ovale (PFO) or atrial septal defect (ASD) also results in a positive saline contrast study with echocardiography, PAVM can be easily misdiagnosed as an intracardiac right-to-left shunt. However, there are unique echocardiographic features that differentiate between intracardiac shunting due to a PFO or ASD and extracardiac shunting such as in PAVM. This case details the course of a patient with recurrent cryptogenic strokes that was initially misattributed to a PFO and was only correctly diagnosed with multiple PAVMs after two failed attempts at PFO closure. This case serves as a reminder of an alternative etiology of right-to-left shunt and its presentation on imaging, which echocardiographers must be familiar with.

Keywords: Arteriovenous malformation, echocardiography, ischemic stroke, patent foramen ovale, saline contrast study

Main Points

- Pulmonary arteriovenous malformations (PAVMs) are commonly misdiagnosed, resulting in significant delays in treatment.
- In the clinical setting, PAVMs are not a rare phenomenon, even in patients without any known associated risk factors.
- Expertise in echocardiography in patients with a positive saline contrast study can improve timely diagnosis in this patient population

Introduction

Despite what was previously thought, pulmonary arteriovenous malformations (PAVMs) are relatively common with an estimated prevalence of 1 in 2,600.[1,2] Depending on the degree of shunting, patients can be asymptomatic or suffer from multisystem complications.[1,3] PAVMs increase the risk of cryptogenic stroke by as much as 25% and have a 25-50% risk of mortality if left untreated.[3,4] Alarmingly, the median delay from cerebral event to diagnosis of PAVM and from diagnosis of PAVM to referral for treatment is 2 and 7.5 years, respectively.[1,2] Despite their relative prevalence, PAVMs remain under-recognized in physician education, resulting in misdiagnosis, delayed treatment, and increased morbidity and mortality.[2-4]

Corresponding author: Sridhar Reddy Musuku, e-mail: musukus@mail.amc.edu

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Case Presentation

After obtaining informed consent, this report presents a 50-year-old man with Gilbert's syndrome, alpha-1-antitrypsin deficiency, and chronic obstructive lung disease who initially presented to an outside institution with a left cerebellar infarct. At that time, a saline contrast study was positive for a right to left shunting (RLS), raising suspicion for a patent foramen ovale (PFO) (Video 1). Percutaneous closure was attempted, but interventionalists were unable to traverse the PFO and as a result, the patient was managed with clopidogrel. During the subsequent year, the patient suffered from recurrent strokes and was referred for surgical closure. At our institution, intraoperative transesophageal echocardiography (TEE) did not reveal an interatrial defect but agitated saline injection during Valsalva maneuver was positive for contrast in the left atrium (LA) within 2 cardiac cycles. The coronary sinus (CS) appeared normal, and the surgical team remained suspicious for a PFO. Subsequently, the patient was placed on cardiopulmonary bypass and a right atriotomy was performed. Surgical visualization of the right atrium revealed an intact fossa ovalis with an opening that was much smaller than anticipated without frank interatrial communication. Examination of the interatrial septum, CS, and vena cava was also unremarkable, prompting consultation with a pediatric cardiothoracic surgeon who confirmed these findings. Post-bypass saline contrast study remained positive with a somewhat delayed appearance of the contrast in the LA from the right pulmonary vein (Video 2), raising suspicion for a PAVM.

Upon examination of the right lung, two prominent PAVMs were identified (Video 3), prompting consultation with a thoracic surgeon who performed wedge resection. Subsequent TEE revealed persistence of a positive saline contrast study, with flow primarily originating from the left pulmonary veins, suggesting additional PAVMs in the contralateral left lung (Video 4). At this time, the surgical team closed the incisions and planned postoperative imaging and potential coiling. Postoperative chest computed tomography (CT) with contrast revealed PAVMs in the left lower, right upper, and right middle lobes (Figures 1-4). The patient was subsequently referred to interventional radiology.

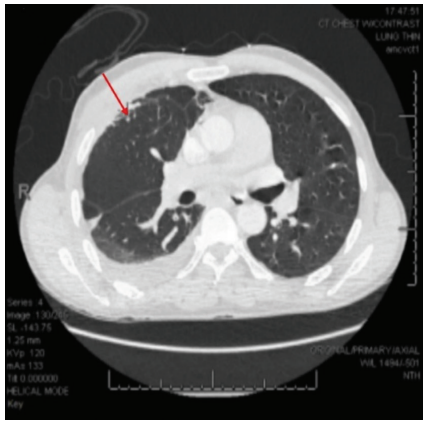

Figure 1. Axial computed tomography with intravenous contrast showing a pulmonary arteriovenous malformation in the right upper lobe measuring 3 mm.

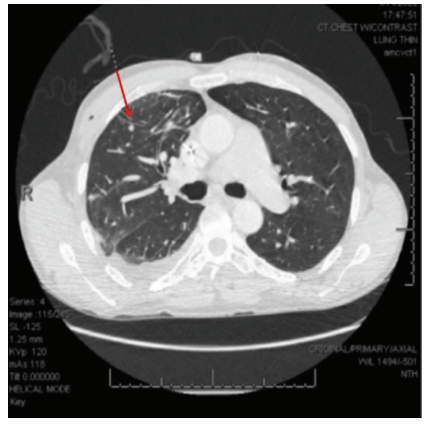

Figure 2. Axial computed tomography with intravenous contrast showing a pulmonary arteriovenous malformation in the right upper lobe measuring 5 mm.

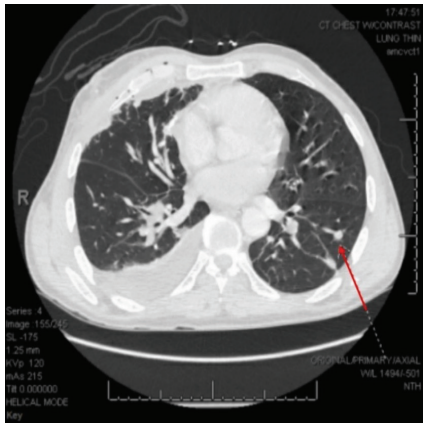

Figure 3. Axial computed tomography with intravenous contrast showing a pulmonary arteriovenous malformation in the left lower lobe measuring 7 mm.

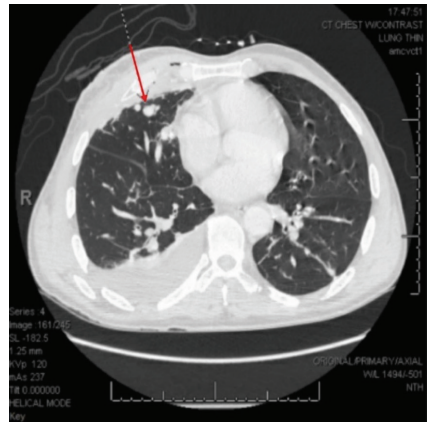

Figure 4. Axial computed tomography with intravenous contrast showing a pulmonary arteriovenous malformation in the right middle lobe PAVM measuring 9 mm.

PAVM, pulmonary arteriovenous malformation.

Discussion

While intracardiac shunting is most commonly the source of paradoxical emboli, it is also necessary to recognize PAVM as an alternative cause. Misdiagnosis dramatically changes the approach to treatment, resulting in delayed care.[5,6] Left untreated, mortality associated with PAVM complications may reach 50%, especially in patients with multiple PAVMs and large feeding arteries.[4] Those with feeding arteries greater than 2.0 to 3.0 mm in diameter are usually treated with percutaneous transcatheter embolization, while larger PAVMs with multiple feeding arteries are treated with thoracoscopic resection.[1,3,5,7] Despite this, long-term follow-up is imperative in this patient population due to possible collateralization and recurrence.[1,8,9]

While PAVMs are most commonly associated with an autosomal dominant condition called hereditary hemorrhagic telangiectasia (HHT), they have also been reported in association with hepatopulmonary syndrome, schistosomiasis, mitral stenosis, previous thoracic surgery, metastatic thyroid carcinoma, and congenital heart disease, with at least 15% of cases attributed to idiopathic causes.[5,9,10] However, PAVMs in the context of non-HHT have not been extensively studied.[2,5] The largest retrospective study of non-HHT PAVMs (n = 77) reported that 61% did not have any known associated risk factors.[9] Despite a history of alpha-1-anti-trypsin deficiency, our patient's hepatic function was within normal limits and he lacked any other risk factors, contributing to his delayed diagnosis.

Saline contrast study with TEE is the gold standard screening test for the evaluation of intracardiac and extracardiac RLS.[5] In RLS due to PFO, it takes 1-2 cycles for microbubbles to appear in the LA in contrast to 3-8 cycles in the case of PAVM.[3,5,11] Visualization of microbubbles in the pulmonary vein (Video 2) may be confirmatory for PAVM. In our patient, the bubbles appeared in the LA within 2-3 cardiac cycles (grade 1 shunt) and became more diffuse and prominent as the cardiac cycle progressed through the 7-9th cardiac cycle (grade 3 shunt) (Video 1).[12] Gradual increase in the number of microbubbles in the LA should not be seen in cases of [atrial septal defects (ASDs)/PFOs]. Our patient had a negative Valsalva and Color flow Doppler across the interatrial septum (Video 1), effectively ruling out a PFO.[4] Further, contrast-enhanced chest CT has utility in excluding PAVMs and has a high sensitivity for those with a grade 2 or 3 echocardiographic shunt.[3,5,13] Therefore, in cases of indeterminate shunting and evidence of high-grade shunt by TEE, further evaluation by CT scan is warranted.

The timing of bubble appearance is also dependent on cardiac output, shunt size, and concomitant intracardiac defect. The bubble appearance can be delayed in cases of a PFO with an aneurysmal atrial septum or hastened in extensive PAVMs, especially when they are located proximally to the heart.[14] In our patient, microbubbles appeared in the LA sooner than 3 cardiac cycles, likely due to multiple PAVMs with large feeding arteries. Recently, researchers used acoustic intensity mapping to quantify the saline contrast patterns that differentiate PFOs from PAVMs.[11] Interestingly, they found that the appearance of contrast in PAVMs has a uniquely longer wash-in/wash-out phase, resulting in a greater contrast intensity in the left-sided heart chambers during the wash-out phase. This contrasts with PFOs/ASDs in which the contrast intensity is always higher in the right-sided heart chambers.

Conclusion

When encountering a patient with a positive saline contrast study, one must consider PAVMs as a potential source given that most PAVMs in the context of non-HHT are idiopathic and cannon be excluded in a patient with cryptogenic emboli.[5,9] In doing so, echocardiographers must familiarize themselves with echocardiography features that distinguish between common and rare causes of RLS.

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Video 1. Transesophageal echocardiographic saline contrast study at the time of the patient's initial percutaneous patent foramen ovale closure attempt at an outside hospital. Mid esophageal (ME) bicaval view with and without color flow doppler demonstrating lack of interatrial communication and color flow across the interatrial septum at a color scale of 46.2. ME bicaval view of saline contrast study demonstrating appearance of microbubbles in the left atrium in 2.5 cardiac cycles. Freeze frames at 2.5 and 7th cardiac cycles demonstrate that the microbubbles become progressively more prominent and diffuse later on in the cardiac cycle.

https://doi.org/10.4274/TJAR.2022.221106.video1

Video 2. Intraoperative transesophageal echocardiographic saline contrast studies at our institution. ME bicaval view demonstrates a delayed appearance of microbubbles in the left atrium from the right pulmonary vein. Mid esophageal coronary sinus view does not reveal any patent foramen ovale or atrial septal defect.

https://doi.org/10.4274/TJAR.2022.221106.video2

Video 3. Surgical view of the pulmonary arteriovenous malformation (PAVM) located in the right middle lung which was resected. The air at the top of the PAVM can be visualized due to its distinctly light-colored appearance.

https://doi.org/10.4274/TJAR.2022.221106.video3

Video 4. Saline contrast study performed after surgical resection of two pulmonary arteriovenous malformations. The study demonstrates a positive contrast study with reduced number of microbubbles in the left atrium, raising concern for additional sources of right-to-left shunt.

https://doi.org/10.4274/TJAR.2022.221106.video4

DOI: 10.4274/TJAR.2022.221038

Case Report
Paediatric Anaesthesia

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Challenging Anaesthesia Management of a Patient with Fryns Syndrome: A Case Report

Celal Kaya, Pınar Kendigelen, Kadir Melih Yılmaz, Ayşe Çiğdem Tütüncü, Güner Kaya

Department of Anaesthesiology and Intensive Care, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

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Abstract

Fryns syndrome cases with variable characteristics require careful preoperative evaluation and have challenges for airway management. Craniofacial anomalies can complicate both ventilation and intubation. Extubation can also be problematic because of limited pulmonary reserves.

Keywords: Airway management, Fryns syndrome, pediatric anaesthesia, perioperative care, regional anaesthesia

Main Points

- Fryns syndrome with craniofacial anomalies should be regarded as candidates for difficult airway and preparations should be made accordingly.
- Anaesthesia and analgesia management must be done with utmost care and patients may require postoperative intensive care, especially for respiratory problems.
- Sugammadex as a reversal agent might be a good choice when there are concerns over airway management.

Introduction

Fryns syndrome (FS) is a rare condition with multiple congenital malformations frequently including congenital diaphragmatic hernia (CDH), together with pulmonary hypoplasia, distal extremity hypoplasia, craniofacial, and internal anomalies.[1] Although surgical interventions for CDH, gastrointestinal anomalies, and cleft palate are carried out in surviving infants, there are inadequate data on anaesthesia procedures for FS in the literature.[2]

Case Presentation

Preoperative evaluation of the 16-month-old 9 kg male, who was in the 8th percentile for weight and 2nd percentile for height, with FS diagnosis showed typical features of coarse broad face, broad and flat nasal bridge, cleft palate, micrognathia, short and thick neck, widely spaced nipples, and hypoplastic extremities (Figure 1).

The patient, without a history of anaesthesia experience, was admitted for Nissen fundoplication following diagnosis of gastroesophageal reflux with frequent aspiration.

Preoperative echocardiography showed a thin (tubular) patent ductus arteriosus and focal septal hypertrophy. The results of laboratory tests were within normal limits. The patient's heart rate (HR) was 145 min^{-1}. There were secretory rales with lung auscultation due to chronic aspiration; his respiratory rate was around 50 min^{-1} and SpO_2 was 96% in the room air.

Corresponding author: Pınar Kendigelen, e-mail: pinarken@gmail.com

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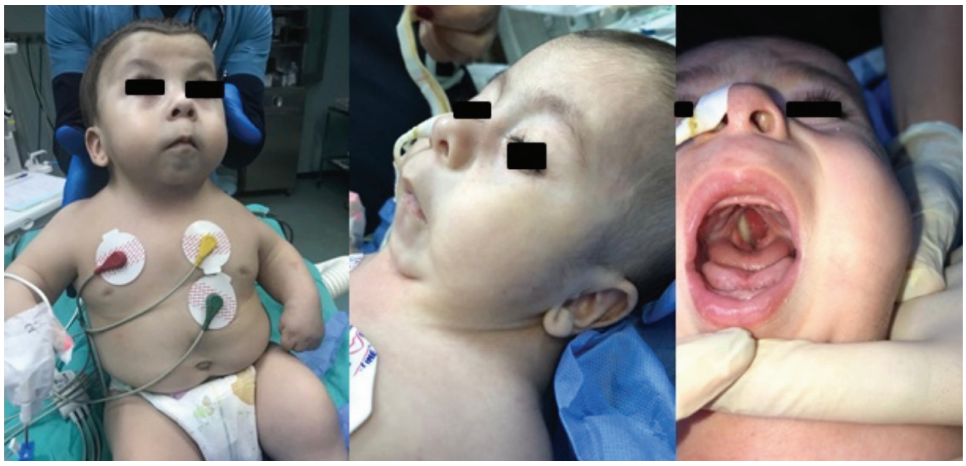

Figure 1. Fryns syndrome with short thick neck, micrognathia, coarse face, hypoplasic extremities and cleft palate.

Considering the patient's neck and lower jaw structures, preparation for difficult intubation including laryngoscope blades, laryngeal masks, endotracheal tubes of various sizes, intubation stylets, and bougie endotracheal introducers was organised. Unfortunately, pediatric flexible fiberoptic bronchoscope was not available, so an ear-nose-throat surgeon was also called for an emergency.

First, a nasogastric tube was inserted and aspirated to avoid pulmonary aspiration, which was followed by anaesthesia induction with inhalational anaesthesia. Following successful face mask ventilation with 6% sevoflurane, a 26-gauge intravenous cannula was inserted and remifentanil (0.5 mg kg^{-1} min^{-1}) infusion was commenced; finally, rocuronium (0.6 mg kg^{-1}, IV) was administered. Neuromuscular monitoring was carried out with train of four (TOF) measurements. Before inhalational anaesthetic, the first TOF ratio was documented as 0.96 and "zero" TOF ratios was observed in the 55th second after rocuronium. Afterwards, intubation was tried using the Macintosh laryngoscope size 1. During the first attempt neither the glottis nor the epiglottis could be seen, so Cormack Lehane classification[3] was recorded as grade 4, but with the head in the sniffing position and cricoid pressure epiglottis and lower arytenoids were observed during second attempt and the trachea was intubated with the bougie, followed by sliding the 3.5 cuffed endotracheal tube over it. Next, the bougie was withdrawn, ventilation was commenced, and the endotracheal tube was fixed at 12 cm depth. Remifentanil infusion was decreased to 0.1 mg kg^{-1} min^{-1}, sevoflurane was maintained at 2%, and IV dexamethasone (0.1 mg kg^{-1}) was administered.

Ultrasound-guided central venous catheterization through the right internal jugular vein was performed. Subsequently, the distance between the skin and the dura was measured at the T10-11 level with ultrasound, which was approximately 18 mm. 6 mL of 0.125% bupivacaine was injected into epidural space with a 20 G Tuohy needle. The epidural space was reached at 15th mm depth.

The total duration of surgery was 180 min. Perioperatively, HR was 100-140 min^{-1}, mean blood pressure was 72-48 mmHg, SpO_2 and $EtCO_2$ ranges were 98-100% and 40-45 mmHg, respectively. Neuromuscular blockade monitoring was achieved and additional rocuronium (0.15 mg kg^{-1}) was administered once during the operation. The patient without distinct haemorrhage was given 320 mL crystalloid intravenously and total diuresis was 50 mL. The operation ended without any complications.

Following 2 mg kg^{-1} IV sugammadex administration, 0.9 TOF ratio, which was used as a threshold for removing the intubation tube, was observed. Then, he was followed up in the recovery room for one hour using a modified Aldrete scoring system. Pain was monitored with visual analog scale score and additional analgesia was not needed after surgery even in the intensive care unit. Despite having an Aldrete score of 10, he was transferred to the pediatric intensive care unit for close monitoring and further treatment. He was transferred to the ward the day after surgery and discharged 2 days later.

Discussion

Patients with FS present with differing clinical symptoms and anatomical defects.[1] In cases indicated for surgery, complete cooperation with the surgical team is of primary importance. Preoperative anaesthesia examination must be performed with utmost care, evaluating all anomalies of the patient.

Given craniofacial malformations, the prospect of difficult ventilation and intubation should be kept in mind and preparations should be made accordingly.[4] Despite being good options for difficult airways, video laryngoscopy

and flexible fiberoptic bronchoscopy may not be available in many hospitals. Unluckily, we did not have them, so laryngoscope blades, laryngeal masks, endotracheal tubes of various sizes, intubation stylets, and bougie endotracheal introducers were prepared. At least two other experienced anaesthetists were also available during the procedure as recommended by studies in literature[4]. However, an ENT surgeon also presented for possible surgical airway in this particular case.

NMB monitoring was performed to make certain decisions about relaxation and complete reversal. The initial TOF ratio was recorded before induction to compare it after reversing with sugammadex. It has been shown that rocuronium-induced neuromuscular block can be fully reversed via sugammadex in a short time, which is comparable with succinylcholine; thus, it is possible to avoid succinylcholine-related side effects. However, there are many studies reporting the use of sugammadex in a "cannot ventilate and cannon intubate" situation.[5,6]

Intravenous cannulation can be difficult with hypoplastic extremities and hypotonia. A short and thick neck with limited extension can complicate central venous cannulation. Ultrasound guided catheterization is a safe approach as we have experienced.

Fluid therapy was maintained according to German guideline.[7] A balanced isotonic electrolyte solution with 1% glucose was administered. The initial infusion rate was adjusted to 10 mL kg^{-1}, then additional balanced isotonic solution was given due to patient loss from the nasogastric tube and surgical area. Fluid responsiveness was monitored with HR, blood pressure, skin turgor, venous blood gas analysis, and diuresis.

CDH is a significant cause of neonatal mortality and the associated pulmonary hypoplasia is frequently encountered in FS. Cases without CDH can present with diaphragmatic muscle weakness and elevated location of the diaphragm, which complicates respiration.[8] In our patient, the diaphragm was elevated, causing tachypnoea and aspiration, which produced secretory rales. Therefore, during perioperative monitoring, possible mechanical complications were circumvented by avoiding high positive end-expiratory pressure and high tidal volume.

Providing effective analgesia is one of our main tasks to ensure rapid and comfortable postoperative recovery. Analgesia can be accomplished by a single dose epidural blockade in such patients.[9] Opioid-spared analgesia was achieved using ultrasound-guided epidural bupivacaine to prevent nausea, vomiting, persistent sedation, and respiratory depression that complicate recovery, which has been a common practice of ours.

Conclusion

Airway management can be challenging for syndromic patients with craniofacial anomalies. All necessary preparations must be done preoperatively. Opioid-spared analgesia achieved via regional techniques and complete antagonism with sugammadex for early extubation may prevent postoperative complications, enabling an early discharge from the hospital.

Informed Consent: Written informed consent was obtained from the parents.

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Letter to the Editor
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Postoperative Anisocoria-need not be Concerned Always

Ashutosh Kaushal[1], Roshan Andleeb[2], Priyanka Gupta[2], Praveen Talawar[2]

[1]Department of Anaesthesiology, All India Institute of Medical Sciences, Bhopal, India
[2]Department of Anaesthesiology, All India Institute of Medical Sciences, Rishikesh, India

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Dear Editor,

Anisocoria in the postoperative period may indicate life-threatening conditions, and the possible causes are intracranial pathologies, Horner syndrome, acute angle closure glaucoma, ocular injury, or pharmacological blockade.[1,2] We report a unique case of postoperative anisocoria in a patient who underwent cervical spine surgery in a prone position with the patient's head secured on a head clamp.

A 30-year-old female patient underwent posterior cervical spine surgery because of a C5-C6 fracture following a road traffic accident under standard general anaesthesia in a prone position with her head secured on a Mayfield 3-pronged head clamp. In preoperative anaesthesia check-up, she was ASA I, had a stable vitals, 15/15 Glasgow coma score (GCS), normal bilateral size reacting pupils, and no neurological deficit. The patient had a history of migraine for five years. The surgery continued for three and a half hours. The intraoperative period was uneventful and there was 100-200 mL blood loss. Before extubation, the right-sided pupil was dilated (7 mm), sluggishly reacting to light, and the left pupil was 4 mm in size, normally reacting to light. Since the patient's head was fixed on a Mayfield 3-pronged head clamp, non-contrast computed tomography (NCCT) was performed to rule out extradural haemorrhage, which was expected. The trachea was extubated as the patient was fully awake and moving all four limbs on command. During her stay in the post-anaesthesia care unit, the vitals and GCS remained normal, but anisocoria persisted. There was no associated headache, orbital pain, ptosis, facial anhidrosis, periorbital oedema, conjunctival chemosis, or lacrimation. Ophthalmology evaluation revealed 6/6 visual acuity in both eyes, normal intraocular pressure, and normal fundus examination. Thus, it was advised to wait for spontaneous recovery. The anisocoria gradually resolved more than one day, and the pupillary reaction also returned to normal. The patient and her relative were asked about any episode of anisocoria before, but they were unaware of it. She was followed up daily until discharge on the 10th day and was uneventful.

Acute angle-closure glaucoma due to raised intraocular pressure may also cause unilateral dilation, but there are associated ocular pain, conjunctival hyperemia, or corneal edema.[3] Horner syndrome also leads to anisocoria, but there is an associated triad of miosis, anhidrosis, and ptosis.[1,2]

Stroke, cerebral oedema, or intracranial hematoma could be the cause of anisocoria. An abnormal NCCT head and GCS deterioration are hard to miss in such scenario.[1]

Inability to maintain a neutral head position causing impaired venous return also leads to unilateral dilated pupil but concurrent exophthalmos due to venous congestion. The accidental direct pressure on the globe in a prone position may lead to postoperative anisocoria when the patients head is kept on a horseshoe headrest.[3]

Corresponding author: Ashutosh Kaushal, e-mail: drashutosh.kaushal@gmail.com

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In this case report, pressure-induced ocular injury could not be the reason for anisocoria because the head was secured on the Mayfield head frame. Pin site epidural hematoma was also overruled in view of normal NCCT head and full GCS. Pharmacological blockade can cause mydriasis without pain, ptosis, or diplopia, but such a dilation usually bilateral.

Adie's pupil is a benign and idiopathic condition in which anisocoria can be precipitated by disruption of the sympathetic-parasympathetic balance.[1,2] All these possible causes were ruled out in our case.

Benign episodic unilateral mydriasis (BEUM) is an isolated benign reason for intermittent pupil asymmetry, which may be associated with migraine. It can be present in migraine without aura or ophthalmoplegia.[4] Functional exhaustion of parasympathetic fibers running within the IIIrd cranial nerve, ischemia or oculomotor nerve demyelination caused by neuropeptides secreted at the level of the circle of Willis upon activation of the trigeminovascular system causing edema and inflammation may explain the reason for mydriasis in ophthalmoplegic migraine.[5] These isolated benign episodic mydriasis have a benign neurological prognosis and do not necessitate further neurodiagnostic workup.

We assumed that it was a rare case of BEUM in the postoperative period in a female patient with a migraine history after excluding all possible causes of anisocoria. Migraine may be precipitated due to stress caused at the time of extubation. More research is needed to fully understand the underlying pathophysiology of BEUM in association with migraine.

Anisocoria during the perioperative period should be thoughtfully evaluated, as etiology ranges from serious life-threatening situations to benign local causes. Anaesthesiologists should be aware of this rare association of anisocoria with migraine in operative settings.

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