EISSN 2667-6370

Turkish Journal of Anaesthesiology & Reanimation

Volume 51 • Issue 4 • August 2023

Official journal of the TURKISH SOCIETY OF ANAESTHESIOLOGY AND REANIMATION

galenos publishing House

turkjanaesthesiolreanim.org

Turkish Journal of Anaesthesiology & Reanimation

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Publisher Contact
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
Web: www.galenos.com.tr **Publisher Certificate Number:** 14521

Publishing Date: August 2023
E-ISSN: 2667-6370
International scientific journal published bimonthly.

Turkish Journal of Anaesthesiology & Reanimation

Aims and Scope

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Chief Editor: Aslı Dönmez
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E-mail: aslidonmez@hotmail.com
Web: www.turkjanaesthesiolreanim.org

Publisher: Galenos Publishing House
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Turkish Journal of Anaesthesiology & Reanimation

Contents

Review Articles

Original Articles

Turkish Journal of Anaesthesiology & Reanimation

Contents

DOI: 10.4274/TJAR.2023.221093

Review Article
Perioperative Care

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):280-289

Vasoplegic Syndrome and Anaesthesia: A Narrative Review

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Cite this article as: Gökdemir BN, Çekmen N. Vasoplegic Syndrome and Anaesthesia: A Narrative Review. *Turk J Anaesthesiol Reanim.* 2023;51(4):280-289.

Abstract

Vasoplegic syndrome (VS) is defined as low systemic vascular resistance, normal or high cardiac output, and resistant hypotension unresponsive to vasopressor agents and intravenous volume. VS is a frequently encountered complication in cardiovascular and transplantation surgery, burns, trauma, pancreatitis, and sepsis. The basis of the pathophysiology is associated with an imbalance of vasodilator and vasoconstrictive structure in vascular smooth muscle cells and is highly complex. The pathogenesis of VS has several mechanisms, including overproduction of iNO, stimulation of ATP-dependent K^+ channels and NF-κB, and vasopressin receptor 1A (V1A-receptor) down-regulation. Available treatments involve volume and inotropes administration, vasopressin, methylene blue, hydroxocobalamin, Ca^{++}, vitamin C, and thiamine, and should also restore vascular tone and improve vasoplegia. Other treatments could include angiotensin II, corticosteroids, NF-κB inhibitor, ATP-dependent K^+ channel blocker, indigo carmine, and hyperbaric oxygen therapy. Despite modern advances in treatment, the mortality rate is still 30-50%. It is challenging for an anaesthesiologist to consider this syndrome's diagnosis and manage its treatment. Our review aims to review the diagnosis, predisposing factors, pathophysiology, treatment, and anaesthesia approach of VS during anaesthesia and to suggest a treatment algorithm.

Keywords: Anaesthesia management, diagnostic and therapeutic approach, perioperative period, vasoplegic syndrome

Main Points

- Vasoplegic syndrome (VS) is defined as low systemic vascular resistance, normal or high cardiac output, and resistant hypotension unresponsive to vasopressor agents and intravenous (IV) volume.
- VS is an essential complication in cardiac and transplantation surgery, burns, trauma, pancreatitis, and sepsis.
- VS is related to highly increased perioperative morbidity and mortality.
- Overproduction of iNO, activation of ATP-dependent K^+ channels and NF-κB, and vasopressin receptor 1A (V_1A-receptor) downregulation are responsible for the pathogenesis of VS.
- Rapid identification and diagnosis of at-risk patients should implement an optimal therapeutic approach.
- Treatment strategies involve IV administration of volume and inotropes, vasopressin, methylene blue, angiotensin II, corticosteroids, hydroxocobalamin, Ca^{++} vitamin C, and thiamine, and should also restore vascular tone and improve vasoplegia.

Introduction

Vasoplegic syndrome (VS) is defined as low systemic vascular resistance (SVR), normal or high cardiac output (CO), and resistant hypotension unresponsive to vasopressor agents and intravenous (IV) volume. VS should be considered when perioperative refractory hypotension develops in cardiovascular and transplantation surgery.[1]

Normal organ and tissue functions are provided by adequate tissue perfusion and oxygen.

Requires adequate mean arterial pressure (MAP), CO, heart rate (HR), stroke volume, CO, and SVR for average systemic circulation. Physiologically, factors that determine hemodynamics are MAP, SVR, and CO. It is defined by the formula [SVR=(MAP-RAP)/CO].[1,2] Studies recommend this component for the diagnosis of VS:

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Received: October 06, 2022 Accepted: February 23, 2023

1) Low SVR (SVR<700 dyn s cm^{-5});

2) Systolic blood pressure <90 mmHg or severe hypotension (MAP) <60 mmHg refractory to vasopressors use (norepinephrine = NE);

3) Unchanged or high CO;

4) Cardiac index (CI >2.2 L min^{-1} m^{-2});

5) Refractory to adequate volume expansion (Table 1).[1,3,4]

VS can also lead to significant organ dysfunction, manifested by systemic tissue hypoperfusion and high lactate, due to insufficient cellular oxygen utilization.[5]

Although no rate is specified in the literature on the overall incidence of VS, it has been reported in all age groups and various clinical circumstances, such as sepsis, cardiopulmonary bypass (CPB), anaphylaxis (including protamine reactions), hemodialysis, all shock states, cardiac arrest, blood transfusion, transplantation, burns, trauma, and pancreatitis.[3,5-8] VS is a common complication of major cardiovascular surgery: The incidence of VS in patients undergoing CPB is between 9% and 44%,[8] and it accounts for 4.6% of all forms of circulatory shock.[6-8] The incidence of VS after heart transplantation ranged between 8.8 and 54% and 42% after pulsatile left ventricular assist device (LVAD) implantation.[3,5,6] The most typical cause of VS in the intensive care unit (ICU) is sepsis. The incidence depends upon the definition used and the patient population under consideration.[5,8-10]

Despite modern advances in treatment, the mortality rate is still 30-50%. VS can lead to systemic tissue hypoperfusion due to insufficient cellular oxygen use. As a result, it leads to multi-organ failure, especially acute kidney injury, resulting in longed duration hospital and ICU stays and raised costs.[6-8,10-12] Thus, VS is associated with increased morbidity in the perioperative period.[7,8,12-16] It is challenging for an anaesthesiologist to consider this syndrome's diagnosis and manage its treatment.

Our review aims to review the diagnosis, predisposing factors, pathophysiology, treatment, and anaesthesia approach of VS during anaesthesia and to suggest a treatment algorithm.

Pathogenesis in Vasoplegic Syndrome

The pathogenesis of VS has several mechanisms, including overproduction of iNO, stimulation of ATP-sensitive K^+ channels and NF-κB, and vasopressin receptor 1A (V_1A-receptor) down-regulation (Figure 1).[5,8-12] The basis of the pathophysiology is associated with an imbalance of vasodilator and vasoconstrictive structure in VSMC and is highly complex and multifactorial.[17] The release of intracellular Ca^{++} from the sarcoplasmic reticulum and an increase in extracellular Ca^{++} via voltage-sensitive channels triggers the contraction of vascular smooth muscle cells (VSMC). The contractile activity of VSMC determines SVR. Intrinsic and extrinsic mechanisms regulate vascular tone. Intrinsic regulators include NO, prostanoids, oxygen free radicals, endothelin-1 (ET-1), and non-endothelial factor as K^+ channel hyperpolarisation, vasoactive metabolites as acidosis, hypoxia, hydrogen peroxide physiologically active substance as (such as serotonin, prostaglandins, thromboxane A_2 (TXA_2), bradykinin).[5,17,18] Extrinsic regulators include epinephrine, vasopressin, angiotensin II, and sympathetic control. NO is an important mediator that regulates vascular function produced from endothelial L-Arginine via NO synthase. NO causes relaxation and vasodilation in VSMC.

Table 1. The Diagnostic Criteria of Vasoplegic Syndrome

SVR <700 dyn s cm^{-5}
SBP <90 mmHg or MAP <60 mmHg
CO ↔/>5 L min^{-1}
CI >2.2 L min^{-1} m^{-2}

SVR, systemic vascular resistance; SBP, systolic blood pressure; MAP, mean arterial pressure; CO, cardiac output; CI, cardiac index

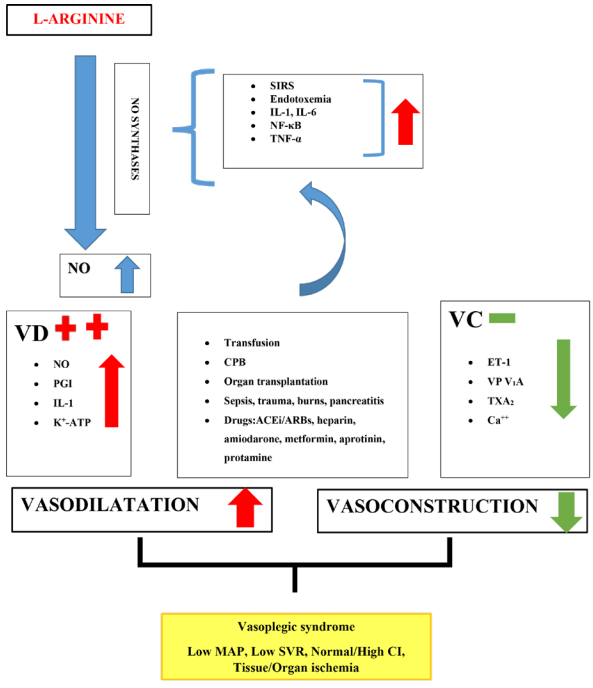

Figure 1. The basic pathogenesis of vasoplegic syndrome.

SIRS, systemic inflammatory response syndrome; IL, interleukin; NF-κB, nuclear factor kappa B; TNF-α, tumor necrosis factor alpha; NO, nitric oxide; PGI, prostacyclin; ET, endothelin; VP, vasopressin V1A; TXA2, thromboxane A2; VD, vasodilatation; VC, vasoconstriction; MAP, mean arterial pressure; SVR, systemic vascular resistance; CI, cardiac index.

In addition, NO prevents coagulation by inhibiting platelet aggregation and adhesion.[18] Prostacyclin (PGI_2) is mainly synthesized in vascular endothelial cells and VSMC. PGI_2 is synthesized from membrane phospholipids via COX-2 and PGI synthase. PGI_2's primary functions inhibit platelet aggregation, effect relaxation, and cause vasodilation via cAMP-protein kinase A in VSMC[19], significantly increasing inflammation.[5,17,19] Overproduction of PGI_2 causes the induction of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 β (IL-1 β), IL-6, pathogen-associated molecular pattern molecules, and lipopolysaccharide.[5,8,10,11] ET-1 activates endothelin A receptors in VSMC released from the endothelium, producing a rise in intracellular Ca^{++} and acting as a potent vasoconstrictor. However, ET-1 leads to an increased pro-inflammatory process in inflammatory stress conditions by activating many signals.[20] TXA_2 is a short-lived prostanoid that increases vasoconstriction and platelet aggregation.[21] As a result, the main reason for the pathogenesis of VS is the decrease in ET-1 against excessive NO release. With the deterioration of this balance, refractory hypotension develops with changes in SVR and CO, and VS occurs with heterogeneous events (Figure 1).[5,8-12]

Perioperative Risk Factors in Vasoplegic Syndrome

Many risk factors increase the development of VS. The most important risk factors are blood transfusion, CPB, transplantation, burns, trauma, pancreatitis, sepsis, and drugs (Table 2).[3,5,8,11-16]

a) Blood transfusion

The first known and essential risk factor for VS is blood transfusion. Transfusion of blood products contributes to the development of VS by inducing inflammation. In addition, blood products used in the treatment of anemia may worsen the condition by activating inflammatory pathways due to their immunomodulatory effects.[22]

Table 2. Risk Factors for Vasoplegic Syndrome
Blood transfusion
CPB
Organ transplantation
Trauma, burns, and sepsis
LVAD
Pancreatitis
ACEi/ARBs use
The use of other drugs: Heparin, amiodarone, metformin, aprotinin, and protamine

CPB, cardiopulmonary bypass; LVAD, left ventricular assist device; ACEi, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers.

b) CPB surgery

VS is frequently seen in 9-44% of patients during or after CPB surgery.[8] The pathophysiologic basis of VS is also based on patient characteristics, comorbidities, and surgical procedures. The contact of blood elements, which starts with surgical trauma, with the foreign surface of the pump system initiates inflammation. In addition, many systems are activated with ischemia/reperfusion injury, hypothermia, endotoxemia, surgical stress, and exacerbation of inflammation with anaesthesia.[5,8] As a result, cytokines (IL-1β, IL-6, TNF-α), complement system, coagulation-fibrinolysis cascade, neurohumoral (bradykinin-kallikrein-kinin system) and endothelial (iNO, PGI_2) factors, and cellular immune system are induced causing systemic inflammatory response syndrome.[8-10] Adjuvant factors other than NO cause VS development by activating ATP-dependent K^+ channels in myocytes and stimulating the release of endothelium-derived hyperpolarizing factor.[5,8-10]

Ultimately, VS is a transient vascular dysfunction caused by inflammation, vasodilation, refractory to fluid replacement, and vasopressors.[5] This causes hypoperfusion and metabolic acidosis. If not treated adequately, it results in high mortality and morbidity.[5-7] If VS continues for 36-48 hours, the prognosis gets worse, and the mortality rate increases by 16-27%.[6-8]

Risk factors for VS during CPB include male gender, higher body mass index, elderly (>65 years), anemia, high EuroSCORE, ejection fraction (EF) <35%, myocardial ischemia, diabetes mellitus, dialysis-dependent renal failure, LVAD use, prolonged of CPB, hypotension soon after the onset of CPB, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) use, infected endocarditis, and the use of inodilators (milrinone, dobutamine, levosimendan) in the perioperative period (Table 3).[8,11-16]

The cardiac anaesthesiologist should evaluate essential risk factors that worsen VS, such as acid-base and fluid-electrolyte disorders, hypothermia, and hypoxia before surgery. Cardiovascular surgery requires a multidisciplinary and comprehensive assessment and management approach.

c) Organ transplantation

Liver and kidney transplantation surgery has a significantly higher risk of developing VS in the perioperative period, which is usually confronted following graft reperfusion.[23,24] VS occurs in 2% to 20% of patients who undergo liver transplantation (LT) and may result in mortality.[23] The cause of VS during LT is multifactorial. The development of VS during the new hepatic phase of LT is an essential challenging clinical scenario, requiring rapid diagnosis and treatment and appropriate management.[23,24]

Hepatic failure is characterized by activation of the renin-angiotensin-aldosterone system and arteriolar vasodilation despite the excessive release of endogenous catecholamines. Hyperdynamic circulation with increased CO, increased HR and SVR, hypotension, and hypovolemia are seen mainly due to vasodilation in the splanchnic circulation in hepatic failure. Portal hypertension causes a significant endothelial change followed by endothelial cell stretching and sheer stress, leading to a rise in endogenous NO, carbon monoxide, and hydrogen sulfide (H_2S) release. This results in VSMC relaxation, decreased SVR, vasodilatation, as well as a deficiency of vasopressin. This condition contributes to VS.[25] Additionally, it contributes to the development of VS during LT in situations such as acidosis, hypothermia, hypocalcemia, bleeding, hyperkalemia, and pre-operative renal dysfunction.[3,5] This hemodynamic deterioration becomes more pronounced during LT, usually requiring a vasopressor, and puts the LT patient at risk.[23]

Transesophageal echocardiography (TEE) can guide evaluation information on cardiovascular function and intravascular volume status, exclude pulmonary embolism and ischemia, evaluate ventricular function, and assess SVR.[26] Considering the diagnosis of VS, necessary vasopressor and other treatments should be promptly started. However, the main goal is to maintain adequate organ perfusion and hemodynamics.[3,5]

Suppose volume replacement and resistance to vasoactive drugs and hemodynamic instability continue after hemodynamic, laboratory, TEG findings, and TEE evaluation. Vasoactive drug selection should be made carefully based on clinical findings. Considering the relative deficiency in liver failure, vasopressin should be considered the first choice.[23,27] MB may be an essential option for us in transplant surgery in post-reperfusion syndrome (PRS) and VS. If PRS continues after graft reperfusion, VS should be considered.[27]

Table 3. Risk Factors for Vasoplegic Syndrome During Cardiopulmonary Bypass

EF <35%
Male gender
Elderly (>65 years)
Higher BMI (>30 kg m^2)
High EuroSCORE
MI
DM
Presence of anemia
DDRF
Presence of LVAD
Prolonged of CPB
Hypotension immediately upon initiation of CPB
Perioperative ACEi/ARB use
Infected endocarditis
Use of inodilators

EF, ejection fraction; BMI, body mass index; LVAD, left ventricular assist device; CPB, cardiopulmonary bypass, ACEi, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers; MI, myocardial ischemia; DM, diabetes mellitus; DDRF, dialysis dependent renal failure.

d) Trauma, burns, pancreatitis, and sepsis

Necessary conditions such as polytrauma, burns, severe pancreatitis, and sepsis cause hypermetabolism, systemic inflammation, and significant tissue damage, thus predisposition to developing VS and organ dysfunction.[28,29]

e) Pharmacologic agents

There are many different categories of drugs used to be associated with VS. Among these, the most common drugs causing are ACEi/ARBs.[3] Drugs such as metformin, protamine, aprotinin, heparin, amiodarone, nitrates, Ca^{++} channel blockers, phosphodiesterase inhibitors, and β-blockers[3,8,10,15] have been reported to cause VS potentially but have not been fully proven; however, administration of ACEi 24 hours before surgery is a reported risk factor for VS with an incidence of 26.9%. It should always be kept in mind that VS may develop in the presence of important risk factors in patients using these drugs and undergoing major surgery.[30]

Monitoring and TEE in Vasoplegic Syndrome

Central venous catheters and intraoperative TEE are routinely used in cardiovascular and transplantation surgery. TEE provides comprehensive information about the heart's anatomy, contraction, ventricular function, and wall motions. If VS is suspected, the first action is to exclude pathologies such as ventricular and valve dysfunction, wall motion abnormalities, ischemia, pulmonary embolism, volume status, or pericardial tamponade. The diagnosis of VS should be confirmed by evaluating these findings observed in TEE and the hemodynamic data obtained from PICCO.[3,5,26] After hemodynamic, laboratory, TEG findings, TEE evaluation, volume replacement, and vasoactive drugs should be considered if hemodynamic instability continues.

Management of Vasoplegic Syndrome

Early recognition of VS is essential for correct treatment and management. That is, the clinician should always consider and confirm VS in the presence of low SVR, hypotension, and standard/high CO.[5,6,11,12] Current treatment strategies include volume and vasopressors administration vasopressin, MB, high dose hydroxocobalamin, angiotensin II, vitamin C, thiamine, and corticosteroids. Other treatments could involve NO inhibitors, ATP-dependent K^+ channel blockers, NF-κB inhibitors, indigo carmine, and hyperbaric oxygen therapy.[11,12,31] When we suspect VS in our clinic during CPB,

organ transplantation, and other surgeries, the diagnosis and treatment are summarized in Figure 2 as indicated and recommended in the literature.[10-12]

Vasoactive Drugs

VS management is based on restoring vascular tone. For this reason, vasoactive agents are preferred first in the treatment. These agents act on various receptors to elevate MAP and SVR. If MAP remains low (<60 mmHg) despite adequate fluid resuscitation, vasopressors should be initiated. It is suggested to start NE or vasopressin as first-line agents to provide systemic perfusion pressure.[5,11,12] These vasoactive agents are of three types depending on their mechanism of action. 1) Catecholamines, 2) Non-catecholamines (Hormones), 3) NO inhibitors (Table 4).[11,12]

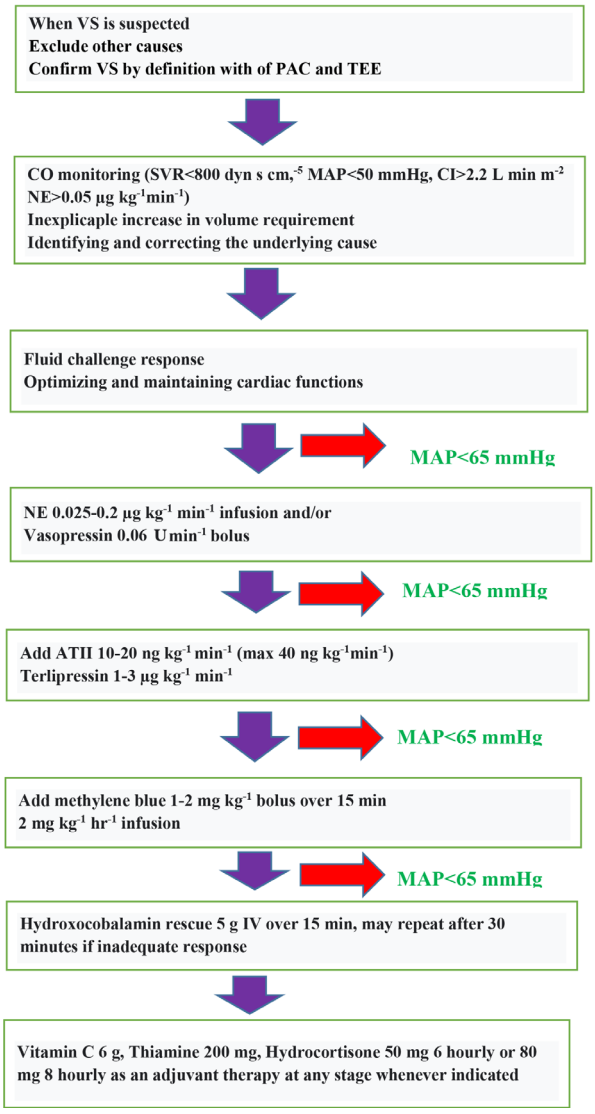

Figure 2. A systematic practical approach to the management of vasoplegic syndrome during anesthesia.

VS, vasoplegic syndrome; PAC, pulmonary artery catheter; TEE, transesophageal echocardiography; CO, cardiac output; SVR, systemic vascular resistance; MAP, mean arterial pressure; CI, cardiac index; NE, norepinephrine.

1. Catecholamines

Catecholamines form the basis of treatment. These drugs induce the contraction of VSMC by stimulating adrenergic receptors and increasing cytosolic Ca^{++}.[5] This group includes NE, epinephrine, phenylephrine, and dopamine. These drugs are agents that increase MAP and should be considered first.[5,10]

2. Non-catecholamines (Hormones)

Vasopressin, terlipressin, and angiotensin II are vasopressors that increase non-adrenergic cytosolic calcium. They are more effective than catecholamines in providing vascular tone without affecting L-type Ca^{++} channels.[11,12]

Volume resuscitation

Determination of volume response is essential in treating VS. In major surgeries, hypovolemia due to bleeding, hypoperfusion, and acidosis may deepen, and VS may be more mortal. According to hemodynamic data, appropriate fluid and blood products should be used cautiously to correct hypovolemia due to bleeding. Optimal perfusion and oxygenation as adequate as possible for tissues and organs should be ensured. However, excessively aggressive volume resuscitation (>20-30 mL kg^{-1}) causes excessive vascular endothelial fluid shear stress, unnecessary systemic pressures, and increased extravascular lung water. Meanwhile, both hypovolemia and hypervolemia are associated with increased mortality and morbidity, and both should be avoided as much as possible.[32,33]

3. Nitric oxide inhibitors

Methylene blue (MB)

MB should be considered an alternative treatment drug in cases resistant to fluid and inotrope in VS.[34] MB reduces NO production by inhibiting iNO synthase and guanylate cyclase, potentially reducing NO concentration and other physiological stress. As a result, MB inhibits NO-mediated phosphorylation of myosin and associated vasodilation, includes coronary vasoconstriction, reduces splanchnic blood flow, and increases pulmonary vascular resistance.[32] Additionally, MB administration has demonstrated an increase in MAP and SVR, a decrease in CI from supranormal level, lower TNF-α concentration, and a gradual reduction in vasopressors requirements.[34] Boluses of 1-2 mg kg^{-1} at VS can usually be given over 10-20 minutes or up to 1 hour. Intravenous administration generally has a terminal half-life of 5-6 hours, and a continuous infusion of 1 mg kg^{-1} hr^{-1} after an initial bolus for up to 48-72 hours without sacrificing splanchnic perfusion may be beneficial.[11,12,32,34] Although adverse reactions are rare with

MB, they can sometimes be severe. This may exacerbate hemolytic anemia due to MB's inhibition of pulmonary vasoconstriction, especially in patients with hypoxia and glucose-6-phosphate dehydrogenase deficiency. In addition, since MB and leucomethylene blue are excreted in the urine, they stain the urine green. MB infusion also has dose-dependent, mild to severe side effects like nausea and vomiting, chest pain, hypertension, interference with pulse oximetry readings without PaO_2, compromised splanchnic perfusion, methemoglobinemia, hyperbilirubinemia, and

Table 4. Drugs Used in the Treatment of Vasoplegia Syndrome

	Mechanism of action	Treatment dose	Outcome benefits
Catecholamines			
Norepinephrine	α_1 receptor agonist	0.02-0.5 μg kg^{-1} min^{-1}	First-line catecholamine to restore and maintain systemic perfusion pressure
Epinephrine	α_1, β_1 receptor agonist	0.01-0.2 μg kg^{-1} min^{-1}	No benefits. Also, the risk of end-organ damage and cardiotoxicity
Dopamine	α_1, β_1, D_1, D_2 receptor agonist	10 μg kg^{-1} min^{-1}	To increase CO and maintain systemic perfusion pressure
Non-catecholamines			
Vasopressin	AVPR1a receptor and blunts NO	0.03-0.04 U min^{-1}	Decreases requirement of other vasopressors, used as a first-line rescue agent, improves the outcome
Methylene blue	Inhibits NO synthesis	2 mg kg^{-1} over 15-30 min^{-1} bolus	Used as preventive and rescue therapy, it decreases the requirement for other vasopressors, and early use reduces mortality
Angiotensin II	Stimulates aldosterone release Increases ADH synthesis, acts on angiotensin type I receptors	2-10 ng kg^{-1} min^{-1} and max. 20-40 ng kg^{-1} min^{-1}	Used in refractory VS by working α1 adrenoceptor agonists Decreases the requirement of other vasopressors
Terlipressin	Selective vasopressin V_1a receptor activator	1.3 μg kg^{-1} hr^{-1} 1 mg bolus	Decreases the requirement of other vasopressors More selective than vasopressin at AVPR1 receptors Decreases rebound hypotension
Hydroxocobalamin (Vitamin B12)	Inhibition of NO directly and iNOS Inhibition of hydrogen sulfide	5 g over 15 min^{-1} max. 10 g	Decreases the requirement of other vasopressors Decreases mortality Used as a rescue agent
Adjuvants			
Ascorbic acid (Vitamin C)	Increases catecholamine and vasopressin synthesis	6 g in divided doses in 24 hr	Synergistic effect with other vasopressors
Thiamine (Vitamin B1)	Cofactor of lactate dehydrogenase (increase in lactate clearance)	200 mg day^{-1}	Prevents conversion of ascorbic acid to oxalate Clears lactate Decreases the requirement of other vasopressors
Hydrocortisone	Increased vascular catecholamine response	Bolus 50 mg every 6 hr or 100 mg every 8 hr Infusion: 10 mg hr^{-1}	A combination of ascorbic acid, thiamine, and hydrocortisone decreases vasopressor requirements and mortality
Calcium	Increased vascular calcium signaling	Bolus: 1-2 g Infusion: 20-50 mg kg^{-1} hr^{-1}	No benefits, but it improves SVR
Sodium bicarbonate	Reverse metabolic acidosis	1-2 mEq kg^{-1}	To combat acidosis

NO, nitric oxide; iNOS, inducible nitric oxide synthetase; ADH, anti-diuretic hormone; SVR, systemic vascular resistance; AVPR1, arginine vasopressin receptor-1; VPS, vasoplegic syndrome.

serotonin syndrome.[32] Finally, MB treatment can improve vascular tone and improve mortality and morbidity in VS.[34]

Other Treatments

Corticosteroids

Corticosteroids guide inflammatory tissue responses, including cytokine release and circulating immune cell function. Corticosteroids probably inhibit the arachidonic acid cascade and the NF-κB transcription factor.[35] These activities are driven by the regulation of many intermediate pathways involving iNOS-mediated NO synthesis and COX-2 activity. Accordingly, these drugs reduce pro-inflammatory cytokine, leukotriene, and endotoxin levels, such as IL-10 increases anti-inflammatory mediators.[5,11,12,35] Corticosteroid receptors are found in endothelial and VSMC, and under normal conditions, they increase the response to circulating catecholamines and angiotensin II.[5,35] Presumably, corticosteroids increase the efficacy of vasopressors by increasing the sensitivity of vascular adrenergic receptors and alleviating the underlying inflammatory process that causes loss of vascular tone.[5,31,35] In the treatment of VS, low doses of corticosteroids seem to increase the vascular response to NE.[5,11,12,31,35] In our clinic, we give low-dose corticosteroids and inotrope in cases where VS develops.

Vitamin C

Vitamin C (ascorbic acid) is a micronutrient that has begun to be used in the treatment of VS. Vitamin C cannot be synthesized endogenously and is an essential cofactor in the biosynthesis of endogenous catecholamines.[36] Vitamin C deficiency in critically ill patients may worsen the clinical picture by decreasing the production of endogenous vasopressors such as NE and vasopressin.[5,36] Vitamin C may reduce inflammation and improve microcirculation with its anti-inflammatory effects. In addition, due to antioxidative properties, vitamin C scavenges reactive oxygen species, decreases NO_S induction, and increases susceptibility to catecholamines by decreasing adrenergic receptors back to baseline conditions. These properties, presumably similar to corticosteroids, may restore systemic vascular tone and reduce the vasopressors needed to maintain hemodynamic goals.[7,31,36-38] It has been shown that administering high-dose IV vitamin C (25 mg kg^{-1} or 1.5 g every 6 hours) can ameliorate hemodynamic changes, inflammation, and body functions in seriously ill patients, even in the absence of vitamin C deficiency.[7,37] However, high doses of vitamin C can cause hyperoxaluria, so it should be carefully monitored.[7,36-38]

Vitamin B12

Vitamin B12 (hydroxocobalamin) effectively scavenges NO released in endothelial blood vessels or diffuses into the perivascular space and reduces NO signals, resulting in reduced vasodilation. Vitamin B12 may also act as a catalyst for vitamin C, and O_2 is applied to inactivate NO signalling in VS.[39] Vitamin B12 has also been shown to increase the clearance of H_2S and endothelial hyperpolarization factors. Although traditionally used in treating cyanide poisoning, the reason vitamin B12 produces raised vascular tone is unknown. A critical side effect of vitamin B12 infusion is increased MAP in patients. Although vitamin B12 can cause chromaturia, its difference from MB is that there is no risk of serotonin syndrome.[40,41]

Non-cardiac surgery

Following major non-cardiac surgery, patients may develop hypotension due to vasodilation. Vasopressors usually need to maintain optimal MAP, with suitable resuscitation to correct hypotension. Hypotension due to sympathetic blockade often occurs in neuraxial blocks. VS should be considered when the need for volume replacement and vasopressors develops against the systemic vasodilator effects of neuraxial blockade.[42]

Discussion

There are many studies on VS in the literature. A systematic review by Egi et al.[43] compared multiple agents in the treatment of VS, including norepinephrine, dopamine, and phenylephrine. They suggested that no particular vasopressor was superior to the others but suggested using a second agent with a different mechanism of action in line with BP targets. Hajjar et al.[9] in the Vasoplegic Shock After Cardiac Surgery study, compared vasopressin and norepinephrine as first-line therapy for the treatment of VS after cardiothoracic surgery, reporting a lower incidence of atrial fibrillation and acute renal failure, as a combined consequence of mortality or serious complications, in the vasopressin group.

Intraoperative MB application has been described widely in the literature. Mehaffey et al.[34] retrospectively analyzed 118 patients who underwent CPB and were given MB in the early (intraoperative) and late (postoperative) period to prevent VS. They reported that mortality and incidence of renal failure were lower in patients who were given MB in the early period compared to those given in the late period, and the results were more positive.[34] We do not provide MB prophylactically in CPB surgery in our clinic, but we use MB for treatment in cases where VS develops. Gunt and Çekmen[44] reported successfully treating MB in a patient who underwent LT and developed VS. Wieruszewski et al.[38] noted in the case series of three cardiac surgery patients that there was a decrease in vasopressor requirements in all three patients after ascorbic acid administration in the treatment of refractory VS. In two patients they reported that they did not need vasopressor support after 24 hours.

Recently, published case reports and series have shown an increase in MAP in patients with VS when hydroxocobalamin is administered at 5 g over 15 minutes.[39,45-48] Shah et al.[39] retrospectively examined 33 patients who had undergone cardiac surgery and reported that hydroxocobalamin administration could provide a beneficial alternative treatment for refractory hypotension and VS, but more controlled clinical studies are needed to evaluate its efficacy.

Currently, no data supports or favours non-catecholamine therapy over other therapies. A balanced approach of catecholamine and non-catecholamine treatments is crucial in managing VS. It may be by allowing more optimal doses to avoid toxicity risks. Based on the best available evidence in the literature, vasopressin may be considered the first-choice agent among non-catecholamine drugs in combination with catecholamines.[11] Jha[49] reported that although vasopressin is recommended for high EF patients with good heart function, NE is preferred for cardiac surgery patients with poor ventricles and low EF.

The basic approach to VS is presented in Table 4.[11,12] Non-catecholamine agents should be started with lower catecholamine doses (0.1 μg kg^{-1} min^{-1}), with vasopressin as the first-line non-catecholamine agent followed by MB. Subsequently, hydroxocobalamin and/or angiotensin II should be used when catecholamine doses are increased to 0.2 μg kg^{-1} min^{-1}.[8,11,12] Care should be taken to identify potential risk factors for intolerance or adverse reaction and to avoid or discontinue the drug with an adverse reaction. In addition, the response to each agent should be evaluated along with the absence of an increase in MAP or the simultaneous up-titration of other agents, and the dose should be adjusted accordingly. Finally, attention should be paid to the titration of adjustable agents to avoid high-dose or prolonged use.[10-12]

Conclusion

VS is a severe and life-threatening condition that continues to challenge anaesthesiologists. When VS is encountered in the perioperative period, the anaesthesiologist should deal with difficulties correctly and effectively. VS is a significant complication that increases morbidity and mortality but is reversible if treated correctly and effectively within the first 6 hours. The use of intraoperative TEE should be considered to establish the diagnosis of VS early and quickly and to rule out other causes in the differential diagnosis. Vasopressors should be started if MAP remains low (<60 mmHg) despite adequate volume administration and optimization of cardiac functions. It is recommended to start NE as a first-line agent to restore and maintain systemic perfusion pressure. An anesthesiologist must consider risk factors, diagnose VS, and manage treatment.

Peer-review: Internally and externally peer-reviewed.

Author Contributions: Concept - N.Ç.; Design - N.Ç.; Literature Search - N.Ç., B.N.G.; Writing - N.Ç., B.N.G.; Literature Review - N.Ç.

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

Funding: The authors declared that this study had received no financial support.

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DOI: 10.4274/TJAR.2023.231264

Review Article
Other

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):290-296

Safety in Healthcare: From the Flight Deck to the Operating Room

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Cite this article as: Fuzier R, Izard P, Petiot E, Jaulin F. Safety in Healthcare: From the Flight Deck to the Operating Room. *Turk J Anaesthesiol Reanim.* 2023;51(4):290-296.

Abstract

The recent health crisis has increased the workload and the stress levels of healthcare professionals around the world. Such stressful working environments are conducive to an increased incidence of medical errors. Implementing education and training specifically focused on human and organizational factors can promote teamwork and decrease the risk of error. Such techniques have been extensively deployed, most notably in commercial aviation. Numerous tools have been developed to reduce the risk of error associated with routine tasks, forgetting a task and handling alarm situations during commercial flights. Many of these tools can be transferred to the healthcare sector. After a brief recap about the importance of the working environment, this narrative review aims to highlight several specific tools used in commercial aviation that can be readily transferred to the operating theatre.

Keywords: Check-list, cross-check, flow, human factors, readback

Main Points

- To improve quality and safety in healthcare environment, it is important to integrate the work on human factors into everyday practice.
- Based on the aeronautics' experience, it therefore seems conceivable to adapt some of these procedures to the healthcare sector.
- The development of non-technical skills (various tools, communication techniques, and teamwork simulation) training courses should be encouraged at the very early training stages of healthcare professionals.
- These tools must be used routinely on a daily basis, in order to be even more effective in stressful situations.
- This review provides useful tools that can be easily and quickly implemented in our healthcare institutes.

Introduction

At a time when the world is faced with the Coronavirus disease-2019 pandemic, healthcare professionals are confronted with work overloads in the context of increased stress levels. These specific work conditions increase the risk of medical errors. In fact, medical errors represent the 3rd leading cause of death in the United States. The vast majority of medical errors do not result from an individual action, but rather from the collective actions, of teams, systems and/or procedures.[1] A lack of awareness of the importance of Human Factors (or more accurately Organizational and Human Factors) as the primary cause of healthcare complications is no longer a matter of debate.[2,3] It is therefore becoming increasingly important to develop non-technical skills to improve safety in the field. Lessons drawn from a range of industries (aeronautics, nuclear power plants, car industry, etc.) can be applied to the medical field, and particularly to surgical and anaesthetic activities.[4] The aviation safety model is the one most often cited as example. Lessons learned from aviation may help reduce operating theatre errors.[5] These practices would need to be adapted by healthcare professionals and tailored to their specific practices.[3] The reason model defines several different types of errors.[6] Specialists are particularly susceptible to routine errors, which

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Received: March 18, 2023 Accepted: April 29, 2023

occur whilst performing routine tasks or simply forgetting to perform a task. The management of alarms also warrants a mention. The objective of this article is to present tools used in commercial aviation that can be readily transferred to the operating room, but also more generally to the healthcare institutions themselves.

The Working Environment

The working environment is a significant independent factor that increases the risk of errors.[7] Numerous components of the working environment can indeed disrupt the ability to concentrate whilst performing a given task, increase the risk of becoming distracted and thereby increase the likelihood of an error occurring. Disturbing any one of the five senses of an operator may affect a healthcare worker's performance in the operating theatre.

In terms of the auditory system, surgery generates many different types of sounds (electric scalpel, electric syringe, suction, ventilation, alarms, telephone, discussions between operators, etc.). Background music is also often played during the operation. The type of music played may induce sleepiness, apathy or conversely excitement. Excessively loud music can interfere with communication, resulting in a word or a phrase being misunderstood or not heard at all. Conversations that are not related to the actual procedure (external phone calls, non-medical discussions, etc.) may also increase the risk of distraction. Smartphone use and the management of personal or professional messages have recently been identified as independent risk factors of reduced vigilance.[8,9] These risks are compounded by lack of sleep, fatigue, taking narcotic drugs or other specific drugs.[10-12] Factors such as hunger and particularly dehydration, further increase these risks (the recommendation in the aviation industry is to drink 1 litre of water every 4 flight hours).

The commercial aviation industry, limits communications below 10,000 feet - approximately 3,000 m (in non-emergency situations). This is commonly known as the "sterile cockpit rule".[13] The choice of words is both specific and conventional. In terms of the visual system, several sources of light may be used in an operating theatre (surgical lamp, ceiling light, desk lamp, lights emitted by computer screens or medical devices, etc.) and may impact performance. Healthcare workers are also exposed to night shifts and sleep deprivation.

These same issues have been investigated in aeronautics. The time allocation of pilots' working hours takes into account biological rhythms and disruptions caused by some types of flights, in particular long-haul flights, and their impact on sleep patterns.

In Europe, work hours in the medical field are defined by European regulations.[14] However in practice, this regulation is not integrated into healthcare organization, with many healthcare workers doing shifts of longer than 12 hours straight, for more than 48 hours a week.[15] The work hours of professional pilots, regulated by the International Civil Aviation Organization, are limited to a fixed number of hours per rolling week: regardless of the actual date, their time on duty never exceeds 60 hours over the previous 7 days.[16] Both in-flight and land-based hours are taken into account and there is little margin for exceeding these hours. Some flights may even be diverted from their final destination to comply with these working hours regulation (on 22 February 2015, flight AF007 from Paris to New-York, was for instance, diverted via Manchester).

Routine Tasks

There are many routine tasks that need to be performed during a flight (entering data into the on-board computer, changing radio frequency, setting heading and altitude, adjusting the altimeter setting, performing weight and balance calculations, etc.). Many of these tasks, which are repeated several times a day, can have devastating consequences if carried out incorrectly. Several procedures have been implemented to limit the risk of such errors. First and foremost, certain instruments are fitted with "mistake proofing" functions. This ensures that any input that does not correspond to the expected value is rejected by the on-board computer. It is also common practice to keep the last communication frequency with the controller on stand-by until a new communication has been established on the new frequency. Cross-checks are another technique which is used to mitigate the risk of error when setting heading, altitude and speed. It requires any changes to these parameters made by the Pilot on Duty (PD) to be confirmed by the Monitoring Pilot. For altimeter settings, checking the concordance of the two altimeter readings is done systematically. Most of these different measures can also be applied to healthcare.

The increasingly widespread use of electronic medical records, including in the operating theatre, may help to improve safety. This type of software should for instance incorporate the option of rejecting absurd entries (e.g., to prevent reversing the patient's weight and height). It is likewise feasible to envisage color-coded caps on vials to eliminate mix-ups during the preparation of specific drugs. Cross-checks may also be readily deployed in the healthcare sector. When a nurse at the Cancer University Institute programs a morphine PCA pump, he/she systematically asks a colleague to confirm that the settings correspond to the prescription. The same applies to the final check of blood type matching before blood transfusions. Similarly, when a nurse assists a healthcare professional and transfers a drug from its original packaging, in addition to reading the name of the drug out aloud, the ampoule or vial label is also systematically shown to the operator. This practice has recently averted the injection of water for injection instead of saline. One last example involves the concordance of

components, namely when preparing medicines before anaesthesia. The vial (or ampoule) is kept until the label stating the name and dilution of the medicine has been placed on the syringe and checked against the label of the vial. This practice ought to be generalized for all syringe and infusion bag labelling. It allows to check that the names are consistent and to identify any potential errors before administration to the patient.

Forgetting a Task

Forgetting a task can have dramatic consequences in certain circumstances. In aeronautics, for example, there are key actions that may result in an accident, if not carried out correctly. Examples include forgetting to extend flaps to the take-off position before taxiing on the runway, forgetting to switch on the engine anti-icing devices in freezing conditions (risk of engine shutdown), forgetting to activate the approach phase during an instrument landing or forgetting to extend the landing gear on the final approach. Accidents caused by such lapses have prompted airlines to put in place procedures to limit the risk of such oversights occurring. The use of checklists is the best-known recourse. The aim of a checklist is to list only a few items, which are deemed essential at specific stages of the flight, and which if forgotten could have potentially dangerous consequences. Manufacturers and airlines have also introduced flows at key stages of the flight. These flows consist of carrying out the same actions, in a set order that remains unchanged, during different phases of the flight for each of the pilots. The repetitive and immutable nature of these flows limits the risk of forgetting an action, even in the presence of disruptive external factors. The system is further complemented with color-coded and audible alarms to help pilots recall their tasks. During maximum thrust at take-off, for instance, an alarm will sound and a red message will appear (warning) if the flaps are not in the correct position, prompting the pilots to abort take-off. The same applies during the final approach, in the event of a landing gear extension oversight (indicator light for each landing gear and audible alarm), triggering a go-around by the pilot before touch down. And finally, when pilots communicate with each other or with the air traffic controllers, the principle of collation is applied. This consists of banning answers such as "yes", "ok" and "agreed" in response to an order. Instead, the information must be repeated, so that the instructing party can ascertain that the recipient of the information has understood the message. This collation principle applies to numerous phases of flight: take-off clearance, heading or altitude changes, clearances etc.

The risk of forgetting a task and its potentially harmful consequences also exists in the healthcare sector. In the operating room, before a general anaesthetic, forgetting to connect the suction, start monitoring, open the oxygen flowmeter, check the functionality of the peripheral venous line, connect the capnograph or adjust the hypnotic agent after induction, are just a few such examples. The frequency of task interruptions is an important component to consider as an additional risk factor which may increase the risk of oversight. These task interruptions are related to interactions between the different participants in an operating room, but also with external parties (colleagues in the operating room, telephone calls, etc.).

Most of the aeronautical tools used and presented at the beginning of this review can be applied to the healthcare sector. The World Health Organization (WHO) has made it compulsory to use a checklist, at specific times, in operating theatres since 2009:[17] before inducing anaesthesia, before surgical incision, and at the end of the operation. To be effective, these checklists must be carried out during an adequate pause and each individual team member must feel implicated by items listed. Where a team considers it necessary, and bearing in mind the reservations mentioned above, it is possible to incorporate a number of additional specific items to these lists. A recent study concluded that the implementation of a specific check-list to standardize handover process in adult patients post-surgery was associated with a reduction in the rate of hypoxemic events in the post-anaesthesia care unit.[18] It is also important to put in place safeguards to limit the risk of task interruptions. In some institutions, staff wear obvious badges when performing specific procedures (e.g. preparation of chemotherapy), which prompts those around them not to interrupt. It is important to train healthcare workers to refuse to be interrupted. One such practice involves raising one's hand to say "wait" or "I am not available right now" or "stand-by" all at the same time. It is also important to be familiar with the rules which apply to interrupting tasks: Knowing when to interrupt (this is essential), knowing how to help the person get back to where they were at the time of the interruption, etc.

The use of flows may also be of interest to the medical field. A visual circuit pointing to blood pressure, oxygen saturation, capnography curve and maintaining anaesthesia ensures that the induction phase of anaesthesia is completed without any complications. A flow can also be used to double check all the connections of a patient's ventilator circuit, from the intubation tube (or laryngeal mask) to the ventilator. Flows may also be applied to connecting an electric syringe pump. It is common practice to give numerous orders to paramedics verbally. To ensure that the information has been correctly understood, we recommend using collation. This means that when a drug is administered, the person receiving the command responds by repeating the name and dosage of the drug, and not simply by saying "ok" or "right".

Managing Alarms

Alarm management is a specific situation associated with a higher risk of error because it occurs in an emergency

context, when stress-levels are increased. Rushing may increase the risk of precipitated decision making and may have final repercussions that are more or less disconnected from the initial objectives. In aeronautics, the first thing taught in such situations is to start by doing nothing and to breathe calmly and deeply for a few seconds, in order to re-equilibrate the sympathetic and parasympathetic nervous systems.There are two types of alarms in the cockpit: "warnings" and "cautions". "Warning" alarms refer to urgent situations that require a certain number of actions to be taken quickly (e.g. jet engine fire). These alarms are indicated by a "red" signal and a distinctive sound. In all cases, the audible alarm should be switched off after the cause has been identified. This enables the alarm to be triggered again in the event of a new incident.

Training on a simulator allows pilots to acquire good practices. Situational awareness is integrated into performance (e.g. managing the flight path to a safe altitude before dealing with the engine fire that occurred on take-off). Each pilot has a well-defined role. Once the first actions are completed and the situation is under control, a number of actions are carried out with the help of "do-lists" which are used to complete the procedure during the secondary phase. The pilots then perform a comprehensive analysis of the situation with team decision support [Time, Facts, Options, Risks, Decision, Execution and Checking (T-FORDEC) of some airlines] taking into account T-FORDEC the implementation. Informing the controller services, the airline, the crew and the passengers is all part of the procedure. These situations are the most stressful. The triggering of a "caution" alarm represents a reduced level of urgency. The signal is visual (amber color) and a single sound is normally emitted. It indicates a situation requiring a rapid response. Generally, the PD manages the aircraft's flight path and communications with the controllers, while the second pilot manages the alarm itself. The second pilot immediately refers to do-lists and ensures that the PD is kept in the loop. The procedure is again completed by a comprehensive analysis of the situation (such as T-FORDEC as previously described).

A similar management of alarms may be envisaged in the healthcare sector. Some healthcare procedures require a rapid response, the equivalent of a warning alarm (e.g. cardiac arrest in the operating theatre). This is when technical skills take over. Once the alert has been raised and resuscitation initiated, the use of "do-lists" may guide the clinicians' diagnostic and therapeutic processes (e.g. by evoking some of the diagnoses applicable after cardiac arrest). The procedure could be completed with the equivalent of a "T-FORDEC" process among all the team members (stopping or continuing the surgical procedure, hospitalization in intensive care, etc.).

There are other healthcare situations which would be more akin to triggering a "caution" alarm (e.g., a power outage of the monitoring system, a drop in fluid pressure, a progressive drop in capnography, etc.). The use of a "do-list" right at the beginning of the procedure would avert the oversight of an important component. The division of tasks (such as management and monitoring of anaesthesia on the one hand and management of the alarm on the other) is perfectly feasible when reinforcements arrive. A discussion on whether or not to continue the procedure and the subsequent transfer of the patient to the appropriate department would complete the process, similarly to aviation type "warning" alarms. Improvements in cognitive ergonomics should be envisaged in healthcare, as alarms are currently not defined at all or are not very clearly defined and are therefore prone to being misinterpreted or of not being clearly understood.

General Discussion

Many tools that focus on managing human factors have been developed to improve safety in commercial aviation. Broadly speaking, the question arises as to whether these tools can also be applied to the healthcare sector.[19] Some teams believe that aviation is not a good model for improving safety in healthcare.[20] Other teams, conversely, go further and stress the importance of digitizing surgical checklists on giant screens, based on current practices in aeronautics.[21] This review attempts to illustrate the benefits of adapting safety culture practices from commercial aviation to healthcare teamwork (Table 1). One of the main research studies addressing this issue was published some ten years ago and demonstrated that using checklists prior to several key stages of surgery decreased perioperative morbidity and mortality.[17] It resulted in the WHO making checklists mandatory in the operating theatre. Subsequent studies later validated the importance of checklists.[22]

In addition to checklists, a number of other tools from aeronautics have been tested in the healthcare sector. This has been the case for debriefings, incident analyses (feedback) and the implementation of team-based resource management [i.e., crew resource management, (CRM)].[23] A meta-analysis specifically demonstrated the positive impact of CRM training on teamwork in the healthcare sector.[24] Other studies have highlighted the benefits of CRM training for anaesthetic teams in terms of improving performance and reducing errors in the operating theatre.[25] The growing interest in further developing CRM training has been confirmed in recent years. There are, however, many different approaches to CRM training in the healthcare sector.[26]

More recent publications have specifically focused on determining the impact of the normalization of deviance, the Swiss cheese model[27] as well as the issue of threats

Table 1. Examples of Tools Derived From Aeronautics that are Applicable to the Operating Room

	Aeronautics	Medicine
"Sterile cockpit"	• Flight below 10,000 feet • Take-off • Landing • Alarms	• Drug preparation • Induction of anesthesia • Emergence from anesthesia • Complex surgery
Coding system	• Wrong ICAO field code inserted in the FMS • Incoherence between left and right QNH settings	• Connection of fluids to the wall socket • Different cap colors for injection and infusion bottles
Cross-check	• Setting heading, speed, altitude • Selection of appropriate check-list	• Setting up a morphine PCA • Identification of drugs transferred from the original packaging
Data concordance check	• Altitude difference between QNH and standard pressure	• Name of drug on the vial and sticker on the syringe • Surgical side concordance between patient's words, medical record and skin mark
Rejection of absurd data	• QNH setting beyond normal range	• Weight and height in electronic patient care reporting
Check-list	• Before start C/L • Before take-off C/L • After take-off C/L	• Before induction of anesthesia • Before skin incision • Before waking-up • Before awake intubation
Flows	• After engine ignition • Before line-up and take-off • Emergency descent	• Connection from airway device (tracheal tube, laryngeal mask…) to ventilator • Visual pattern after intubation to check oximetry, ventilation, blood pressure and anesthesia drug delivery
Readback	• All clearances from ATC • Speed, altitude, heading changes ordered by the ATC	• All orders (drug preparation and/or injection) • Unusual demand

ICAO, International Civil Aviation Organization; FMS, flight management system (computer of the plane); QNH, barometric altimeter setting (height above sea level); PCA, patient-controlled analgesia; C/L, check-list; ATC, air traffic control.

and errors.[28] Accident reporting procedures, such as those advocated in aeronautics by the National Transportation Safety Board, and the use of simulations have been introduced and encouraged, particularly in the field of anaesthesia.[29]

It is therefore important to focus on team training as part of this process. A one-day CRM training session can already improve non-technical skills.[1]

These practices must be complemented by procedural improvements. The importance of standardized protocols for the administration of drugs, the management of analgesia, the management of an emergency such as cardiac arrest, etc., has indeed been emphasized.[30-32] Similarly, electronic systems which issue reminders (e.g. for administering antibiotics) or alerts for allergies or anomalies in the laboratory work-up may also be useful.[33,34]

Conclusion

Given that human error is primarily a loss of human performance in the working environment, it is important to integrate the work on human factors into everyday practice. There is a real need for systems to limit the consequences of these errors. This is exactly the premise upon which CRMs, various other tools, communication techniques, and teamwork simulations have been based in the initial and ongoing training of pilots. The experience gained from aeronautics, has enabled to reduce the risk of the consequences of human errors, it therefore seems conceivable to adapt some of these procedures to the healthcare sector, and also to the initial and ongoing training of healthcare professionals. The development of non-technical skills training courses should be encouraged at the very early training stages of healthcare professionals. These new tools must be used routinely on a daily basis, in order to be even more effective in stressful situations. Ultimately, these approaches are expected to reduce the incidence and impact of medical errors. This review provides useful tools that can be easily and quickly implemented in our healthcare institutes.

Acknowledgements: The authors want to thank Dr. Petra Neufing, Biomedical Editing and Translation in A4 Helix, for her help in the English translation of the manuscript.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - R.F., E.P., F.J.; Design - R.F., E.P., F.J.; Supervision - P.I., E.P.; Literature Review - R.F., F.J.; Writing - R.F., P.I., E.P., F.J.; Critical Review - P.I., E.P.

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

Funding: The authors declared that this study has received no financial support.

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DOI: 10.4274/TJAR.2023.221140

Original Article
Obstetric Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):297-303

Effect of Intrathecal Morphine on Postdural Puncture Headache in Obstetric Anaesthesia

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Cite this article as: Onay M, Şanal Baş S, Işıker A, Akkemik Ü, Bilir A. Effect of Intrathecal Morphine on Postdural Puncture Headache in Obstetric Anaesthesia. *Turk J Anaesthesiol Reanim.* 2023;51(4):297-303.

Abstract

Objective: Intrathecal morphine is used as an effective component of multimodal analgesia in postoperative analgesia in cesarean section patients. We aimed to analyze the relationship between intrathecal morphine administration and postdural puncture headache (PDPH), pain score and analgesia consumption in the postoperative period, and maternal fetal effects.

Methods: One hundred four pregnant women aged ≥18 years (American Society of Anesthesiology physical status I or II, >36 weeks gestation) who were scheduled for elective cesarean section under spinal anaesthesia were included in this study. Spinal anesthesia consisted of bupivacaine with or without morphine (Group M: 10 mg heavy marcaine + 25 mcg fentanyl + 100 mcg morphine; Group F: 10 mg heavy marcaine + 25 mcg fentanyl). The effect of intrathecal morphine on PDPH, postoperative pain score, analgesia consumption, and maternal and fetal effects were recorded for 5 days.

Results: PDPH developed in a total of 33 patients (Group M: 18 and Group F: 15, P=0.274). When we evaluated PDPH with the VAS, there was no significant difference between the groups. The postoperative visual analogue scale (VAS) was lower in the morphine group, and no statistically significant difference was found in the VAS 1st hr and VAS 2nd hr, whereas the VAS 6th hr and VAS 24th hr were found to be statistically significant. There was no difference in terms of PDPH, the first analgesic requirement and postoperative nausea-vomiting, but meperidine consumption was lower in the morphine group.

Conclusion: Low-dose intrathecal morphine did not affect the incidence of PDPH. It is an effective method that can be used in cesarean section patients without increasing the maternal and fetal side effects from postoperative analgesia.

Keywords: Intrathecal morphine, obstetric anaesthesia, postdural puncture headache, postoperative analgesia, spinal anaesthesia

Main Points

- The administration of neuraxial morphine in postoperative analgesia is considered the gold standard and provides superior analgesia compared to systemic practice.
- Epidemiologically, postdural puncture headache (PDPH) is the most common complication and is observed in approximately 10-30% of patients with lumbar puncture, while the risk increases in young and obstetric patients.
- Low-dose intrathecal morphine is an efficient and effective component of multimodal analgesia without increasing maternal and fetal side effects in cesarean section patients.
- Low-dose 0.1 mg morphine had no protective efficacy in reducing PDPH incidence and pain severity.

Introduction

The use of neuraxial techniques has increased because of their safer and postoperative analgesia contribution compared with general anaesthesia at childbirth.[1] Morphine, which is applied with neuraxial blocks (spinal, epidural anaesthesia) during cesarean section, is an effective and easily applicable part of postoperative multimodal

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Received: November 14, 2022 Accepted: June 13, 2023

analgesia. Considering the risk factors for the patient, it is recommended that a low dose of morphine can be used safely in postoperative analgesia during cesarean section when the respiratory monitoring frequency and duration are monitored.[2] Intrathecal morphine exerts its analgesic efficacy through opioid receptors, which are also found in the substantia gelatinosa in the dorsal horn of the spinal cord. The respiratory depression effect of neuroaxial morphine administration is biphasic. In epidurally administered morphine, systemic absorption occurs in the early period (30-90 min), and in epidurally or intrathecally administered morphine, late period effects (6-18 hours) occur with rostral spread into the cerebrospinal fluid and with slow penetration into the brain stem. Its low fat resolution explains why its effect starts slowly and lasts for a long time.[3]

During cesarean section, spinal anaesthesia is the first choice owing to advantages such as simplicity of the technique, rapid application, rapid action start, increased block density, and low risk of systemic toxicity compared to other techniques.[4,5] Epidemiologically, PDPH is the most common complication and is observed in approximately 10-30% of patients with lumbar puncture, while the risk increases in young and obstetric patients.[1] The mother's inability to meet the needs of her baby is a cause of morbidity, which increases the length of hospital stay and health care costs.[6] PDPH is usually benign and not long term but is sometimes associated with chronic headaches and back pain.[7] Recommendations on risk factors and treatment for PDPH have been identified, and the effect of neuraxial morphine on prophylaxis has been discussed.

Our primary objective in the present study was to assess the relationship between low-dose intrathecal morphine administration and postdural puncture headache (PDPH). Our secondary aim was to analyze the need for the first analgesia, meperidine consumption, maternal visual analogue scale (VAS) and side effects (nausea, vomiting, itching, and respiratory depression) in the postoperative period.

Methods

Because of the high incidence of PDPH in the pregnant population, pregnant women who have neuraxial blocks in our clinic are closely monitored, and regular records are kept. This study was planned retrospectively. The data of 128 patients were examined after obtaining approval from the Eskişehir Osmangazi University Non-Invasive Clinical Research Ethics Committee (approval no: 28, date: 12.01.2021). Twenty-four patients were excluded from the study due to missing documents or different doses of morphine administered. Pregnant women aged ≥18 years with a physical classification of American Society of Anesthesiology (ASA) I-II who underwent spinal anaesthesia for cesarean section under elective conditions were included in the study. A fentanyl group (Group F: 10 mg heavy marcaine + 25 mcg fentanyl) and a morphine group (Group M: 10 mg heavy marcaine + 25 mcg fentanyl + 0.1 mg morphine) were included in the study and had standardized doses. The patients' age, body mass index (BMI), gestational week, migraine or other PDPH history, intrathecal opioid (fentanyl and morphine), level of spinal anaesthesia, number of trials, intraoperative hemodynamic response, perioperative complications, postoperative VAS, meperidine consumption and first analgesic requirement, pH of infant blood gas, Apgar score of the baby in the 1st min and 5th min, and PDPH presence and severity were checked from the records. PDPH is defined as bilateral and non-throbbing positional headache, occurring within 5 days after dural puncture, intensifies within 15 minutes in a sitting or standing position, decreases within 15 minutes in a back position and is usually present in the fronto-occipital position. Neck stiffness can be accompanied by vestibular, visual, and auditory symptoms.[8,9]

In our clinic, headache severity is evaluated using the VAS (0 represents no pain and 10 represents the worst pain), and patients are evaluated in the preoperative period. Patients with VAS <4 are considered to have mild headache, and conservative methods, such as bed rest, analgesia, oral caffeine and hydration, are recommended. In the patients who do not respond to these treatments, those who have VAS >4 and those who have challenges in infant care are referred to our algology clinic, and opioids, epidural blood patches or sphenopalatine ganglion blocks may be added to the standard pain control regimen. Clinically stable patients are discharged on the 2nd day following the operation. Although the frequency of the patients who have follow-up evaluations is increased in the first 24 hours, the patient's 5-day follow-up is completed with a phone call.

Statistical Analysis

Assuming that a relative decrease of at least 50% would be necessary to support the clinical usefulness of this treatment, we determined that a sample size of 64 patients in each group would be required to achieve an 80% power to detect this difference between intrathecal morphine and fentanyl administration. Group sample sizes of 64 were required to achieve an 80% power in detecting a difference between the group proportions of 0.25. The proportion in the treatment group is assumed to be 0.5 under the null hypothesis and 0.25 under the alternative hypothesis. The proportion in the control group is 0.5. A superiority trial test was performed using the two-sided Fisher's exact test. The significance level of the test was targeted at 0.05. The sample size was calculated using PASS 11, version 11.0.7, release date June 28, 2011 (NCSS Inc., USA).

Continuous data are given as the average ± standard deviation. Categorical data are given as percentages (%).

The Shapiro-Wilk test was used to investigate the compliance of the data with a normal distribution. In the comparison of the normally distributed variables, an Independent Samples t-test analysis was used to compare the variables between the two groups. The Mann-Whitney U test was used for the comparison of the variables that did not conform to the normal distribution to determine the differences between the two groups. Pearson's chi-squared and Pearson's exact chi-squared analyses were used in the analysis of the created cross tables. Logistic regression analysis was used to determine risk factors. In the implementation of the analyses, the IBM SPSS Statistics 21.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) program was used. A value of $P < 0.05$ was accepted as the criterion for statistical significance.

Results

The study included 104 elective cesarean section patients with ASA I-II. The data of a total of 128 patients were analyzed. Since data from 24 patients were not available, these patients were excluded from the study (Figure 1). The patients were divided based on the doses given and into Group M (Group M: 10 mg heavy marcaine + 25 mcg fentanyl + 0.1 mg morphine) (n = 47) and Group F (Group F: 10 mg heavy marcaine + 25 mcg fentanyl) (n = 57) using the above standard doses. Demographic data (age, BMI, and gestational week), migraine and PDPH history are included in Table 1.

Spinal anaesthesia was administered in the L3-4 or L4-5 vertebral space. The number of attempts and the levels applied were similar between the groups ($P > 0.05$). There was no statistically significant difference between intraoperative hypotension (P=0.94), itching (P=0.89), nausea and vomiting (P=0.53), need for vasoconstrictor (P=0.87), and given fluid volumes (P=0.35).

There was no statistically significant difference in the newborn's blood gas regarding pH (P=0.54) and Apgar score at the 1st minute (P=0.93) and at the 5th minute (P=0.79).

The sensory block, Ramsay sedation scale, and Bromage scale checked postoperatively were similar in the 0th, 1st, and 6th hours. The postoperative VAS scores were lower in the morphine group, and VAS in the 1st hour (P=0.197), VAS in the 2nd hour (P=0.23), VAS in the 6th hour (P=0.01), and VAS in the 24th hour ($P < 0.001$) were statistically significant (Figure 2).

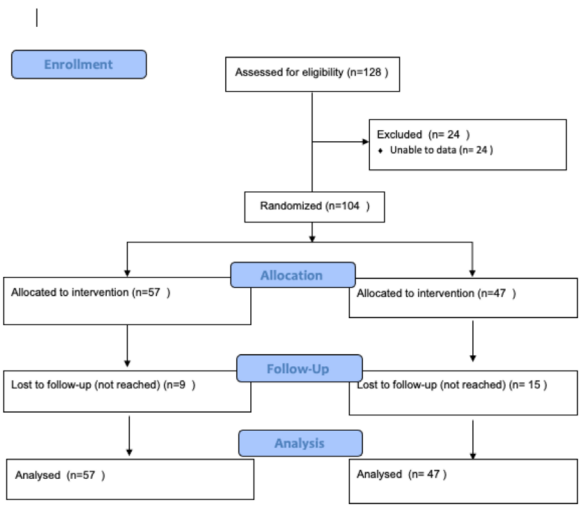

Figure 1. Consort flow diagram of patient flow in the study.

Table 1. Demographic Data

	Fentanyl (n = 57)	Morphine (n = 47)	*P* value
Age (year)	30.6 ± 5.21 30.0 (27.0-34.0)	31.0 ± 4.42 31.0 (29.0-33.0)	0.413*
Body mass index	31.6 ± 5.57 30.9 (27.4-35.8)	29.3 ± 4.71 28.9 (26.1-32.0)	0.0319*
Gestational week	37.4 ± 2.14 38.0 (37.0-38.0)	37.7 ± 1.94 38.0 (37.0-39.0)	0.21*
Migraine Yes No	 8 (14.0%) 49 (86.0%)	 6 (12.8%) 41 (87.2%)	1.00**
PDPH Yes No	 2 (3.5%) 55 (96.5%)	 4 (8.5%) 43 (91.5%)	0.505***

*Independent-Samples t-test; **Pearson's chi-squared test; ***Pearson exact chi-squared test.
PDPH; postdural puncture headache.

There was no statistically significant difference between PDPH, the first analgesic requirement, postoperative nausea-vomiting, hospitalization duration, and patient satisfaction, but meperidine consumption was lower in the morphine group (Table 2). In-group PDPH was analyzed through VAS and was found to be similar between the groups (Figure 3) (Group M: 47 and Group F: 57, n = 104).

The incidence of PDPH was 38.3% (n = 18) in Group M and 26.3% (n = 15) in Group F. PDPH developed in a total of 33 patients, and given the risk factors for PDPH, it was observed that its incidence was increased in those with a history of PDPH (*P*=0.019) and in those with lower arterial blood pressure (*P*=0.017).

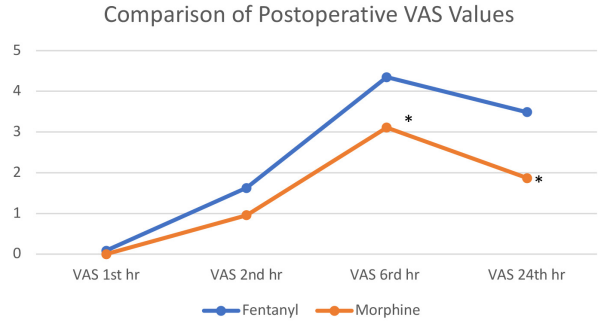

Figure 2. Comparison of postoperative VAS values.

VAS, visual analogue scale.

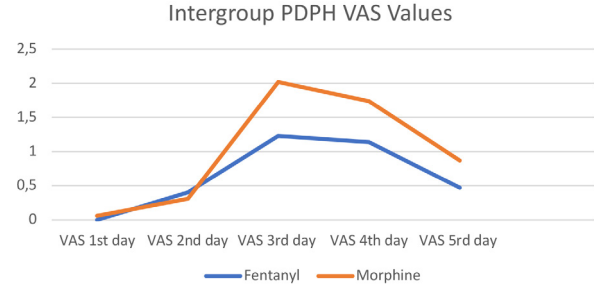

Figure 3. Intergroup PDPH VAS values.

VAS, visual analogue scale; PDPH, postdural puncture headache.

Table 2. Need for Postoperative Analgesia

		Fentanyl (n = 57)	Morphine (n = 47)	*P* value
First analgesic requirement (min)		234 ± 88.4 210 (180-300)	301 ± 149 240 (180-405)	0.0639**
Meperidine consumption				
Yes		44 (77.2%)	23 (48.9%)	**0.00527*** **
No		13 (22.8%)	24 (51.1%)	
Postoperative nausea-vomiting				
None		46 (80.7%)	38 (80.9%)	
Mild		9 (15.8%)	4 (8.5%)	0.331***
Moderate		2 (3.5%)	4 (8.5%)	
Severe		0 (0%)	1 (2.1%)	
Length of stay (days)		2.35 ± 1.06 2.00 (2.00-2.00)	2.13 ± 0.536 2.00 (2.00-2.00)	0.406*
Satisfaction		1.77 ± 0.598 2.00 (1.00-2.00)	1.66 ± 0.600 2.00 (1.00-2.00)	0.334*
PDPH				
Yes		15 (26.3%)	18 (38.3%)	0.274***
No		42 (73.7%)	29 (61.7%)	
PDPH (days)	**1**	0 ± 0	0.0638 ± 0.438	0.271*
	2	0.404 ± 1.60	0.319 ± 1.24	0.898*
	3	1.23 ± 2.43	2.02 ± 2.84	0.119*
	4	1.14 ± 2.26	1.74 ± 2.73	0.241*
	5	0.474 ± 1.47	0 (0-0)	0.57*

*Independent-Samples t-test; **Mann-Whitney U test; ***Pearson's chi-squared test.
PDPH; postdural puncture headache.

Discussion

Neuroaxial morphine is considered the gold standard for postoperative analgesia in cesarean section. In the present study, 0.1 mg morphine was administered only intrathecally for postoperative analgesia, and the effect of low-dose morphine on PDPH incidence was not observed. The postoperative VAS scores were lower in the morphine group, and the VAS in the 6th and 24th hours was especially significant. Complications, such as perioperative nausea-vomiting and itching, were similar between the two groups.

In the present study, in the pregnant women, the spinal blocks were applied with routine 25 G Quincke needles. Conservative treatment was applied in PDPH treatment; only 2 patients from the morphine group were given opioids. PDPH occurs by the transition of BOS from the dural puncture region to the epidural and paravertebral area faster than BOS production. It is the most common complication, with an incidence of 36.5% after dural puncture. Female sex, low BMI, young age, large needle size, needle direction, number of lumbar punctures, and needle design (cutting-tip needles compared to pencil point needles) are risk factors. Twenty-five gauge cutting and noncutting-tipped spinal needles were used in the pregnant women. The incidence of PDPH was shown to be 36.7% in the group in which cutting-tipped needles were used and 6.7% in the group in which non-cutting needles were used.[10,11] Conservative treatments such as analgesics, caffeine, hydration and bed rest can be used in the treatment of PDPH. However, in cases where conservative treatment is not effective in PDPH, the efficacy of prophylactic epidural blood patch, long-term intrathecal catheter placement, epidural or intrathecal morphine and epidural saline is discussed.[8,12] In the morphine group, the incidence of PDPH was similar to that in the present study, and no reduction was observed.

Given an effective volume (10 cc saline) to the epidural space, slow systemic absorption of epidural morphine, and given it twice with an interval of 24-hour suggest that it may be effective in reducing the incidence of PDPH. The effect of epidural morphine on PDPH was evaluated in the Al-metwalli[13] prospective randomized controlled study. The incidence of PDPH was 78-85% after accidental dural puncture with a 17 G epidural needle in obstetric patients. After accidental dural puncture in pregnant women with increased PDPH risk, 3 mg of morphine + 10 cc saline and 10 cc of saline were applied to the control group with a 24 hr interval and were placed at the same or different level of the epidural catheter. The PDPH incidence has been shown to be associated with reducing therapeutic blood patching and delaying the onset of PDPH symptoms in the epidural morphine group. Although the mechanism is unclear, the PDPH incidence decreased to 48% in the saline group and 12% in the morphine group.[13]

Diamorphine has a higher lipid resolution than morphine. It reaches neural tissues faster, and it is less commonly involved in central side effects such as respiratory depression due to the onset time and shortening of the half-life in the BOS.[14] Spinal anaesthesia was performed with a 25 G Whitacre needle in the study, which analyzed 4559 cesarean patients. They were grouped into those who did not receive intrathecal opioids and those who received intrathecal 10-20 mcg fentanyl and 300 mcg diamorphine. The results show that reduced the incidence of PDPH was not associated with intrathecal fentanyl, but with diamorphine.[15]

In the retrospective study by Brinser et al.[16], the patients were classified into Group M, who received epidural or intrathecal morphine during a cesarean section by placing a catheter after dural puncture, and Group C, who did not receive neuroaxial morphine. The act of childbirth (NVD or CS) was not standard. There was no decrease in PDPH risk, severity of headache or need for epidural blood patches in the patients with neuroaxial morphine.[16] Although morphine doses are not standard in the present study, the applied areas (epidural and intrathecal) are different. As a result, there are studies that showed a reduced PDPH risk when an effective volume was given as an epidural.

Intrathecal route was preferred over the neuraxial pathway, and the morphine doses were kept constant. Although analgesic efficacy of intrathecal morphine occurs through opioid receptors in the spinal cord, the effect of rostral spread is attributed to the emergence of undesirable effects. However, systemic absorption factor also disappears when using intrathecal administration. The mechanism to explain the impact of intrathecal administration on PDPH is unclear. In another randomized controlled trial, a single dose of 150 μg administered after accidental dural puncture with a 17 G needle shortly after delivery did not decrease the incidence or severity of PDPH. The etiology of PDPH is multifactorial. That study does not support the clinical usefulness of prophylactic intrathecal morphine after accidental dural puncture, as in our study.[12]

The administration of neuraxial morphine in postoperative analgesia is considered the gold standard, provides superior analgesia compared to systemic practice and does not increase the risk of respiratory depression. With the increased dose, the action time is prolonged, and the maternal side effects increase. However, the perioperative respiratory monitoring period and frequency should be determined based on postoperative complications according to the intrathecal or epidural morphine dose in at-risk patients in particular (cardiopulmonary/neurological comorbidity, obesity (BMI >40), obstructive sleep apnea, sedative agent or chronic opioid use, and magnesium use in preeclamptic pregnancy). Low-dose morphine administration can provide effective analgesia and minimizes undesirable side effects such as itching, nausea-vomiting, and respiratory depression

when combined with multimodal analgesics (non-steroidal anti-inflammatory drugs, acetaminophen, etc.). The recommended intrathecal low dose of morphine in healthy people is >0.05 to ≤0.15 mg, and the epidural dose is <1 mg to >3 mg.[2]

In our clinic, we used fentanyl and a combination of fentanyl-morphine as adjuvant. The sedation scales were similar in the postoperative follow-up, and no patients experienced respiratory depression. The analgesia duration was prolonged with the increased dose, but with low doses of morphine, statistically significant results were achieved at the end of VAS in the 6th and 24th hours. Cesarean section is the most common surgery performed in women worldwide. Postoperative analgesia during cesarean section is important for the mother to be active to meet the needs of the newborn baby in the early period and to support mother-baby communication psychologically.[12,17] The addition of intrathecal bupivacaine and opioids for spinal anaesthesia improves the intraoperative conditions and contributes to postoperative analgesia. The combination of intrathecal morphine and fentanyl is effective and safe in cesarean analgesia.[18] Because of the lipophilic properties of fentanyl, it's effect begins early, and it is 10-20 times more effective than intravenous administration.[19] Intrathecal morphine with an onset time of approximately 30 minutes contributes to postoperative analgesia. Adding lipophilic fentanyl to accelerate the slow action onset improves intraoperative analgesia, reduces the local anaesthetic need, and decreases intraoperative hypotension.[20,21]

In a meta-analysis by Sultan et al.[18], analgesia duration and side effects of morphine at different doses [0.05-0.1 (low dose) and >0.1-0.25 mg morphine (high dose)] in cesarean section cases were analyzed. First analgesic requirement was longer in the high-dose morphine group. First analgesic requirement in the high-dose morphine group was between 13.8 hours and 39.5 hours, while it was between 9.7 hours and 26.6 hours in the low-dose group. Pain scores were not different between the different morphine consumption level groups in the 12th hour and 24th hour. Side effects, such as nausea, vomiting, and itching, were less common in the low-dose group. Having an Apgar score of <7 in the 1st minute was not different between the groups.[18]

In the present study, intrathecal 0.1 mg morphine was administered, and the initial need for analgesia was between 1.5 hours and 7 hours in Group F and 2 hours to 11 hours in Group M. However, the first analgesic requirement was not statistically significant among the groups. Low pain score in Group M in the 6th and 24th hours was statistically significant. The need for postoperative meperidine was significantly lower in Group M. The APGAR score in the 1st min was 8.51 ± 1.28 in Group F and 8.62 ± 0.945 in Group M, and there was no statistically significant difference between the groups. The patients with an APGAR score <7 in the 1st min were included in Group F (n = 3) and Group M (n = 1), and those with pH <7.2 were included in Group F (n = 1) and Group M (n = 1). While low doses of morphine contributed to the reduction of postoperative analgesia and meperidine consumption, no adverse effects were observed in the newborns.

Study Limitations

Our study limitations were that this study was retrospective, and it was a single-centered study. Despite being retrospective, cesarean section patients are closely monitored for postspinal headaches and complications in our clinic, as obstetric patients are at risk for PDPH. Five-day follow-up forms with a high frequency of routine first 24-hour follow-ups were created for the patients. VAS scores were based on the subjective evaluations of the patients, and the evaluations on the 5th day were completed by telephone calls. Our original estimated sample size could not be reached due to the retrospective nature of the study.

Conclusion

In conclusion, there was no protective efficacy of low-dose morphine in reducing PDPH incidence and pain severity. Low-dose intrathecal morphine is an efficient and effective component of multimodal analgesia that does not increase maternal and fetal side effects in cesarean section patients. Further studies are needed to evaluate the effect of morphine on PDPH at different doses and with different routes of neuroaxial administration.

Ethics Committee Approval: Ethical approval was obtained from the Eskişehir Osmangazi University Non-Invasive Clinical Research Ethics Committee (approval no: 28, date: 12.01.2021).

Informed Consent: This study was planned retrospectively.

Peer-review: Internally and externally peer-reviewed.

Author Contributions: Concept - M.O.; Design - M.O.; Data Collection and/or Processing - A.I., Ü.A.; Analysis and/or Interpretation - S.Ş.B.; Writing - M.O.; Critical Review - A.B.

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

Funding: The authors declared that this study has received no financial support.

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DOI: 10.4274/TJAR.2023.221085

Original Article
Obstetric Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):304-310

The Efficacy of Dural Puncture Epidural Performed by 27-gauge Whitacre Needle in Labour Epidural Analgesia: Randomized Single-Blinded Controlled Study

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Cite this article as: Pazur I, Ožegić O, Lijović L, Jaić KK, Pešić M. The Efficacy of Dural Puncture Epidural Performed by 27-gauge Whitacre Needle in Labour Epidural Analgesia: Randomized Single-Blinded Controlled Study. *Turk J Anaesthesiol Reanim.* 2023;51(4):304-310.

Abstract

Objective: Dural puncture epidural technique is refinement of standard epidural technique. Its goal is to overcome drawbacks of standard epidural. We assessed whether dural puncture epidural technique performed by 27-gauge spinal needle would provide higher quality of labour epidural analgesia by using 10 mL epidural bolus of 0.125% bupivacaine. Additionally, the impact of dural puncture epidural on epidural analgesia onset, course of labour and occurrence of maternal side effects was examined.

Methods: We designed prospective, randomized, single-blind study. A total of 76 healthy nulliparous parturients were randomly allocated to dural puncture or standard epidural group. After identification of epidural space, spinal Whitacre needle was used for dural puncture. Intrathecal drug administration was omitted at that point. Both groups received a bolus of local anaesthetic mixture, followed by a continuous infusion of diluted local anaesthetic via epidural catheter. Pain was assessed by numeric pain rating scale. The number of top-ups and mode of delivery were recorded in both groups.

Results: After 10 minutes, there was a statistically significant difference in numeric pain rating scale ≤3 reported (P=0.028), with 97.4% subjects in dural puncture epidural group achieving adequate analgesia after 10 minutes. There was no statistically significant difference in the number of additional boluses, time to delivery, Bromage scale achieved or maternal outcomes between groups.

Conclusion: Dural puncture epidural technique appears to be effective in providing faster onset of epidural analgesia. However, the need for additional boluses remains unchanged. It can be safely used in obstetrics, without deleterious effect on the course of labour.

Keywords: Dural puncture epidural, epidural analgesia, labour pain, neuraxial analgesia, obstetric anaesthesia

Main Points

- Dural puncture epidural technique enables faster onset of epidural labour analgesia.
- The clinical significance of dural puncture epidural technique in obstetrics remains equivocal.
- Dural puncture epidural technique could be helpful in conformation of epidural space.
- It is a safe technique for mother and child.

Introduction

Dural puncture epidural (DPE) technique is a modification of combined spinal epidural, but it is devoid of intrathecal drug administration. It was introduced to obstetric anaesthesia clinical practice in a comparative study done by Chau et al.[1] in 2017. Although epidural analgesia (EA) has been acknowledged as the most effective tool in relieving labour pain and is considered the gold standard in obstetric anaesthesia, the incidence of breakthrough

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Received: September 26, 2022 Accepted: April 25, 2023

pain under EA varies from 0.9 to 25% due to inconsistency in defining breakthrough pain.[2] Slow onset of analgesia, block asymmetry, failed block, and insufficient analgesia in sensory distribution of sacral roots are the most common challenges in attainment of effective EA, especially during second labour stage.[2,3] The aim of DPE in obstetric anaesthesia is to overcome these obstacles in providing satisfactory analgesia in parturients. Dural perforation by a spinal needle allows translocation of local anaesthetic (LA) from epidural space to cerebrospinal fluid (CSF) and greater caudal spread of medications, targeting sacral roots.[4,5] Moreover, it represents additional confirmation that epidural space has been encountered. Notably, the risk of postdural puncture headache (PDPH) is being mitigated by using an atraumatic spinal needle.[6] Primary aim of our study was to investigate whether DPE performed by 27 G spinal needle would provide higher quality of labour EA by using relatively small volume of epidural boluses, namely 10 mL of 0.125% bupivacaine. We hypothesized that the quality of EA would be improved by DPE technique. The secondary goal was to assess the impact of DPE on EA onset, course of labour and occurrence of maternal side effects related to neuraxial procedure.

Methods

We performed a single centre, prospective, single-blinded, randomized controlled study to assess the effectiveness of DPE technique in comparison with standard epidural technique in labour analgesia. The study was conducted in Sestre Milosrdnice University Hospital Centre in Zagreb, Croatia from April 2021 to February 2022 after obtaining Institutional Ethics Board of Sestre Milosrdnice University Hospital approval on the 5th of November 2020 (251-29-11-20-01-6). Trial registration was performed via Australia and New Zealand Clinical Trials Registry (ACTRN12622000976785). The study was conducted in accordance with the Helsinki Declaration. All participants recruited in the study provided written informed consent. The trial was blinded for patients but not for clinical investigators. Due to lack of anaesthesiologists in obstetric ward in our hospital we decided to conduct a single-blinded study with participants who were unaware of group allocation, while the members of anaesthesia team were informed about participant allocation. Seventy-six nulliparous parturients were randomly assigned using sealed opaque envelope technique to receive DPE or standard EA. Patients who met enrolment criteria were aged between 18 and 45 years in active labour with cervical dilatation from 3 to 6 cm at the moment of epidural insertion and with verbal numeric pain rating scale (NPRS) value greater than 3 during an uterine contraction. All parturients were at 38 to 42 weeks of gestation with healthy singleton pregnancy and foetal vertex position, classified as American Society of Anesthesiologists (ASA) physical status II. Exclusion criteria included hypertensive disorders in pregnancy (gestational hypertension, preeclampsia, eclampsia), placental disorders, contraindications for neuraxial anaesthesia, opioid addiction, allergy reaction on drugs used in the study, morbid obesity (body mass index >40 kg m^{2-1}), patient refusal and unintended dural puncture by epidural needle. All procedures were performed by an anaesthesiologist experienced in the field of obstetric anaesthesia, defined as at least ten years of clinical experience.

The local clinical protocol was followed during procedure of epidural catheter placement. All participants were provided with peripheral venous access with 18-gauge cannula and maternal noninvasive blood pressure monitoring and pulse oximetry was initiated. A cardiotocography monitor was placed and monitored by obstetric personnel.

All participants received an intravenous co-loading of 500 mL of saline (0.9% NaCl) infusion before neuraxial procedure. Maternal hypotension was defined as a systolic blood pressure (SBP) less than 100 mmHg and/or a drop of more than 10% compared with the baseline preprocedural SBP.[7] Treatment of hypotension consisted of placement in left or right decubital position and/or administration of vasopressor and additional bolus of fluids. For the purpose of this study we used individual epidural set and spinal kit. Lumbar epidural puncture was performed in a sitting position with an 18-gauge, 8 cm long Tuohy needle (Vygon, 5 rue Adeline - 95440 Ecouen, France), at the level between third and fourth or fourth and fifth lumbar vertebra. Epidural space was identified by using loss of resistance technique with syringe containing 10 mL of saline. DPE parturients received a dural puncture by atraumatic Whitacre needle of 27-gauge and 12 mm of length (Vygon, 5 rue Adeline - 95440 Ecouen, France). Spinal needle was inserted through epidural needle until free flow of CSF was obtained. Afterwards, the Whitacre needle was withdrawn and intrathecal drug administration was withheld. All epidural catheters of 19-gauge were introduced 5 cm into epidural space. Upon epidural catheter insertion and negative aspiration of blood or CSF, all participants were given a test dose (3 mL of 2% lidocaine) to rule out intrathecal epidural catheter placement. After the test dose came negative, EA was initiated with a 10 mL bolus of 0.125% bupivacaine administered over 5 minutes in both groups. We used fentanyl 1.5 mcg mL^{-1}, as an analgesic adjuvant to LA. Analgesia was evaluated by verbal NPRS value between 0 and 10 during an uterine contraction (where 0 indicates no pain and 10 indicates the worst pain imaginable). After completion of epidural bolus (starting point), NPRS values were recorded at 5, 10 and 15 minutes. Further assessments of NPRS, level of sensory blockade and motor function were evaluated and recorded in 60 minute intervals until delivery or earlier on parturient's request. If the pain was still present after 15 minutes had elapsed since

the first bolus, the epidural catheter was withdrawn by 1 cm and a manual bolus was repeated. In case of inadequate response on second bolus or any other bolus given during labour, epidural catheter replacement was discussed with the parturient. Assessment of sensory block was done in each dermatomal level bilaterally for loss to blunt pinprick, cold and light touch sensation from cranial to caudal direction. Targeted upper dermatomal distribution of EA was bilateral Th10 level. The level of motor blockade was assessed by modified Bromage scale after bolus administration. Motor strength was assessed with a modified Bromage score (0 = full flexion of knees and ankles, 1 = partial flexion of knees, full flexion of ankles, 2 = inability to flex knees and partial flexion of ankles, and 3 = inability to flex knees and ankles, 4 = no movement). Examination of NPRS, sensory and motor block was done before and after administration of every additional bolus to ensure adequate analgesia with preserved motor function. The study team member who performed the assessment of sensory and motor function did not perform the block. The value of NPRS equal or less than 3 in the presence of an uterine contraction was defined as adequate analgesia. After the first bolus was given, continuous epidural infusion of 0.08% bupivacaine mixed with fentanyl 1.5 mcg mL^{-1} was immediately commenced at 8 mL per hour in both groups. Breakthrough pain was defined as NPRS >3 despite administration of continuous epidural infusion. The number of additional manual epidural boluses and NPRS values after bolus administration were recorded in both groups. Each bolus consisted of 10 mL of 0.125% bupivacaine mixed with fentanyl 1.5 mcg mL^{-1}. Manual boluses were given by attending anaesthesiologist upon parturient's request. Maximal allowed overall volume of LA mixture administered via epidural catheter was 25 mL per hour. Occurrence of maternal hypotension, pruritus, nausea and vomiting were recorded. Apgar scores were assessed by neonatologists after vaginal delivery and caesarean sections. Other collected data included record of side effects related to neuraxial procedure demanding intervention (hypotension, pruritus, nausea and vomiting), as well as failed conversion to epidural anaesthesia in case of emergency caesarean section. All participants were visited on postpartum day 1 by the member of study team who assessed the presence of headache, low back pain, nerve injury or any other complication related to neuraxial procedure.

Statistical Analysis

Before the beginning of the study, power analysis showed that to achieve the power of 80% with α=0.05 and effect size of 0.5 a sufficient sample size would be n = 32. Normality of distribution of variables was tested using the Shapiro-Wilk test. The differences between quantitative variables were analysed using t-test for normally distributed variables, and Mann-Whitney U test was applied to variables that were not normally distributed. Continuous variables are shown as mean (standard deviation) or median (interquartile range). The differences between qualitative variables were compared using χ^2 (chi-squared) test or Fisher's exact test (for frequencies less than 5), where necessary. Values are presented as number and corresponding percentage, unless specified otherwise. All tests were two-tailed. *P* value of less than 0.05 was considered statistically significant. Statistical analysis was done using IBM SPSS 27.0.

Results

Seventy-eight parturients requesting EA were assessed for the eligibility for the study, two of them were excluded (Figure 1). A total of 76 patients were recruited. The groups were similar at baseline. Our results showed a significant difference in body mass index (BMI) between groups with mean value of BMI in DPE group 27.2 versus 29.7 in EA group (*P*=0.023). Moreover, we did not record cephalad spread of LA above targeted Th 10 level. Participants flow and baseline characteristics are summarized in Figure 1 and Table 1.

No significant difference in adequate analgesia achieved after 5 minutes was measured. After 10 minutes, there was statistically significant difference in NPRS score ≤3 achieved (Fisher's exact test, *P*=0.028), with 97.4% subjects in DPE group achieving adequate analgesia after 10 minutes. However, the NPRS values were comparable between groups after 15 minutes (Figure 2). There was no statistically significant difference in additional boluses applied, time to delivery, Bromage scale achieved, mode of delivery and foetal outcomes between groups. Results are presented in Table 2. None of participants reported adverse reactions related to EA (PDPH, pruritus, hypotension, nausea and vomiting). The presence of CSF flow was successfully confirmed in

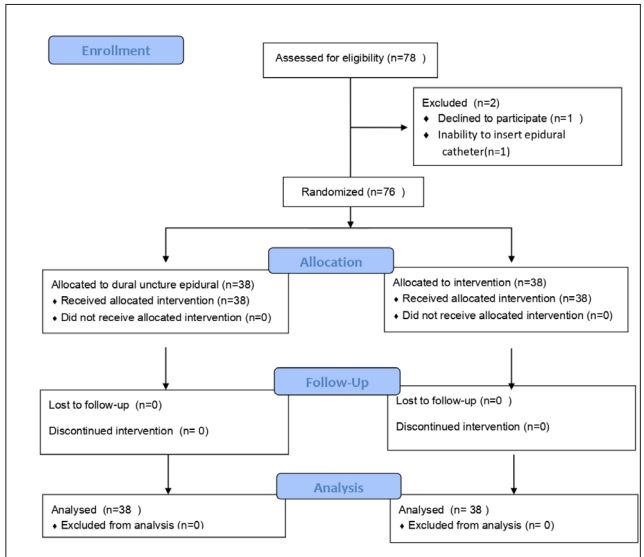

Figure 1. CONSORT flowchart of the patients progress throughout different phases of the study.

Table 1. Subject Baseline Characteristics			
Variable	**DPE (n = 38)**	**EA (n = 38)**	***P* value**
Age, years	31.7 (4.7)	31.5 (5.1)	0.853
Height, cm	169.5 (5.6)	168.3 (5.1)	0.334
Weight, kg	79.5 (15.0)	84.0 (18.0)	0.103
BMI, kg m^{2-1}	27.2 (4.5)	29.7 (5.8)	0.023
Primipara, n (%)	27 (71.0)	27 (71.0)	0.999
Cervical dilation at the time of epidural placement, cm	4.0 (2.0)	4.0 (2.0)	0.385
Initial NPRS score	8.0 (3.0)	8.0 (2.0)	0.932

Values are mean (SD), median (IQR) or n (%). Student's t-test was used for analysis of age, weight and height, and Mann-Whitney U test for analysis of BMI and cervical dilatation. Chi-square test was used for evaluation of parity and initial NPRS score. *P* value of < 0.05 was considered significant.
DPE, dural puncture epidural; EA, epidural analgesia; BMI, body mass index; SD, standard deviation.

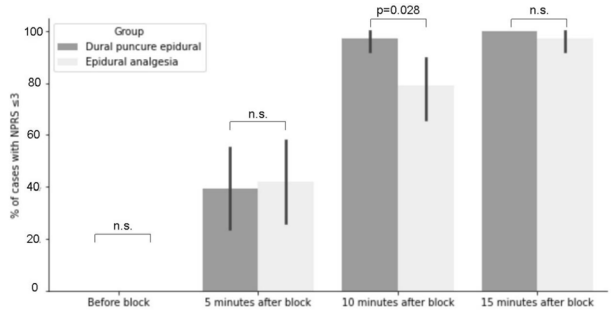

Figure 2. Epidural analgesia quality. NPRS was initially recorded 5, 10 and 15 min after first epidural bolus. Adequate NPRS value, defined as NPRS ≤3, was achieved in 97.4% of participants in subject group after 10 min following initial bolus. However, 5 min later there was no significant difference in NPRS value between groups.

NPRS, numeric pain rating scale.

all parturients in DPE group. There were no episodes of unintentional dural puncture by epidural needle. Also, there was no record of failed conversion to epidural anaesthesia in case of an emergency caesarean section.

Discussion

There is paucity of data regarding the role of DPE in the field of obstetric anaesthesia, while the results of previous researches are often equivocal.[1-4,8-10]

In this randomized clinical trial we examined the effect of DPE in labouring women on EA onset time and quality of EA considering DPE influence on course of labour, mode of delivery and foetal outcome.

Table 2. Neuraxial Block Quality and Maternal Outcomes			
Variable	**DPE (n = 38)**	**EA (n = 38)**	***P* value**
NPRS score after 5 minutes	4.0 (2.0)	4.0 (2.0)	0.631
NPRS score after 10 minutes	1.0 (3.0)	2.0 (3.0)	0.123
NPRS score after 15 minutes	1.0 (2.0)	1.0 (2.0)	0.086
Adequate analgesia achieved			
NPRS score ≤3 after 5 minutes	15 (39.5)	16 (42.1)	0.815
NPRS score ≤3 after 10 minutes	37 (97.4)	30 (78.9)	0.028
NPRS score ≤3 after 15 minutes	38 (100.0)	37 (97.4)	0.314
Additional boluses			
0	22 (57.9)	23 (60.5)	0.451
1	15 (39.5)	11 (28.9)	
≥2	1 (2.6)	4 (10.6)	
Time to delivery (min)	216.5 (180.0)	280.0 (260.0)	0.139
Induction of labour (yes)	29 (76.3)	29 (76.3)	0.999
Bromage scale			
0	28 (73.7)	30 (78.9)	0.309
1	8 (21.1)	8 (21.1)	
2	2 (5.3)	0 (0.0)	
APGAR 1 min <10	4 (10.5)	3 (7.9)	0.692
APGAR 5 min <10	0 (0.0)	0 (0.0)	0.999
Cesarean section	11 (28.9)	12 (31.6)	0.803
Imminent asphyxia	3 (7.9)	1 (2.6)	0.615
CTG disturbance	1 (2.6)	1 (2.6)	0.999
Inadequate analgesia	0 (0.0)	1 (2.6)	0.999
Dystocia	4 (10.5)	2 (5.3)	0.674
Missing data	3 (7.9)	7 (18.4)	-
Vacuum extraction	1 (2.6)	1 (2.6)	0.999

Values are median (IQR) or n (%). Mann-Whitney U test was used for analysis of NPRS 5, 10 and 15 minutes and time to delivery. *P* value of < 0.05 was considered significant.
DPE, dural puncture epidural; EA, epidural analgesia; NPRS, numeric pain rating scale.

The principal finding of our study was that DPE performed by 27-gauge Whitacre needle provided faster onset of adequate labour EA compared to standard epidural technique. However, the number of additional boluses, time from first bolus to delivery, parturients' motor function and Apgar scores did not differ significantly among groups. Our study also showed that the incidence of caesarean

section and instrumented vaginal delivery were comparable between groups as well as the incidence of side effects.

Different sizes of spinal needles, LA concentrations and volumes of epidural catheter boluses and infusions were utilized in previous studies. In general, translocation of epidural medication in subarachnoid space is initiated by creating the dural hole. Intrathecal drug migration is influenced by the speed and the pressure of an injection applied via epidural catheter. Likewise, size of dural hole and volume of epidural bolus may also play important role in transmeningeal flux of anaesthetic drugs. Following this, it can be assumed that larger needle size and higher concentration of LA are related to faster analgesia onset and improved quality of EA but at the expense of compromised motor function and increased occurrence of side effects such as hypotension and pruritus.[2,3] Potentially favourable effect of DPE in labour analgesia has been explained by improved coverage of sacral roots with LA offering better pain relief during second stage of labour. Ideal EA would provide satisfactory analgesia throughout the entire labour, while preserving motor function enabling smooth vaginal delivery.

According to literature, ropivacaine and bupivacaine are equally effective in regard to pain control. Although, ropivacaine showed higher specificity for sensory fibres due to its lower lipophilicity and slower spread to thick motor fibres in comparison with bupivacaine.[11]

However, our decision to use bupivacaine was based on the fact that bupivacaine in low doses (0.125% or less) has proved to be a safe LA in labour EA and is related to fewer additional top-ups in comparison with ropivacaine.[11-13]

Although epidural opioids are considered safe for mother and child, the effect of neuraxial opioids on foetal heart rate still remains a matter of debate.[14] In our study fentanyl was administered as an analgesic adjuvant in slightly lower dose then in the majority of previous studies,[1,15,16] namely 1.5 mcg per mL according to our local institutional protocol. We chose this approach trying to minimize the risk of foetal bradycardia and maternal pruritus.

There is a lack of consensus in literature whether to give test dose in labour analgesia or not. Moreover, there is heterogeneity in concentration, volume and type of LA used as a test dose.[17] In the study by Yadav et al.[15] after identification of epidural space, test dose was not administered. Instead, upon epidural catheter placement, epidural bolus of LA was immediately given in fractionated manner, using small aliquots of low concentration of LA as an alternative to traditional test dose. In our study, a test dose consisting of 3 mL of 2% lidocaine without adrenaline, was given prior the epidural bolus as part of local institutional protocol. Administration of test dose was devoid of any complications in terms of intravascular injection, high spinal or motor weakness of lower extremities.

To the best of our knowledge, in comparison with previous studies in the field of labour DPE, we used the smallest volume of bupivacaine as an induction dose for labour EA (namely, 10 mL of 0.125% bupivacaine). Unlike the majority of published studies, in our research larger volume of additional top-ups were deploy. The rationale for this is as the labour progresses and second labour stage begins, larger volume of single top-up is necessary to enable spread of LA around sacral roots which innervate birth canal. In contrast to previous studies which utilized patient controlled EA (PCEA), we decided to deploy a combination of manually given boluses on parturient's request with continuous infusion of LA via epidural catheter. We opted for this approach because PCEA devices are not available in our facility.

Our choice to use 27-gauge Whitacre needle was based on results obtained in the study by Contreras et al.[18] They showed that DPE with 25-gauge pencil point needle enabled 1.6 min shorter onset of EA in comparison with 27-gauge pencil point needle. Nonetheless, authors concluded that this result was of vague clinical relevance.[18]

Moreover, young pregnant woman are at very high risk for development of PDPH which is associated with long-term morbidity (persistent headache and backache) and some possibly life-threating complications (cerebral haemorrhage, dural sinus thrombosis).[19,20] Considering these facts, we decided to test the efficacy of 27-gauge Whitacre needle in DPE procedure as more favourable option in comparison with larger spinal needle size.

Recent studies obtained faster onset of adequate EA in DPE group regardless of spinal needle size. Concerning request for additional top-ups and course of labour, most of authors showed no significant difference among DPE and standard epidural. Song et al.[21] found that a combination of DPE with programmed intermittent epidural boluses showed most favourable results regarding EA onset, number of additional boluses and LA consumption.

According to Yadav et al.,[15] higher quality of EA was reported in DPE group. The number of parturients achieving adequate analgesia in 5 and 10 min was significantly higher in DPE group than in control group.[15] Although we used similar protocol, in our study significantly higher number of parturients reported adequate analgesia in DPE group only 10 min after first epidural bolus. The possible explanation could lie in the fact that study by Yadav et al.[15] and our trial were conducted on different type of population (Indian versus European). Also, there was difference in LAs

(ropivacaine versus bupivacaine) as well as in mode of LA delivery (solely epidural boluses versus epidural boluses in addition to continuous epidural infusion of LA and opioid).

Thomas et al.[16] pointed out that when no CSF returned from the 27-gauge spinal needle after an attempted dural puncture, the catheter inserted into the epidural space might be less functional with a higher replacement rate. Nevertheless, EA quality was not improved in DPE group.[16] Potential beneficial effect of DPE was examined in population of obese parturients (BMI >35 kg m^{2-1}) who are at higher risk for epidural failure, so the dural puncture technique may have particular utility in this population. Authors showed no additional benefit of DPE to support routine use of DPE in obese parturients.[22]

Cappiello et al.[23] demonstrated improved quality and onset of EA with DPE with 25-gauge spinal needle but at the cost of increased incidence of instrumented vaginal delivery. This might be explained by using larger spinal needle size and higher concentration of LA (0.25% bupivacaine bolus followed by 0.125% bupivacaine epidural infusion).[23] Chau et al.[1] also utilized 25-gauge needle in their study, comparing efficiency of DPE with epidural and combined spinal epidural techniques (CSE). Contrary to majority of studies in this field, they found no difference in analgesia onset between DPE and standard epidural technique, while most rapid onset of analgesia was recorded in CSE group. This could be attributed to the large volume of initial epidural bolus (20 mL of 0.125% bupivacaine) applied in both groups, DPE and standard epidural technique. Parturients' motor function remained preserved probably due to lower LA concentration (0.125% bupivacaine bolus and infusion). Notably, DPE provided improved block quality in comparison with standard epidural and fewer maternal and foetal side effects than the CSE technique. In our study, we did not find increased incidence of side effects related to DPE.

The reason why we did not achieve more beneficial effect of DPE might be explained by the fact that we used low concentration of LA mixture, along with relatively small volume of LA bolus in comparison to some studies in which boluses up to 20 mL were utilized.[1] We decided for aforementioned approach trying not to jeopardize the obstetric outcome by provoking assisted vaginal delivery.[24,25]

Study Limitations

This study does have some limitations. Exact time of EA onset is sometimes difficult to establish considering that we assessed the pain during uterine contractions which could occur in irregular intervals.[26] Moreover, in our opinion, it is difficult to precisely assess the pain by the conventional diagnostic tools (visual analogue scale, NPRS, etc.) in labouring women population. A second limitation is the lack of blinding. However, all NPRS assessments were done by a member of anaesthesia team not directly involved in the epidural catheter placement and participants were unaware of group allocation.

In our opinion, DPE provides faster onset of EA regardless of the spinal needle size. We consider DPE as a valuable tool in confirmation of subarachnoid space, which strongly indicates that the tip of epidural needle is in epidural space. What remains to be established is the optimal combination of spinal needle size, dosing regimen of epidural boluses and the concentration of LA.

Conclusion

In conclusion, DPE provides faster onset of adequate labour EA by using 27-gauge Whitacre needle. However, the clinical importance of this finding is uncertain. We deem that quality of labour EA is not improved, because the request for additional epidural boluses alongside continuous epidural infusion of a LA and an opioid remains unchanged compared to standard epidural technique. It possesses no adverse effect on the course of labour.

Ethics Committee Approval: Ethical approval was obtained from Institutional Ethics Board of Sestre Milosrdnice University Hospital on the 5th of November 2020 (251-29-11-20-01-6).

Informed Consent: All participants recruited in the study provided written informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - I.P.; Supervision - K.K.J.; Fundings - I.P.; Materials - L.L.; Data Collection and/or Processing - I.P., O.O., K.K.J., M.P.; Analysis and/or Interpretation - I.P., O.O., L.L.; Literature Review - I.P., O.O., K.K.J., M.P.; Writing - I.P., O.O.; Critical Review - O.O., L.L., K.K.J., M.P.

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

Funding: The authors declared that this study has received no financial support.

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DOI: 10.4274/TJAR.2023.221071

Original Article

Pain

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):311-317

Assessment of Factors Affecting the Preference of Pain Medicine Subspecialty Choices and Training Course in Turkey: A Cross-Sectional Survey Study

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Cite this article as: Bayramov T, Çetingök H, Köknel Talu G. Assessment of Factors Affecting the Preference of Pain Medicine Subspecialty Choices and Training Course in Turkey: A Cross-Sectional Survey Study. *Turk J Anaesthesiol Reanim.* 2023;51(4):311-317.

Abstract

Objective: The aim of this study is to assess the factors affecting the preference for the Pain Medicine subspecialty and the fellowship training programs by the pain specialists who have completed or continued the Pain Medicine fellowship training program from 2014 to 2021 in Turkey.

Methods: The study was conducted in October 2020 and March 2021. By reaching out to the pain specialists who completed their fellowship or had been continuing their training by getting the right to receive a Pain Medicine fellowship. Via e-mail or WhatsApp application, an e-questionnaire link was sent to the participants, and data were collected on demographics, factors affecting the choice of Pain Medicine subspecialty, level of realization of the expectations during the training course and the level of proficiency in the field of pain specialization. Data analysis was performed using IBM SPSS Statistics 20.0 software, and tests were considered statistically significant if $P < 0.05$.

Results: Participants reported that the factors that most affected their preferences were personal interest (55.1%), more comfortable working conditions (43.6%), and interest in an academic career (38.5%). Seventy-six participants answered the level of realization of expectations about performing interventional pain procedures using ultrasound imaging, and 31.6% reported that their expectations were not met, and 25% reported that their expectations were partially realised.

Conclusion: We hope that our findings will lead to improving Pain Medicine subspecialty training programs, upgrading standards, and more comprehensive studies on these issues.

Keywords: Medical fellowship, medical subspecialty training, pain doctor, pain management, pain medicine

Main Points

- In 2008, Pain Medicine (Algology) was defined as a subspecialty requiring a two-year education under Anaesthesiology and Reanimation, Physical Therapy and Rehabilitation, and Neurology departments in Turkey.
- Taking subspecialty examinations annually by the Measuring, Selection and Placement Center in Turkey since 2014, specialists can be qualified as Pain Medicine (algology) doctors.
- Personal interest (55.1%), more comfortable working conditions (43.6%), and interest in an academic career (38.5%) were the factors most affecting the preference for Pain Medicine (Algology) in our study.
- The area where the participants' expectations were met the most during the subspecialty training was the interventional procedures under fluoroscopy.
- Anaesthesiology and Reanimation departments are more integrated into Pain Medicine (Algology) fellowship program and therefore contributes more.
- Ultrasound is an essential tool for examining and treating pain patients in the practice of Pain Medicine, and this subject should be included more extensively in training programs.

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Received: September 09, 2022 Accepted: June 04, 2023

Introduction

The first clinic for treating patients suffering from chronic pain was established by anaesthesiologist E. Rovenstine at Bellvue Hospital, New York, before World War II. After 1947 the idea spread to Europe; the first pain clinic was opened at University College Hospital in London, followed by other institutions in a short time.[1]

International Association for the Study of Pain (IASP) was founded in 1974 and was the first multidisciplinary and international pain association.[1] One year later, the first issue of the "Pain" journal was published.[2] The establishment of other national pain societies followed the establishment of the IASP. The first Pain Unit in Turkey was established in 1986 at İstanbul University, İstanbul Faculty of Medicine, and the Turkish Algology-Pain Society was established in 1987.[3] In Turkey's Medical Specialization Board (MSB) published in 2001, Pain Medicine (Algology) subspecialization was only for anaesthesiologists. In the MSB of Turkey published in 2008, Pain Medicine was defined as a subspecialty requiring a two-year education in Anaesthesiology and Reanimation, Physical Therapy and Rehabilitation, and Neurology departments. The content of the subspecialty of Pain Medicine was determined by the Curriculum Commission convened in 2010 and organised by the Ministry of Health of Turkey. In 2011, the Ministry of Health evaluated past studies and experiences of doctors who applied and approved the first Pain Medicine (Algology) specialists in Turkey and were given specialization diplomas. Currently, there are 27 Pain Medicine training programs in Turkey whose protocols have been accepted since 2014.[3]

To be able to be admitted to a program qualifying for Pain Medicine fellowship in Turkey is determined according to the success of the subspecialty exam and staff preferences after completing education in Physical Therapy and Rehabilitation, Neurology, or Anaesthesiology and Reanimation residency. Usually, participants with the highest scores succeed in becoming Pain Medicine fellows. The duration of the training is two years, and the main hallmarks are determined in accordance with MSB in the form of rotations in the departments of Anaesthesiology and Reanimation, Physical Therapy and Rehabilitation, Neurology and Psychiatry during the training process of the fellows.

In the last decade, interest in the subspecialty of Pain Medicine and the number of doctors receiving specialization training in this field has increased in Turkey. Despite this, there is no published data on the preferences, training and post-training career period of pain specialists in this field.

The aim of this study is to assess the factors affecting the preference of pain management subspecialty and training courses by the pain specialists who have completed or continue the Pain Medicine fellowship program from 2014 to the present. The secondary gain of the study is to determine the programs' low conditions and lacking facilities in the educational period, which would help improve Pain Medicine fellowship programs and training processes based on the results of the study.

Methods

A 19-item e-questionnaire consisting of 6 sections (Supplementary File 1) was applied to physicians who were continuing or have completed their fellowship program in Pain Medicine (Algology) using Google Forms (Mountain View, California, USA).

The ethical approval of the İstanbul University, İstanbul Faculty of Medicine Clinical Research Ethics Committee was obtained for the study (no: 2020/1171, date: 25/09/2020). This study has been reported according to the principles in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guide.

The study was carried out in the period covering October 2020 and March 2021. It was carried out by reaching out via e-mail or WhatsApp application to the pain specialists who completed their fellowship or who had been continuing their training by getting the right to receive Pain Medicine fellowship training as a result of the annually taken subspecialty exam in the period from 2014 to the present in Turkey.

An e-questionnaire link was sent to the participants, who were asked to fill it out. Contact information of pain specialists and fellows was obtained through the Turkish Algology Association.

The e-questionnaire link was sent to 114 physicians four times, and 78 participants filled out the e-questionnaire. The first two parts of the e-questionnaire contained information about the participant's e-mail address, the date of filling out the questionnaire and the consent form; the 3rd part contained demographic information about the participant; the 4th part contained the factors affecting the choice of Pain Medicine subspecialty. The 5th part had the level of realization of the expectations during the training course, and the 6th part was the level of proficiency of the participants who have completed the training course. Likert scale was used for evaluation in the 4th and 5th sections of the questionnaire. And blank spaces were left in sections 4, 5 and 6 for additional assessments of the participants (see Supplementary File 1).

The questionnaire was created after interviewing a Pain Medicine fellowship program director, based on the surveys conducted among Anaesthesiology and Reanimation residents in Turkey and Canada and Physical Therapy and

Rehabilitation residents in Turkey.[4-6] Eight Pain Medicine fellows participated in the piloting to ensure that the questionnaire was understandable and complete.

Statistical Analysis

Shapiro-Wilk test was used to determine whether the distributions of continuous variables were normal or not, and the Levene test was used to evaluate the homogeneity of variances and mean, percentage distribution and standard deviation values were calculated using descriptive statistical methods. Independent Samples t-test or ANOVA test was used to compare parametric data. Cronbach's alpha value was used to measure the internal consistency of a set of survey items. Data analysis was performed using IBM SPSS Statistics 20.0 software (IBM Corporation, Armonk, NY, USA), and tests were considered statistically significant if $P < 0.05$.

Results

The number of participants in our study was 78 pain physicians. Response rate was 68.4%. Thirty-eight (48.7%) of the participants were female, and 40 (51.3%) were male. The mean age of the participants was 37 years (SD=4), the youngest 31 y, and the oldest 47 y.

The training profile of the participants is shown in Table 1.

Pain Medicine was the first choice of all participants, except for 5 (6.4%) participants, at the stage of subspecialty preferences after the subspecialty exam. It was seen that 4 participants whose first choice wasn't Pain Medicine were Neurology, and 1 participant was Physical Therapy and Rehabilitation specialists.

A 4-point Likert scale was used to determine the factors affecting the Pain Medicine subspecialty preferences: 0 - no effect, 1 - little effect, 2 - moderate effect, and 3 - high effect. This section was composed of 11 items, and if any other condition affected the participant's choice, it was reported that it should be indicated together with the impact score (Table 2).

The Cronbach α value was calculated as 0.693 for this evaluation, which included 11 items. The factors affecting the preference for the algology subspecialty (P=0.21) and the groups with different main specialities (P=0.34) were compared, and no statistically significant difference was found in either comparison.

Participants reported the three factors that had the most influence on their preferences, in order: personal interest

Table 1. Training Profile of the Participants

Main specialty	1st year of training participants (n)		2nd year of training participants (n)		Pain specialist participants (n)	
	University Hospital	Training and Research Hospital	University Hospital	Training and Research Hospital	University Hospital	Training and Research Hospital
Anaesthesiology and Reanimation	4	0	5	1	31	4
Neurology	5	0	2	0	11	1
Physical Therapy and Rehabilitation	4	0	2	0	9	0

Table 2. Factors Affecting the Preference of Subspecialty Pain Medicine

	N	Mean points*	Standard deviation
Personal interest	78	2.35	0.865
Subspecialty exam score	78	1.46	1.203
Comfortable working conditions	78	1.92	1.171
High income	78	1.54	1.053
Influence of colleagues	78	.91	1.009
Social and family factors	78	1.14	1.170
City of training	78	1.36	1.269
Hospital of training	78	1.53	1.192
Opportunities on research	78	1.71	1.082
Interest in an academic career	78	1.92	1.066
Social status	78	1.63	0.982

*A 4-point Likert scale was used: 0 - no effect, 1 - little effect, 2 - moderate effect, and 3 - high effect.

(55.1%), more comfortable working conditions (43.6%), and interest in an academic career (38.5%). It was observed that the most negligible affecting factor was the influence of colleagues.

A 4-point Likert scale was used to determine at what level the different expectations of the participants were realised in the Pain Medicine fellowship training course: 0 - my expectations were not realised, 1 - my expectations were partially realised, 2 - my expectations were fully realised, 3 - above my expectations. This section covers nine areas, and if any other condition affects the participant's choice, it was reported that they should specify it with the impact score.

The Cronbach α value was calculated as 0.730 for this evaluation, which included nine items. The results of the level of realization of expectations in the subspecialty training course are shown in Table 3.

The level of realization of expectations in the Pain Medicine subspecialty training process was compared between male and female participants (P=0.17) and the groups with different main specialities (P=0.77), and no statistically significant difference was found in both comparisons.

The level of realization of expectations in the training course, was compared the participants from university hospitals and training-research hospitals, and no statistically significant difference was found (P=0.28).

The three areas in which the participants' expectations were met the most during the training course were: practice on fluoroscopy-guided interventions, Anaesthesiology and Reanimation rotation, and outpatient practice. The area where the least expectations were realised was reported as the psychiatry rotation (Table 3).

Table 3. The Level of Realization of Expectations in the Subspecialty Training Course

	N	Mean points*	Standard deviation
Outpatient practice	75	1.87	0.791
Physical Therapy and Rehabilitation rotation	72	1.55	0.964
Anesthesiology and Reanimation rotation	67	1.90	0.877
Neurology rotation	71	1.27	0.936
Psychiatry rotation	72	1.08	0.907
Inpatient practice	75	1.10	1.145
Conducting scientific research	75	1.23	1.015
Practice on fluoroscopy-guided interventions	76	2.00	0.991
Practice on ultrasound-guided interventions	76	1.23	1.064

*A 4-point Likert scale was used: 0 - no effect, 1 - little effect, 2 - moderate effect, and 3 - high effect.

Among the participants, 56 people completed the algology subspecialty training and the distribution of hospitals they work are shown in Figure 1.

Just after completing the subspecialty training programme, the participants were asked to evaluate themselves in X-ray and ultrasound (US)-guided interventional pain procedures and the management of the pain patient. Although the participants mostly found themselves thoroughly competent (58.9%) in fluoroscopy-guided interventional procedures and patient management with pain, 46.4% of the participants found themselves partially competent in US-guided interventional procedures, while 25% reported that they were incompetent (Figure 2).

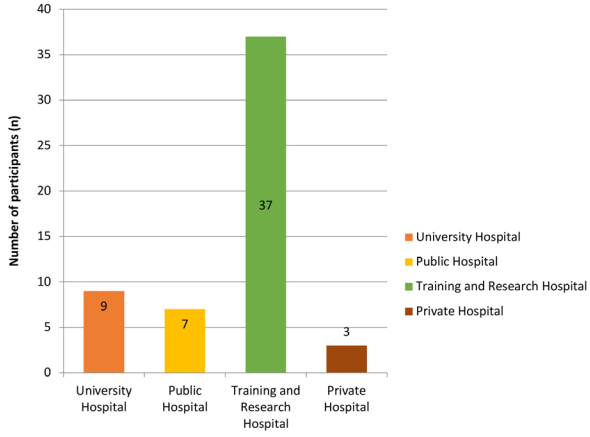

Figure 1. Hospitals where pain specialists work after subspecialty training.

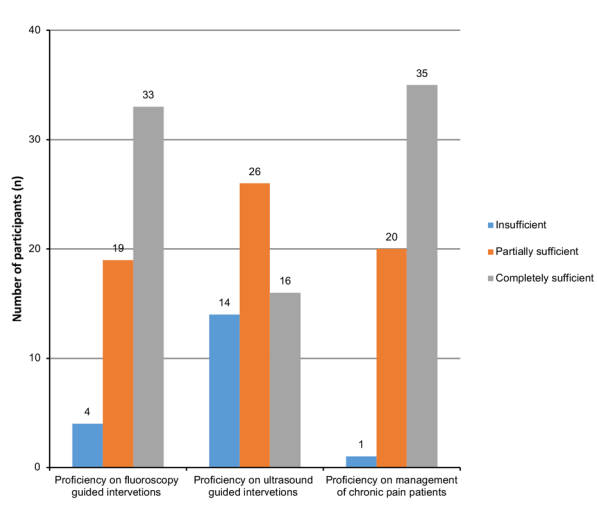

Figure 2. Proficiency in Pain Medicine right after completing subspecialty training.

In the questionnaire, the participants were asked again what level of proficiency they gained after working as a pain specialist for at least six months on the same subjects. One participant did not evaluate because he worked for less than six months; the other 55 participants made their evaluations. The results of the evaluation are shown in Figure 3.

After working for at least six months, the participants improved themselves on US-guided interventional procedures and the rate of those who found them thoroughly competent increased from 28.6% to 34.5%.

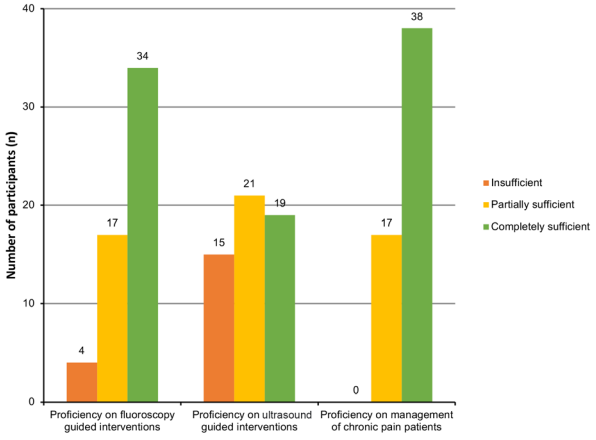

Figure 3. Proficiency in Pain Medicine after completing the subspecialty training and working for at least 6 months.

Discussion

In our study, the factors affecting the preference for Pain Medicine subspecialty in Turkey by physicians who have completed or are continuing their training in pain medicine, the expectations during the fellowship and the level of self-proficiency of the physicians in the post-fellowship period were evaluated. As far as we know, there has been no previous study in Turkey investigating which factors affect the career choices of Pain Medicine physicians, their expectations, and the Pain Medicine fellowship training process and beyond with 68.4% response rate. We found that the most important factor in the preference of a Pain Medicine specialty is personal interest, and learning the procedures performed with fluoroscopy during the training process meets the expectations the most. And during the training of fellows, Anesthesiology and Reanimation departments are more integrated into the Pain Medicine (Algology) fellowship program and therefore contribute more.

In a study conducted in Turkey by Izgi et al.[4] among 284 Anaesthesiology and Reanimation residents, it was reported that 35.2% of the participants planned a subspecialty training after their residency, and 2/3 of this group planned Pain Medicine. In addition, among those who decided to take a subspecialty training, the most common factors affecting this decision were working in a better place during compulsory service (47.2%), improving earning potential (43.1%) and personal interest (40.4%). Sena et al.[6] in a study with 181 physical therapy and rehabilitation residents in Turkey, only 9.4% of the participants reported that they were planning to get Pain Medicine subspecialty fellowship program. In this study, the most common factors affecting this decision were prestige (social status) (54.7%), interest in an academic career (50%) and the possibility of doing compulsory service in a better place (34.4%) among residents who were planning to take a subspecialty training.[6] In our study, participants reported that the factors that most affected their preferences were personal interest (55.1%), more comfortable working conditions (43.6%) and interest in an academic career (38.5%). Only 29.9% of the participants reported that the score obtained from the subspecialty exam was one of the most influential factors. These results show that the participants think that the working conditions in their primary speciality in Turkey are more difficult than in Pain Medicine and that academic career opportunities are more in the field of Pain Medicine. This situation is supported by the number of pain specialists (82.1%) who have completed their fellowship program and are currently working in training and research hospitals (37 specialists) and university hospitals (9 specialists). Participants were allowed to write their own opinions in the questionnaire. Pain specialists have a compulsory duty for two years after the completed fellowship, do not always have the opportunity to do their subspecialty in compulsory duty, or cannot apply all they have learned because of the lack of infrastructure and equipment. And the contributions, such as the possibility of private practice and high job satisfaction among the influential factors of some participants drew attention.

In the section about the realization of expectations during the fellowship, 72 participants reported that they completed the Psychiatry rotation, and 31.9% of the participants reported that their expectations were not fulfilled. Only 4 (5.6%) participants gained an experience beyond their expectations during the psychiatry rotation. These results suggest a need to integrate psychiatry departments more into the process and standardize the training programs in rotations in hospitals that provide Pain Medicine fellowship programs. The rotation with the highest fulfilment of expectations was the Anaesthesiology and Reanimation rotation. This result shows us that Anaesthesiology and Reanimation departments are more integrated into the Pain Medicine fellowship program and therefore contribute more.

Nowadays, fluoroscopy remains the most commonly used technology for interventional procedures by pain specialists. The advantage of fluoroscopy is the clear visualization

of the bony structures and allows precise identification of the anatomical structures necessary to perform these procedures. In our study, the area where the expectations of the participants were met the most during the subspecialty training was the interventional procedures under fluoroscopy. In pain management practice, pain specialists have started to use US imaging for examination and interventional pain procedures to reduce the use of fluoroscopy. In our study, 76 participants answered the level of realization of expectations about performing interventional pain procedures using US imaging, and 31.6% (24 participants) reported that their expectations were not met, and 25% (19 participants) reported that their expectations were partially realised. Some participants wrote that factors such as the COVID-19 pandemic, the economic difficulties of the hospital, the insufficient number of faculty members in the departments and the non-compliance with the training curriculum have an important place in the failure of the expectations.

71.8% (56) of the participants completed their Pain Medicine fellowship program. Of these participants, 4 (7.1%) reported that they found themselves insufficient in fluoroscopy-guided interventions after completing a Pain Medicine fellowship and working for at least six months. Although one participant felt inadequate at the end of the training on proficiency in managing patients with chronic pain, he could eliminate this insufficiency after working for six months. In light of these data, we see that fluoroscopy-guided interventional pain management training and management of pain patients in outpatient and inpatient are standardized throughout Turkey. At the end of the fellowship program on US in Pain Medicine practice, 14 (25%) participants reported feeling insufficient, and 26 (46.4%) partially sufficient. US not only reduces the risk of radiation exposure but is also less costly and easily transported and can be used in multiple locations. Some interventional procedures that cannot be performed with fluoroscopy can be easily performed under US guidance. Considering these advantages, it can be predicted that US will be an essential tool for examining and treating pain patients in the practice of Pain Medicine in the future, and this subject can be included more extensively in training programs.

In a survey study conducted in the USA by Asaad et al.[7] reported that the main barriers to the use of US in the pain subspecialty training program were the lack of education of the instructors and lack of access to equipment. Although we did not get opinions from the participants on this issue in our study, we think that the same problems exist in Turkey.

The short history of Pain Medicine subspecialty training in Turkey, such as six years, and the low number of specialists (114 physicians) receiving this training are the factors limiting our study. In the Turkish and English language literature, we could not find studies conducted in other countries on the Pain Medicine subspecialty training, and this prevented us from providing the opportunity to compare the experiences of other countries. In addition, the high rate of participation in our study (68.4%), the fact that 71.8% of the participants have completed their education, and therefore they can make a more comprehensive assessment, are the advantages of our study, as it is the first research on Pain Medicine subspecialty training in the national and international arena.

Conclusion

In conclusion, we found that the most important factors affecting Pain Medicine subspecialty preferences in Turkey are personal interests for our physicians, more comfortable working conditions and interest in an academic career. Anaesthesiology and reanimation rotation during the training process was best organized in the participants' opinion.

In order for Psychiatry rotation to be more efficient, it should be better integrated into the Pain Medicine fellowship training process. Considering that the use of US will become more common as time progresses, there is a need to identify and solve the deficiencies in this issue in institutions providing subspecialty training on Pain Medicine, and there is a need to establish training programs on the use of US.

We hope that our study will lead to improve Pain Medicine fellowship programs, the advancement of standards and more comprehensive studies on these issues.

Acknowledgments

Authors would like to thank Assoc. Prof. Dr. Mert Akan for his valuable and helpful recommendations during writing the manuscript.

Ethics Committee Approval: The ethical approval of the İstanbul University, İstanbul Faculty of Medicine Clinical Research Ethics Committee was obtained for the study (no: 2020/1171, date: 25/09/2020). This study has been reported according to the principles in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guide.

Informed Consent: It is an e-questionnaire study.

Peer-review: Internally and externally peer-reviewed.

Author Contributions: Concept - T.B., H.Ç., G.K.T.; Supervision - T.B., H.Ç., G.K.T.; Materials - T.B., H.Ç., G.K.T.; Data Collection and/or Processing - T.B., H.Ç., G.K.T.; Analysis and/or Interpretation - T.B., H.Ç., G.K.T.; Literature Review - T.B., H.Ç., G.K.T.; Writing - T.B., H.Ç., G.K.T.

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

Funding: The authors declared that this study has received no financial support.

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DOI: 10.4274/TJAR.2023.221133

Original Article
Airway Management

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):318-323

Nasogastric Tube Insertion in Intubated Patients: Comparison of Three Different Positions; Standard Sniffing Position, Additional Flexion of the Neck, and Standard Sniffing Position with Lateral Neck Pressure

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Cite this article as: Mohanan S, Gupta M, Dabas M. Nasogastric Tube Insertion in Intubated Patients: Comparison of Three Different Positions; Standard Sniffing Position, Additional Flexion of the Neck, and Standard Sniffing Position with Lateral Neck Pressure. *Turk J Anaesthesiol Reanim.* 2023;51(4):318-323.

Abstract

Objective: Our study aimed to evaluate two modified nasogastric tube (NGT) insertion techniques in intubated patients compared to the conventional method in respect of first attempt success rate, time taken for insertion, and complications.

Methods: In this prospective interventional study, patients with orotracheal intubation requiring NGT insertion were randomly allocated into three groups by SNOS Group A (control group- standard sniffing position, n = 40), Group B (additional flexion of the neck, n = 40), Group C (standard sniffing position with lateral neck pressure, n = 40). The number of attempts for successful NGT insertion, time for insertion, and complications were compared.

Results: Modified positions showed a high first-attempt success rate in Group B (55%) and Group C (85%) as compared to conventional Group A (32.50%) ($P < 0.001$). On intergroup analysis of modified groups (B and C), Group C was superior to Group B in 1st attempt success rate with a significant P value of 0.003.

Conclusion: In intubated patients, NGT insertion in standard sniffing position with lateral neck pressure has the highest first attempt success rate followed by additional flexion of neck position. Both the modified positions are better positions for NGT insertion in intubated patients.

Keywords: Anaesthesia, intubation, nasogastric, position

Main Points

- Nasogastric tube (NGT) insertion in intubated patients is many a times difficult to perform due to anatomical reasons as most commonly it gets impacted at the pyriform sinus and arytenoid cartilage.
- Insertion of NGT in an awake state is easier due to the act of deglutition by the patient but in anesthetized and intubated patients, the act of deglutition is not possible.
- Simple manoeuvrers such as additional flexion of the neck and standard sniffing position with lateral neck pressure can overcome the impaction sites and helps in easier and quicker NGT insertion in intubated patients.
- In our study, we found that the standard sniffing position with lateral neck pressure is a superior technique compared to additional neck flexion and standard sniffing position for NGT insertion in anesthetized intubated patients in terms of first-attempt success rate, less time taken, and fewer complications.

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Received: December 16, 2022 Accepted: April 19, 2023

Introduction

The conventional way to insert nasogastric tube (NGT) is often difficult in intubated patients, the failure rate to insert NGT in the first attempt is as high as 50%.[1] The reasons for failure in inserting NGT in intubated patients are anatomical as well as mechanical. Most of the difficulties are due to anatomical reasons as resistance is felt at the pyriform sinus and arytenoid cartilage while inserting NGT.[2] Mechanical reasons for difficulty in inserting NGT are due to multiple openings at the distal end of NGT making it prone to kink, coil, and knot,[3] and the "memory effect" i.e. after a failed attempt followed by subsequent attempts using the same technique, NGT tends to kink again at that location itself[4] and flexibility of silicone NGT making insertion difficult. When the mechanical reasons add upon the pre-existing anatomical causes further aggravates the difficulty in the insertion of NGT. Simple maneuvers such as additional flexion of the neck,[5] lateral neck pressure,[4] and reverse Sellick's maneuver[3] were used by several authors for increasing the success rate of NGT insertion. Studies using instruments such as forceps, angiography catheters,[6] and wire rope[7] as stylets, and the use of video laryngoscopes such as C-Mac[8] resulted in success rate, but with complications.

Several authors have reported different techniques with varying success rates. However, we couldn't find any studies comparing "additional flexion of the neck" and "standard sniffing position with lateral neck pressure" for inserting NGT in intubated patients. The primary objective of this study was to compare 1st attempt success rate between modified positions of inserting NGT ("additional flexion of the neck" and "standard sniffing position with lateral neck pressure") in comparison to the conventional method. The secondary objective was to find the overall success rate, time taken for insertion, and complications if any.

Methods

This study was a prospective interventional randomized comparative study conducted after obtaining the permission from Institutional Ethical Committee of ESI-Post Graduate Institute of Medical Sciences and Research and registered in Clinical Trial Registry- India with CTRI registration number CTRI/2020/08/027360. Total of 120 adults of either gender aged between 18 years - 65 years of American Society of Anesthesiologists I and II physical status were included in the study. Exclusion criteria were patients with airway distortion or trauma, neck mass, cervical spine pathology, significant deviated nasal septum, and those taking aspirin or anticoagulants. Informed consent was taken from patients after discussing the study procedure and complications.

The pre-anaesthetic check-up was done in all the patients. A more patent nostril was selected in the pre-operative area based on better fogging on the metal tongue depressor while expiring through each nostril. After giving premedication with midazolam (0.03 mg kg^{-1}) and fentanyl (1-2 mcg kg^{-1}), induction of anaesthesia was done by propofol (2-2.5 mg kg^{-1}) IV and muscle relaxation with vecuronium (0.1 mg kg^{-1}) was followed by intubation with appropriate - sized cuffed endotracheal tube. After intubation, oxymetazoline (0.05%) drops were instilled in both nostrils. Sterile, lubricated, 14Fr POLYMED NGT was used.

In Group A, NGT was inserted while the patient's head is in the standard sniffing position. In Group B, additional flexion of the neck was used by placing a non-compressible 10 cm width pillow under the patient's head (Figure 1). In Group C, NGT was inserted while the patient's head was in the standard sniffing position with applying lateral neck pressure on the same side of the selected nostril (Figure 2). Lateral neck pressure was applied with three fingers placed about an inch lateral to the trachea, at the level of the cricoids cartilage. The successful placement of NGT was confirmed by auscultation at the epigastrium during which a characteristic whooshing sound was heard by injecting 20 mL of air fast into the NGT-called the whoosh test. The time for insertion (seconds) was started from NGT insertion through the selected nostril up to the successful placement of NGT within a maximum of two attempts which includes cleaning and re-lubricating the NGT in case of first attempt failure. If both attempts failed, then the technique was considered a failure, and an alternative technique was used. The following observations were documented: a number of attempts for successful insertion of NGT, time for insertion of NGT, and complications like kinking, coiling, and bleeding (Figure 3).

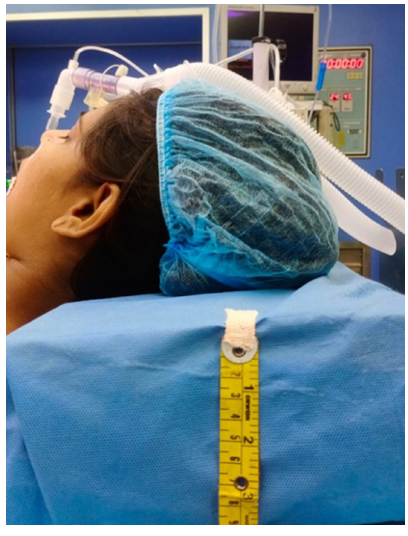

Figure 1. (Group B) NGT insertion in additional flexion of the neck.

NGT, nasogastric tube.

Sample Size Calculation

The study by Jonnavithula et al.[5] observed that the success rate of nasogastric tube insertion in 2 or fewer attempts in the sniffing position was 68% and in the additional flexion position was 92%. Taking these values as a reference, the minimum required sample size with 80% power of the study and 5% level of significance is 40 patients in each study group. So total sample size taken is 120 (40 patients per group).

Figure 2. (Group C) NGT insertion in standard sniffing position with lateral neck pressure.

NGT, nasogastric tube.

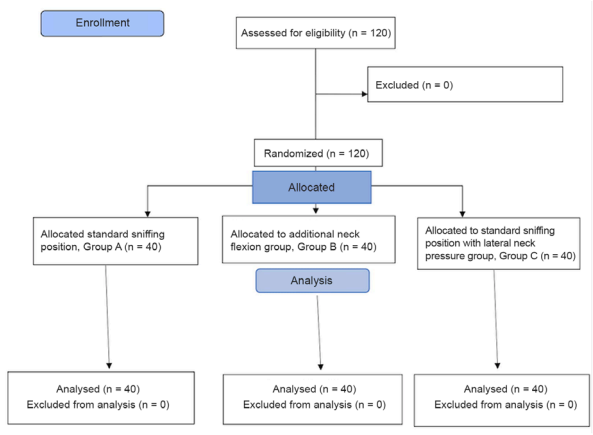

Figure 3. Consortflow diagram of participants in the study group: standard sniffing position group, additional neck flexion group, and standard sniffing position with lateral neck pressure group

Analyses were done using IBM SPSS 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. Categorical variables were presented in frequency and percentage (%), and continuous variables were presented as mean ± standard deviation and median (minimum-maximum).

The following statistical tests were applied for the results:

1. The comparison of the variables which were quantitative in nature were analyzed using ANOVA test and post hoc comparison was done using Bonferroni correction for significant parameters.

2. Qualitative variables were compared using the Pearson chi-square test and Fisher-Freeman-Halton test.

For statistical significance, *P* value of less than 0.05 was considered as significant.

Results

The study was conducted from October 2019 to April 2021. A total of 120 patients were included in the study who had indications for nasogastric tube insertion for elective surgeries. There were no statistically significant differences in terms of age and gender among the three groups (Table 1).

The first-attempt success of NGT insertion in intubated patients was highest in Group C in 34 patients (85%) as compared to Group B and Group A with first-attempt success in 22 patients (55%) and 13 patients (32.5%) respectively ($P < 0.001$). Successful NGT insertion (NGT insertion within 2 attempts) was highest (97.5%) in Group C as compared to Group A (55%) and Group B (80%) ($P < 0.001$). Time taken for successful insertion of NGT (seconds) was less in Group C (23.9 ± 7.5) as compared to Group B (30.09 ± 6.18) and Group A (43.04 ± 12.74) ($P < 0.001$) (Table 2). Intergroup analysis (A vs. B, B vs. C, A vs. C) of the above mentioned procedure parameters were also statistically significant (Table 2).

The occurrence of overall complications was highest in Group A (50%) as compared to fewer complications that occurred in Group B (27.5%) and Group C (7.5%) ($P < 0.001$). Fewer complications were seen in Group C with coiling complication of 7.5% and no complications of kinking and bleeding (Table 3).

Table 1. Demographic Parameters

Parameters	A (n = 40)	B (n = 40)	C (n = 40)	Total	*P* value
Age (years)	33.83 ± 5.41	36.7 ± 6.99	36.42 ± 6.42	35.65 ± 6.39	0.083
Female	17 (42.50%)	14 (35%)	18 (45%)	49 (40.83%)	0.639
Male	23 (57.50%)	26 (65%)	22 (55%)	71 (59.17%)	

Table 2. Procedure Parameters

Parameters	Group A (n = 40)	Group B (n = 40)	Group C (n = 40)	*P* value
1st attempt success	13 (32.50%)	22 (55%)	34 (85%)	<0.001
Successful NGT insertion (within 2 attempts)	22 (55%)	32 (80%)	39 (97.50%)	<0.001
Time taken for successful insertion of NGT (seconds)	43.04 ± 12.74	30.09 ± 6.18	23.9 ± 7.5	<0.001
Intergroup analysis	Parameters	A vs B	A vs C	B vs C
	1st attempt success	0.043	<0.001	0.003
	Successful NGT insertion (within 2 attempts)	0.017	<0.001	0.029
	Time taken for successful insertion of NGT (in sec)	0.015	0.003	<0.001

Table 3. Complications

Complications	A (n = 40)	B (n = 40)	C (n = 40)	Total	*P* value
Overall complications	20 (50%)	11 (27.5%)	3 (7.50%)	34 (28.33%)	0.001
Bleeding	3 (7.50%)	1 (2.50%)	0 (0%)	4 (3.33%)	0.322
Coil	8 (20%)	8 (17.50%)	3 (7.50%)	19 (15.83%)	0.209
Kinking	10 (25%)	2 (5%)	0 (0%)	12 (10%)	0.004
Parameters	A vs B	A vs C	B vs C		
Overall complications	0.066	<0.001	0.037		

Discussion

This prospective interventional randomized comparative study revealed that modified techniques of NGT insertion, such as additional neck flexion and the standard sniffing position with lateral neck pressure, are effective techniques in inserting NGT in intubated patients in the first attempt with less time and with fewer complications than the conventional method.

The usual sites of resistance while inserting NGT in an intubated patient are seen at the piriform sinuses and the arytenoid cartilages at the same side of the NGT passage.[2] In an awake state, the upper esophageal sphincter is open during deglutition, thus helping in NGT passage into the esophagus. Inserting NGT after general anaesthesia is difficult because deglutition is impossible, and the sphincter remains closed[9] and due to compression by the inflated cuff of an endotracheal tube at the esophagus.[10]

There are various studies with high success rate for NGT insertion in intubated patients, which includes slit endotracheal tube assisted,[11,12] stylet, or guidewire methods,[3,4,6] using glide scope for placement.[13] However, these methods have limitations in patients with inadequate mouth opening and are also time-consuming with various complications. Various maneuvers for insertion of NGT such as reverse Sellick's maneuver,[3,10,14] neck flexion,[1] and turning the head to one side[2,15] have been studied for insertion of NGT.

In our study, additional flexion of the neck (Group B) and standard sniffing position with lateral neck pressure (Group C) were used for NGT insertion in intubated patients. The advantages of these techniques are that the structural changes that occur when the neck is flexed along with the curve of NGT help in the easy passage of NGT into the esophagus by keeping it in the posterior pharyngeal wall and it also prevents glossoptosis.[5] Lateral neck pressure applied at the same side of NGT insertion compresses the pyriform sinus and medially moves the arytenoid cartilage, allowing NGT to enter the hypopharynx in the usual position[3] thereby bypassing the anatomical resistance followed by preventing the mechanical reasons for difficult NGT insertion.

Our study revealed that both Group B and C improved the first attempt success rate as compared to Group A by overcoming the anatomical resistance sites. Group C showed highest success rate of NGT insertion within two attempts as compared to Group B and Group A by overcoming the mentioned sites of NGT impaction.

In 2009, Appukutty and Shroff[4] found that both the head flexion with lateral neck pressure method and slit endotracheal tube method increased the success rate by 82% in the first-attempt insertion of NGT in intubated patients but the bleeding was the persistent complication in the slit endotracheal tube. Observations of Appukutty and Shroff[4] and that of the present study show that the first attempt success rate of NGT insertion by standard sniffing position with lateral neck pressure happens to be highest with fewer complications. In 2019, Jonnavithula et al.[5] found higher first-attempt success (76%) in additional neck flexion using a pillow under the head as compared to the standard sniffing position group (63%). Two independent studies by Mandal et al.[3] and Siddhartha et al.[10] found good results in neck flexion with lateral neck pressure and reverse Sellick's group with higher first-attempt success rates of 86% and 77.55% respectively. The present study hasn't included

reverse Sellick's maneuver to prevent complications during excessive manipulation of the neck.

The time taken for successful NGT insertion in intubated patients was least in the standard sniffing position with lateral neck pressure group (23 ± 7.5 seconds) as compared to the additional neck flexion group (30.09 ± 6.18 seconds) and standard sniffing position group (43.04 ± 12.74 seconds). In 2019, Siddhartha et al.[10] observed that the time required for NGT insertion was less in reverse Sellick's group and neck flexion with lateral neck pressure group of 13.05 ± 2.57 seconds and 20.48 ± 4.52 seconds respectively.

In our study, Group C had fewer complications as compared to Group A and B due to the ease of inserting NGT in its usual pathway after the lateral neck pressure. Group C had only coiling complication as compared to coiling, kinking and bleeding complications in Group B and Group A. Thus standard sniffing position with lateral neck pressure technique can be used to avoid unanticipated complications during NGT insertion in anaesthetized intubated patients.

Illias et al.[16] found that lifting of the thyroid cartilage group and neck flexion with lateral neck pressure group had a lower incidence of complications as compared to the control group. They have emphasized the fact that choosing a procedure with a high success rate that does not require the use of additional instruments can reduce the risk of these complications. In our study, we used simple techniques to avoid all possible complications during NGT insertion.

Study Limitations

In our study, we avoided obese, pregnant, paediatric, and emergency patients with a full stomach. In the coming years, more studies involving such populations may be required to find the superiority of these modified techniques in such special situations.

Conclusion

The standard sniffing position with lateral neck pressure technique is the best and most superior technique as compared to the additional neck flexion technique and standard sniffing position for successful and quick NGT placement without instrumentation and hence with less complication. As compared to additional flexion on the neck, the standard sniffing position with lateral neck pressure group is a better technique for successful NGT placement in less time and with fewer complications.

Ethics Committee Approval: Ethical permission was obtained from Institutional Ethical Committee of ESI-Post Graduate Institute of Medical Sciences and Research and registered in Clinical Trial Registry- India with CTRI registration number CTRI/2020/08/027360.

Informed Consent: Written and informed consent was obtained from all the patients who participated in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.M., M.G.; Design - S.M., M.G.; Supervision - M.G; Resources - S.M., M.G., M.D.; Materials - S.M., M.G., M.D; Data Collection and/or Processing - S.M., M.D.; Analysis and/or Interpretation - S.M., M.G., M.D.; Literature Search - S.M., M.G., M.D.; Writing Manuscript - S.M., M.G., M.D.; Critical Review - S.M., M.G., M.D.

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

Funding: The authors declared that this study has received no financial support.

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DOI: 10.4274/TJAR.2023.22856

Original Article
Cardiovascular and Thoracic Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):324-330

Preoperative Anemia and Female Gender are Risk Factors for Transfusion in Patients Undergoing Coronary Artery Bypass Grafting with a Restrictive Transfusion Strategy

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Cite this article as: Koçyiğit ÖI, Koçyiğit M, Güllü AÜ, Şenay Ş, Toraman F, Alhan C. Preoperative Anemia and Female Gender are Risk Factors for Transfusion in Patients Undergoing Coronary Artery Bypass Grafting with a Restrictive Transfusion Strategy. *Turk J Anaesthesiol Reanim.* 2023;51(4):324-330.

Abstract

Objective: Red blood cell (RBC) transfusion in cardiac surgery is associated with increased morbidity and mortality. Even when using patient blood management methods, blood transfusions may still be needed in cardiac surgery. This study examined the risk factors for blood transfusion in isolated coronary artery bypass graft (CABG) surgery with a restrictive transfusion strategy, along with individualized patient blood management.

Methods: We enrolled 198 patients (age, 61.8 ± 9.9 years; 28 females and 170 males) who underwent isolated CABG surgery in a single private hospital using a restrictive transfusion strategy between April 2015 and October 2020. Pre-, intra-, and postoperative parameters were compared between patients with and without RBC transfusions. The risk factors for transfusion and transfusion probability were analyzed.

Results: Patients who received RBC transfusions had higher European System for Cardiac Operative Risk Evaluation values (13.60 ± 18.27%). Preoperative hematocrit (Hct) [odds ratio (OR)=0.752; 95% confidence interval (CI) 0.639-0.884; *P*=0.001] and female gender (OR=7.874; 95% CI 1.678-36.950; *P*=0.009) were significant independent risk factors for RBC transfusion in logistic regression analysis. When the preoperative Hct was 30%, the RBC transfusion probability was 61.08% in females and 16.6% in males. Patients who received RBC transfusions had longer intensive care unit (31.40 ± 25.42 hours) and hospital (11.18 ± 6.75 days) stays.

Conclusion: Risk factors for RBC transfusion in isolated CABG surgery with a restrictive blood transfusion strategy were preoperative anemia and female gender.

Keywords: Anemia, blood transfusion, coronary artery bypass, patient blood management, restrictive blood transfusion

Main Points

- Red blood cell transfusion during cardiac surgery is associated with increased morbidity and mortality.
- Cell saving is one of the main ways to conserve blood during cardiac surgery.
- Preoperative anemia and female gender were the only significant independent risk factors for blood transfusion during isolated coronary artery bypass graft surgery with a standardized operating technique and restrictive transfusion protocol.

Introduction

Red blood cell (RBC) transfusion during cardiac surgery is associated with increased morbidity and mortality.[1] Population aging is leading to an increase in the consumption of blood products and a decrease in donations, which poses a challenge for blood services globally.[2,3] Various studies have compared restrictive and liberal blood

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Received: March 31, 2022 Accepted: February 23, 2023

transfusions in cardiac surgery,[4,5] and guidelines have been created to limit the use of RBC transfusion.[6,7] However, despite such efforts, blood transfusion is not completely avoidable.

Patient blood management, which is the major method for reducing RBC transfusion, proceeds via three stages: detecting/treating preoperative anemia; reducing perioperative blood loss; and managing anemia.[8] Cell saving is one of the main ways to conserve blood during cardiac surgery.[9] Although cell salvage systems can decrease the odds of blood transfusion by recovering blood, blood transfusion may still be required.

This study identified independent risk factors for RBC transfusion in patients undergoing isolated coronary artery bypass graft (CABG) surgery using a restrictive transfusion strategy, along with individualized patient blood management.

Methods

After receiving Institutional Review Board of Acıbadem University Ethical Approval (ATADEK; 2022-07/30), patient data were retrieved from the electronic medical records of our institution's database. Informed consent was obtained from all patients and the study was conducted in accordance with the principles of the Declaration of Helsinki.

This study enrolled 198 patients (age, 61.8 ± 9.9 years; 28 females and 170 males) who underwent isolated CABG surgery using a restrictive transfusion strategy between April 2015 and October 2020. Patients who had off-pump or concomitant surgery were excluded.

All operations were performed by the same surgical team and anaesthesiologist. Where possible, enoxaparin sodium, rivaroxaban, apixaban, and antiplatelet drugs (clopidogrel and ticagrelor) were discontinued for 24 hours to 7 days preoperatively.

Patients were monitored perioperatively (five-lead electrocardiogram, pulse oximetry, invasive blood pressure, central venous pressure, bispectral index, and cerebral oximetry). Transesophageal echocardiography was used routinely for hemodynamic monitoring. All patients underwent balanced anaesthesia using clinical protocols. The initial dose of heparin was 300 U kg^{-1}. After achieving an activated clotting time of >400 s, aortic and caval cannulation were performed and cardiopulmonary bypass (CPB) was initiated. Ringer's lactate solution was used for CPB priming. The pump flow rate was set at 2.2-2.4 L $min\ m^{-2}$ (30-32°C). Cold blood cardioplegia was used for myocardial protection. Heparin activity was reversed with a 1:1 dose of protamine sulfate.

Postoperatively, all patients were transferred to the intensive care unit (ICU) and extubated once the weaning criteria were met.

The patients' demographic characteristics, European System for Cardiac Operative Risk Evaluation (EuroSCORE), ejection fraction, hematocrit (Hct) and creatinine levels, use of medication, and comorbidities were analyzed. Cross-clamp and CPB of distal anastomoses were also analyzed (times and numbers). The durations of endotracheal intubation and ICU and hospital stays, and the morbidity and hospital mortality rates, were evaluated. Patients with and without RBC transfusion were compared.

Restrictive Transfusion Strategy

All patients were infused with tranexamic acid (25 mg kg^{-1}, IV) after inducing anaesthesia within 10 minutes. Meticulous hemostasis and careful tissue handling were of paramount importance in all steps of the operation. The bypass circuit volume used to reduce hemodilution was 1.150 mL of crystalloid in all operations. We do not use retrograde autologous priming, venous autologous priming, or acute normovolemic hemodilution. An autotransfusion device was used in all cases (Sorin XTRA; LivaNova, Arvada, CO, USA). Throughout the cardiac procedure, blood was collected from the pericardial and pleural spaces into the collection reservoir of the cell salvage device. The bloody sponges were squeezed and blood was suctioned into the cell saver system. All remaining pump contents were added to the cell saver reservoir and washed before being returned to the patient. After closing the sternum, chest drainage tubes were connected to the autotransfusion circuit. Autotransfusion continued in the ICU for the first 6 hours postoperatively; a new device was used after 6 hours. If the bleeding amount was >200 mL h (over >2 hours) in the absence of a coagulation disorder, re-exploration for bleeding was carried out (Figure 1).

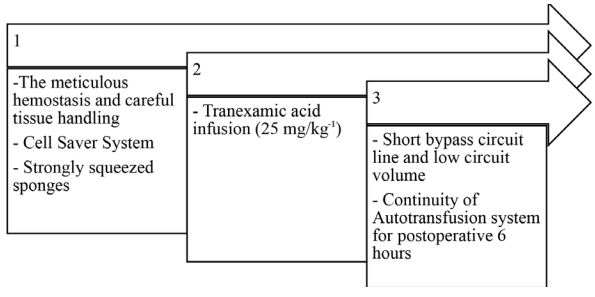


Figure 1. Blood conservation strategy.

If the Hct was <17% during the hypothermic period of CPB, <20% after CPB, or <21% during the postoperative period, RBC transfusion was considered. However, blood transfusion was not based on a numerical value alone; rather, a restrictive RBC transfusion policy was implemented according to the Hct level and hemodynamic and clinical parameters.

Hct was measured before, during, and after CPB, on arrival in the ICU, and on days 1, 2, 4, and 7 (while the patient was still hospitalized) at a minimum. If the Hct fell below the threshold at any time, red cells were administered (1 unit at a time) and the Hct was reassessed.

Statistical Analysis

The statistical analyses were performed using SPSS software (version 23, IBM Corp., Armonk, NY, USA). The normality distribution of variables was checked with the Shapiro-Wilk test. Normally distributed data were presented using mean ± standard deviation. Categorical variables were compared with the chi-square test or Fisher's exact test and expressed as numbers and frequency (%). Continuous variables were compared with Student's t-test or the Mann-Whitney U test. Variables significant at $P < 0.05$ were included in the binary logistic regression model. The Hosmer and Lemeshow goodness-of-fit test was also performed. Binary logistic backward regression analysis was used to investigate the impact of several pre- and perioperative factors on the likelihood of receiving at least RBC transfusion. A P value < 0.05 indicated statistical significance in all tests. Regression analysis as odds ratio (OR) with 95% confidence intervals (CIs) are reported. The probability of blood transfusion was calculated using a probability formula.

The power analysis was performed using G*Power version 3.1.9.7 (Heinrich Heine Universität Düsseldorf, Germany) software. The sample size was calculated based on a study by Kim et al.[10] who compared the patients with blood transfusion or without blood transfusion and preoperative hemoglobin (Hb) levels. It was determined that the effect size was 85% at the power 86% and 5% alfa error significance level in our study.

Results

The baseline demographic and clinical characteristics of the patients were compared (Table 1). Of the 198 patients who underwent CABG using a restrictive transfusion strategy, only 11 (5.6%) had RBC transfusions. The patients who received transfusions were significantly older and had higher logistic EuroSCOREs than those who did not receive RBCs (P=0.007 and P=0.026, respectively); the former patients were also more likely to be females undergoing reoperations (Table 1). The preoperative Hct was significantly lower ($P < 0.001$), and the total fluid balance was higher (P=0.001), in the transfusion group (Table 1).

Table 1. Patients' Demographics and Clinical Data

	RBC transfusion (n = 11)	No-RBC transfusion (n = 187)	*P* value
Age (years)	69.70 ± 6.06	61.38 ± 9.96	0.007
BMI (kg m^{-2})	27.79 ± 4.08	28.76 ± 4.25	0.483
Sex (female:male)	8:3	20:167	<0.001
Logistic EuroSCORE	13.60 ± 18.27	5.71 ± 10.84	0.026
NYHA class 3 and 4	18.2% (n = 2)	8.0% (n = 15)	0.242
Left ventricle EF (%)	52.36 ± 9.83	55.76 ± 10.03	0.276
Previous cardiac operations	18.2% (n = 2)	2.1% (n = 4)	0.003
Hypertension	63.6% (n = 7)	64.7% (n = 121)	0.960
Diabetes mellitus	54.5% (n = 6)	42.7% (n = 80)	0.758
Hypercholesterolemia	45.5% (n = 5)	56.1% (n = 105)	0.575
COPD	0.0% (n = 0)	6.4% (n = 12)	0.386
Cerebrovascular attack	18.2% (n = 2)	5.3% (n = 10)	0.083
Preoperative AF	0.0% (n = 0)	2.1% (n = 4)	0.624
Smoking			
Smokers	20.0% (n = 2)	36.1% (n = 66)	0.140
Former smokers	20.0% (n = 2)	33.9% (n = 62)	
Never smoked	60.0% (n = 6)	30.1% (n = 55)	

Table 1. Continued			
	RBC transfusion (n = 11)	**No-RBC transfusion (n = 187)**	***P* value**
Preoperative medications			
Beta blockers	36.4% (n = 4)	50.8% (n = 95)	0.352
ACE inhibitors	45.5% (n = 5)	33.2% (n = 62)	0.402
Aspirin	45.5% (n = 5)	32.1% (n = 60)	0.359
Clopidogrel	18.2% (n = 2)	7.5% (n = 14)	0.206
Non-elective surgery	18.2% (n = 2)	26.2% (n = 49)	0.554
Pre-operative hematocrit level (%)	32.82 ± 3.63	41.03 ± 4.11	<0.001
Hct level - Female (%)	32.67 ± 1.52	36.87 ± 4.89	0.169
Hct level - Male (%)	33.3 ± 4.16	41.76 ± 3.41	<0.001
Pre-operative creatinine level (mg dL^{-1})	1.10 ± 0.29	0.96 ± 0.28	0.108
CC time (min)	57.44 ± 20.43	55.64 ± 16.97	0.759
CPB time (min)	91.60 ± 23.18	87.40 ± 23.34	0.580
Number of distal anastomosis (mean)	3 (min 2 - max 4)	4 (min 1 - max 7)	0.263
Total fluid balance after CPB (mL)	1560 ± 603.6	998.37 ± 529.94	0.001

BMI, body mass index; NYHA, New York Heart Association; EF, ejection fraction; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; ACE, angiotensin-converting enzyme; CC, cross clamp; CPB, cardiopulmonary bypass.

The intubation time and ICU and hospital stays were significantly longer in the blood transfusion than non-transfusion group, and there were more ICU readmissions in the former group (Table 2). There were no cases of new-onset dialysis or stroke, no hospital readmissions within 4 weeks after discharge, and no deaths during the hospital stay or first postoperative month (Table 2).

RBCs were transfused in three patients during, and three patients after, CPB because of low Hct (<17% and <20%, respectively). Three patients had RBC transfusions on the second and fourth postoperative days because of low Hct (<21%). One patient had an RBC transfusion because of hemodynamic instability during revision for bleeding on the day of surgery. One patient had an RBC transfusion because of gastrointestinal bleeding on postoperative day 4.

Table 2. Patients' Postoperative Data			
	RBC transfusion (n = 11)	**No-RBC transfusion (n = 187)**	***P* value**
Total recycled RBC volume (mL)	519 ± 238	581 ± 302	0.545
Intubation time (hr)	11.57 ± 10.61	5.93 ± 2.04	<0.001
Chest tube output (mL)	239.09 ± 100.84	282.73 ± 160.31	0.374
ICU duration (hr)	31.40 ± 25.42	19.24 ± 4.19	<0.001
Post-operative hematocrit level	27.01 ± 3.53	33.93 ± 4.92	<0.001
Hct level - Female	28.73 ± 2.55	29.02 ± 4.66	0.888
Hct level - Male	27.40 ± 2.10	34.76 ± 4.70	0.008
Postoperative AF	18.2% (n = 2)	6.4% (n = 12)	0.139
Platelet use	9.1% (n = 1)	0.5% (n = 1)	0.108
Platelet use (U/patient)	0.27 ± 0.9	0.11±0.15	0.36
Fresh frozen plasma use	18.2% (n = 2)	2.7 % (n = 5)	0.051
Fresh frozen plasma use (U/patient)	0.55 ± 1.3	0.05 ± 0.32	0.237
Pulmonary complication	9.1% (n = 1)	0.0% (n = 0)	0.057
Inotropic support >4 hours	9.1% (n =1)	1.06% (n = 2)	0.172
Revision for bleeding	9.1% (n = 1)	0.5% (n = 1)	0.108

Table 2. Continued

	RBC transfusion (n = 11)	No-RBC transfusion (n = 187)	*P* value
Discharge hematocrit	30.87 ± 3.89	29.30 ± 4.07	0.218
Hct level - Female	31.55 ± 4.40	26.94 ± 2.76	0.008
Hct level - Male	30.43 ± 2.66	29.78 ± 4.09	0.785
Discharge creatinine (mg dL^{-1})	1.05 ± 0.27	0.91 ± 0.27	0.163
ICU readmission	18.2% (n = 2)	3.2% (n = 6)	0.029
Reintubation	9.1% (n = 1)	0.0% (n = 0)	0.056
Hospital stay (days)	11.18 ± 6.75	7.07 ± 4.28	0.003
Mortality	0.0% (n = 0)	0.0% (n = 0)	Ns

RBC, red blood cell; AF, atrial fibrillation; ICU, intensive care unit.

There was a significant negative correlation between preoperative Hct and age (r=-0.363, $P < 0.01$). Age, sex, EuroSCORE, previous cardiac operations, total fluid balance after CPB, and preoperative Hct were subjected to logistic regression analysis. The Hosmer and Lemeshow test indicated a good fit (P=0.991). Preoperative Hct (OR 0.752; 95% CI 0.639-0.884; P=0.001) and female gender (OR 7.874; 95% CI 1.678-36.950; P=0.009; "constant variable", 6.967; "coefficient variable", -0.286) were significant independent risk factors for blood transfusion (Table 3).

We calculated the blood transfusion probability according to the Hct using the probability formula in Table 3.

$$p = \frac{1}{1 + e^{-a-bx}}$$

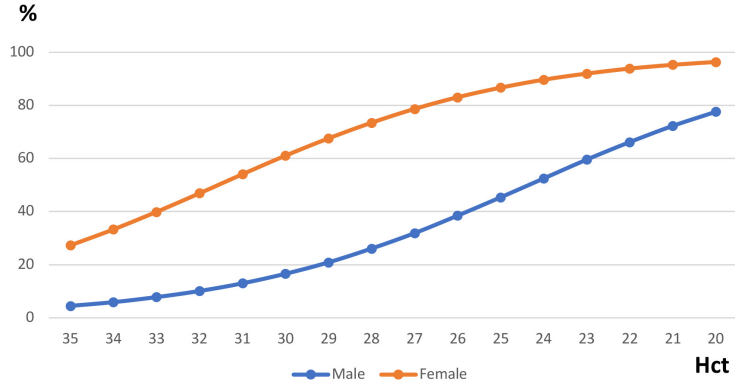
$$P\ \text{female} = \frac{1}{1 + e^{-6.967-(-0.286xHct+2.064)}}$$

$$P\ \text{male} = \frac{1}{1 + e^{-6.967-(-0.286xHct)}}$$

According to this formula, if the preoperative Hct is 25%, 30%, and 35%, the probability of blood transfusion is 86.7%, 61.08%, and 27.3% in females, and 45.4%, 16.6%, and 4.5% in males, undergoing isolated CABG surgery, respectively (Figure 2).

Table 3. Predictive Factors for Blood Transfusion

	Odds ratio	95% Confidence interval	*P* value
Female gender	7.874	1.678-36.950	0.009
Preoperative hematocrit	0.752	0.639-0.884	0.001



% Hct	35	34	33	32	31	30	29	28	27	26	25	24	23	22	21	20
% P_{MALE}	4.5	5.9	7.8	10.1	13	16.6	20.9	26.1	31.9	38.5	45.4	52.5	59.6	66.2	72.3	77.6
% P_{FEMALE}	27.3	33.3	39.9	46.9	54.1	61.1	67.6	73.5	78.7	83.1	86.7	89.7	92	93.9	95.3	96.4

Figure 2. Preoperative Hct level and blood transfusion probability.

Hct, hematocrit; P, probability.

Discussion

This study identified risk factors for blood transfusion during isolated CABG surgery with a standardized operating technique and restrictive transfusion protocol. Age, sex, EuroSCORE, previous cardiac operations, total fluid balance after CPB, and preoperative Hct were risk factors for blood transfusion in the univariate analyses; however, preoperative anemia and female gender were the only significant independent risk factors.

Recent studies found that perioperative anemia was an independent risk factor for unfavorable outcomes following CABG, such as acute renal failure, neurological injury, and mortality.[11-13] Although Hb alone does not accurately reflect the available oxygen or RBC volume, it is still the most widely used transfusion trigger, and perioperative anemia is frequently managed with blood transfusion.[14,15] However, independent of anemia, blood transfusions have also been reported to be associated with an increase in the rate of major complications, including kidney and lung injury, infections, and mortality after cardiac surgery.[16]

Therefore, many studies have examined how to prevent damage due to anemia and blood transfusion. Importantly, protocols have been prepared for guiding allogeneic RBC transfusion in patients with anemia.[4,17]

Despite evidence from numerous randomized clinical trials, meta-analyses, and guidelines, blood transfusion strategies after cardiac surgery differ among centers; some groups use liberal blood transfusions, while others prefer a restrictive strategy.[4,17,18] In a study of the variation in use of blood transfusion in CABG surgery (involving 82,446 cases at 408 sites), the rates of blood transfusion ranged from 7.8% to 92.8% for RBCs, 0% to 97.5% for fresh-frozen plasma, and 0.4% to 90.4% for platelets.[19]

Factors influencing blood transfusion include preoperative anemia, older age, female gender, small body size, preoperative antiplatelet or anti-thrombotic medication, redo and complex procedures, and emergency operations.[20,21] However, risk factors for blood transfusion in the context of restrictive strategies have not been adequately investigated.

We have long used a restrictive blood transfusion policy in our clinic, and have shown the benefits of this strategy. In our previous study, the total blood transfusion rate was 29.6% in isolated CABG,[22] which decreased gradually to 5.6% when using blood conservation methods and a restricted transfusion strategy. In the univariate analyses in the present study, female gender, older age, higher EuroSCORE, previous cardiac surgery, fluid balance after CPB, and low preoperative Hct were associated with RBC transfusion. However, in logistic regression analysis, only preoperative anemia and female gender remained as independent risk factors for RBC transfusion.

The finding that preoperative anemia and female gender were risk factors for RBC transfusion in our study can be explained by the influence of other factors, such as older age and higher EuroSCORE, on preoperative Hct levels. In females, prior pregnancies, menstruation, nutrient insufficiency in the elderly, and chronic inflammation all lower Hct levels.[22,23] Females also have lower body mass index and circulating blood volume, which influence RBC transfusion.[24,25] The priming volume of the CPB circuit was the same in all of our patients, indicating that females are more prone to dilutional anemia and, ultimately, RBC transfusion.

One of the most important reasons why transfusion is needed in some cardiac surgeries is excessive peri- or postoperative bleeding. However, the amount of bleeding and rate of blood transfusion were not correlated in our study. This might be related to factors such as meticulous bleeding control, the use of autotransfusion during the operation and the first 6 hours postoperatively, and a strict perioperative transfusion policy. These factors might explain why other variables significant in the univariate analyses were not significant in the multivariate analysis.

Study Limitations

The main limitations of our study were the non-randomized, observational design and relatively small number of patients. Moreover, there were no preoperative interventions for patient blood management. However, as a strength of the study, all operations were performed by the same team using similar blood transfusion practices.

Conclusion

Although many risk factors for transfusion have been identified in patients undergoing cardiac surgery, we found that preoperative anemia and female gender were risk factors specifically for those undergoing coronary bypass surgery using a restrictive blood strategy. Other identified risk factors may be associated with preoperative anemia. Prospective randomized controlled studies with large numbers of patients are needed to validate our findings.

Ethics Committee Approval: This study was approved by Institutional Review Board of Acıbadem University (ATADEK; 2022-07/30).

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Internally and externally peer-reviewed.

Author Contributions: Concept - M.K., C.A.; Design - Ö.I.K., C.A.; Supervision - F.T., C.A.; Materials - M.K., A.Ü.G., Ş.Ş.; Data Collection and/or Processing - Ö.I.K., M.K. C.A.; Analysis and/or Interpretation - M.K., C.A.; Literature Review - Ö.I.K., A.Ü.G., Ş.Ş.; Writing - Ö.I.K., M.K., A.Ü.G.; Critical Review - A.Ü.G., Ş.Ş., F.T., C.A.

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

Funding: The authors declared that this study has received no financial support.

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DOI: 10.4274/TJAR.2023.22995

Original Article

Cardiovascular and Thoracic Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):331-340

Atrial Fibrillation and Perioperative Inflammation (FIBRILLAMMED Study): A Retrospective Analysis of the Predictive Role of Preoperative Albumin-Adjusted Platelet-Leukocytic Indices in OPCABG

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Cite this article as: Magoon R, Shri I, Kashav RC, et al. Atrial Fibrillation and Perioperative Inflammation (FIBRILLAMMED Study): A Retrospective Analysis of the Predictive Role of Preoperative Albumin-Adjusted Platelet-Leukocytic Indices in OPCABG. *Turk J Anaesthesiol Reanim.* 2023;51(4):331-340.

Abstract

Objective: New-onset atrial fibrillation (NOAF), an important postoperative complication, has pertinent inflammatory links. Motivated by the encouraging literature on the prognostic role of hypoalbuminemia, leukocytic indices [LIs: neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR)], systemic inflammation response index (SIRI=NLR×monocyte) and platelet-leukocytic indices [PLIs: platelet-to-lymphocyte ratio (PLR)], systemic immune inflammation index (SII=NLR×platelet), aggregate index of systemic inflammation (AISI=NLR×platelet×monocyte), we sought to investigate the NOAF-predictive value of preoperative albumin-adjusted indices (aa-LIs and aa-PLIs) in an off-pump coronary artery bypass grafting (OPCABG) setting.

Methods: Of 899 patients, 151 patients (16.79%) developed the primary outcome i.e. NOAF that was analyzed further retrospectively for its predictors instead of the highlighted text perioperative data of 899 patients undergoing elective OPCABG, were retrospectively analyzed. The study participants were categorized into non-NOAF and NOAF groups (defined as new-onset atrial arrhythmia with irregular RR interval with indistinct *P* wave in the first week postoperatively).

Results: One hundred and fifty-one patients (16.79%) developed NOAF. On univariate analysis: age, smoker status, The European System for Cardiac Operative Risk Evaluation (EuroSCORE) II, systemic hypertension, diabetes mellitus, prior congestive heart failure (CHF), and a higher preoperative NLR, PLR, SII, and albumin were significant predictors of NOAF. While age, CHF, and EuroSCORE II retained predictive significance in multivariate analysis, LI-PLIs and albumin did not emerge as independent NOAF predictors. Notably, aa-NLR, aa-PLR, and aa-SII independently predicted NOAF on the computation of model-estimates in the regression analysis (Odds ratio; 95% confidence interval: 31.05;15.75-70.61, 1.04;1.02-1.05, 1.12;1.10-1.14, respectively, $P < 0.001$). aa-NLR ≥1.32, aa-PLR ≥52.64, and aa-SII ≥344.38 predicted NOAF with the respective AUC;sensitivity;specificity of 0.66;63.6%;73.3%, 0.63;66.2%;59.0%, and 0.65;58.3%;78.2%. Preoperative aa-NLR, aa-PLR and aa-SII also positively correlated with CHA_2DS_2-VASc score (R=0.40, 0.45 and 0.42; $P < 0.001$).

Conclusion: The independent NOAF predictive value of aa-NLR, aa-PLR, and aa-SII reiterates the inflammatory relationship of the arrhythmic complication following OPCABG.

Keywords: Albumin, coronary artery bypass grafting, neutrophil-to-lymphocyte ratio, new-onset atrial fibrillation, perioperative inflammation, platelet-to-lymphocyte ratio, systemic immune-inflammation index

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Received: July 05, 2022 Accepted: April 17, 2023

Main Points

- New-onset atrial fibrillation (NOAF), a common complication (15-36%) following coronary artery bypass grafting (CABG) has relevant inflammatory etiology.
- Literature is accruing that emphasize the NOAF predictive and prognostic value of inflammatory hematological parameters viz. leukocytic indices (LIs), and platelet-leukocytic indices (PLIs) following cardiac surgery.
- There also exist some studies suggestive of possible role of hypoalbuminemia in predicting AF.
- Therefore we retrospectively evaluated our large set of off-pump CABG data to evaluate the NOAF predictive value of albumin adjusted LIs and PLIs.

Introduction

New-onset atrial fibrillation (NOAF), frequently compounds the postoperative course following coronary artery bypass grafting (CABG) with an overall reported incidence of 15-36%, entailing a substantial postoperative morbidity-mortality.[1,2] Hence, NOAF risk-stratification constitutes an area of active research interest, particularly in order to efficiently prioritize preventive and/or therapeutic interventions.

In this context, perioperative inflammation is being increasingly scrutinized for its' role in attributing a higher risk of NOAF.[2,3] This is largely motivated by the pathophysiological proposition of an enhanced atrial conduction "anisotropy" owing to a pro-inflammatory milieu and the concomitant description of novel promising parsimonious inflammatory biomarkers.[2] With regards to inflammatory prognostication, encouraging literature is accumulating on the AF-predictive role of leukocytic ratios such as neutrophil-to-lymphocyte ratio (NLR) and platelet-leukocytic ratios and indices [platelet-to-lymphocyte ratio (PLR)] and systemic immune inflammation index (NLR×platelet), from diverse operative and non-operative predilected settings.[4-9]

Hypoalbuminemia too has considerable significance from the inflammatory standpoint and its' association with poor cardiac surgical outcomes (including NOAF).[10,11] Recent literature points towards co-existence of hypoalbuminemia with a pro-inflammatory leukocytic alteration pattern conferring a likely incremental prognostic value to the composite evaluation of the parameters.[10,12,13] Therefore, we sought to retrospectively evaluate the NOAF predictive value of albumin-adjusted leukocytic indices [aa-LIs, including aa-NLR, monocyte-to-lymphocyte ratio (aa-MLR), and aa-systemic inflammation response index (aa-SIRI=NLR×monocyte/albumin)] and platelet-leukocytic indices [aa-PLIs, including aa-PLR, aggregate index of systemic inflammation (aa-AISI=NLR×platelet×monocyte/albumin)] and albumin adjusted systemic immune inflammation index (aa-SII=NLR×platelet/albumin) in our study aiming for a simultaneous account of AF and perioperative inflammation (FIBRILLAMMED study) in patients undergoing off-pump CABG (OPCABG). The secondary objectives of the study were to derive the NOAF predictive cut-offs of aa-LIs and aa-PLIs and evaluate the correlation of preoperative hematological inflammatory indices with the CHA_2DS_2-VASc score[14] (a scoring system widely described to be associated with an elevated NOAF-risk).

Methods

After obtaining the ethical approval by Institutional Ethics Committee of Atal Bihari Vajpayee Institute of Medical Sciences & Dr. Ram Manohar Lohia Hospital [554(90/2021)/IEC/ABVIMS/RMLH/735], the present retrospective case-control study was conducted at our tertiary care referral center, on patients scheduled for elective OPCABG surgery between January 2017 and October 2021. Patients with pre-existing arrhythmia or amiodarone therapy, pre-existing neurological deficit, thyroid disorder, anemia with hemoglobin (Hb) <10.0 g dL^{-1}, unavailability of hematological investigations within 72 hours of surgery, hepatic dysfunction [serum glutamic-oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT) greater than twice the baseline], end-stage renal disease (glomerular filtration rate <30 mL min^{-1} or hemodialysis), undergoing either concomitant valve surgery and emergency CABG were excluded at the beginning of the study. Apart from these any condition affecting leukocyte counts and albumin levels were also excluded eg. active infection, patient on steroids, lymphoproliferative disorders, or systemic hypoalbuminemic disorder.

Preoperative demographical characteristics evaluated were age, sex, history of smoking, hypertension (HTN), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), history of prior congestive heart failure (CHF), history of previous myocardial infarction (MI), hyperlipidemia. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) II was evaluated for each patient from the calculator available on official website www.euroscore.org. A detailed preoperative drug history was also recorded.

Preoperative laboratory investigations compared between the groups were Hb, total leukocyte count, differential leukocyte count (DLC), platelet count, blood urea, serum creatinine, albumin, SGOT and SGPT levels, triglycerides, and on echocardiogram, left-ventricular ejection fraction and regional wall motion abnormality were noted. From the DLC, NLR, PLR, MLR, SII, SIRI and the AISI values were derived.[15] The albumin-adjusted LIs and PLIs were computed by dividing the corresponding values by serum albumin levels, eg: aa-NLR=NLR/albumin. Intraoperatively duration of surgery, the total number of grafts, vessel grafted, and number of blood and blood product units transfused were noted.

Postoperatively, the parameters recorded were duration of mechanical ventilation (DOMV), length of intensive care unit (LOS-ICU) stay, length of hospital stay (LOS-H), postoperative mean lactate levels, mean vasoactive inotropic score (VIS), incidence of major adverse cardiac events (MACE), cerebrovascular accident (CVA), acute kidney injury (AKI), intra-aortic balloon pump (IABP) insertion, and in-hospital mortality.

VIS was calculated as dopamine (μg kg^{-1} min^{-1})+dobutamine (μg kg^{-1} min^{-1})+milrinone (μg kg^{-1} min^{-1})×10+ epinephrine (μg kg^{-1} min^{-1})×100+norepinephrine (μg kg^{-1} min^{-1})×100+ vasopressin (μg kg^{-1} min^{-1})×10000.[15]

MACE was characterized by any of the following: ST-segment elevation Myocardial Ischemia, low cardiac-output syndrome (LCOS, cardiac index <1.5 L min^{-1} m^2), and cardiac-arrest.[15] Perioperative CVA was defined as any new temporary or permanent, focal or global neurologic deficit in accordance with the standardized Valve Academic Research Consortium-2 guidelines for cerebrovascular events after Trans Catheter Aortic Valve Implantation.[16] New-onset renal failure was defined according to Kidney Disease: Improving Global Outcomes Foundation as an increase in serum creatinine by ≥0.3 mg dL^{-1} (≥26.5 μmol L^{-1}) within 48 h; or an increase in serum creatinine to ≥1.5 times the baseline value, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 mL kg^{-1} h^{-1} for 6 h.[17]

CHA_2DS_2-VASc score consists of CHF, HTN, age (between 64-75, and if above 75 assigned a score of 2), diabetes, sex, history of stroke (assigned a score of 2), and vascular disease. Higher the CHA_2DS_2-VASc score, higher the stress on the atria and hence an increased incidence of NOAF and subsequent stroke.[14]

The anaesthetic induction and maintenance were as per institutional protocol. After standard premedication, arterial line was inserted and the patient was induced with 3-5 μg kg^{-1} fentanyl, 0.2 mg kg^{-1} etomidate, and 1.2 mg kg^{-1} rocuronium, titrated to hemodynamics. Patient was put on volume control mechanical ventilation at a ratio of inspired oxygen and air at 1:1, tidal volume 6-8 mL kg^{-1} to maintain end-tidal carbon dioxide at 34-35 mmHg. Central venous line and pulmonary artery catheter were placed. Anaesthesia was maintained with fentanyl, rocuronium, and isoflurane. Arterial blood gas analysis was performed at regular intervals to monitor arterial oxygen concentration, electrolyte balance, mixed venous oxygen saturation ($ScVO_2$), Hb and hematocrit, and blood sugar levels. Temperature was monitored and maintained at 35-36°C. Blood sugar values were maintained between 140-180 mg dL^{-1} by using insulin infusion if required. Blood and blood products were transfused if Hb below 10 g dL^{-1} or hematocrit <28-30% and based on Sonoclot ACT machine results respectively.

After midline sternotomy, the left internal mammary artery (LIMA) was harvested. Simultaneously saphenous venous graft too was harvested. Heparin 200 IU kg was administered after LIMA harvest to achieve an activated clotting time of >300 sec. The Octopus Evolution Tissue Stabilizer (Medtronic, Inc, Minneapolis, MN) was used to stabilize the target coronary artery and after placing intracoronary shunts as to prevent distal ischemia and maintain graft patency, distal anastomosis was performed with 7-0 prolene suture, and for proximal anastomosis 5-0 prolene sutures were used.

At the end of anastomosis, heparin was reversed with protamine in a ratio of 1 mg/100 IU of heparin and the patient shifted to ICU for elective mechanical ventilation, and extubated once the extubation criteria were satisfied. Strict hemodynamic monitoring was followed in the ICU using invasive pressure monitoring and rhythm monitoring. In addition, a 12-lead electrocardiogram was performed daily, and on the detection of arrhythmias. Occurrence of NOAF was defined as a new onset atrial arrhythmia with irregular RR intervals without discernible *P* wave on 12 lead ECG or as recorded in the case files, in the first 7 days postoperatively.[18]

Statistical Analysis

For descriptive statistics, after dividing the patients into NOAF and non-NOAF groups, continuous variables are expressed as mean, median, and standard deviation and compared across the groups using Mann-Whitney U test (on applying Shapiro-Wilk's test, the data was appropriate for non-parametric tests and hence Mann-Whitney U test was used employing respective median values), while categorical variables are expressed as number and percentage of patients and compared across the groups using Pearson's chi-square test for independence. Odds ratio (OR), 95% confidence interval (CI) and significance level is provided for variables significant in the univariate logistic regression analysis. Multivariate analysis was done using binary logistic regression. Furthermore, for the analysis of albumin-adjusted parameters three multivariate binary logistic regression analysis models were designed for variables discriminating

two groups. The threshold value effect of albumin, each hematological parameter, and albumin-adjusted ratios on NOAF was observed by receiver operating characteristic (ROC) curve, and calculated relative predictive powers as measured by area under the curve (AUC). The sensitivity, specificity, and predictive values were reported using these generated cut-offs. Association between continuous variables is captured by Spearman's rank correlation coefficient. The statistical software SPSS version 22 has been used for the analysis. An alpha level of 5% i.e. any *P* value less than 0.05 is considered significant.

Results

Out of total 1121 patients initially inducted, after accounting for the exclusion of 134 patients at the baseline, 70 patients due to intraoperative conversion to on-pump, and concomitant unavailability of adequate follow up data in 18 patients; 899 patients were eventually included in the study. The patient enrolment is illustrated in Figure 1. Of these, 151 (16.79%) developed NOAF. The perioperative variables including patient demographics, comorbidities, preoperative investigations, and intraoperative parameters were compared between the NOAF and non-NOAF groups, as depicted in Table 1.

Subsequent to univariate regression analysis, factors predicting NOAF after OPCABG were: advanced age, higher EuroSCORE II, smoker status, comorbidities viz systemic HTN, DM, prior CHF, and a higher NLR, PLR, SII and serum albumin level as outlined in Table 2. A multivariate regression analysis was further computed using the aforementioned parameters to ascertain variables independently affecting occurrence of NOAF. It was found that age (OR: 1.12; 95% CI: 1.07-1.17; $P < 0.001$), EuroSCORE II (OR: 1.95; 95% CI: 1.53-2.48; $P < 0.001$), and history of prior CHF (OR: 2.43; 95% CI: 1.43-4.11; $P=0.001$) were independent predictors of NOAF (Table 2). However, albumin and the leukocytic parameters (serum albumin and LI-PLIs) were non-significant following multivariate regression analysis, as illustrated in Table 2. Hence, model estimates were calculated for aa-LIs and aa-PLIs, after adjusting the respective NLR, PLR, and SII values for the corresponding serum albumin levels as outlined in Table 3. In model aa-NLR, it is our variable of interest and other confounding variables found significant on univariate analysis were adjusted with aa-NLR to assess if it can independently predict the occurrence of NOAF. Similarly in models B and C, confounding variables were adjusted with aa-PLR and aa-SII respectively. After computation of model estimates using aa-LIs and aa-PLIs and other parameters predicting NOAF on univariate analysis, aa-NLR, aa-PLR, and aa-SII independently predicted the occurrence of NOAF (OR; 95% CI: 31.05; 15.75-70.61, 1.04; 1.02-1.05, 1.12; 1.10-1.14, respectively; $P < 0.001$).

Subsequently, ROC analysis of serum albumin, LI-PLIs revealed the cut-off values for the development of NOAF

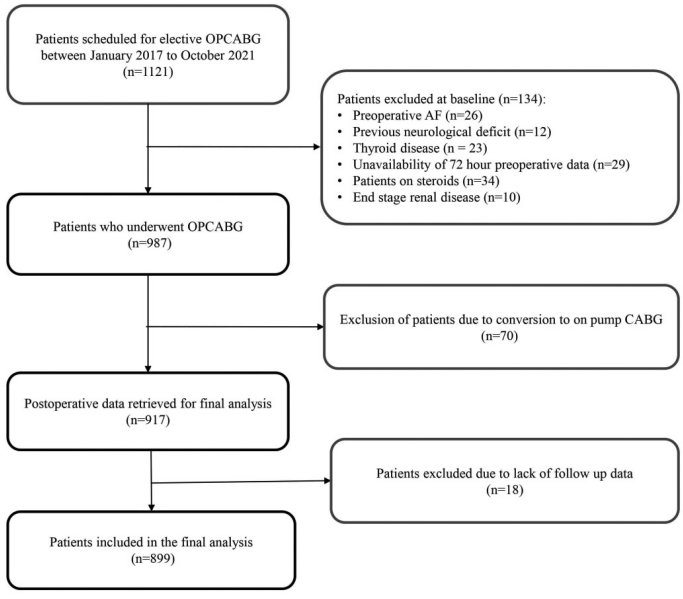

Figure 1. Flowchart depicting patient enrolment.

OPCABG, off-pump coronary artery bypass grafting; AF, atrial fibrillation.

Table 1. Comparison of Baseline Demographic and Laboratory Parameters, and Intraoperative Parameters Between NOAF and Non-NOAF Groups

Patient characteristics		NOAF (n = 151)	Non-NOAF (n = 748)	*P* value
Age (years)		67 (69-65)	66 (68-59)	<0.001
Gender	**Male**	74 (49.01%)	408 (54.54%)	0.214
	Female	77 (50.99%)	340 (45.45%)	0.213
HTN		103 (68.21%)	435 (58.16%)	0.021
DM		46 (30.46%)	165 (22.06%)	0.026
History of MI		32 (21.19%)	152 (20.32%)	0.809
History of prior CHF		30 (19.87%)	79 (10.56%)	0.001
Smoker		90 (59.60%)	365 (48.80%)	0.015
COPD		40 (26.49%)	217 (29.01%)	0.532
PVD		18 (11.92%)	111 (14.84%)	0.351
Dyslipidemia		67 (44.37%)	337 (45.05%)	0.878
Drugs	**Beta blockers**	142 (94.00%)	708 (94.65%)	0.748
	Statins	138 (91.39%)	688 (92.10%)	0.769
	Aspirin	142 (94.00%)	705 (94.30%)	0.885
	ACEIs	144 (95.36%)	712 (95.30%)	0.974
EuroSCORE II		6.36 (7.0-6.0)	5.61 (6.0-5.0)	<0.001
LVEF (%)		56.0 (60.0-55.0)	55.0 (60.0-50.0)	0.133
Hb (g dL^{-1})		10.80 (10.9-10.7)	10.60 (11.3-10.4)	0.557
TLC (cells/mm^3)		8300 (9200.0-7600.0)	8150 (9000.0-7700.0)	0.623
NLR		4.21 (4.63-3.67)	3.80 (3.95-3.75)	<0.001
PLR		174.5 (195.65-141.72)	154.80 (179.69-137.93)	0.004
MLR		0.13 (0.18-0.10)	0.13 (0.16-0.10)	0.869
SII / mm^3		1040 (1185.0-874.0)	950 (1036.32-900.95)	<0.001
SIRI / mm^3		806.25 (1040.0-577.78)	866.33 (1014.6-614.6)	0.466
AISI / mm^6		197777.78 (250593.73-141540.0)	212187.0 (253650.0-147646.61)	0.453
Platelets (cells/mm^3)		250000.0 (260000.0-230000.0)	248000.0 (260000.0-240000.0)	0.161
Urea (mg dL^{-1})		40.0 (45.0-35.0)	43.0 (45.0-36.0)	0.481
Serum creatinine (mg dL^{-1})		0.90 (1.1-0.70)	0.90 (1.1-0.7)	0.434
Albumin (g dL^{-1})		2.90 (3.2-2.6)	3.10 (3.3-3.0)	<0.001
Triglycerides		2.11 ± 0.17	2.13 ± 0.16	0.270
SGOT (U L)		55.0 (66.0-45.0)	55.0 (66.0-45.0)	0.857
SGPT (U L)		56.0 (66.0-45.0)	55.0 (66.0-45.0)	0.320
Duration of surgery (hours)		4.0 (4.0-4.0)	4.0 (4.0-4.0)	0.354
No. of vessels grafted		3.0 (3.0-3.0)	3.0 (3.0-3.0)	0.842
Type of vessel grafted	**LAD**	122 (80.79%)	605 (80.88%)	0.980
	LCx	31 (20.53%)	142 (19.12%)	0.689
	OM	110 (72.85%)	546 (72.99%)	0.970
	Diagonal	40 (26.49%)	202 (27.01%)	0.896
	RCA / PDA	124 (82.12%)	582 (77.81%)	0.239
	Ramus	26 (17.225)	164 (21.93%)	0.196
RBC transfusion (units)		1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.186
Blood products transfusion (units)		1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.921

Data is presented as a median with interquartile range (IQR) or number (%). *P* values < 0.05 are italicized.

AISI, aggregate index of systemic inflammation; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EuroSCORE II, European system for cardiac operative risk evaluation II; Hb, hemoglobin; HTN, hypertension; LAD, left anterior descending artery; LCx, left circumflex artery; LVEF, left ventricular ejection fraction; MLR, monocyte-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; OM, obtuse marginal artery; PDA, posterior descending artery; PLR, platelet-lymphocyte ratio; PVD, peripheral vascular disease; RBC, red blood cell; RCA, right coronary artery; RWMA, regional wall motion abnormality; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; SII, systemic immune inflammation index; SIRI, systemic inflammation response index; TLC, total leukocyte count.

Table 2. Univariate and Binary Logistic Regression Analysis of Parameters Predicting NOAF						
Parameter	**Univariate Analysis**			**Multivariate Analysis**		
	OR	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Patient parameters						
Age	1.127	1.080-1.177	<0.001	1.118	1.066-1.172	<0.001
HTN	1.544	1.064-2.240	0.021	1.152	0.755-1.757	0.511
DM	1.548	1.051-2.280	0.026	1.258	0.816-1.939	0.299
CHF	2.100	1.322-3.335	0.001	2.426	1.433-4.107	0.001
Smoking	1.548	1.051-2.209	0.015	1.395	0.940-2.072	0.099
EuroSCORE II	2.052	1.629-2.585	<0.001	1.948	1.529-2.482	<0.001
Laboratory parameters						
NLR	1.677	1.255-2.241	<0.001	1.556	0.773-3.314	0.216
PLR	1.007	1.002-1.011	0.004	1.002	0.995-1.009	0.539
SII (/mm^3)	1.002	1.001-1.003	<0.001	1.999	0.999-2.999	0.539
Albumin (g dL^{-1})	0.127	0.073-0.220	<0.001	0.154	0.084-0.280	0.078

P values < 0.05 are italicized.

CHF, congestive heart failure; CI, confidence interval; DM, diabetes mellitus; EuroSCORE-II, European system for cardiac operative risk evaluation II; HTN, hypertension; NLR, neutrophil-lymphocyte ratio; OR, odds ratio; PLR, platelet-lymphocyte ratio; SII, systemic immune inflammation index.

Table 3. Models for Individual NOAF Predictive Ability of Albumin Adjusted Leukocytic Indices			
Parameter	**Odds ratio**	**95% Confidence interval**	***P* value**
Model A			
Age	1.125	1.069-1.184	<0.001
HTN	1.259	0.803-1.972	0.315
DM	1.193	0.755-1.886	0.449
CHF	2.381	1.369-4.143	0.002
Smoking	1.154	0.763-1.747	0.498
EuroSCORE II	1.908	1.483-2.456	<0.001
aa-NLR	31.044	15.745-70.610	<0.001
Model B			
Age	1.127	1.073-1.184	<0.001
HTN	1.203	0.785-1.845	0.397
DM	1.268	0.815-1.973	0.292
CHF	2.273	1.328-3.891	0.003
Smoking	1.348	0.906-2.005	0.141
EuroSCORE II	2.002	1.562-2.567	<0.001
aa-PLR	1.036	1.023-1.049	<0.001
Model C			
Age	1.122	1.067-1.179	<0.001
HTN	1.226	0.790-1.904	0.364
DM	1.167	0.743-1.835	0.502
CHF	2.398	1.395-4.124	0.002
Smoking	1.180	0.785-1.774	0.426
EuroSCORE II	1.958	1.524-2.516	<0.001
aa-SII	1.120	1.100-1.140	<0.001

P values < 0.05 are italicized.

aa-NLR, albumin adjusted neutrophil-lymphocyte ratio; aa-PLR, albumin adjusted platelet-lymphocyte ratio; aa-SII, albumin adjusted systemic immune inflammation index; CHF, congestive heart failure; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; OR, odds ratio; EuroSCORE II, European system for cardiac operative risk evaluation II.

following OPCABG as illustrated in Figure 2. The derived respective cut-off values were: serum albumin ≤2.85 (sensitivity: 41.1%, specificity: 85.4%, AUC: 0.646), NLR ≥4.01 (AUC: 0.605; sensitivity: 58.9%, specificity: 80.2%), PLR ≥174.74 (AUC: 0.574; sensitivity: 46.4%, specificity: 72.9%), SII ≥1066.23 (AUC: 0.601; sensitivity: 47.0%, specificity: 82.1%). The cut-off values of aa-LI and aa-PLIs were: aa-NLR ≥1.32 (AUC: 0.661; sensitivity: 63.6%, specificity: 73.3%), aa-PLR ≥52.64 (AUC: 0.629; sensitivity: 66.2%, specificity: 59.0%) and aa-SII ≥344.38 (AUC: 0.654; sensitivity: 58.3%, specificity: 78.2%). Of note is that the AUC values for the aa-ratio indices were higher as compared to the lone ratio-indices. Secondarily, it was also found that the patients in the NOAF group had a significantly escalated incidence of poor outcomes as depicted in Table 4. Patients in the NOAF group had a significant increase in the incidence of MACE, CVA, AKI, LCOS, and the requirement of IABP. Similarly, NOAF was also found to significantly increase DOMV, LOS-ICU, and LOS-H with a higher postoperative mean lactate level, and mean-VIS score value. The in-hospital mortality, however was similar in both groups (1.99% versus 1.07%, P=0.350).

On applying Spearman's correlation analysis between CHA_2DS_2VASc, and aa-LIs and aa-PLIs, a significant linear correlation (aa-NLR: R=0.40, aa-PLR: R=0.45, aa-SII: R=0.42; $P < 0.001$) was revealed between the two parameters as depicted in Figure 3.

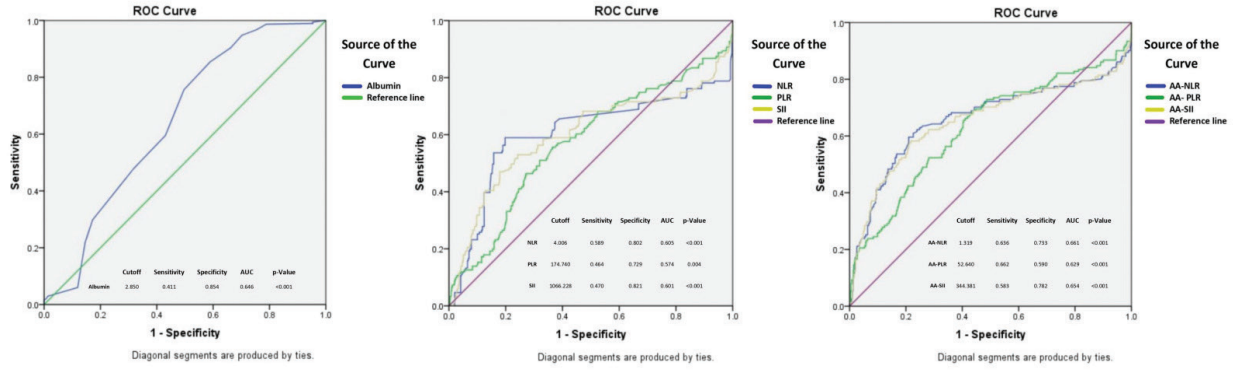

Figure 2. The receiver operating characteristic curve depicting cut off values with sensitivity, specificity and area under the curve of albumin, leukocytic and platelet leukocytic indices, albumin adjusted leukocytic indices for predicting NOAF.

ROC, receiver operating characteristic; AUC, area under the curve; NOAF, new onset atrial fibrillation; aa-NLR, albumin adjusted neutrophil-lymphocyte ratio; aa-PLR, albumin adjusted platelet-lymphocyte ratio; aa-SII, albumin adjusted systemic immune inflammation index.

Table 4. Comparison of Postoperative Outcomes in the NOAF and Non-NOAF Groups

Postoperative outcomes	NOAF group (n = 151)	Non-NOAF group (n = 748)	*P* value
DOMV (hours)	25.09 ± 6.32	12.18 ± 1.86	<0.001
Mean-Lactate (mmol L)	4.70 ± 1.04	2.03 ± 0.50	<0.001
Mean-VIS	22.32 ± 2.17	16.32 ± 2.60	<0.001
IABP	8.00 (5.30%)	12.00 (1.60%)	0.005
LCOS	14.0 (9.27%)	30.0 (4.01%)	0.006
MACE	25.0 (16.56%)	51.0 (6.82%)	<0.001
CVA	6.00 (3.97%)	10.0 (1.34%)	0.025
AKI	37.0 (24.50%)	127 (16.98%)	0.029
LOS-ICU (hours)	95.49 ± 19.02	24.68 ± 3.19	<0.001
LOS-H (Days)	13.81 ± 3.51	6.11 ± 1.49	<0.001
Mortality	3.00 (1.99%)	8.00 (1.07%)	0.350

Data is presented as a mean ± standard deviation or number (%). *P* values < 0.05 are italicized.
AKI, acute kidney injury; CVA, cerebrovascular accident; DOMV, duration of mechanical ventilation; IABP, intra aortic balloon pump; LCOS, low cardiac output syndrome; LOS-ICU, length of stay in intensive care unit; LOS-H, length of stay in hospital; VIS, vasoactive inotropic score.

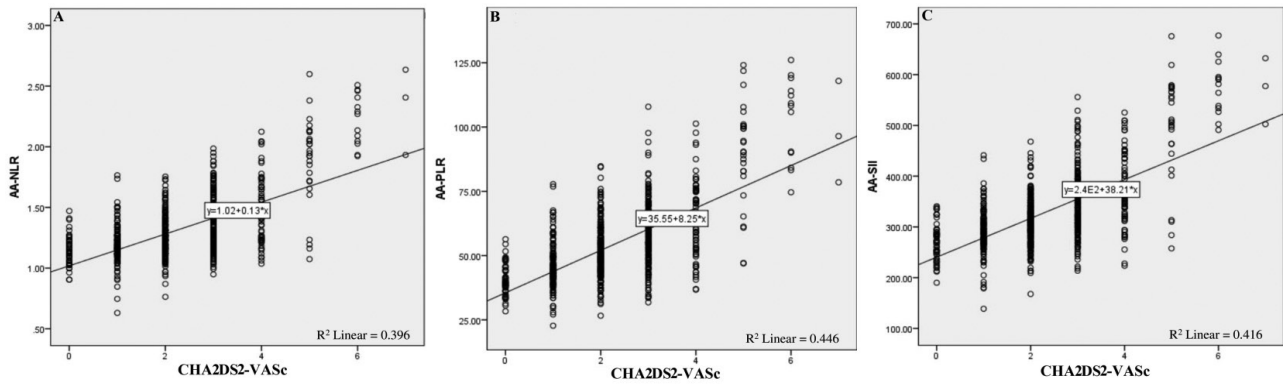

Figure 3. Spearman's rank correlation coefficient analysis of aa-NLR, aa-PLR, and aa-SII with CHA_2DS_2-VASc score.

aa-NLR, albumin adjusted neutrophil-lymphocyte ratio; aa-PLR, albumin adjusted platelet-lymphocyte ratio; aa-SII, albumin adjusted systemic immune inflammation index.

Discussion

The index elucidation of an independent NOAF-predictive significance of the aa-LIs and aa-PLIs in an OPCABG setting (ahead of the albumin and LI-PLIs alone), is congruent with the recent studies from non-operative settings suggesting an augmented inflammatory prognostic potential of a combined account of the leukocytic and albumin levels.[13,19] The 16.79% incidence of NOAF in our study relates closely to the existing literature on the research subject.[1] As far as postoperative NOAF predisposition is concerned, the risk-factors emerging from our retrospective analysis are also largely comparable to the NOAF literature in cardiac surgical arena.[14,20]

Inflammatory conditions such as pericarditis, postoperative period, and histological findings of inflammatory infiltrates in cases of lone AF suggest inflammation is intimately associated with the occurrence of AF, the major research element in the index study.[21] The postoperative inflammatory atrium is "anisotropic" i.e. variegated with cells having different refractory periods and conduction velocities, enhancing its susceptibility to aberrant electrical activity.[2] A 2014 systematic review by Jacob et al.[3] highlighted the importance of white blood cell elevations in predicting NOAF after cardiac surgery. Furthermore, the 2020 meta-analysis by Liu et al.[4] distinctively addressed the research subject of NLR predictive value of AF in cardiac surgery by a pooled analysis of 12 studies and 9,262 patients. They outlined preoperative NLR as a significant predictor of NOAF (OR: 1.42, 95% CI: 1.16-1.72) and concluded that the former emerges as a promising NOAF prognostic marker but simultaneously flagged the residual potential sources of heterogeneity.[4] Our study also delineated preoperative NLR as a NOAF predictor in univariate but not in multivariate analysis. The preoperative NLR cut-off of 4.01 derived in our study, also corroborates with the threshold NLR values described in the studies included in the Liu et al.[4] meta-analysis. Interestingly, the Liu et al.[4] meta-analysis additionally demonstrated that an elevated postoperative NLR fails to predict NOAF. Meanwhile, OPCABG is considered to be associated with lower incidence of NOAF in view of the absence of side effects of extracorporeal circulation and inadequate myocardial protection as well as due to advances in the OPCABG techniques.[22] The incidence of AF in our study is 16.79%, commensurate with that in the literature and less than on-pump CABG which is 21.7%.[22]

Ahead of NLR, PLR and SII have received research attention in the purview of NOAF prediction following cardiac surgery. A preoperative NOAF-predictive PLR cut-off of 174.74 emanating from our study exceeds the 119.3 cut-off of PLR outlined by Gungor et al.[5]. Nonetheless, there is a dearth of literature on PLR cut-offs for post-cardiac surgery NOAF prediction in order to draw holistic comparisons. As far as preoperative SII is concerned, our cut-off value of 1066.22 mm^3 adds to the recent studies by Selcuk et al.[7] and, Ata and Abanoz[23] highlighting NOAF-predictive SII cut-offs of 807.8 mm^3 and 986 mm^3, in their respective operative settings of isolated CABG.

Specific to the post-CABG NOAF links of hypoalbuminemia, Akgül et al.[11] outlined significantly lower albumin levels of 2.87 ± 0.34 g dL^{-1} in NOAF-patients versus 3.77 ± 0.47 g dL^{-1} in non-NOAF patients. The corresponding NOAF-predictive cut-off was 3.05 g dL^{-1} in the Akgül et al.[11] study whereas 2.85 g dL^{-1} emerged as the NOAF-predictive albumin cut-off in our OPCABG cohort. More importantly, the higher OR of C-reactive protein (CRP) albumin ratio (OR: 1.85; 95% CI: 1.60-2.14; $P < 0.001$) in comparison to the serum CRP and albumin levels alone (OR: 1.16; CI: 1.11-1.20; $P < 0.001$; OR: 0.44; CI: 0.26-0.86; $P < 0.001$, respectively) outlined by Karabacak et al.[24] in 830 CABG patients, epitomizes the basic concept of our study

propounding the need for a comprehensive inflammatory assessment.

Appropriate to the context of the prognostic value-addition owing to a combined account for hypoalbuminemia and inflammatory leukocytic alterations, Zhang et al.[13] recently highlighted the association of systemic inflammation score (SIS, a score computed by relative weight analysis of albumin and leukocytic ratios) with AF in 376 pairs of cases and controls using a propensity score matching system. However, our study evaluated a homogeneous surgical cohort (CABG) and adjusted the individual leukocytic ratios and the indices to the albumin levels motivated by the recent Yoon et al.[12] elucidation of the co-existence of lower albumin levels with higher SII, in cardiac surgical patients.

The perioperative inflammatory response plays a pivotal role in the genesis of NOAF.[3,4] Alongside the comprehension of an inflammatory alliance of neutrophilia and lymphocytopenia, albumin also has vital physiological functions including the maintenance of vascular endothelial integrity, anti-oxidative and anti-inflammatory properties.[10,11,13,24,25] From a NOAF-pathophysiological perspective, perioperative inflammation renders the myocardium as a tissue mosaic of varying refractory periods and/or conduction velocities which enhances the susceptibility to aberrant electrical-activity, and conduction re-entry - the so called "anisotropic" atrium.[2]

Study Limitations

To the best of our knowledge, the index study classifies as a seminal research endeavour focusing on the NOAF-predictive value of aa-LIs and aa-PLIs in OPCABG. Needless to say, the large homogeneous surgical cohort is the major strength of the study. Moreover, the additional evaluation of the correlation of the preoperative aa-LIs and aa-PLIs with well-established patient-centric NOAF-risk scoring systems like the CHA_2DS_2-VASc score, adds further credibility to the research findings. It is worthwhile to point out that the CHA_2DS_2-VASc score employs certain patient-risk factors such as age (which are continuous parameters, speaking strictly statistically) as categorical parameters for the scoring purposes (eg: age >75 years: scored 2 and age 65-74 years scored as 1).[14] Nonetheless, we studied such risk-parameters in their original continuous statistical connotations.

The study had its' own limitations given the retrospective design being peculiarly susceptible to residual confounding.[26] Although, as mentioned above, the Liu et al.[4] meta-analysis failed to attribute NOAF-predictive value to the postoperative NLR, the inclusion of postoperative LIs and PLIs in our study could have rendered the analysis more comprehensive. With that said, the isolated evaluation of an off-pump patient subset in our study potentially prevents the hematological and biochemical perturbations associated with the conduct of extracorporeal circulation. The lack of echocardiographic data on the concomitant atrial dimensions of the study participants, is also an important limitation considering NOAF was being evaluated as the primary outcome.[27] Lastly, inclusion of other markers like CRP could have further strengthened the inflammatory relationship proposed in the present research endeavour.[24]

Conclusion

The independent NOAF predictive value of aa-LIs and aa-PLIs reiterates the inflammatory relationship of the arrhythmic complication following cardiac surgery. While awaiting future prospective literature in this area of clinical importance, it only becomes imperative to reflect upon the need of an inflammatory account in the comprehensive risk-stratification and subsequent positive risk-modulation, aligned with the ultimate goal of improving postoperative outcomes in cardiac surgical subset.

Ethics Committee Approval: This study was approved by Institutional Ethics Committee of Atal Bihari Vajpayee Institute of Medical Sciences & Dr. Ram Manohar Lohia Hospital [554(90/2021)/IEC/ABVIMS/RMLH/735].

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer-reviewed.

Author Contributions: Concept - R.M., R.C.K., J.K.K., V.G., V.Gu.; Design - R.M., I.S.; Supervision - R.M., R.C.K., J.K.K., V.G., V.Gu.; Materials - R.M., I.S., S.D.; Data Collection and/or Processing - R.M., I.S., S.D.; Analysis and/or Interpretation - R.M., I.S., S.D.; Literature Review - R.M., I.S.; Writing - R.M.; Critical Review - R.C.K., J.K.K., V.G., V.Gu.

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

Funding: The authors declared that this study has received no financial support.

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DOI: 10.4274/TJAR.2023.221166

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Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):341-346

A Feasible Web-Conference-Style Remote Simulation using Demonstration Video Clips in Anaesthesia under the COVID-19 Outbreaks: A Preliminary Survey Study

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Cite this article as: Kojima T, Kawatsu Y. A Feasible Web-Conference-Style Remote Simulation using Demonstration Video Clips in Anaesthesia under the COVID-19 Outbreaks: A Preliminary Survey Study. *Turk J Anaesthesiol Reanim.* 2023;51(4):341-346.

Abstract

Objective: The Coronavirus disease-2019 (COVID-19) outbreak has deprived simulation-based medical education for health care workers. Attendees are strictly prohibited to converge at a simulation training venue because of the COVID-19 outbreaks. To address this issue, we developed a web-conference-style remote simulation program using demonstration video clips. This report introduced the method and described participants' satisfaction.

Methods: This preliminary survey study evaluated learners' satisfaction in multiple institutions. The Satisfaction Scale Questionnaire with High-Fidelity Clinical Simulation (SSHF) by a 5-degree scale was used to evaluate participants' satisfaction. The survey was conducted immediately after completing the simulation sessions.

Results: Ten (100%) participants (7 anaesthesia individuals, 2 anaesthesia residents and 1 nurse anaesthetist) from nine institutions responded to the survey. All median values of the satisfaction scores were ≥4.0, whereas the median values of scores for environmental fidelity and psychological insecurity were 3.5 and 3.0, respectively (P=0.005).

Conclusion: A web-conference-style remote simulation using demonstration video clips is a feasible method for conducting simulation-based medical education under COVID-19 that showed high satisfaction scores. Further, additional studies are required to explore the internal and external validity and the effectiveness of mastery learning.

Keywords: Anaesthesia, COVID-19, remote, simulation, web-conference-style

Main Points

- A web-conference-style complete remote simulation using demonstration video clips can be a feasible approach under the coronavirus disease-2019 outbreaks.
- A web-conference-style complete remote simulation using video clips focused on teaching the two aspects of team dynamics and medical management.
- The overall satisfaction scores of the participants for a complete remote simulation using video clips were generally high.

Introduction

Simulation-based medical education (SBME) is commonly performed as an effective training method to enhance individual clinical skills, judgment, team dynamics and resource management.[1] However, the Coronavirus disease-2019 (COVID-19) outbreaks have become a major obstacle in providing manikin-based SBME practices because of social distancing as participants must travel from different places and gather at a training venue

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Received: December 12, 2022 Accepted: February 02, 2023

(e.g. simulation centre or hospital). Thus, a new SBME technique that does not require learners to congregate in one place is desired.

Even under the COVID-19 outbreaks, remote simulation using telecommunication technologies can be a viable method in providing SBME since the learners can remotely participate in the simulation sessions via the internet.[2] However, a remote simulation was originally designed to remotely provide facilitation from the outside of the simulation site for the learners gathered at the simulation venue to perform a hands-on training. Therefore, the proposed method for remote simulation is not ideal to conduct SBME owing to the potential risks of COVID-19 outbreaks.

To address this issue, we modified the structure to prevent learners from gathering at the simulation venue, and they, along with the facilitators, participated in the SBME sessions remotely via the internet. The learners were unable to practice on-site simulation scenarios. Thus, we created demonstration video clips that were used as materials for discussion-based learning.

This report presents the web-conference-style remote simulation using demonstration video clips and the survey results of participants' perceptions.

Methods

Study Design, Participants

This was a preliminary survey study on anaesthesia providers, who participated in a web-conference-style remote simulation programme in October, 2021. This study obtained the approval of the Local Institutional Ethics Committee of Aichi Children's Health and Medical Center (approval number: 2021053, September 11, 2021).

Course of Web-Conference-Style Remote Simulation

Learners and facilitators remotely participated in the online conference sessions. The remote simulation was structured into a 50 min simulation session each for two scenarios (i.e. cardiac arrest and difficult airway). Two facilitators experienced in *in situ* anaesthesia simulation separately conducted each simulation session. After a brief explanation of the cases in each scenario, the learners watched a video clip of an unsuccessful demonstration. Further, the participants analysed the actions of the actors in the video clip in terms of teamwork/communication and medical expertise along with the prepared questions that were created based on the pre-determined checklists (Table 1). Between each discussion, the essential knowledge of teamwork/communication and medical knowledge was addressed by a brief didactic lecture series to enhance learners' understanding. After the discussion and a brief lecture, learners watched a successful demonstration video clip and discussed improvements in the unsuccessful demonstration video clip (Figure 1). Regarding medical knowledge, participants analysed the Pediatric Advanced Life Support (PALS) algorithm for cardiac arrest and American Society for Pediatric Anesthesia (SPA) critical events checklists for difficult airways in real-life clinical scenarios via demonstration video clips that re-enacted clinical scenes.

Simulation Scenarios

Two distinct paediatric critical scenarios during general anaesthesia (i.e. cardiac arrest and difficult airway) were created. These simulation scenarios were designed to cover the pre-determined checklists of the learners' expected actions for effective management in each critical event, and their expected actions were classified into two major categories: teamwork/communication and medical knowledge. The teamwork/communication checklists included team dynamics and interpersonal communication

Table 1. Questions that were Discussed by Learners During the Simulation Sessions of Cardiac Arrest and Difficult Airway Scenarios

Cardiac arrest scenario	Difficult airway scenario
1. What happened to the patient in the early part of the scenario?	1. What happened to the patient in the early part of the scenario?
2. What did the team do immediately after the patient's health deteriorate?	2. What did the team do immediately after the patient deteriorate?
3. What are the reasons for the insufficient functioning of a team when a patient suddenly collapsed?	3. What are the reasons for the insufficient functioning of a team when a patient suddenly collapsed?
4. What were the possible reasons for hypotension after anaesthesia induction?	4. What necessary actions should be considered if you encounter a situation of "no ventilation"?
5. What will you do if pulseless ventricular tachycardia is suspected?	5. What are the purposes of team communication during a sudden deterioration in the patient's health?
6. What is high-quality cardiopulmonary resuscitation?	6. When do you start chest compression after you encounter bradycardia?
7. Please explain the algorithm of pulseless ventricular tachycardia management.	7. Please explain the algorithm of difficult airway management.

skills (i.e. role assignment, sharing mental models/critical information, closed-loop communication), whereas, medical knowledge checklists were developed based on the critical event checklists of SPA and PALS.[3,4] The learners were expected to perform all of the pre-determined tasks in the checklists.

Demonstration Video Clips for Successful and Unsuccessful Instances

Two types of demonstration video clips were developed for successful and unsuccessful instances for each scenario (i.e., cardiac arrest and difficult airway) (Figure 2). For successful instances, actors playing the roles of anaesthesiologists and operating room nurses implemented the pre-determined tasks in the checklists regarding teamwork/communication and medical knowledge. In contrast, these were not sufficiently implemented in the unsuccessful instances. The following three major components were incorporated into the successful instances, while not into the unsuccessful instances: 1) crisis management (i.e., situation awareness, resource management), 2) team dynamics (i.e., statement of emergency, sharing mental models, role assignment, frequent mutual verbal communication, closed-loop communication), 3) medical management (i.e., background knowledge, algorithm implementation). These video clips mainly focus on learning how to prevent human errors in a resuscitation scene. We applied the anaesthetists' non-technical skills scoring tool.[5] This tool has four major categories (i.e., task management, team working, situation awareness, and decision making) with three to four subcategories rated from 1 to 4. We selected most components from the tool based on the capability to learn them in discussion-style, knowledge-based learning.

The demonstration video clips show: 1) the scene of implementing the pre-determined tasks by anaesthesiologists and operating room nurses, 2) the monitor displaying vital signs of the manikin and 3) subtitles describing the conversation among actors in the demonstration scenes. In advance, to create demonstration video clips for successful and unsuccessful instances, the demonstration scenes by actors in the operating rooms and the monitor of manikin's vital signs were recorded simultaneously using video cameras. The recorded video files (i.e. MP4 format) of demonstration scenes were edited into the final demonstration video clips with subtitles of actors' conversation using a video editing software (Filmora X®, Wondershare, Shenzhen, China) (Figure 2).

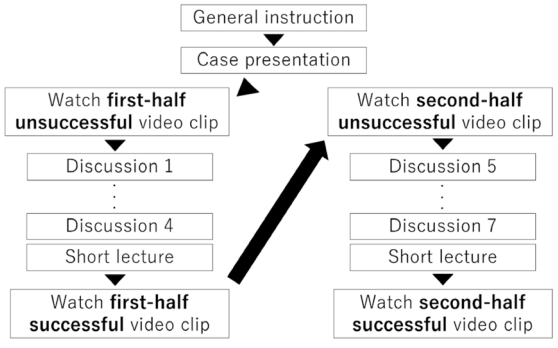

Figure 1. Flowchart of the web-conference-style simulation session of the difficult airway scenario.

Two Parts of Demonstration Video Clips

The duration of both final video clips was ~7 min, which is divided into two parts because of the progression of each scenario. The first half focused on the situation awareness regarding the patient's sudden deterioration and the team dynamics for early transition to initial treatments (e.g. declaration of the patient's deterioration, call for help, role assignment and initiation of cardiopulmonary resuscitation). In the second half, the patient's condition deteriorated more, such that individual clinical skills, judgement, team dynamics and resource management were focused on situations requiring advanced medical management (e.g. implementation of PALS and difficult airway management algorithms, closed-loop communication, recap the situation, request necessary resources).

Data Collection

Anonymous survey forms were distributed to learners after completing the simulation sessions. The data regarding the characteristics of learners, including age, sex, post-graduate year and simulation experience (i.e. none, limited, moderate or extensive) were collected. The Satisfaction Scale Questionnaire with High-Fidelity Clinical Simulation (SSHF) was used to determine the participants' satisfaction with the remote simulation sessions.[4,6] SSHF is a validated evaluation tool of simulation sessions that originally comprised 38 closed questions evaluated by a 5-degree Likert scale, integrating into eight domains: 1) simulation utility, 2) scenario cases and applications, 3) team communication, 4) self-reflection on performance, 5) increase in self-confidence,

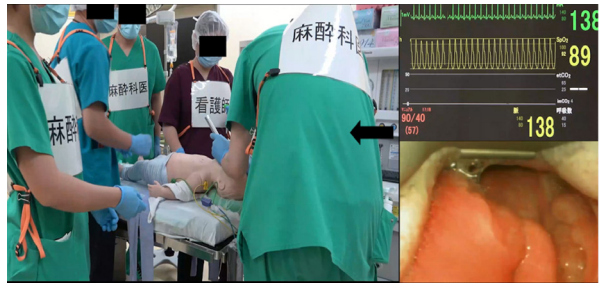

Figure 2. Screenshot of the demonstration video clip in the difficult airway scenario. An actor anaesthesiologist (black arrow) was attempting endotracheal intubation.

Left, the scene in the scenario; right upper, vital signs; right lower, a picture of the laryngeal exposure.

6) connection between theory and practice, 7) facilities and equipment and 8) negative aspects of the simulation session.[4,6] The two questions in the original SSHF: 1) were removed because of their irrelevance to the simulation scenarios in the current study since learners did not have the opportunities to improve their communication skills with the patient and family members during general anaesthesia in the operating room.

Statistical Analysis

The primary investigator collected the survey forms and summarised the descriptive statistics of the results. The summary statistics were described in median [interquartile range (IQR)] or number (%). The median values of the score in each questionnaire item were compared using the Kruskal-Wallis test. All summary statistics were calculated using STATA 17.0 (StataCorp, College Station, TX, USA).

Results

The simulation sessions involved 10 learners (7 anaesthesia individuals, 2 anaesthesia residents and 1 nurse anaesthetist) from nine institutions. The response rate was 100%.

Learners' Characteristics

The following are the learner's characteristics: age, median (IQR), 30 (27-33); female, 5/10 (50%); previous experiences of manikin-based simulation, none 4/10 (40%); limited 4/10 (40%); moderate 2/10 (20%).

Learners' Satisfaction

The median values of the scores of learners' satisfaction for the remote simulation were ≥4.0, except for the median values for the two items "the reality of facilities and equipment" (3.5) and "I was thrown off balance during some of the cases" (3.0) (Table 2). There was a significant difference among the scores (P=0.005).

Table 2. Median and Interquartile Values of SSHF[a] Items (1-19) in Participants (n = 10)

SSHF[a] items	Median (IQR[b])
1. Facilities and equipment were real	3.5 (3-4)
2. Objectives were clear cases	5 (4-5)
3. Cases recreated real situations	4 (4-5)
4. Timing for each simulation case was adequate	4.5 (4-5)
5. The degree of case difficulty was appropriate for my knowledge	4 (4-5)
6. I felt comfortable and respected during sessions	5 (5-5)
7. Clinical simulation is useful to assess a patient's clinical situation	4.5 (4-5)
8. Simulation practices help you learn to avoid mistakes	5 (4-5)
9. Simulation has helped me to set priorities for action	5 (4-5)
10. Simulation has improved my ability to provide my patients with care	4 (4-5)
11. Simulation has made me think about my upcoming clinical practice	5 (5-5)
12. Simulation improves communication and teamwork	4.5 (4-5)
13. Simulation has made me more aware/ concerned about clinical practice	4 (4-5)
14. Simulation is beneficial to relate theory to practice	4.5 (4-5)
15. Simulation allows us to plan patient care effectively	4 (4-5)
16. I have improved my technical skills	4 (4-4)
17. I have reinforced my critical thinking and decision-making	4 (3-5)
18. Simulation helped me assess a patient's condition	4 (4-5)
19. This experience has helped me prioritise care	4 (4-5)
20. Simulation promotes self-confidence	4 (3-4)
21. I have improved communication with the team	4 (4-4)
22. This type of practice has increased my security	4 (4-5)
23. I was thrown off balance during some of the cases	3 (2-4)
24. Interaction with simulation has improved my clinical competence	4 (4-4)
25. The teacher gave constructive feedback after each session	5 (4-5)
26. Debriefing has helped me reflect on the cases	4.5 (4-5)

Table 2. Continued

SSHF[a] items	Median (IQR[b])
27. Debriefing at the end of the session has helped me correct mistakes	4.5 (4-5)
28. I found out about the cases' theoretical side	4 (4-5)
29. I learned from the mistakes during the simulation	4.5 (4-5)
30. Practicality	5 (4-5)
31. Overall satisfaction with the sessions	5 (5-5)

Summary statistics were described as median (interquartile range) for each item.
[a]SSHF denotes Satisfaction Scale Questionnaire with High-Fidelity Clinical Simulation.
[b]IQR denotes interquartile range.

Discussion

This was the preliminary survey study to conduct a web-conference-style remote simulation using demonstration video clips and evaluate the perceptions of the learners. The overall satisfaction scores of the learners were generally high, whereas the scores for environmental fidelity and psychological safety were relatively lower compared with the other items.

The COVID-19 outbreaks have enforced medical educators to conduct SBME using virtual platforms. A remote simulation in operating rooms can now be a solution to provide *in situ* simulation training for anaesthesia providers to avoid participants from different sites assembling in a single venue. In the remote simulation, two potential methods exist: 1) trainees assemble in the operating room to begin a simulation scenario as a resuscitation team and the facilitator remotely teaches learners via the internet and 2) faculty members assemble in the operating room to proceed with a simulation scenario as a resuscitation team and learners remotely lead the team via the internet, However, proceeding a simulation scenario requires several participants (learners or faculty members), in both methods, to conduct the simulation scenario in each simulation training session. Therefore, we developed a web-conference-style remote simulation technique using video clip materials that allow all participants (i.e., faculty members and learners) to independently participate in the simulation sessions.

The present study showed high learners' satisfaction despite a lack of opportunities for learners to physically conduct the simulation scenario in the operating room. However, scores for environmental fidelity and psychological safety were relatively lower than that for other domains. These results are attributed to several explanations. First, learners participated in the simulation session to engage in the discussion for improving situation awareness, team dynamics, medical knowledge and clinical judgement from clinical scenes in the video clip materials that they watched on their computer screens. The absence of in-situ training in the operating room might have unsatisfied learners regarding environmental fidelity. Advanced virtual technologies (e.g. virtual reality) providing realistic remote simulation are considered a solution for providing sufficient environmental fidelity to learners participating in the remote simulation via the internet. Second, our simulation programme was developed as a practical session at an academic conference. Therefore, the simulation sessions that can endanger the learners' psychological safety because these simulation sessions were watched by other audiences via the online video-sharing platform. Our web-conference-style remote simulation can be performed within a closed community enabling facilitators to provide a psychologically safe environment for learners.

There are several strengths in our web-conference-style remote simulation technique, except for minimising the risk of COVID-19 outbreaks. First, compared with the conventional manikin-based simulation, this web-conference style simulation can accommodate more participants. Despite the number of roles in a simulation scenario being limited (e.g. leader, chest compressor and recorder), the current new remote simulation is performed in a discussion-based style, which allows numerous individuals to participate simultaneously via the internet. Second, the participants can repeatedly review the performance of the actors by comparing successful and unsuccessful instances. Comparisons of failed and ideal instances can clarify issues happening in real-life critical situations and provide solutions in that clinical context.

Study Limitations

There are several significant limitations in this study. First, a small sample size was used in this preliminary survey study. However, this new method can accommodate more people compared with conventional in-situ manikin-based simulation. Thus, further prospective studies with larger sample sizes are considered feasible. Second, most participants were unfamiliar with all components (crisis management, team dynamics, and medical management) due to a lack of knowledge and skills. The unfamiliarity with the simulation training could result in high satisfaction scores for the current simulation program. However, our simulation program did not provide opportunities for skill training.

This simulation program mainly focused on learning the knowledge aspects of the major components (i.e., crisis management, team dynamics, medical management) for successful resuscitation because a COVID-19 surge eliminated learning opportunities for novice trainees regarding team resuscitation. Third, the mastery of learning teamwork/communication and medical knowledge was not evaluated. Fourth, this remote simulation was performed in paediatric anaesthesia scenarios, which require further validation assessment in other clinical scenarios (e.g., emergency department, general paediatrics). Finally, this study does not dismiss the significance of manikin-based simulation procedures. However, in critical situations, the currently modified remote simulation cannot substitute manikin-based simulation practices to improve situation awareness and review the local response systems. Further, this new method is situated between the knowledge and practice levels in Miller's pyramid, which facilitates learners to develop a realistic image of appropriate actions to maximise the team dynamics during critical events.[7]

Conclusion

Under the COVID-19 outbreaks, a web-conference-styled remote simulation, which uses demonstration video clips can be a feasible approach for simulation-based education. Further additional prospective investigations that evaluate the effectiveness of mastery learning and validation study are required.

Acknowledgment

We would like to thank Enago (https://www.enago.jp/) for the English language review.

Ethics Committee Approval: This study obtained the approval of the Local Institutional Ethics Committee of Aichi Children's Health and Medical Center (approval number: 2021053, September 11, 2021).

Informed Consent: Written consents were obtained by all study participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.K., Y.K.; Design - T.K., Y.K.; Supervision - Y.K.; Materials - T.K.; Data Collection and/or Processing - T.K., Y.K.; Analysis and/or Interpretation - T.K.; Literature Review - T.K.; Writing - T.K.; Critical Review - Y.K.

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

Funding: The authors declared that this study has received no financial support.

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DOI: 10.4274/TJAR.2023.221010

Original Article
Paediatric Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):347-353

Comparison of Clinical Performance of C-MAC Video Laryngoscope Guided vs Blind Placement of I-Gel® in Paediatric Patients: A Randomized Controlled Open-Label Trial

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Cite this article as: Kumar R, Binahi P, Mohammed S, Syal R, Bhatia P, Jaju R. Comparison of Clinical Performance of C-MAC Video Laryngoscope Guided vs Blind Placement of I-Gel® in Paediatric Patients: A Randomized Controlled Open-Label Trial. *Turk J Anaesthesiol Reanim.* 2023;51(4):347-353.

Abstract

Objective: Placement of the supraglottic airway devices under direct vision has been shown to decrease the incidence of malposition in adults. This study was designed to compare the clinical performance of C-MAC guided and blind placement of i-gel® in paediatric patients.

Methods: The present prospective, randomized controlled study was conducted on 102 paediatric patients scheduled to undergo elective infraumbilical surgeries under general anaesthesia. Patients were randomly divided into group "B" (blind) and group "C" (C-MAC) based on the technique used for placement of i-gel®. The primary objective of the study was to compare the incidence of malposition based on the fiberoptic bronchoscope (FOB) score of the glottic view. Oropharyngeal leak pressure (OPLP), hemodynamic parameters, and insertion characteristics (time taken to insert and the number of attempts) were secondary objectives. Categorical data were presented as ratio or percentage and continuous data were presented as mean ± standard deviation or median [95% confidence interval (CI)].

Results: The incidence of malposition (Brimacombe score 1 or 2) was significantly lower in group C compared to group B (7.8% vs 49% respectively) ($P < 0.001$); implying a relative risk reduction of 2.42 (95% CI 1.72 to 3.40) with C-MAC. On FOB assessment, the median (interquartile range) Brimacombe score was significantly better in group C [4 (4-4)] compared to group B [3 (2-3)] ($P < 0.001$). The OPLP was significantly higher in group C compared to group B. Other insertion characteristics were comparable in both the study groups.

Conclusion: Compared to blind placement, C-MAC guided placement ensures proper alignment of i-gel® with periglottic structures and proper functioning of i-gel®.

Keywords: Bronchoscope, children, functional performance, general anaesthesia, supraglottic airway device

Main Points

- Supraglottic airways (SGA) have become the cornerstone for paediatric airway management. But routinely SGAs are inserted blindly.
- Radiological studies have shown that the incidence of malposition after blind insertion of SGA may exceed more than 50%.
- Malpositioned SGA devices may result in failed insertion, displacement after insertion, multiple attempts at insertion, leak during ventilation, airway trauma, aspiration of gastric contents, postoperative hoarseness, and extubation related problems.
- In this randomized controlled trial, compared to blind insertion, video laryngoscope guided insertion ensures proper alignment of i-gel® with periglottic structures and proper functioning of i-gel®.

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Received: August 08, 2022 Accepted: February 09, 2023

Introduction

The second-generation supraglottic airway (SGA) devices have revolutionized airway management in patients scheduled for surgery under general anaesthesia (GA). Each device possesses some unique features and has been used extensively in paediatric patients with varying degrees of success.[1] The i-gel® (Intersurgical Ltd, Wokingham, Berkshire, UK), a second-generation SGA, can be placed easily with fewer attempts and provide an effective seal around the airway enabling both spontaneous and controlled ventilation. The blind insertion technique is routinely used to insert the i-gel®. Radiological studies have shown that incidence of malposition after blind insertion of LMA may range up to 50-80%.[2] A study in paediatric patients undergoing magnetic resonance imaging found that radiologically proven malposition of LMA-unique was seen in 42.9% of children, though the clinical performance of LMA-unique was not hampered.[3] The consequences of the malpositioned SGA devices include failed insertion, displacement after insertion, multiple attempts at insertion, leak during ventilation, airway trauma, aspiration of gastric contents, postoperative hoarseness, and extubation related problems such as airway edema or laryngospasm.[4]

Video laryngoscope (VL) or other devices to assist under vision placement of SGA devices in adults have been shown to provide optimal placement with higher oropharyngeal leak pressure (OPLP) and better ventilation.[5,6] However, very few studies have evaluated VL-guided placement of SGA devices in paediatric patients.[7] Therefore, we planned a study to compare the C-MAC guided i-gel® insertion with that of the blind insertion technique in paediatric patients with regard to correct positioning. We hypothesized that there would be no difference in the incidence of malpositioning of i-gel® between the C-MAC guided and blind insertion technique in paediatric patients. The primary objective of the study was to compare the incidence of malposition of i-gel® between blind and C-MAC guided insertion. Simultaneously, the insertion characteristics such as the number of attempts, ease of insertion, and time required for successful insertion and the OPLP were also compared between two insertion techniques of i-gel® in paediatric population.

Methods

The present prospective, open-label, randomized controlled trial was conducted in a tertiary care referral institute, after obtaining approval from the Institutional Ethics Committee of All India Institute of Medical Sciences (AIIMS/IEC/2019-20/783) and informed written consent from parents. The study was prospectively registered with the Clinical Trial Registry of India (CTRI: www.ctri.nic.in) (ref. no- CTRI/2019/05/019405; Date of registration-29/05/2019; Patient enrolment date- 05/06/2019). We recruited 110 children aged between 2 and 6 years, belonging to the American Society of Anesthesiologists (ASA) physical status I or II, and scheduled for elective infra-umbilical surgery in supine position under GA. Children with an anticipated difficult airway, having a history of upper respiratory tract infection, gastroesophageal reflux, mass in the pharyngeal/laryngeal cavity and syndromic babies were excluded from the study.

Enrolled children were randomly assigned in a 1:1 ratio into 2 groups using the block randomization technique. An equal number of blocks of size 4 were used to divide all the patients into two groups (group B and group C). A sealed opaque envelope method was used for allocation concealment and was opened just before shifting the child inside the operating room (OR). Because of the intervention selected it was not possible to practice the double-blinding however, the outcome assessor (bronchoscopy and OPLP measurement) was not aware of the group allocation.

An appropriately lubricated i-gel was inserted blindly in group B and under direct vision using C-MAC (C-MAC® Karl Storz, Tuttlingen, Germany) VL of size 2 MAC blade in group C. The appropriate size of i-gel® was selected as per the manufacturer's recommendation i.e. size 1.5, 2, and 2.5 for children weighing 5-12, 10-20 and 20-30 kg respectively.

All patients underwent pre-anaesthesia evaluation a day before scheduled surgery and were kept fasted preoperatively according to the Indian Society of Anesthesiologists fasting guidelines.[8] As per our department protocol, premedication with intravenous (IV) ketamine 0.5 mg kg^{-1} was given in the preoperative area on the day of surgery. In children who were not having IV access preoperatively, oral midazolam syrup 0.5 mg kg^{-1} was given 20 minutes before induction of anaesthesia. Inside the OR, monitoring such as electrocardiography, non-invasive blood pressure, and oxygen saturation were attached and induction of anaesthesia was carried out with IV fentanyl 2 µg kg^{-1} and IV propofol 2.5 mg kg^{-1}. In children without having IV access, IV cannula was secured after inhalational induction using sevoflurane. After assessing the adequacy of the bag and mask ventilation, IV atracurium 0.5 mg kg^{-1} was given. After 3 min, the appropriate size i-gel® was inserted using either of two techniques according to group allocation. In both groups, i-gel® was inserted by the anaesthesiologist with having minimum experience of 5 years in anaesthesia field and who have inserted at least 100 i-gel® in paediatric patients.

In group B, the patient was placed in a "sniffing" position and lubricated i-gel® was inserted blindly by keeping it parallel to the chest wall and then glided downwards and backward along the hard palate with a continuous but gentle push until a definitive resistance was felt. In group C, the

C-MAC VL blade was inserted in the vallecula and the epiglottis lifted anteriorly under vision on the video monitor screen. The i-gel® was then advanced till the proximal bowl of the i-gel® gets positioned just below the epiglottis and its placement was labeled satisfactory when the tip of the epiglottis is aligned with the tip of the rim of the proximal cuff of the i-gel®.

After insertion, the device was connected to a breathing circuit and correct placement was assured with continuous end-tidal CO_2 ($ETCO_2$) monitoring and the presence of bilateral equal chest rise. When the device was not placed properly on the first attempt, the chin lift followed by chin lift plus jaw thrust maneuvers were used sequentially to correctly place the device. Depending upon the number of maneuvers required to correctly place the i-gel®, the ease of insertion was graded as very easy, easy, or difficult, with no maneuver, one maneuver, and two maneuvers respectively required to place the device.

Anaesthesia was maintained with 1-2% sevoflurane in a mixture of air and oxygen (40:60). Mechanical ventilation was commenced with a tidal volume (V_T) of 8 mL kg^{-1} and increased to 10 mL kg^{-1} if some leak was encountered. However, if V_T of 10 mL kg^{-1} was not delivered, reinsertion was attempted. The respiratory rate was adjusted to maintain an $ETCO_2$ of 32-38 mmHg. The OPLP was measured by closing the expiratory valve of the circle system and setting the fresh gas flow to 3 L min and the OPLP was recorded as airway pressure at which equilibrium was reached and an audible leak occurred at the neck. A well-lubricated gastric tube was inserted through the gastric port of the i-gel®. For detection of malposition (alignment with laryngeal opening) of the device, a fiberoptic bronchoscope (FOB) was inserted through the airway tube and placed 0.5 cm proximal to the distal end of the i-gel®. The fibreoptic glottis view was graded using Brimacombe score[9] (1-vocal cords not seen, 2-vocal cords plus anterior epiglottis seen, 3-vocal cords plus posterior epiglottis seen, and 4-only vocal cords visible). We considered grades 3 and 4 as correct positions while scores 1 and 2 as malposition of i-gel® as per our study protocol.

The insertion time (seconds) was defined as the time from picking up the device to the first appearance of continuous $ETCO_2$ tracing on the anaesthesia monitor. The number of attempts to insert the i-gel® was also recorded and a maximum of three attempts were allowed, after which patients were excluded from the study and an alternative device was used to secure the airway.

At the end of the surgery, neuromuscular blockade was reversed with IV glycopyrrolate and neostigmine, and after the return of adequate muscle power; the i-gel® was removed and observed for any blood staining on the device. The child was observed in the post-anaesthesia care unit (PACU) for two hours for any episodes of desaturation, PONV, sore throat, or hoarseness of voice.

Statistical Analysis

The sample size was calculated using G*Power software (version 3.1.9.2, Institute of Experimental Psychology, Heinrich Heine University, Dusseldorf, Germany).[10] Prior study indicates that the incidence of malposition using the blind insertion technique ranges from 50-80%.[4] Assuming an incidence rate of malposition with C-MAC guided technique as 0.5 or 50%, 47 subjects in each group were required at 90% power (1-β) and 5% significance (α) to reject the null hypothesis of equal incidence of malposition for C-MAC and blind insertion technique. We assumed a 10% dropout rate so our sample size was 51 subjects in each group. We used a continuity-corrected chi-squared statistic or Fisher's exact test to evaluate this null hypothesis.

The recorded data were tabulated in a Microsoft Excel spreadsheet and analyzed using SPSS version 23 (Statistical Package for Social Sciences, Inc., Chicago, IL). The data normality was tested with Kolmogorov-Smirnov one-sample test. Categorical data were presented as a ratio or percentage. Continuous data were expressed as mean ± standard deviation or median [interquartile range (IQR)] (range). The chi-square test or Fisher's exact test was used to analyze the categorical variables while the intergroup comparison of continuous outcomes was analyzed using an Independent Samples t-test or Mann-Whitney U test. The strength of association between insertion technique and the anatomical fit of the device was calculated in terms of the relative risk reduction. The statistical significance was represented as a confidence interval and the level of significance was set at $P < 0.05$.

Results

A total of 110 children were assessed for eligibility. Three patients developed desaturation after induction so the airway was secured with an endotracheal tube (ETT) and 5 patients had an upper respiratory tract infection. So, a total of 102 children were finally recruited for the trial and randomized evenly into two treatment groups. Data from both groups were collected and analyzed according to the assigned groups (Figure 1). The demographic characteristics (age, gender, weight, height, and body mass index) and the size of the device used were comparable between both groups (Table 1).

On FOB assessment, the median [(IQR) (range)] of Brimacombe score was significantly better in group C [4 (4-4) (1-4)] compared to group B [3 (2-3) (1-4)] ($p \leq 0.001$). The incidence of malposition (Brimacombe score 1 or 2) was significantly lower in group C compared to group B (7.8% vs 49% respectively) ($P \leq 0.001$); implying a relative risk reduction of 2.42 (95% CI 1.72 to 3.40) with C-MAC (Figure 2).

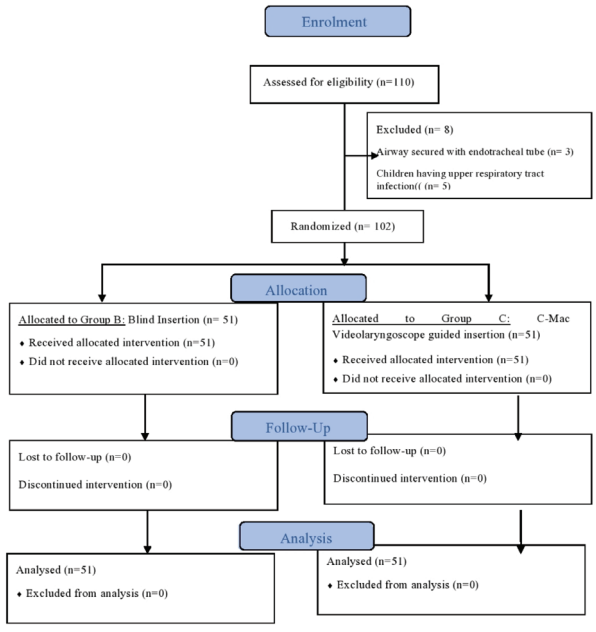

Figure 1. CONSORT flow diagram.

The insertion time (sec) was significantly higher in group C compared to group B [mean difference (95% CI) -7.1 (-8.7 to -5.5); $P \leq 0.001$] (Table 2). The OPLP was also significantly higher in group C compared to group B [mean difference (95% CI) -4.3 (-4.9 to -3.6); $P \leq 0.001$] (Table 2). The first attempt success rate was significantly higher in group C compared to group B (44 vs 35) (P=0.033). The ease of device insertion as calculated from the no of maneuvers required for correct positioning of the device was more in group C than in group B. The median [(IQR) (range)] of maneuvers required for correct positioning in groups B and C was 2 [(1-2) (1-3)] and 1 [(1-2) (1-2)] respectively with a median difference (95% CI) 1.0 (0.05 to 0.5); $P \leq 0.018$ (Table 2).

Table 1. Comparison of Demographic Profile and Size of I-Gel® Used Between Study Groups

Parameter	Group B (n = 51)	Group C (n = 51)	*P* value
Age (years)[1]	3.539 ± 1.69	3.661 ± 1.26	0.343
Weight (kg)[1]	14.51 ± 3.5	15.48 ± 3.78	0.391
Gender (male / female) (%)[2]	40 / 11 (78.4 / 21.6)	42 / 9 (82.4 / 17.6)	0.618
Size of i-gel® (1.5 / 2 / 2.5) (%)[3]	14 / 34 / 3 (27.5 / 66.6 / 5.9)	9 / 38 / 4 (17.6 / 74.6 / 7.8)	0.307

Values are presented as mean ± standard deviation and numbers (n). [Test applied- independent samples t-test ([1]); chi-square test ([2]) and Fisher's exact test ([3])]

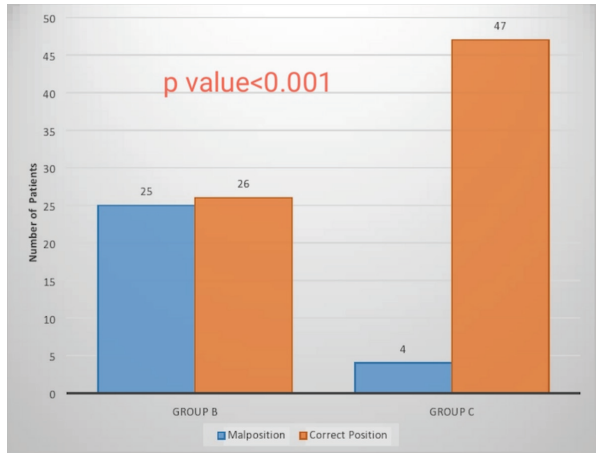

Figure 2. Comparison of malposition of i-gel® between both the groups.

In group B, 4 patients while in group C one patient had blood on the device after removal. One patient in group B had a minor dental injury (Table 3). None of the children in either group experienced hoarseness of voice or sore throat.

Table 2. Comparison of Insertion Characteristics and Oropharyngeal Leak Pressure Between Study Groups

Variable	Group B (n = 51)	Group C (n = 51)	Mean difference (95% CI)	Relative risk reduction (95% CI)	*P* value
Brimacombe score (Correctly placed/Malpositioned)[1]	3 [(2-3) (1-4)][#] (26 / 25)	4 [(4-4) (1-4)][#] (47 / 4)	-	2.420 (1.721- 3.404)	<0.001[†]
Insertion time (sec)[2]	14.5 ± 3.8[##]	21.6 ± 4.6[##]	-7.1 (-8.7 to -5.5)	-	<0.001[†]
OPLP (cmH_2O)[2]	21.8 ±1.9[##]	26 ± 1.4[##]	-4.3 (-4.9 to -3.6)	-	<0.001[†]
Ease of insertion (1 / 2 / 3)* (%)[1]	22 / 24 / 5 (43.1 / 47.1 / 9.8)	31 / 20 / 0 (60.8 / 39.2 / 0)	-	-	0.018[†]
Insertion attempts (1 / 2 / 3) (%)[1]	35 / 16 / 0 (68.6 / 31.4 / 0)	44 / 7 / 0 (86.3 / 13.7 / 0)	-	-	0.033[†]

Values are presented as median (IQR) (range) or mean ± standard deviation or number/proportion. [([#]represents median (IQR) (range)], ([##]represents mean±SD), (*1: easy, 2: moderate, 3: difficult) ([†]denote statistically significant p-value) (OPLP: oropharyngeal leak pressure). [Test applied- Mann-Whitney U test ([1]); independent samples t-test ([2])]

Table 3. Comparison of Postoperative Complications of I-Gel® Insertion Techniques		
	Group B (n = 51) (%)	Group C (n = 51) (%)
Dental injury	0 (0)	1 (1.96)
Blood stained device	4 (7.8)	1 (1.96)

Discussion

The present study found that the C-MAC guided insertion of i-gel® was associated with a significantly lower incidence of malposition and significantly higher OPLP compared to the blind insertion technique. Also, C-MAC guided insertion of i-gel® was associated with significantly better first-attempt success rate and ease of device insertion, and lower device-related adverse effects.

The advancement in anaesthesia practice is towards performing procedures under the vision and includes ultrasound assistance for regional blocks, ultrasound-guided central venous cannulation, fiberoptic/VL guided endotracheal intubation, etc. Anaesthesiologists almost confirm the correct position of the ETT and corrective measures are immediately taken in the context of misplaced ETT but often accept suboptimally placed SGAs.[11] The Difficult Airway Society and the ASA difficult airway guidelines recommend blind airway management unreliable and VL has become an integral part of airway management.[12,13] The correct placement of SGAs after blind insertion is often assessed by indirect measures such as adequate chest rise, $ETCO_2$ monitoring, measurement of OPLP, leaks during ventilation and cuff pressure. The fiberoptic assessment of the glottis view provides the most reliable assessment of the correct position of SGA but is not practiced routinely. VL offers better glottis visualization on the screen and enables correct placement of SGA beneath the glottis, thereby preventing epiglottic down folding or distal cuff displacement and improving functional or anatomical optimization of SGA.[14]

Fiberoptic evaluation after blind insertion of SGAs has shown the tip of the epiglottis in the bowl of SGA in over 50% of patients.[3] Other suboptimal positions described are epiglottis downfolding during device insertion, misalignment between the epiglottis and SGA cuff, inappropriate intra cuff pressure or epiglottis obstructing the airway in the bowl of SGA.[2] In adults, several adjuncts such as Macintosh laryngoscopes, lightwand, C-MAC VL and other VL have been used to guide under vision placement of SGA.[5,6,14-18]

In our study, we observed a 2.42 times risk reduction of malpositioned i-gel® in group C compared to group B in pediatric patients. Behera et al.[7] evaluated the effectiveness of under vision placement (direct laryngoscopy or VL) of Ambu AuraGain in paediatric patients. The incidence of malposition was 44% in blind insertion, 48% in DL group, and 64% in the VL group with no statistical difference. In fact, the reported incidence of malposition in vision-guided group was higher compared to previous studies as they considered the only laryngeal view without the epiglottis as the optimal position of the SGA.[6] In paediatric patients, the difficulty might be encountered in lifting the large-sized epiglottis which might be caught in the bowl of Ambu AuraGain. They also found no impact on ventilation and the absence of leaks in the majority of the patients in all three groups.

VL offers distinct advantages over the standard Macintosh blade for LMA insertion. First, the camera on the VL blade offers a wider 60° angle of view compared to just a 15° angle of view with a standard laryngoscope blade. Second, due to the proximity of the camera and light source to the tip of the VL, the glottis can be visualized in proximity allowing optimal insertion and correction of any malposition of the SGA. Third, others can also visualize the screen simultaneously and may help in maneuvers for correcting any suboptimal placement of the device.[18] Other direct viewing methods such as visual stylet-guided insertion of SGA also allow visual confirmation of positioning of SGA and allow better placement compared to conventional blind technique.[19] In fact, Van Zundert et al.[20] proposed the development of a SGA which is to be equipped with cameras and fiberoptic illumination to provide under vision device insertion to enable correct placement of SAD position and to take corrective measures immediately if required.

Apart from bronchoscopic visualization of glottis view, measurement of OPLP is another method for evaluation of functional performance of SGA and defining the seal of the device around the airway. Similar to our results, under vision placement of SGA has reported a higher OPLP compared to blind insertion in adults.[4,14-18] Under vision optimal placement, cuff inflation to a recommended pressure of 60 cmH_2O, and immediate corrective measures result in a better seal of i-gel® and higher OPLP. Behera et al.[7] reported comparable OPLP in all the three groups, blind/DL and VL guided group as they didn't calculate the exact values of OPLP rather, noted the number of patients who had an audible leak in the mouth at 20 cmH_2O in each group.

Under vision placement of SGAs has shown a higher success rate over conventional blind insertion.[14-18] As for blind insertion, we rely on the manufacturer's recommendation for correct sized device selection, so many times the device had to be replaced by a larger-than-recommended size or a smaller size due to ventilation failure resulting in multiple attempts at insertion or sometimes securing the airway with an ETT. The reason for a better first attempt success rate with VL is that the VL blade displaces the tongue laterally and lifts the epiglottis making a room for i-gel® insertion

so it prevents any epiglottic down folding during placement of the device and maneuvers like chin lift/head tilt/jaw thrust can be given by the assistant by directly visualizing the screen.

The time taken to insert the device was more in the vision-guided group as more time was required to do the laryngoscopy, making a room for insertion of the i-gel®, lifting up the epiglottis, and then correctly positioning the device. However, from the clinical point of view, this long time is not important.

In the present study, we highlight the importance of under vision placement of SGA compared to blind insertion for optimal sealing conditions. However, there are a few limitations of the present study. First, all the device insertions were carried out by experienced anaesthesiologists for better generalization of the study result. A learning curve and practice is essential for skill acquisition and better hand-eye coordination during the operation of C-MAC VL. But practice is essential for any procedures so we recommend under vision placement of SGA should also be considered during the training of residents or less experienced anaesthesiologists. Second, we selected i-gel®, a second-generation SGA for comparison, studies may be needed to verify the efficacy of VL guided placement with other available SGAs. Third, we enrolled children above the infantile age group so the result of the study cannot be extrapolated to this vulnerable population. Finally, babies with difficult airway or syndromic babies were excluded from the trial for better generalization of the study result, but the vision-guided placement of SGA might be a useful technique in this population. Future studies with larger sample sizes and using other SGAs are required for better validation of our study results.

Conclusion

C-MAC guided i-gel® insertion prevents or corrects any malposition, offers better sealing characteristics, and improves postoperative pharyngolaryngeal outcomes. We suggest that i-gel® should be inserted under vision using VL to expand the safety of already available second-generation SGAs in paediatric airway management.

Ethics Committee Approval: Ethical approval was obtained from the Institutional Ethics Committee of All India Institute of Medical Sciences (AIIMS/IEC/2019-20/783).

Informed Consent: Written informed consent was obtained from parents.

Peer-review: Externally peer-reviewed.

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

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

Funding: The authors declared that this study has received no financial support.

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DOI: 10.4274/TJAR.2022.221042

Case Report
Regional Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):354-357

Clinical Experience for Modified Thoracoabdominal Nerve Block Through Perichondrial Approach (M-TAPA) in Five Patients. Dermatomal Evaluation and Application of Different Volumes: A Case Series and Review of Literature

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Cite this article as: Çiftçi B, Güngör H, Alver S, Akın AN, Özdenkaya Y, Tulgar S. Clinical Experience for Modified Thoracoabdominal Nerve Block Through Perichondrial Approach (M-TAPA) in 5 Patients Dermatomal Evaluation and Application of Different Volumes: A Case Series and Review of Literature. *Turk J Anaesthesiol Reanim.* 2023;51(4):354-357.

Abstract

Thoracoabdominal nerves block through perichondrial approach (TAPA) is a novel block and provides abdominal analgesia. TAPA block targets the both anterior and the lateral branches of the thoracoabdominal nerves. Modified-TAPA (M-TAPA) was defined due to the need for blocking certain dermatomes depending on the surgical incision sites. In the literature, the knowledge about the efficiency and dermatomal coverage of M-TAPA is limited. In this case series, we want to report our experiences with this issue.

Keywords: Abdominal surgery, dermatomal coverage, modified thoracoabdominal nerves block, postoperative analgesia, regional anaesthesia

Main Points

- Modified thoracoabdominal nerves block through perichondrial approach (M-TAPA) is a novel abdominal wall block and it targets anterior and the lateral branches of the thoracoabdominal nerves.
- In the literature, there are several case reports and studies about the analgesic efficacy of M-TAPA.
- However, there is still a need for the knowledge about the dermatomal coverage of M-TAPA.

Introduction

Thanks to the use of ultrasound, novel plane blocks have been defined in recent years. Recently Tulgar et al.[1] defined the thoracoabdominal nerves block through perichondrial approach (TAPA) for abdominal analgesia. TAPA block targets the both anterior and the lateral branches of the thoracoabdominal nerves. It provides effective analgesia in a large dermatomal area due to this mechanism of action. Following the description of TAPA, again Tulgar et al.[2] redefined the TAPA block and named this novel technique as modified-TAPA (M-TAPA). They defined the M-TAPA block due to the need for blocking certain dermatomes depending on the surgical incision sites. They applied 50 mL of local anaesthetic (LA) (bupivacaine 0.25%) only to the lower surface of the perichondrium. After

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Received: August 23, 2022 Accepted: December 21, 2022

the first description of M-TAPA, it has been successfully used for several abdominal procedures such as ventral hernia repair, and laparoscopic sleeve gastrectomy.[3,4] We have read with great interest the M-TAPA articles.[1-4] However, the volumes of LA used are different in each case report. Fascial plane blocks are volume-related blocks, the efficacy may depend on the LA volume.[5] Therefore, we decided to perform lower volume M-TAPA than in the literature for different laparoscopic abdominal surgeries.

Case Presentation

We performed bilateral M-TAPA in our patients after the end of the surgery before extubation (Figure 1). A high-frequency linear transducer (11-12 MHz) was placed deep into the costochondrium at the level of the 9th-10th ribs (Figures 2, 3). We used 0.25% bupivacaine for the block. We performed 400 mg ibuprofen and 100 mg tramadol on our patients 20 min before the end of the surgery. We evaluate the dermatomal area with a pin-prick test in our patients during the postoperative 1st hour. We ordered a dose of 400 mg ibuprofen IV every 8 hours for the routine postoperative analgesia protocol. We evaluated pain scores with the numeric rating scale (NRS).

Case 1 was a 25-year-old female patient (165 cm, 61 kg) with no co-morbidity, who underwent laparoscopic cholecystectomy surgery. The operation was uneventful (surgery lasted 60 min), and her hemodynamic parameters were stable during the surgery. We performed bilateral M-TAPA with 15 + 15 mL for each side (30 mL total). NRS was <2 at the postoperative 24-hour period. No additional analgesia was needed. The dermatomal area was between T6-T12 dermatomes (Table 1).

Case 2 was a 53-year-old male patient (156 cm, 68 kg) with regulated hypertension, who underwent laparoscopic cholecystectomy surgery. The operation was uneventful (surgery lasted 65 min), and his hemodynamic parameters were stable during the surgery. We performed bilateral M-TAPA with 15 + 15 mL for each side (30 mL total). NRS was <1 at the postoperative 24-hour period. No additional analgesia was needed. The dermatomal area was between T6-T11 dermatomes (Table 1).

Case 3 was a 47-year-old male patient (170 cm, 82 kg) with no co-morbidity, who underwent laparoscopic cholecystectomy surgery. The operation was uneventful (surgery lasted 50 min), and his hemodynamic parameters were stable during the surgery. We performed bilateral M-TAPA with 15 + 15 mL for each side (30 mL total). NRS was <3 at the postoperative 24-hour period. No additional analgesia was needed. The dermatomal area was between T8-T12 dermatomes (Table 1).

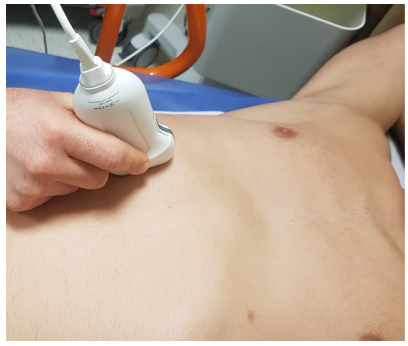

Figure 1. Patient position and probe placement during M-TAPA. Minimal compression from caudal to cranial over the probe may improve visualization.

M-TAPA, modified-through perichondrial approach.

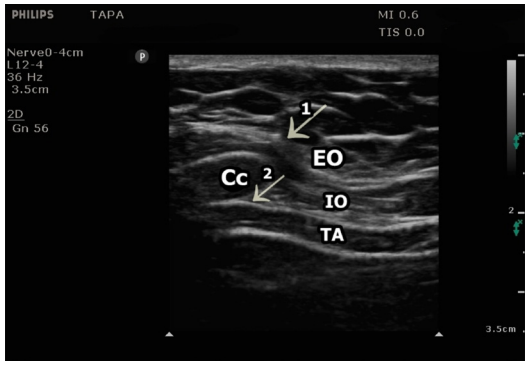

Figure 2. Sonographic anatomy of TAPA and M-TAPA. Arrows indicate the needle directions. 1 + 2 = TAPA, only 2 = M-TAPA.

Cc, costal cartilage; EO, external oblique muscle; IO, internal oblique muscle; TA, transversus abdominis muscle, M-TAPA, modified-through perichondrial approach.

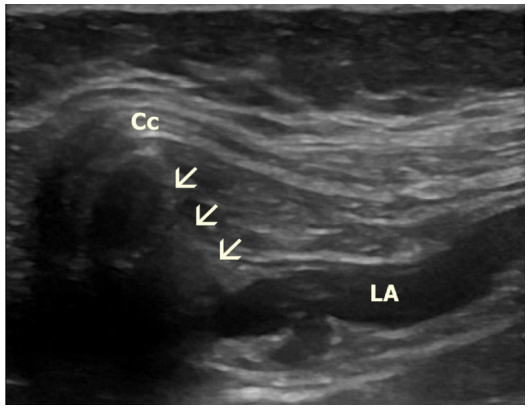

Figure 3. Sonographic visualization of LA. Arrow indicates the needle.

Cc, costal cartilage; LA, local anesthetic.

Table 1. The Demographic Data, Pain Scores, and Dermatomal Evaluation of the Patients

Case	Gender	Age	Height/weight	ASA/comorbidity	Surgery time	Volume	NRS	Dermatome anterior	Dermatome lateral
1	Female	25	165 cm, 61 kg	I/none	60 min	Totally 30 mL	<2/10	T6-T12	T7-T10
2	Male	53	156 cm, 68 kg	II/hypertension	65 min	Totally 30 mL	<1/10	T6-T11	T8-T11
3	Male	47	170 cm, 82 kg	I/none	50 min	Totally 30 mL	<3/10	T8-T12	T9-T11
4	Female	46	170 cm, 82 kg	II/hypothyroidism	180 min	Totally 40 mL	0/10	T6-T12	T7-T11
5	Male	65	185 cm, 79 kg	II/hypertension	80 min	Totally 40 mL	<4/10	T7-T11	T7-T10

Case 4 was a 46-year-old female patient (170 cm, 82 kg) with regulated hypothyroidism, who underwent laparoscopic incisional hernia repair surgery. The operation was uneventful (surgery lasted 180 min), and her hemodynamic parameters were stable during the surgery. We performed bilateral M-TAPA with 20 + 20 mL for each side (40 mL total). NRS was 0 during the postoperative 24-hour period. No additional analgesia was needed. The dermatomal area was between T6-T12 dermatomes (Table 1).

Case 5 was a 65-year-old male patient (185 cm, 79 kg) with regulated hypertension, who underwent laparoscopic inguinal hernia repair surgery. The operation was uneventful (surgery lasted 80 min), and his hemodynamic parameters were stable during the surgery. We performed bilateral M-TAPA with 20 + 20 mL for each side (40 mL total). NRS was <4 at the postoperative 24-hour period. No additional analgesia was needed. The dermatomal area was between T7-T11 dermatomes (Table 1).

The demographic data, pain scores, and dermatomal evaluation of the patients are shown in Table 1.

Discussion

M-TAPA is a novel plane block and has been used successfully for several abdominal surgeries with its opioid-sparing effect. According to our case series presentation, there are nearly similar results with different volumes of LA. The NRS of our patients was low, however, the dermatomes were different.

In the first description of M-TAPA, Tulgar et al.[2] performed 50 mL volume of LA bilaterally (25 mL for each side) for a patient who underwent laparotomy due to metastatic ovarian cancer. They performed M-TAPA just after the anesthesia induction. They reported that there was no need for extra analgesia during surgery, even though they stopped the infusion of remifentanil. They reported a dermatomal area that included T7-T11 dermatomes from the anterior axillary line to the midline bilaterally, and NRS scores <3/10. Altıparmak et al.[3] performed M- TAPA with 40 mL of LA bilaterally for a patient who underwent laparoscopic ventral hernia repair. They preferred M-TAPA instead of TAPA due to technical difficulty performing TAPA. They reported that the NRS score of the patient was 2-3/10 at the postoperative 15th and 30th minutes. The dermatomal coverage was between T5-T10 levels at the postoperative 60th min. de Oliveira et al.[6] performed M-TAPA in 12 patients who underwent laparoscopic sleeve gastroplasty surgery. They used a total of 40 to 60 mL volume of LA (4 patients to 6, respectively). They evaluated pain scores and quality of recovery scores (QoR-15) after surgery. They reported that higher pain levels were observed in patients performed with 40 mL of LA. According to their case series, the QoR-15 scores were between moderate and excellent. The authors concluded that M-TAPA may be an alternative analgesia technique for the upper abdomen levels and the lateral wall of the abdomen. Aikawa et al.[4] performed M-TAPA on a patient with co-morbidities who underwent laparoscopic sleeve gastrectomy surgery. The authors did not prefer epidural anesthesia due to previous thoracic spine surgery. They performed M-TAPA bilaterally with a 60 mL volume of LA (30 mL for each side). They reported that the patient had no pain and needed no extra analgesia during the postoperative period. They evaluated the dermatomal area between T3-T12 from the posterior axillary line to the midline. They reported that the effect of the sensorial block disappeared at 56 h after the block. Additionally, we can see different usage areas for M-TAPA in the literature. Balaban et al.[7] performed M-TAPA for surgical anesthesia after failed erector spinae plane block (ESPB) in a patient who underwent pericholecystic drainage catheter placement. They reported that the patient had a chronic obstructive pulmonary disease and had cyanosis with 86% peripheral saturation. They performed M-TAPA with a 30 mL volume of LA (bupivacaine + lidocaine) for surgical anesthesia after the failure of ESPB. After 30 min from the M-TAPA procedure, they determined sensorial coverage between T6-T11. On the other hand, a continuous catheter may be used in M-TAPA. Ohgoshi et al.[8] performed continuous M-TAPA in 2 patients who underwent adhesion surgery. They reported that patients had no pain during the postoperative period, and needed no extra analgesic.

Clinical research articles are limited to M-TAPA, yet. Bilge et al.[9] compared M-TAPA vs no block control group in their prospective and randomized study. They concluded that M-TAPA reduced pain scores and opioid consumption during the postoperative period. They reported that the QoR-40 scores were higher in the M-TAPA group. Aikawa

et al.[10] performed a dermatomal analyses study on patients who underwent gynecological laparoscopic surgery. In their prospective observational surgery, they performed M-TAPA with a 25 mL volume of LA. They reported that the highest sensory level was T7 (T5-T8) in the anterior and T9 (T7-T10) in the lateral area. They did not observe a sensory loss in the lateral area in 5 patients. A recent dermatomal analyses study was performed by Ohgoshi et al.[11] They compared external oblique muscle plane block (EXOP) vs M-TAPA in ten volunteers. They used a 20 mL volume of LA for each block. They concluded that M-TAPA anaesthetized only the anterior branches from T6/7 to T11/12, whereas EXOP anaesthetized the lateral cutaneous branches of T7-10 and T11-12. They concluded that the combined use of M-TAPA and EXOP may anaesthetize the entire abdominal wall. However, in our case series, we observed that there was a sensorial block in both the anterior and lateral abdominal walls.

Ciftci et al.[12] performed a cadaveric investigation and they compared the spread of dye between TAPA and M-TAPA. They reported that there was dye on the thoracoabdominal nerves (T4-T12), and over external and internal oblique muscles. Additionally, they reported that the spread of M-TAPA over the transversus abdominis muscle [transversus abdominis plane (TAP)] was in a wider area than TAPA. Since the thoracoabdominal nerves run through the TAP, here is important for the mechanism of action. In our patients, M-TAPA provided adequate pain control and dermatomal coverage. In a recent prospective observational pilot study, Tanaka et al.[13] evaluated the efficacy of M-TAPA in open gynecological surgery, and they performed a cadaveric evaluation. They reported that M-TAPA had dermatomal coverage in the areas supplied by the anterior branches of T8-T11. They observed dye spread between T8-T11 in both 2 cadavers.

Conclusion

In our patients, M-TAPA provided adequate pain control and dermatomal coverage. Further studies and cadaveric examinations are needed to evaluate the exact mechanism and efficiency of M-TAPA. In summary, M-TAPA provides effective pain control after laparoscopic abdominal surgeries.

Informed Consent: Written informed consent for the procedure and future publishing was obtained from patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.Ç., H.G., S.A., A.N.A., Y.O., S.T.; Supervision - B.Ç., H.G., S.A., A.N.A., Y.O., S.T.; Data Collection and/or Processing - B.Ç., H.G., S.A., A.N.A., Y.O., S.T.; Analysis and/or Interpretation - B.Ç., H.G., S.A., A.N.A., Y.O., S.T.; Literature Review - B.Ç., H.G., S.A., A.N.A., Y.O., S.T.; Writing - B.Ç., H.G., S.A., A.N.A., Y.O., S.T.; Critical Review - B.Ç., H.G., S.A., A.N.A., Y.O., S.T.

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

Funding: The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

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DOI: 10.4274/TJAR.2023.221115

Case Report
Paediatric Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):358-361

Mode of Mechanical Ventilation in a Case of Venolymphatic Malformation: Spontaneous-Saves, Positive-Precludes

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Cite this article as: Arora P, Singha SK, Mujahid OM, Kumari S, Prakashbabu A. Mode of Mechanical Ventilation in a Case of Venolymphatic Malformation: Spontaneous-Saves, Positive-Precludes. *Turk J Anaesthesiol Reanim.* 2023;51(4):358-361.

Abstract

Mediastinal venolymphatic malformations (VLM) are rare tumours, with very few reported cases in the literature. Arising often from the anterior mediastinum, VLM manifests symptoms based on invaded surrounding structures. Masses from the anterior and superior mediastinum pose an anaesthetic challenge for airway and hemodynamic management. A 7-month-old male child presented with a progressively growing mass over the left anterior chest wall for one month, about 4x4 cm, with diffuse margins and now expanded to involve the root of the neck and into the axilla. The patient was free from any apparent systemic illness. The breathing difficulty worsened in the past week with noisy respiration associated with feeding difficulty and hence sought medical admission to the paediatrics emergency unit. In conclusion, such huge mediastinal masses are managed better under spontaneous ventilation with an adequate surgical depth of anaesthesia to maintain appropriate respiratory compliance and necessitate lower peak inspiratory pressure. Given rare cases reported in the literature, similar topics would help choose the modus of ventilation and their safe management.

Keywords: Congenital abnormalities, intermittent positive-pressure ventilation, mediastinal diseases, paediatric emergency medicine

Main Points

- Mediastinal VLMs are rare tumors with no clear-cut guidelines as to how to proceed.
- Moreover, whether to maintain the patient on spontaneous ventilation or perform surgery under muscle relaxation needs to be judged on a case-to-case basis and depends upon the expertise and logistics of the setup.
- Spontaneous ventilation is preferred in patients with difficult airways and with airway compromise.

Introduction

Mediastinal venolymphatic malformations (VLM) are rare tumours, with very few reported cases in the literature. Arising often from the anterior mediastinum, VLM manifests symptoms based on invaded surrounding structures. Masses from the anterior and superior mediastinum pose an anaesthetic challenge for airway and hemodynamic management.[1] The mass can compromise the airway, where the patient's spontaneous ventilation and respiratory muscle tone may be indispensable in keeping the airway patent. Preservation of spontaneous ventilation and avoiding neuromuscular paralysis are desired to keep the airway patent by a trans-pleural gradient. Although not commonplace, cardiovascular compromise by anterior mediastinal masses can present with pericardial invasion, may compress the pulmonary artery or its branches, or cause superior vena cava compression.[2] This can trigger a cardiovascular collapse on induction of general anaesthesia. A delicate balance of anaesthetic drug usage, ventilatory strategy and understanding of the mass effect will preempt any cardiopulmonary embarrassment.

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Received: November 02, 2022 Accepted: March 20, 2023

Case Presentation

A 7-month-old male child weighing 9 kg presented with a progressively growing mass over the left anterior chest wall for one month, initially about 4 x 4 cm with diffuse margins and now expanded to involve the root of the neck and into the axilla (Figure 1). The patient was free from any apparent systemic illness. The breathing difficulty worsened in the past week with noisy respiration associated with feeding difficulty.

A contrast-enhanced computerized tomography scan (Figure 2) of the chest showed a large heterogeneously hypodense mass lesion predominantly involving the upper and partially anterior, middle, and posterior mediastinum. Superiorly the lesion was cystic. In the neck, the lesion displaced left carotid vessels, completely compressing the left internal jugular vein, with mild compression of the right internal jugular vein. The larynx was displaced anteriorly and towards the right side.

The child presenting to the paediatric intensive care unit was dehydrated; the respiratory rate was 40/min^{-1}, heart rate was 130 min^{-1}, and SpO_2 was 96% on a face mask with 4 L of oxygen. There was biphasic audible stridor, indrawing of the chest wall, and intercostal retractions. The child was posted for surgery with informed consent from the parent. The patient was pre-oxygenated and sedated using intravenous (IV) midazolam, a bolus of 0.5 mg, and IV fentanyl with a bolus dose of 10 mcg for induction anaesthesia. The trachea was intubated using an uncuffed 4.0 ID endotracheal tube (ETT) and fixed at 12 cm. The child was ventilated on SIMV-PC mode with FiO_2 of 0.4%, PEEP 6 hPa, and Pinsp of 16 hPa. On the day of surgery, the American Society of Anesthesiologist's standard monitoring, anaesthesia gas monitoring, and invasive blood pressure was applied in the operating room. The tube position was confirmed with bilateral air entry on auscultation, Rocuronium 5 mg IV was administered, and the ventilatory mode was put to PCV with a Pinsp of 23 cmH_2O (Figure 3). The tidal volume achieved was 50-60 mL, and end-tidal carbon dioxide was maintained between 35-40 mmHg. The dynamic compliance reflected was around 4-5 mL cmH_2O and airway resistance of 53 cmH_2O L^{-1} sec^{-1}.

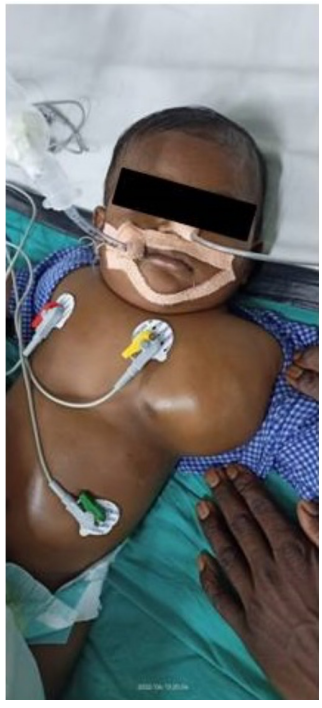

Figure 1. 4 x 4 cm mass in the anterolateral part of the neck.

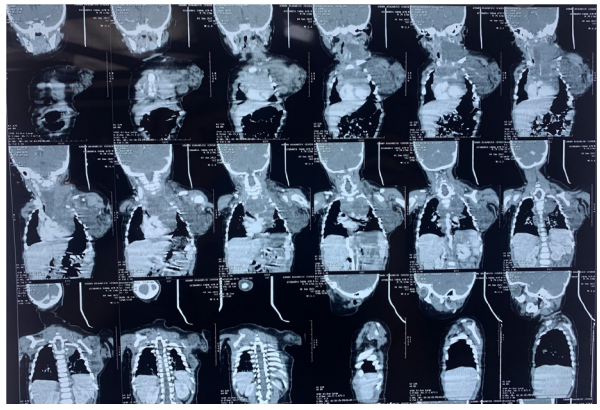

Figure 2. In the anterior, middle, and posterior mediastinum solid lesion measuring 10 cm (CC) x 7.5 cm (TR) x 7 cm (AP) and located primarily on the left side displacing the trachea, brachiocephalic artery, and superior vena cava towards the left side, encasing the arch of the aorta & its proximal branches and partially compressing the trachea above the diaphragm. Solid cystic lesion extending into the left axilla and along the left chest wall, measuring around 7.1 cm (TR) x 7.5 cm (AP) x 8 cm (CC).

Figure 3. The monitor shows intra-operative ventilatory parameters as well as the compliance of the lungs.

The surgery commenced, and the ventilation parameters remained the same after the sternotomy and the radiological findings were confirmed. After the muscle relaxation effects wore off, the patient was put on pressure support (PS) of 8 cmH_2O, generating a tidal volume of 60-65 mL with a rate of 22-24 min^{-1}. A multimodal analgesia plan comprising IV paracetamol, fentanyl, and ultrasound-guided bilateral erector spinae plane block at T3 & T5 levels with 0.125% of 14 mL ropivacaine and (1 mg) dexamethasone was instituted. The mass debulking involved extensive harmonic scalpel as vital neurovascular structures were in the vicinity or within the mas. The surgery subsequently had an uneventful course, and the child was shifted to the paediatric intensive care unit on ETT with CPAP support as the muscle relaxant effects wore off. The patient was extubated the next day in the afternoon and was on supplemental oxygen till the 5th postoperative day. The patient was on a semisolid diet for the first two days following extubation and thereafter put on a solid diet. The mass had decreased by the 4th postoperative day because of the bleomycin injection into the mass, and the rest of the course in the hospital was uneventful.

Discussion

The cyclical pressure changes inside the thorax play a central role in regulating the heart and lung function.[1] With mechanical ventilation, the atrial filling and cardiac output decrease due to increased intrathoracic pressure.[2] This primarily affects the right ventricle (RV). The work done by the RV (afterload) mainly depends on pulmonary vascular resistance (PVR), which is affected by lung volumes.[2,3] It is uncommon to see a clinically significant change in the PVR at physiological lung volumes and a PEEP of less than 10 cm H_2O.[2] However, mediastinal masses and chest wall tumours can undeniably reduce lung and chest wall compliance, hampering ventilation and compromising venous return. Spontaneous ventilation and avoiding muscle relaxant are advocated to reduce the risk of central airway occlusion in patients with mediastinal masses and even video-assisted thoracic surgeries.[4-6] Problems with ventilation are often encountered after paralysis despite the apparent prior ability to ventilate. Hence short-acting paralytic agents, if needed, are preferred,[4,7,8] usher the practice of spontaneous breathing being safer and better at preserving airway patency than positive pressure ventilation and paralysis.[5] In a recent prospective observational study on seventeen adult patients with mediastinal mass, continuous video bronchoscopy recordings of the compromised airway portion were assessed in spontaneous and controlled ventilation modes. Hartigan et al.[5] hypothesised that in adult patients with moderate to severe mediastinal mass-mediated tracheobronchial compression, anaesthetic interventions, including positive pressure ventilation and neuromuscular blockade, could be instituted without compromising central airway patency and challenged the general physiologic concepts regarding positive pressure ventilation and use of neuromuscular blocking agents.[5] However, such an observation does not extend to paediatric airways since poor reserves and higher metabolic demand are present owing to a smaller field.[9] Therefore, even though muscle relaxation was administered to ensure a still child, it increased the airway resistance as the splinting pressures were taken off and the respiratory dynamics were better maintained later with the PS mode of ventilation under deeper levels of sedation, as observed in our case. There are no clear-cut guidelines in such massive anterior mediastinal mass as to the mode of ventilation (spontaneous vs paralysis) and maintenance of the ventilation & oxygenation. The decision would depend on the morbidity of the patient and the involvement of the vital structures in the neck and anterior mediastinum, as conflicting views are found in the limited literature published about such a case.

To conclude, such huge mediastinal masses are better managed under spontaneous ventilation with an adequate surgical depth of anaesthesia to maintain appropriate respiratory compliance and necessitate lower peak inspiratory pressure. Such masses tend to involve the neurovascular structures in proximity, and their identification is paramount during debulking of the tumour. Similar rare cases in literature will help shed some insight into the ventilatory issues faced by this rare morbid condition.

Informed Consent: The child was posted for surgery with informed consent from the parent.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - P.A., S.K.S., O.M.M., S.K., A.P.; Supervision - P.A., S.K.S., O.M.M., S.K., A.P.; Data Collection and/or Processing - P.A., S.K.S., O.M.M., S.K., A.P.; Analysis and/or Interpretation - P.A., S.K.S., O.M.M., S.K., A.P.; Literature Review - P.A., S.K.S., O.M.M., S.K., A.P.; Writing - P.A., S.K.S., O.M.M., S.K., A.P.

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

Funding: The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

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DOI: 10.4274/TJAR.2023.221172

Letter to the Editor

Cardiovascular and Thoracic Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):362-363

Comment on: "Transversus Thoracic Muscle Plane Block for Attenuating the Haemodynamic Response to Median Sternotomy"

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Cite this article as: Sethuraman RM. Comment on: "Transversus Thoracic Muscle Plane Block for Attenuating the Haemodynamic Response to Median Sternotomy". *Turk J Anaesthesiol Reanim.* 2023;51(4):362-363.

Keywords: Cardiac surgeries, cardiovascular and thoracic anaesthesia, regional anaesthesia, sternotomy, transversus thoracic muscle plane block

Dear Editor,

I read with great interest the case series that evaluated the haemodynamic responses to sternotomy in patients in whom bilateral transversus thoracic muscle plane block (TTPB) was administered.[1] I wish to present my reflections on that article.

Walian et al.[1] quoted 3 references from Ueshima et al. (Reference #8-10 of Walian et al.[1]) that were retracted. I believe that these 3 references were cited despite knowing that these referenced articles were retracted because the titles of these references contain "RETRACTED" in bold format. I believe that we are not supposed to cite the retracted articles knowingly and it is the primary responsibility of the authors to be vigilant in avoiding the citation of retracted articles at any stage of publication. Walian et al.[1] could have deleted these 3 articles by Ueshima et al. during the proof check as these were retracted well ahead on the basis of misconduct, and there are other articles by Fujii et al.[2] and Zhang et al.[3] on this topic. Hence, there is no justification to cite these retracted articles. In this context, I wish to point out that recently, the inclusion of a retracted article in a meta-analysis was noted during the production, and remedial measures were taken in the nick of time.[4] Walian et al.[1] also misquoted the article by Taketa et al.[5] for TTPB, while that case series was about erector spinae plane block in thoracoscopic lobectomies; hence, it had nothing to do with TTPB or sternotomy pain.

Walian et al.[1] stated that their case series was unique as it analysed the role of TTPB specifically on haemodynamic responses. However, although it is technically correct, it is not a great difference considering the previous studies focusing on postoperative pain and analgesic consumption,[2,3] as sternotomy pain is the major contributing factor in the postoperative phase. Also, the variations in haemodynamic parameters could be influenced by other factors such as volume status, depth of anaesthesia, etc.

Peer-review: Internally peer-reviewed.

Funding: The author declared that this study has received no financial support.

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Received: December 13, 2022 Accepted: January 02, 2023

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Response to the Letter

Editorial policy note on the use of retracted/withdrawn publications as references for citations

The use of retracted publications as references is a controversial issue in the world of medical literature.

The use of retracted/withdrawn publications hasn't been advocated by the Turkish Journal of Anesthesiology and Reanimation as an editorial policy, unless such information as of basic science, anatomy, historical progress etc. is cited from these publications. The data and results of such articles shouldn't be included into manuscripts that are submitted for publication.

Kind Regards,

Editorial Team

The Turkish Journal of Anesthesiology and Reanimation

DOI: 10.4274/TJAR.2023.231423

Letter to the Editor

Cardiovascular and Thoracic Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):364-365

Authors' Response: Comment on: "Transversus Thoracic Muscle Plane Block for Attenuating the Haemodynamic Response to Median Sternotomy"

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Cite this article as: Walian A, Magoon R, Shri I, Kashav RC. Authors' Response: Comment on: "Transversus Thoracic Muscle Plane Block for Attenuating the Haemodynamic Response to Median Sternotomy"". *Turk J Anaesthesiol Reanim.* 2023;51(4):364-365.

Dear Editor,

We thank Sethuraman[1] for an interested reading of our case series[2] and would wish to respond to the points raised.

Firstly, the correspondence discusses the concerns about referencing in our manuscript.[1,2] Without denying the significance of refraining from citing retracted literature, it remains to be put forth that these articles were cited only from a technical purview of the subject and were in no form capable of affecting our findings.[3] Having said that, we do regret the inability to replace the former with alternative articles, in the later stages of the publication process. Meanwhile, the retraction of the cited literature stands notified to the readers in the bibliography, we simultaneously take the responsibility for having presented our clinical experience with utmost sincerity and again appreciate Sethuraman[1] for pointing out an important shortcoming in our drafting endeavors.[2]

Secondly, Sethuraman[1] questions our choice of citing the Taketa et al.[4] case series which features the use of erector spinae plane block (ESPB). It is understandable that on a superficial perusal, an ESPB paper might not appear to have anything to do with a case series on transversus thoracic muscle plane block (TTPB). Nonetheless, Taketa et al.[4] categorically emphasize the dermatomal role of anterior cutaneous branches of the intercostal nerves in the context of parasternal analgesia. The blockade of these branches becomes pivotal with regards to a sternotomy incision and hence, the citation in a case series proposing to achieve the same with TTPB.[2]

Lastly, being mindful of the multifactorial etiology of acute post-cardiac surgical pain, the findings of our case series specifically focusing on the hemodynamic response to median sternotomy has a distinct meaning in our opinion.[2,5] As far as the continued reliance on hemodynamic surrogates in analgesic research is concerned, the need for reliable alternate intraoperative nociception monitoring is certainly making for some ardent debates amongst the perioperative fraternity.[5]

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Received: August 18, 2023 Accepted: August 18, 2023

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DOI: 10.4274/TJAR.2023.231211

Letter to the Editor
Regional Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):366-367

Social Media Use Amongst Regional Anaesthesia and Pain Practitioners and Residents: Standardization and Ethical Considerations

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Cite this article as: Tulgar S, Ahıskalıoğlu A, Thomas DT, De Cassai A, Gürkan Y. Social Media Use Amongst Regional Anaesthesia and Pain Practitioners and Residents: Standardization and Ethical Considerations. *Turk J Anaesthesiol Reanim.* 2023;51(4):366-367.

Keywords: Algology, ethical consideration, pain, regional anaesthesia, social media

Dear Editor,

Social media has become an everyday part of social interaction and communication. All parties involved in healthcare - physicians, patients, students and educators, use social media for their own benefit. Clinicians and researchers involved in regional anaesthesia and pain management, as well as other medical fields, often share their findings, achievements, personal experiences, radiological/sonographic images on social media platforms such as Twitter, Facebook, YouTube, LinkedIn, Instagram, etc. or on personal blogs.[1]

There were two exemplary studies: one which examined the use of Twitter for communication between pain physicians during Coronavirus disease-2019 (COVID-19)[2] and one which reports changes in regional anaesthesia-related hashtags due to the COVID-19 pandemic.[3] It is possible that, in the near future, social media will become a tool used by medical journals for the rapid dissemination of scientific information.[4] Yet, how will the reliability of the information presented on social media be ensured, and how will ethical considerations be resolved?

Scientific information communicated through medical journals pass a rigorous review process in which scientific integrity and ethical considerations are closely scrutinized. Recently, the American Academy of Neurology (AAN) published a position statement regarding opportunities, challenges and ethical considerations for the use of social media in healthcare.[5] Aimed at neurologists, the article includes detailed recommendations to be followed and situations to be avoided when sharing content on social media. The topic is discussed from not only the point of view of physicians but also that of patients and researchers. Ethical problems that need to be alleviated as well as suggestions about patient education, counseling and treatment are explored. The AAN suggests proper fact checking and scientific vetting of information, use of selection bias and separation of personal and professional content as some suggestions. On the other hand provision of individual medical advice over social media and discrimination on the basis of categories such as race, ethnicity, socioeconomic status, age, gender, religion, national origin, or disability are noted as some situations that need to be avoided.[5] While suggestions made in this position statement may be a guide to regional anaesthetists and pain clinicians, it should be kept in mind that

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Received: January 23, 2023 Accepted: February 01, 2023

patient characteristics, respective training and professional communication significantly differ between neurology and regional anesthesiology clinics.

Amongst healthcare professionals, regional anesthesia and pain professionals are probably amongst those who most frequently use social media.[1] Therefore the authors propose that a more comprehensive position statement for regional anesthesia and pain professionals is required.

Since there are no routine "hashtag" patterns that are standardized or recommended by medical societies, many social media messages can be left out of studies that utilize hashtags on platforms such as Twitter. Just as keywords, terms of bias, etc. are pre-determined in meta-analyses, similarly, when conducting social media research, the type of study, sample selection, and evaluation process should be standardized and pre-determined so that more rational, reliable, consistent, and repeatable studies can be conducted. Furthermore; beneficence, non-maleficence, justice, and autonomy are principles of medical ethics that healthcare professionals should pay attention to in their social media posts, as well as broadcasting ethics which is another problem that is often neglected in social media.

We believe that a recommendation; led by national anaesthesiology societies that includes experts in humanity, law, and ethics, social media consultants, and professional influencers who frequently share regional anesthesia and pain medicine-related social media posts will be useful and informative.

Peer-review: Internally peer-reviewed.

Author Contributions: Concept - S.T., A.A., D.T.T., A.D.C., Y.G.; Design - S.T., A.A., D.T.T., A.D.C., Y.G.; Writing - S.T., A.A., D.T.T., A.D.C., Y.G.; Critical Review - S.T., A.A., D.T.T., A.D.C., Y.G.

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

Funding: The authors declared that this study has received no financial support.

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DOI: 10.4274/TJAR.2022.221120

Letter to the Editor
Intensive Care

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2023;51(4):368-369

A Simple and Novel Modification of the Nebulization Mask to Improve Nebulization in the Supine Position

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Keywords: Angle piece, catheter mount, nebulization, nebulization mask, supine

Dear Editor,

Nebulization therapy is commonly used for pre-hospital and in-hospital (operating theatre, intensive care unit and emergency area) patient care.[1] For this purpose, a nebulisation mask device is widely used, which consists of a Hudson mask, a medicine cup and an oxygen tube (Figure 1A). It is necessary to pass oxygen flow from the bottom of the medicine cup so that oxygen can go through the medicine and the medicine can change from liquid to mist form.

Although the conventional nebulization mask is beneficial when the patient is in a sitting or semi-sitting position, it has some limitations while the patient is in a supine position like drug spillage as the medicine cup becomes parallel to the ground as well as improper mist formation as the flow of oxygen not passed through the medicine from the bottom of the medicine cap (Figure 1B). It is also very difficult and cumbersome to make the drug chamber straight by holding the medicine cup by hand while the patient is in the supine position.

To overcome these problems, we suggest a novel modification of the nebulization mask kit (Romsons Pvt Ltd, India) to improve the nebulization in the supine position. For this purpose, we need one catheter mount and one angle piece (Figure 1A). The Hudson mask is detached from the medicine cup, and the proximal part of the angle piece is attached to the distal part of the medicine cup. Then the distal part of the angle piece is attached to the proximal part of the catheter mount. Finally, the distal part of the catheter mount is attached to the Hudson mask to make the final modified version of the nebulization device (Figure 1C).

The advantages of such a design would be better mist formation and drug delivery, and the medicine cup can be kept vertical so that there will be no drug spillage due to the drug chamber tilting while nebulising patients in the supine position (Figure 1D). Patients like spine injury patients who are restricted to be nebulised in the supine position in the intensive care unit and operation theatre primarily benefit from this technique.

Although, there is the possibility of turbulent flow and drug condensation at angles due to the usage of an angle piece and catheter mount between the mask and medicine cup to straighten the medicine cup.[2]

We recommend this simplified yet useful version of the conventional nebulization mask device for the nebulization of patients in the supine position.

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Received: October 25, 2022 Accepted: December 19, 2022

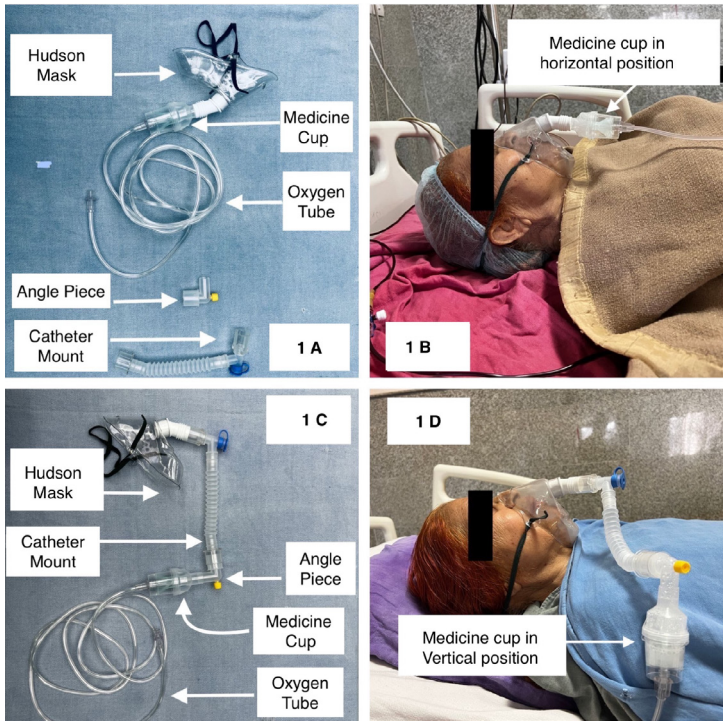

Figure 1. Modification of the nebulization mask.

Informed Consent: Informed written consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.K., H.K., V.W., J.P.S.; Design - A.K., H.K., V.W., J.P.S.; Supervision - H.K., V.W., J.P.S.; Writing - A.K.

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

Funding: The authors declared that this study has received no financial support.

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