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Intravenous Clonidine versus Intraperitoneal Clonidine for Postoperative Analgesia After Total Abdominal Hysterectomy: A Randomised Controlled Trial

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Abstract

Objective: This prospective randomised double-blind study was conducted to compare the effect of intravenous (IV) with intraperitoneal (IP) administration of clonidine with respect to analgesic efficacy and side effects.

Methods: A total of 60 American Society of Anaesthesiologists (ASA) physical status class I and II patients, aged 35–60 years, undergoing total abdominal hysterectomy, were randomly divided into 2 groups. Standard general anaesthesia technique was used. All the patients in group IV received 3 μg kg^{-1} of IV clonidine after resection of the uterus along with 0.25% bupivacaine (20 mL intraperitoneally and 10 mL as wound infiltration), whereas patients in group IP received 10 mL of normal saline intravenously and 3 μg kg^{-1} of clonidine mixed with 0.25% bupivacaine (20 mL intraperitoneally and 10 mL as wound infiltration). Postoperative analgesia was provided with IV diclofenac every 8 hours and IV fentanyl (1 μg kg^{-1}) on demand. Pain at rest, opioid consumption, level of sedation and severity of nausea were recorded for 24 hours. The heart rate (HR) and blood pressure (BP) were recorded at an interval of 15 minutes for 2 hours followed by routine hourly monitoring.

Results: Both the groups were found to be similar with respect to demography and ASA physical status. The maximum pain was felt at 6 hours in both the groups. The mean visual analogue scale score at 6 hours ($p=0.47$) was comparable. However, patients in group IV had significantly higher sedation ($p<0.001$) and nausea ($p=0.013$) scores on arrival at post-anaesthesia care unit along with a significant reduction in HR ($p=0.001$) and BP ($p=0001$) for the first 2 hours postoperatively.

Conclusion: Although IP clonidine is comparable with IV clonidine with respect to postoperative pain scores and supplementary opioid requirement, the side effects are significantly less with IP clonidine.

Keywords: Analgesia, clonidine, intraperitoneal, intravenous, adjunct, postoperative pain

Introduction

Total abdominal hysterectomy (TAH) is associated with moderate to severe postoperative pain scores (1). Various modes of pain relief have been studied with the basic aim of providing effective postoperative analgesia with minimum side effects and lower monitoring requirements and cost. The most frequently used adjuncts are opioids, which provide good pain relief but have a bundle of side effects, the serious ones being respiratory depression and bradycardia. There is limited literature regarding the role of intraperitoneal (IP) non-opioid adjuvants in the armamentarium of pain relief modalities.

Clonidine, an α2-agonist, provides effective analgesia for pain, particularly as an adjunct to local anaesthetics and opioids (2). It inhibits the release of norepinephrine from prejunctional α2-adrenoreceptors in the periphery and potentially inhibits neural activity in nociceptive pathways (3). Moreover, it augments the block by selectively blocking the

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conduction of Aδ and C fibres and by releasing encephalin-like substances, which produce a peripheral analgesic effect (4).

Various studies have been conducted to evaluate the efficacy of clonidine as an adjunct for postoperative pain, but its use as an IP adjunct has not been studied much. Moreover, intravenous (IV) clonidine, which has many side effects, has hardly been compared with its other routes of administration, especially IP (5-8). Till date, IP clonidine has not been compared with IV clonidine in patients undergoing TAH. Our study aimed to compare the postoperative analgesic efficacy of IP clonidine with IV clonidine in patients undergoing TAH and assess its effect on pain scores, the postoperative opioid requirement and, most importantly, the side effects that include nausea, sedation, bradycardia and hypotension.

Methods

After obtaining clearance from the Institutional Ethics Review Committee, this study was conducted at a tertiary care centre over a period of 1 year, where 82 patients, scheduled for the TAH, coming to pre-anaesthetic check-up clinic, were assessed for eligibility. Of them, 60 American Society of Anaesthesiologists (ASA) physical status class I and II patients aged between 35 and 60 years who planned for elective surgery under general anaesthesia were included in the study with prior written informed consent. Patients with Raynaud's disease, using adrenoreceptor agonists, antagonists or narcotics before an operation and having known hypersensitivity to clonidine were excluded. The primary objective of this study was to determine the analgesic efficacy (pain on visual analogue scale [VAS]) and side effects (nausea, sedation, bradycardia and hypotension) of IP administration of clonidine and to compare it with IV administration in patients undergoing TAH. The secondary objective was to evaluate and compare the time for rescue analgesia requirements and the total dose of opioid consumed in 24 hours postoperatively. No changes were made in outcome measures once the study commenced. Standard pre-anaesthetic evaluation was conducted, and all patients were premedicated with oral alprazolam 0.5 mg and routine acid aspiration prophylaxis. Patients were randomly divided using computer-generated random number table into 2 groups of 30 patients each. The allocation of patients into 2 groups was concealed using sealed opaque envelopes that were opened in the operation theatres just before the induction of anaesthesia by the anaesthesiologist who prepared the study drugs but did not participate in the data collection. As the patient and the data collector were unaware of the groups allotted, it was a double-blind study.

Main Points:

- Post total hysterectomy, Intraperitoneal clonidine is as good an adjunct as intravenous clonidine for pain relief.
- Clonidine reduces post-operative opioid requirement when used intravenously or intraperitoneally.
- Intraperitoneal clonidine is safer due to less side effects.
- Intraperitoneal clonidine may be used instead of intravenous clonidine as adjunct analgesic for abdominal surgeries.

Before induction, all patients were premedicated with IV midazolam (1 mg) and fentanyl (2 μg kg^{-1}). Anaesthesia was induced with IV propofol (1.5-2.5 mg kg^{-1}). Tracheal intubation was facilitated by 0.1 mg kg^{-1} of vecuronium injected intravenously. Anaesthesia was maintained with isoflurane and 66% nitrous oxide in oxygen. The patients were monitored according to basic ASA standards. Heart rate (HR) and mean arterial pressure (MAP) were maintained within 20% of the preoperative value. Hypotension (MAP of 20% of baseline or below 60 mmHg) was treated with 200–250 mL bolus of a balanced crystalloid. Bradycardia was treated with 10 μg kg^{-1} bolus of IV atropine. After Pfannenstiel incision, resection of the uterus, removal of all packs and achievement of haemostasis, the surgeon who was unaware of the group allocation instilled 20 mL of the drug solution intraperitoneally. Group IV received 3 μg kg^{-1} of clonidine intravenously, diluted up to 10 mL with normal saline over 10 minutes along with 20 mL of 0.25% bupivacaine (IP wound infiltration) plus 10 mL of 0.25% bupivacaine as skin and subcutaneous tissue infiltration. Group IP received 10 mL of IV normal saline over 10 minutes along with 20 mL (out of 30 mL) of solution containing 0.25% bupivacaine and 3 μg kg^{-1} of clonidine as IP wound infiltration. Rest 10 mL of it was given as skin and subcutaneous tissue infiltration. All patients received 1.5 mg kg^{-1} of diclofenac intramuscularly and 0.1 mg kg^{-1} of IV ondansetron half an hour before the completion of surgery. At the end of the surgery, residual neuromuscular block was reversed with neostigmine (50 μg kg^{-1}) and glycopyrrolate (10 μg kg^{-1}), and the trachea was extubated. The patients were observed for 24 hours after the surgery in the post-anaesthesia care unit (PACU) by an anaesthesiologist who was not aware of the patient's group assignment. Postoperative analgesia was provided with 1.5 mg kg^{-1} of IV diclofenac every 8 hours. The pain at rest was assessed by VAS (0–10; 0-no pain, 10-maximum imaginable pain) at the time of arrival in the PACU and then after 2, 4, 6, 12 and 24 hours after the operation by trained PACU staff. Rescue analgesia was given with 1 μg kg^{-1} boluses of IV fentanyl on demand or when VAS pain score was >3. The number of patients requiring rescue analgesia and total fentanyl consumption during first 24 hours after surgery was recorded. The level of sedation was assessed using modified Wilsons four-point sedation scale (Annexure 1). The incidence and severity of nausea was assessed by a four-point categorical scale (0-none, 1-mild, 2- moderate and 3- severe). In total, 4 mg of IV ondansetron was given for severe nausea or vomiting.

Statistical analysis

The sample size was predetermined on the basis of a previous study (5). At 95% significance level and 80% power, assuming 30% reduction in fentanyl consumption, 27 patients were required in each group. To minimise the effects of data attrition, a total of 60 patients were enrolled. We used the Statistical Package for the Social Sciences 16.0 (SPSS Inc.; Chicago, IL, USA) software, and results were expressed as the mean± standard deviation (SD). The results were statistically evaluated using unpaired and paired *t*-test to compare quantitative variables, and chi-square and Pearson's chi-square tests were used to compare qualitative tests between the different groups. A p-value of <0.05 was accepted as statistically significant and a p-value of <0.001 as highly significant.

Results

Over 1 year, from December 2013 to November 2014, all 60 patients (30 in each group) completed the study. Both the groups were comparable with respect to age, weight and ASA physical status (Table 1). The VAS scores in group IP were comparable with those of group IV (Figure 1). Furthermore, the time (p=0.227) and dose of opioid required (p=0.886) in both the groups were found to be comparable. A total of 5 patients in group IV needed fentanyl, whereas 4 patients needed opioid supplementation in group IP (p=0.718).

The maximum decrease in mean blood pressure (MBP) was seen at 30 minutes in group IV (SD=6.055; p<0.001) and at 90 minutes in group IP (SD=5.56; p<0.001). The decrease in MBP at 15 minutes was highly significant (SD=6.993; p<0.001) compared with the baseline in group IV, whereas in group IP, the decrement was insignificant for MBP (p=0.245) (Figure 2). It was found that HR at 0 minutes was comparable in both the groups, but the decrease in HR was more in group IV at 15 minutes (p=0.021), 30 minutes (p=0.002), 45 minutes (p=0.003), 60 minutes (p=0.005), 90 minutes (p=0.001) and 120 minutes (p<0.001) than that in group IP.

At the time of arrival to PACU, maximum number of patients in group IV (17 of 30) had a sedation score of 2, whereas in group IP, 18 of 30 patients had a sedation score of 1 (Table 2). Thus, the difference in sedation scores at time 0 was significant (p=0.003). Similarly, on arrival to PACU, 16 patients in group IV and 26 patients in group IP had a nausea score of 0. Nausea score of 2 was found in 12 patients in group IV (Table 3).

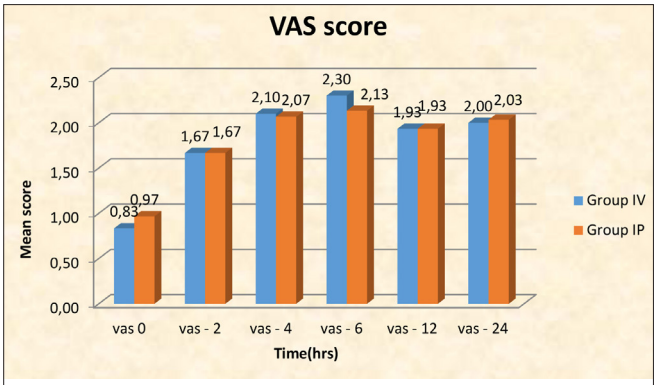

Figure 1. Mean VAS score at various intervals
IV: intravenous; IP: intraperitoneal; VAS: visual analogue scale

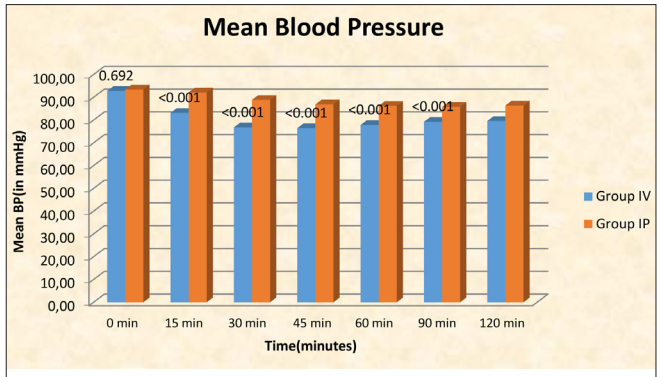

Figure 2. Mean BP at various intervals
IV: intravenous; IP: intraperitoneal; BP: blood pressure

Table 1. Comparison of patient demographics between the 2 groups

	Group	N	Mean	SD	p
Age (years)	Group IV	30	48.77	5.90	**0.61**
	Group IP	30	48.10	3.99	
Weight (kg)	Group IV	30	56.00	7.10	**0.217**
	Group IP	30	53.90	5.87	
ASA grade I	Group IV	24			
	Group IP	19			
ASA grade II	Group IV	6			**0.152**
	Group IP	11	Pearson's chi-square	2.052	

N: number of patients; IV: intravenous; IP: intraperitoneal; SD: standard deviation; ASA: American Society of Anaesthesiologist
All values given in bold are P values>0.05 i.e., insignificant

Table 2. Sedation score distribution in the 2 groups at time 0

At time 0		Number of patients	
		Group IV	Group IP
Sedation scores	0	0	1
	1	7	18
	2	16	11
	3	7	0
Total	30	30	
Chi-square tests	**Value**	**Degree of freedom**	**p**
Pearson's chi-square test	13.766	3	**0.003**
Likelihood ratio	17.031	3	**0.001**
Linear-by-linear association	13.409	1	**0**

IV: intravenous; IP: intraperitoneal
Values given in bold represents significant results

Table 3. Nausea score distribution in 2 groups at time 0 hours

Severity of nausea		Number of patients	
		Group IV	Group IP
Nausea score on	0	16	26
arrival in PACU	1	12	3
	2	2	1
Total	30	30	
Chi-square tests	**Value**	**Degree of freedom**	**p**
Pearson chi-square	8.114	2	**0.017**
Likelihood ratio	8.526	2	**0.014**
Linear-by-linear association	6.055	1	**0.014**

IV: intravenous; IP: intraperitoneal; h: hour; PACU: post-anaesthesia care unit

At 2 hours, a Pearson's chi-square value of 0.554 was noted. At 4, 6, 12 and 24 hours, both groups had a nausea score of 0. No other side effects or untoward incidents were noticed in any patient.

Discussion

During perioperative care, administration of α2-receptor agonists such as clonidine and dexmedetomidine have a multitude of benefits. They provide analgesia, sedation and anxiolysis and mitigate undesirable events such as postoperative shivering, post-operative nausea and vomiting, stress response to surgery and tracheal intubation (9). For postoperative analgesia, clonidine has been utilised through various routes, including oral and systemic, and as an adjuvant to neuraxial and peripheral nerve blocks. The systemic administration of clonidine is found to have moderate analgesic benefit. It decreases cumulative morphine equivalents by approximately 25% in 24 hours postoperatively. This degree of morphine sparing is stronger than with acetaminophen but weaker than with ketamine or nonsteroidal anti-inflammatory drugs. However, the analgesia provided by clonidine comes at a price of increased risk of intraoperative NNT(Number needed to treat) 9 and postoperative (NNT 20) hypotension, bradycardia and sedation (10). Clonidine has also been extensively used as an additive to local anaesthetics for intrathecal and regional nerve blocks. It has demonstrated an increase in the duration as well as quality of sensory and motor block along with prolongation of time for the first analgesic request. However, similar to systemic administration, this route has dose-related side effects (11).

Incisional and IP are alternative routes of administration of clonidine along with local anaesthetics for postoperative analgesia. Infiltration of local anaesthetics around surgical incision is an important component of multimodal analgesia and has been strongly recommended for many enhanced recovery programmes (12). It offers the advantages of being simple and low cost but has a major drawback of limited duration of analgesia. Several strategies to increase the duration of action of infiltrative local anaesthetics have been investigated, including continuous infusion using purposefully designed pumps and catheter and use of newer formulations of local anaesthetics incorporating liposomes or microcapsules. These strategies, although effective, are expensive and have potential limitations (13). The IP route of administration of local anaesthetic is another simple modality for postoperative analgesia. Instillation of LA(Local Anaesthetic) in the peritoneal cavity blocks visceral nociceptive conduction and provides a large surface for their absorption (14). The effectiveness of IP or incisional infiltration of LA alone seems to depend on the magnitude of tissue dissection during surgery. IP instillation of LA is effective for laparoscopic gynaecological procedures but may not be as effective for more invasive and longer surgical procedures such as laparoscopic cholecystectomy and open abdominal procedures. A combination of IP and incisional administration of LA has been suggested for these procedures to block afferent nociceptive transmission from the visceral and cutaneous sites. Ali et al. (15) found no benefits of IP bupivacaine or lignocaine in decreasing opioid consumption. Ng et al. (16) demonstrated that 5 μg mL^{-1} of epinephrine with 30 mL and 20 mL of 0.25% bupivacaine administered into the peritoneum and incision, respectively, produced morphine-sparing analgesia for 4 hours after TAH. We therefore decided to compare the effect of direct addition of clonidine to local anaesthetics for incisional and intraperitoneal instillation with intravenously administered clonidine where local anaesthetics alone are given for incisional and IP instillation. Memis et al. (6) compared IP administration of bupivacaine plus 1 μg kg^{-1} of clonidine to bupivacaine alone and bupivacaine plus

tramadol after TAH. They found that a combination of IP bupivacaine with adjuvants provided more effective analgesia in the early postoperative period. There was a significant difference between the first analgesic request time for IP bupivacaine given with clonidine group (30 minutes versus 110 minutes) and for bupivacaine given alone. However, the total dosage of rescue analgesics was not significantly different for IP bupivacaine alone than for IP bupivacaine plus clonidine, whereas it was significantly lower for IP bupivacaine plus tramadol. This could be attributed to the lower dose of clonidine used and lack of incisional infiltration of bupivacaine as opposed to this study. As pain after TAH is of moderate to severe intensity and has an origin from both visceral and somatic afferents, it is important to target both the components and use multimodal analgesics. We additionally provided intramuscular diclofenac to our patients for background postoperative analgesia. In a dose-response study, Marinangeli et al. (17) have demonstrated that 3 μg kg^{-1} of IV clonidine is more effective than a dose of 2 μg kg^{-1}, whereas a dose of 5 μg kg^{-1} resulted in similar analgesia with significant side effects. We used clonidine at a dose of 3 μg kg^{-1} as adjuvant to IP and incisional bupivacaine because it seems to provide good analgesia without increasing the side effects.

Selvaraj (7) have recently evaluated the role of 3 μg kg^{-1} of clonidine as an adjuvant to 45 mL of 0.25% bupivacaine given as wound infiltration in patients undergoing TAH. Similar to our results, they found the clonidine group to have a better pain score, longer duration of analgesia and lesser requirement of rescue analgesics. There was no incidence of bradycardia and hypotension. Although the appropriate volume of 0.25% bupivacaine is not defined, they used a much higher volume of bupivacaine than our study, and the serum concentration of bupivacaine was not monitored for the possibility of systemic toxicity. Similarly, Nataraj et al. (8) have found that clonidine prolonged the duration of analgesia provided by bupivacaine infiltrated into the wound after a caesarean section with minimal side effects. They had compared 0.25% bupivacaine with the addition of 3 μg kg^{-1} of clonidine to 0.25% bupivacaine as wound infiltration after a caesarean section. Till date, IV clonidine and IP clonidine have been studied separately as adjuvants to local anaesthetic infiltration, but no studies have been conducted to compare the 2 routes for efficacy and side effects.

Bharti et al. (5) have compared 3 μg kg^{-1} of clonidine acting as an adjuvant to bupivacaine administered as wound infiltration with equal dose of clonidine given intravenously in patients undergoing open cholecystectomy. They found postoperative morphine consumption to be significantly less in patients receiving clonidine by either route compared with the consumption in control group. The side effects of hypotension and sedation, however, were significantly higher in the IV clonidine group.

Similar to their results, we demonstrated that clonidine given as an adjuvant to bupivacaine administered intraperitoneally and as wound infiltration provides analgesia similar to IV clonidine, but the side effects of systemic drugs, such as hypotension, bradycardia, nausea, and sedation, are significantly less.

Our study had a few limitations. The serum concentrations of clonidine and bupivacaine were not monitored in the study. The sample size was small, and further studies with larger samples are warranted to establish the benefits of administering clonidine intraperitoneally along with bupivacaine over giving it intravenously.

Conclusion

The use of clonidine intraperitoneally instead of intravenously at the same dose of 3 μg kg^{-1} provides similar pain scores with significantly fewer side effects such as hypotension, bradycardia, nausea and sedation.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Mata Chanan Devi Hospital (No.9-96/DNB/2013-14/MCDH-2876 dated 08/12/2013).

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

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Annexure 1. Modified Wilsons 4-point sedation scale

Score	Response
0	Awake and oriented
1	Drowsy but responding to commands
2	Sleepy but easy to arouse
3	Deep sleep, difficult to arouse

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