Original Research Article

Comparative study of clonidine and dexmedetomidine as adjuvants to bupivacaine in wound infiltration for postoperative analgesia after abdominal hysterectomy: A prospective randomized study

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Abstract

Background: Wound infiltration with local anesthetics is a simple, effective and inexpensive means of providing good analgesia for a number of surgical procedures without any major side-effects. **Aims:** To compare the postoperative analgesic efficacy of clonidine and dexmedetomidine administered in wound infiltration with bupivacaine. **Methods:** Sixty women posted for abdominal hysterectomy belonging to American Society of Anaesthesiologists' Grade 1or 2 were randomly allotted to following two groups: Group BC received wound infiltration with 30 ml 0.25% bupivacaine with 3µg/kg clonidine; Group BD received wound infiltration with 30 ml 0.25% bupivacaine with 1µg/kg dexmedetomidine. A standard general anaesthesia technique was used in all the patients. Postoperative pain score, duration of effective analgesia, number of patients requiring rescue analgesic and side effects were compared between the groups. **Results:** Post-operative pain score was comparable in the two groups ($p>0.05$). There were no significant differences between the groups in terms of duration of analgesia (p value 0.7422) and number of patients requiring rescue analgesia (p value 0.5731) and the level of sedation ($p>0.05$). **Conclusions:** 3µg/kg clonidine and 1µg/kg dexmedetomidine are comparable adjuvants to bupivacaine in wound infiltration for postoperative analgesia with equal efficacy and without any significant side effect.

Key Word: Analgesia, Clonidine, Dexmedetomidine, Bupivacaine, Hysterectomy.

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INTRODUCTION

With advances in imaging techniques and overall improvement in healthcare facilities there is a considerable increase in patients undergoing surgical interventions for therapeutic reasons. Hysterectomy is one of the commonest surgeries being undertaken in women between 20-50 years. In fact it is reported to be only preceded by cesarean section[1]. The common indications for hysterectomy may include benign conditions such as prolapse, endometriosis, dysfunctional uterine bleeding, large and multiple fibroids and malignant conditions such as malignant neoplastic lesion involving uterine body or cervix. In patients undergoing hysterectomy proper pain management is an essential part of overall management. Inadequate pain control may delay patient recovery and prolongs hospital stay[2]. Though the option of epidural analgesia in postoperative period is also effective but complications associated with neuraxial blocks

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discourage its use particularly in elderly patients[3]. Keeping in mind the need to provide effective and adequate analgesia and complications associated with neuraxial blocks an effective alternative would be multimodal analgesia which is becoming a standard and routine practice in modern anaesthesiology practice. Wound infiltration with local anaesthetics is a simple, effective and inexpensive means of providing analgesia for a number of surgical procedures without any major side-effects[4]. Bupivacaine is one of the popular agent for caudal analgesia but the important limitation of bupivacaine is its short duration of action. If used alone its effect usually remains for about 5-6 hours. To overcome this limitation bupivacaine is usually mixed with an adjuvant such as ketamine, midazolam and clonidine. Clonidine, an α_2-adrenoceptor agonist, has antinociceptive properties[5]. There are clinical studies showing peripheral analgesic action of clonidine. Clonidine has been used as an effective adjunct to bupivacaine for wound infiltration[6]. It has also got a potent peripheral analgesic action. It has been in use as an adjuvant to bupivacaine as a part of multimodal analgesia in various surgeries including cholecystectomy, laparoscopic donor nephrectomy and hysterectomy. Dexmedetomidine, a highly selective α_2-adrenoceptor agonist has sedative, analgesic and opiate-sparing effect which is implicated in the management of acute postoperative pain[7]. The peripheral analgesic effect of dexmedetomidine is mediated through α_2-adrenoceptor binding and potentiate the action of local anaesthetics[8]. It has got a potent antinociceptive property on peripheral administration. There are many studies which have concluded that wound infiltration of bupivacaine with dexmedetomidine provides superior pain relief[9]. This study aims to compare the analgesic efficacy of clonidine and dexmedetomidine in wound infiltration with bupivacaine for postoperative analgesia and side-effects in patients undergoing total abdominal hysterectomy.

MATERIAL AND METHODS

With the approval of Institutional Ethics Committee, the study was carried out between January 2017 to August 2017 in the Department of Anesthesiology of a tertiary care medical college situated in a urban area. Sixty women between the age of 30-60 years posted for elective abdominal hysterectomy under general anaesthesia belonging to American Society of Anaesthesiologists' (ASA) physical status of I or II were included in the study. The patients in the following categories were excluded: emergency surgery, expected duration of surgery >2 h, morbid obesity, individuals with chronic pain, Raynaud's disease, previous abdominal surgeries, incision other than Pfannenstiel, malignancy, hepatorenal insufficiency, psychiatric diseases, bronchial asthmatics, or receiving adrenoreceptor agonists, antagonists or narcotics before operation. On the day before surgery, all the patients underwent a pre-anaesthetic evaluation. Written informed consent was also obtained for participation in the study. They were pre-medicated with oral alprazolam 0.5mg 2 h before the operation. Randomization was performed by sealed envelope method. Group BC patients received wound infiltration with 30 ml 0.25% bupivacaine with 3µg/kg clonidine at the end of surgery. Group BD patients received 30 ml 0.25% bupivacaine with 1µg/kg dexmedetomidine at the end of surgery. The person who prepared the study drug solution did not take part in data collection. After adequate preoxygenation for 3 min, anaesthesia was induced with sodium thiopental 3–5 mg/kg, fentanyl 2µ/kg, and tracheal intubation was facilitated with succinylcholine 1–1.5 mg/kg. For maintenance anaesthesia, isoflurane and nitrous oxide in oxygen and vecuronium 0.1mg/kg was used. Intraoperative monitoring included heart rate, non-invasive blood pressure (at 5min intervals), peripheral oxygen saturation. Ringer lactate was infused at maintenance rate. Heart rate and mean arterial pressure (MAP) were maintained within 20% of the preoperative value. Study drug infiltration was done by the primary surgeon after the closure of the peritoneal layer. 30ml of the study drug was infiltrated using a 25-gauge Quincke Babcock spinal needle in these layers: skin, subcutaneous tissue, muscle layers. This surgeon was blinded to the group allotment. All the patients received ondansetron 0.1 mg/kg intravenously, half an hour before the completion of surgery. Residual neuromuscular block was reversed with neostigmine and glycopyrrolate at the end of surgery. Tracheal extubation was carried out according to the standard criteria for extubation. Pain score was recorded immediately after extubation. The patients were shifted to the postoperative ward where they were observed by an anaesthesiologist who was blinded for the study. Pain score was assessed using visual analogue scale (VAS) (0=no pain, and 10=worst possible pain). Pain score was recorded at immediate extubation (taken as 0 h) and after 1, 3, 6, 12, and 24 h. Rescue analgesia was given with tramadol 1mg/kg slow i.v. boluses on demand or whenever VAS pain score was≥4. Duration of effective analgesia before the first rescue analgesic and the number of patients requiring rescue analgesia were recorded. Level of sedation was assessed using Ramsay Sedation Scale (RSS). Adverse effects if any were noted, including nausea and/or vomiting, treated with ondansetron 0.1mg/kg, intravenously. Hypotension (MAP 20% of baseline or 60mmHg) was treated with injection ephedrine 6mg intravenous (i.v.) boluses and bradycardia

(heart rate<60 beats/min) was treated with atropine 0.6mg bolus. The total duration of study was 24 h from the time immediately after extubation.

Statistical analysis: Sample size was calculated on the basis of previous study[8]. At 95% confidence interval, the power of the study was 80%. The data was systematically collected, compiled and statistically analysed by Statistical Package for Social Sciences Version 21.0 software. The results of continuous variables are given as mean ± SD and results of discrete variables as proportion and percentage. The difference between the two groups was assessed by student's t test and chi-square test. For all the tests a 'p' value of < 0.05 was considered as statistically significant.

RESULTS

First demographic details of the patients in both the groups were studied. The analysis of the mean age of the patients showed that the mean age of patients in Group BC and Group BD was 42.83 ± 7.01 and 40.23 ± 6.66 respectively. The mean age was found to be comparable in both the groups (P=0.146). Similarly the other parameters such as height, weight, body mass index, duration of surgery and ASA grades were found to be comparable in both the groups with no statistically significant difference in between 2 groups (P>0.05).

Table 1: Distribution Of Patient Characteristics Among The Two Groups

Patient Characteristics	Group Bc	Group Bd	P Value
Age	42.83 ± 7.01	40.23 ± 6.66	0.1462
Height	154.80 ± 4.22	157.57 ± 6.89	0.0654
Weight	56.43 ± 4.34	59.36 ± 7.72	0.0752
BMI	23.56 ± 1.70	23.84 ± 1.97	0.5579
Asa(I:II)	20:10	18:12	0.5920
Duration Of Surgery	97.47 ± 4.94	97.53 ± 4.97	0.9628

The mean time for the first rescue medication was 662.83 ± 15.63 in the group receiving clonidine along with bupivacaine (Group BC) for local infiltration analgesia while it was 664.16 ± 15.54 in the group receiving dexmedetomidine along with bupivacaine.

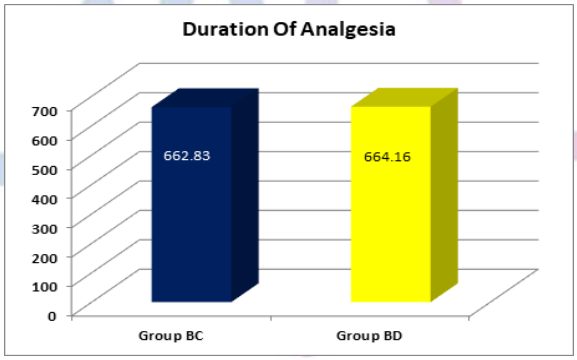

Figure 1: Comparison Of Duration Of Analgesia In Both The Groups.

Duration of analgesia before the requirement for the first rescue analgesic was comparable in both the groups using t test, the values being statistically insignificant (*P* = 0.7422).

Table 2: Comparison Of Duration Of Analgesia In Both The Groups

	Group BC	Group BD
Mean Time (In Minutes)		
	662.83	664.16
Sd	15.63	15.54
P = 0.7422 (Not Significant)		

Degree of pain was assessed by Visual Analogue scores. The mean Pain scores were noted at 0,1,3,6,12 and 24 hours postoperatively and mean pain scores in Group BC and Group BD were compared.

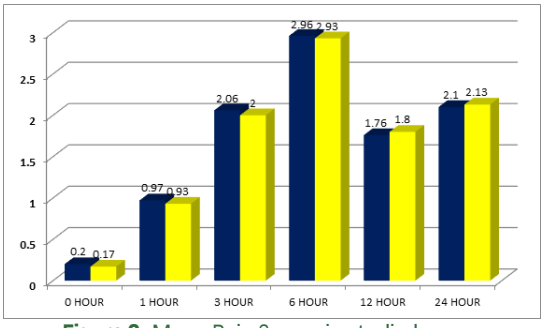

Figure 2: Mean Pain Scores in studied cases.

Analysis of the distribution of mean pain score between the 2 groups showed that the difference in the mean pain score was statistically insignificant at all-time intervals of the study up to 24 h into the postoperative period ($P > 0.05$).

Table 3: Mean Pain Scores in The Studied Cases Upto 24 hours Postoperatively.

Time Interval	Group BC	Group BD	P Value
0 Hour	0.20 ± 0.41	0.17 ±0.38	0.7699
1 Hour	0.97 ± 0.61	0.93 ± 0.58	0.7956
3 Hour	2.06 ± 0.52	2 ± 0.59	0.6776
6 Hour	2.96 ± 0.56	2.93 ± 0.52	0.8305
12 Hour	1.76 ± 0.68	1.80 ±0.71	0.8244
24 Hour	2.10 ± 0.84	2.13± 0.86	0.8918

The analysis of tramadol requirement within first 24 hours after surgery showed that the mean number of tramadol doses in 24 hours in group BC was 0.34 +/- 0.48 whereas in group BD this requirement was 0.26 ± 0.45. There was no statistically significant difference in mean number of tramadol doses in group BC and group BD (P=0.5081)

Table 4: Comparison Of Mean Number Of Doses Of Tramadol In 24hours Between The Groups

Number Of Tramadol Doses In 24 Hours	GROUP BC	GROUP BD	p value
	0.34 ± 0.48	0.26 ± 0.45	0.5081

The requirement of rescue analgesia was studied in both the groups. In group BC 10 (33%) required rescue analgesia whereas in group BD 8 (26%) patients required rescue analgesia. The need for rescue analgesia was found to be comparable in both the groups with no statistically significant difference between both the groups (P=0.5731).

Table 5: Number Of Patients That Required Rescue Analgesia

Number Of Patients Needed Rescue Analgesia	GROUP BC	GROUP BD	p value
	10(33%)	8(26%)	0.5731

Finally the analysis of Sedation scores in both the groups showed that the sedation scores were comparable in both the groups and there was no statistically significant difference amongst the sedation scores of both the groups.

Table 6: Comparison Of Sedation Score Between The Two Groups

Sedation Score	Group BC	Group BD	P Value
0 Hour	3.4± 0.50	3.5± 0.50	0.4417
1 Hour	2.83± 0.37	3.00 ± 0.37	0.0844
3 Hour	1.96 ± 0.18	2.06± 0.25	0.1039
6 Hour	1.73 ± 0.45	1.77± 0.50	0.7458
12 Hour	1.5 ± 0.51	1.6 ± 0.50	0.4417
24 Hour	1.4± 0.50	1.4 ± 0.50	1.0000

The Mean MAP in Group BC was 75.33 +/- 2.33 whereas in group BD mean MAP was found to be 74.22 +/- 2.24. The analysis of mean arterial pressures (MAP) of patients up to 24 hours postoperatively were found to be comparable (P=0.06).

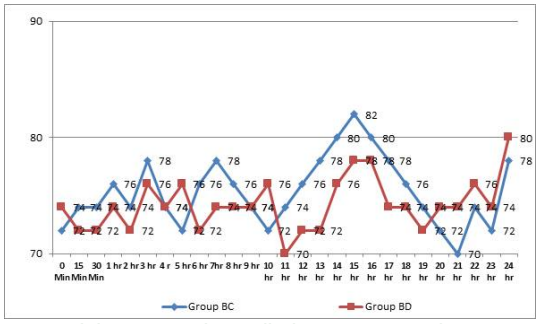

Figure 3: Mean Arterial Pressures in studied cases upto 24 hours post-operatively.

The analysis of heart rates showed that the mean heart rate in Group BC was 82.51 +/- 3.40 whereas in group BD mean heart rate was found to be 83.92 +/- 3.78. The analysis of mean heart rate of patients up to 24 hours postoperatively showed that there was no statistically significant difference in mean heart rate of patients in both the groups (P=0.06).

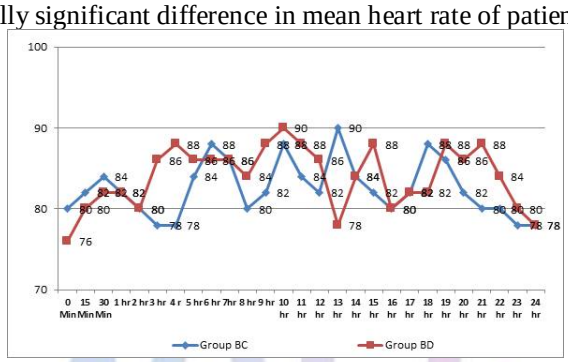

Figure 4: Heart Rates in studied cases up to 24 hours post-operatively.

DISCUSSION

Wound infiltration with bupivacaine is an effective method of minimizing postoperative pain. A wide variety of drugs have been used as adjuvants to local anaesthetics, both non-opioids and opioids[10]. The precise mechanism of topical clonidine analgesia is unclear. It has been put forward that sympathetic neural activity and norepinephrine have an excitatory effect on nociceptive discharge after cutaneous injury[11]. Clonidine inhibits the release of norepinephrine from prejunctional α2-adrenoreceptors in the periphery, and potentially inhibits neural actional potential in nociceptive pathways[12]. Other mechanisms include enhancing the effect of local anaesthetics by selective inhibition of Aδ and C fibres, and release of enkephalin like substances which produce a peripheral analgesic effect. Dexmedetomidine and clonidine are both a2 selective agonists. It is possible that they work in a similar manner and may indicate a class effect. In our study, we have shown that 3µg/kg of clonidine is as effective as 1µg/kg of dexmedetomidine administered with 0.25% bupivacaine in wound infiltration with comparable pain scores, duration of effective analgesia. A recent study by Selvaraj *et al*[13]. showed clonidine 3µg/kg is an effective adjuvant to bupivacaine for local infiltrative analgesia in patients who have undergone total abdominal hysterectomy. They observed that Clonidine group has better pain score, longer duration of effective analgesia, lower percentage of patients requiring rescue analgesic, and less number of doses of rescue analgesia in the first 24 h. A similar study by Singh *et al*[14]. stated that wound infiltration of bupivacaine with dexmedetomidine 1µg/kg provides superior pain relief. They found that post-operative analgesia requirement was significantly less in patients receiving dexmedetomidine in wound infiltration compared to patients receiving bupivacaine alone (P < 0.001). Bharti *et al* found that clonidine 3µg/kg provided effective postoperative analgesia and reduced morphine requirement when administered intravenously or in wound infiltration with bupivacaine[15]. Postoperative morphine consumption was significantly less in patients receiving clonidine by either route when compared with the control group (P =0.0001). In another study, Abd El-Hamid *et al* dexmedetomidine provided effective postoperative analgesia and reduced morphine consumption when administered intravenously or in wound infiltration with bupivacaine[16]. Complications such as hypotension, sedation and bradycardia associated with IV clonidine or dexmedetomidine were negligible when the adjuvants were given as local infiltration[17]. Nataraj, *et al* demonstrated that addition of 3 µg/kg of

clonidine to 0.25% bupivacaine 30 ml for wound infiltration after caesarean section under spinal anesthesia prolongs the duration of analgesia reduces opioid consumption and produces mild sedation without complications[18]. Swami *et al* stated that 1µg/kg dexmedetomidine prolongs the duration of sensory and motor block and enhances the quality of block as compared with 1µg/kg clonidine when used as an adjuvant to Bupivacaine in peripheral nerve block[19]. Ülgey *et al* found that dexmedetomidine added to local anesthetic agent applied to the wound site reduced the analgesic consumption and improved the pain scores in total abdominal hysterectomy surgery[20].

CONCLUSION

3µg/kg clonidine and 1µg/kg dexmedetomidine are comparable adjuvants to bupivacaine in wound infiltration for postoperative analgesia with equal efficacy and without any significant side effects.

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