Original Research Article

Comparison of the efficacy of intrathecal buprenorphine and clonidine as adjuvants to bupivacaine for postoperative analgesia and abdominal muscle relaxation in patients of abdominal hysterectomy

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Abstract

Background and Aims: Various adjuvants have been used with local anesthetics in spinal anesthesia to provide adequate analgesia and muscle relaxation. The aim of this study was to evaluate and compare the two intrathecal adjuvants, buprenorphine and clonidine for postoperative analgesia and intraoperative abdominal muscle relaxation in patients undergoing abdominal hysterectomy. **Methods:** One hundred and fifty adult patients undergoing elective abdominal hysterectomy under spinal anaesthesia were randomly divided into two groups. Group B received 60 µg buprenorphine and Group C received 30 µg clonidine with 3.4 ml of 0.5% hyperbaric bupivacaine. Both groups were evaluated and compared for duration of postoperative analgesia, abdominal relaxation and incidence of adverse effects. Data was analysed with Z-test. **Results:** Duration of postoperative analgesia was more prolonged in Group C (361.6 ± 41.81 min-Group B, 416 ± 50.61 min-Group C). Abdominal relaxation was better in Group C [P = 0.0089]. Onset of sensory (6.08 ± 1.22 min- Group B, 5.88 ± 1.42 min-Group C) and motor (9.93 ± 2.39 min-Group B, 10.33 ± 2.88 min-Group C) blocks were comparable. Duration of sensory (304.8 ± 42.72 min-Group B, 366.4 ± 44.46 min-Group C) and motor (219.2 ± 26.08 min-Group B, 306 ± 35.9 min-Group C) blocks were more prolonged in Group C. The incidence of hypotension was higher in Group C [P = 0.000]. **Conclusion:** Intrathecal clonidine as an adjuvant to bupivacaine provides betterpostoperative analgesia and abdominal relaxation than buprenorphine in patients undergoing abdominal hysterectomy under spinal anaesthesia, but was associated with higher incidence of hypotension.

Key Word: Abdominal hysterectomy, analgesia, buprenorphine, clonidine, hypotension

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INTRODUCTION

The quite regular action of the diaphragm, the contraction of the intestines and the complete relaxation of the abdominal muscles after spinal anaesthesia produce ideal surgical conditions for abdominal hysterectomy. However these advantages of spinal anaesthesia are sometimes offset due to relatively short duration of action of local anaesthetics.[1] Satisfactory abdominal muscular relaxation and effective postoperative pain management leads to improved functional recovery, earlier mobilization and shortened hospital stay.[2] Hence there is always a need for an ideal intrathecal adjuvant which will improve degree of abdominal muscle relaxation and increase the duration of postoperative analgesia. Of all adjuvants, buprenorphine, a powerful agonist and partial antagonist at µ receptors and clonidine, a selective α2-agonist have found to be very useful due to their better profile of desirable effects and lesser adverse effects than others.[3,4] There are no studies

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which compared degree of abdominal relaxation after intrathecal buprenorphine or clonidine during abdominal hysterectomy under spinal anaesthesia. Clonidine is known to potentiate the sensory as well as motor blocking actions of intrathecal local anaesthetics without causing opioid related side effects.[4] Hence in this study we tested this hypothesis against one of the safe and most effective opioid adjuvant, buprenorphine. The primary aim of this study was to compare the duration of postoperative analgesia and the adequacy of abdominal relaxation. The secondary aim was to compare the onset and duration of sensory and motor blocks; and the haemodynamic and adverse effects of intrathecal buprenorphine and clonidine.

METHODS

This was a prospective randomized double blind study. Approval of the hospital ethical committee was obtained. Informed written consent was taken from patients after explaining the procedure in detail. One hundred fifty ASA physical status I or II female patients, aged 18-60 years, scheduled for abdominal hysterectomy under spinal anaesthesia in a tertiary care unit were included in this study. The patients with cardiovascular, respiratory, neurological or renal disease, coagulation abnormalities or spinal deformity were excluded from the study. The patients were then allocated randomly into two equal groups (n = 75 each). The sample size was calculated with the help of the reference of previous study.[5] Minimum sample size calculated by using statistical formula [$n = 2(Z_\alpha + Z_\beta)^2 . \sigma^2/ \delta 2$] was 73.54 per group, where α (level of significance) = 5%, power = 80% and σ = s.d = 12.81 and δ (difference between means) = 59.19.[5] In our study we allocated 75 patients in each group. Group B received intrathecal 3.4 ml of 0.5% hyperbaric bupivacaine plus 0.2 cc (60µg) of injection buprenorphine. Group C received intrathecal 3.4 ml of 0.5% hyperbaric bupivacaine plus 0.2 cc (30µg) of injection clonidine. The total volume of solution in both groups was 4 ml. Randomization was done by a sealed envelope method. The patients and the anesthesiologist performing the block and monitoring the patients were blinded to the procedure. The patients were kept fasting for six hours preoperatively. All patients were instructed about the use of rectus abdominis muscle (RAM) test[6] and VAS score with 0 indicating no pain and 10 indicating the worst imaginable pain. In the operating room, the monitors of electrocardiography (ECG), pulse oxymetry (SpO_2) and non invasive blood pressure (NIBP) were attached to the patient and baseline vitals recorded. An intravenous line was secured with 18 gauge cannula and 10 ml/kg Ringer lactate solution was preloaded over 15 minutes. Under all aseptic precautions subarachnoid block was performed and then patients were turned to supine position immediately to achieve a block level of T4. The surgeon was allowed to start surgery once the sensory block reached T4 level and RAM score[3]. The time at which the injection was given was considered as a zero time of the study and all the study parameters were measured from this point. Sensory block was assessed with loss of sensation to pinprick every two minutes till the levels of T10 (onset of sensory block) and T4 (highest level of sensory block) were achieved. Subsequently the sensory levels were assessed every 15 minutes till two segments regression and thereafter every 30 minutes till the regression of block to L1 (duration of sensory block). Motor block was assessed with modified Bromage scale[7] (0 = able to move hip, knee and ankle, 1 = able to move knee and ankle but cannot move hip, 2 = able to move ankle but cannot move hip and knee, 3 = unable to move hip, knee or ankle). Motor block was assessed every five minutes till Bromage 3 is attained (onset of motor block) and thereafter every 30 minutes till return of motor power to Bromage 0 (duration of motor block). The degree of abdominal muscle relaxation was assessed by using the rectus abdominis muscle (RAM) score at 10, 20 and 30 minutes after the injection of study drug. The procedure of RAM-test was performed as follows: The patient was allowed to lie in the supine position with legs extended. Then the patient was asked to rise slowly from the supine to a sitting position and the block was graded accordingly. RAM score ranges from 0 to 5 with 0 = Able to rise from supine to sitting position with hands behind the head, 1 = Can sit only with arms extended, 2 = Can lift only head and scapulae off the bed, 3 = Can lift only shoulders off the bed, 4 = An increase in abdominal muscle tension can be felt during effort, no other response and 5 = full abdominal muscular relaxation. A minimum score of 3 was required for the surgery.[8] Utmost care was taken to maintain sterility of surgical field and to keep minimum possible surgical interruption during the procedure.

Duration of postoperative analgesia was checked by using VAS score (0-3 = mild pain, 4-7 = moderate pain and 8-10 = severe pain). It was recorded every 30 minutes till three hours and thereafter every hourly till the patient requested for rescue analgesic. The time between completion of the study drug injection (zero time) and the first rescue analgesic demand by the patient was considered as the total duration of postoperative analgesia. Intramuscular injection diclofenac sodium 75 mg was given as a rescue analgesic at VAS ≥ 4. Sedation score was tested according to the modified Ramsay sedation scale[9] as : 1 = Anxious, agitated, restless; 2 = Cooperative, oriented, tranquil; 3 = Responds to commands only; 4 = Brisk response to light glabellar tap or loud noise; 5 = Sluggish response to light glabellar tap or loud noise and 6 = No response. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), oxygen saturation (SpO_2) were recorded

every five minutes for initial 30 minutes, every 30 minutes upto two hours and later on every hourly upto five hours. Hypotension was defined as SBP less than 90mmHg or a fall in SBP of more than 20% from the baseline value. It was decided to treat it with intravenous (IV) crystalloids and injection mephentermine 5 mg IV. Bradycardia (HR < 50/min) was decided to treat with injection atropine 0.6 mg IV. All patients were monitored for the side effects like nausea, vomiting, pruritus, respiratory depression (RR < 8/min), dryness of mouth and shivering. It was decided to treat nausea and vomiting with injection ondensetron 4mg IV, pruritus with injection promethazine 25mg IV and shivering with warm IV fluids and air warmer. At the end of the surgery, the surgical condition was evaluated by the surgeon using a surgeon satisfaction score[10] as: Adequacy of muscle relaxation (yes = 1, no = 0); excessive bleeding (yes = 0, no = 1); patient's response to surgical stimulus (yes = 0, no = 1); patient's movement during the procedure (yes = 0, no = 1). Score 4 was considered as excellent, score 3 as good, score 2 as fair and score 1 as poor. We planned to exclude the cases who required intraoperative supplemental analgesics or who required conversion to general anaesthesia (GA). However no such fallout occurred. Data was compiled in an excel sheet. Quantitative data was expressed as means ± standard deviation. Z – test (standard error of difference between two means) was applied for comparing the data. Mann – Whitney U test was applied to compare ordinal type of data (RAM score and Ramsay sedation score). $P < 0.05$ was considered as statistically significant. Statistical analysis was done using SPSS version 22 for Windows (IBM – Chicago).

RESULTS

The two groups were comparable in respect to age, weight, height and duration of surgery [Table 1]. The results regarding the characteristics of spinal block are summarized in Table 2. The duration of postoperative analgesia was significantly prolonged in Group C as compared to Group B [$P = 0.00$]. There was no statistically significant difference in the onset of sensory and motor blocks between the two groups. There was also no significant difference in the time to achieve the maximum level of sensory block (T4) between the two groups. The time for two segment regression of sensory block was significantly more in Group C than in Group B [$P = 0.00$]. The duration of sensory block was significantly prolonged in Group C as compared to Group B [$P = 0.00$]. The duration of motor block was significantly higher in Group C than in Group B [$P = 0.00$]. Surgical condition according to surgeon satisfaction score was excellent in Group C and good in Group B [$P = 0.00$]. Abdominal muscle relaxation assessed by rectus abdominis muscle (RAM) score was significantly better in Group C than in Group B [$P = 0.03$ at 10 min, $P = 0.00$ at 20 min and $P = 0.001$ at 30 min] [Table 3]. The mean VAS scores were 0 upto 60 minutes in both groups and then 0.92 ± 0.69- Group B, 0.96 ± 0.66-Group C; 1.73 ± 0.66-Group B, 1.43 ± 0.79-Group C; 2.01 ± 0.83-Group B, 2.08 ± 0.56 Group C; 2.35 ± 0.55-Group B, 2.25 ± 0.63-Group C; 2.96 ± 0.62-Group B, 2.99 ± 0.58-Group C; 2.96 ± 0.66-Group B, 3.07 ± 0.74-Group C; 4.0 ± 0.67-Group B, 3.01 ± 0.70-Group C; 4.63 ± 0.63-Group B, 4.17 ± 0.94-Group C and 4.79 ± 0.70-Group B, 4.36 ± 0.67-Group C at 90, 120, 150, 180, 240, 300, 360, 420 and 480 minutes respectively. The postoperative mean VAS scores were higher in Group B than in Group C after 360 minutes [$P = 0.00$ at 360 min, $P = 0.001$ at 420 min and $P = 0.00$ at 480 min] [Figure 1]. The mean heart rate [HR] was found to be lower in Group C as compared to Group B 15 minutes after intrathecal drug administration [$P = 0.02$ at 15 min, $P = 0.006$ at 20 min, , $P = 0.001$ at 30 min, $P = 0.00$ at 60 to 240 min and $P = 0.01$ at 300 min] [Figure 2].There was no incidence of bradycardia (HR < 50/min) in any group.Systolic blood pressure [SBP] was found to be lower in Group C as compared to Group B 60 minutes after intrathecal drug administration [$P = 0.03$ at 60 min, $P = 0.006$ at 90 min, $P = 0.002$ at 120 min and $P = 0.00$ from 180 to 300 minute] [Figure 2]. There were more incidences of statistically significant hypotension in Group C than in Group B [$P = 0.00$] [Table 4] which were successfully treated with intravenous (IV) crystalloids and injection mephentermine 5mg IV. The incidence of side effects was low and not statistically significant in both the groups. No patient in either group developed respiratory depression [Table 4]. There was no statistically significant difference in Ramsay sedation scores between the groups [mean rank 72, sum of ranks 5400 in Group B and mean rank 79, sum of ranks 5925 in Group C; Mann- Whitney U = 2550; $P = 0.25$].

Table 1: Demographic characteristics

Parameters	Group B (n=75)	Group C (n=75)	*P* value
Age (years)	44.83 ± 5.19	45.76 ± 4.18	
Weight (kg)	52.41 ± 5.43	53.24 ± 4.89	
Height (cm)	157.48 ± 3.38	158.53 ± 2.61	
Duration of surgery (minute)	105.73 ± 10.29	107 ± 10.10	0.448

Data presented as mean±SD, SD – standard deviation. $p<0.05$ suggests statistically significant difference. B-buprenorphine, C- clonidine.

Table 2: Characteristics of spinal block

Variables	Group B (n=75)	Group C (n=75)	*P* value
Onset of sensory block (min)	6.08 ± 1.23	5.88 ± 1.42	0.358
Time for highest sensory level (T4) (min)	9.68 ± 1.28	9.49 ± 1.47	0.408
Time for two segment regression (min)	117.4 ± 15.67	140.6 ± 22.71	0.000*
Duration of sensory block (min)	304.8 ± 42.72	366.4 ± 44.47	0.000*
Onset of motor block (min)	9.93 ± 2.4	10.33 ± 2.89	0.357
Duration of motor block (min)	219.2 ± 26.09	306 ± 35.91	0.000*
Duration of postoperative analgesia (min)	361.6 ± 41.82	416 ± 50.62	0.000*
Surgeon satisfaction score	2.95 ± 0.52	3.75 ± 0.47	0.000*

Data presented as mean ± SD. SD- standard deviation, *P<0.05 suggests statistically significant difference. B- buprenorphine, C-clonidine.

Table 3: Rectus abdominis muscle (RAM) score.

RAM score at	Group	Mean rank	Sum of ranks	Mann-Whitney U	*P* value
10 min	Group B	69.21	5190.5	2340.5	*0.030
	Group C	81.79	6134.5		
20min	Group B	62.62	4696.5	1846.5	*0.000
	Group C	88.38	6628.5		
30 min	Group B	64.92	4869	2019	*0.001
	Group C	86.08	6456		

*P<0.05 suggests statistically significant difference. RAM - Rectus abdominis muscle. B- buprenorphine, C- clonidine

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Table 4: Side effects

Parameters	Group B (n=75)	Group C (n=75)	*P* value
Hypotension	7	33	*0.000
Bradycardia	0	0	-
Nausea/vomiting	6	4	0.516
Pruritus	3	1	0.314
Dry mouth	1	3	0.175
Shivering	9	3	0.072
Respiratory depression	0	0	-

*p<0.05 suggests statistically significant difference. (n- number of patients). B- buprenorphine, C- clonidine.

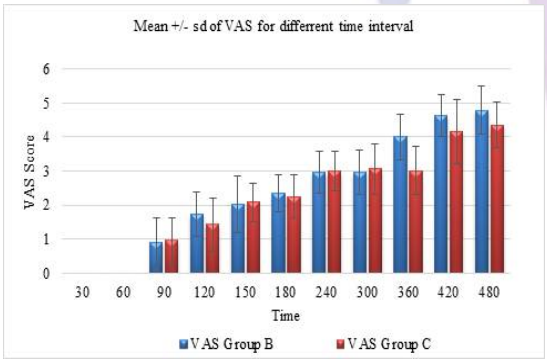

Figure 1

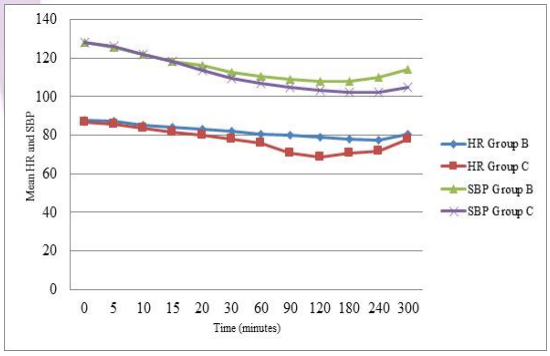

Figure 2

Figure 1: Comparison of mean visual analogue scores (VAS). B- Buprenorphine, C- clonidine. Sd-standard deviation. **Figure 2:** Comparison of mean heart rate and mean systolic blood pressure (HR- heart rate per minute, SBP- systolic blood pressure in mmHg). B- buprenorphine, C- clonidine.

DISCUSSION

To provide adequate abdominal relaxation and analgesia intraoperatively and to extend this analgesia into the postoperative period is an essential part of anaesthesia management. Adequate surgical relaxation decreases chances of haemorrhage, thrombosis, ileus, chest complications, surgical time and infections of the wound.[11] Various opioid and non- opioid intrathecal adjuvants have been used to improve the quality of spinal blockade and to prolong the duration of postoperative analgesia.[12] Buprenorphine is a centrally acting partial opioid agonist. It has been found that buprenorphine causes local

anaesthetic-like inhibition of voltage-gated Na(+) channels and this mechanism may be responsible for prolongation of action of spinal anaesthesia.[13] According to Capogna *et al.*[14] buprenorphine diffuses quickly into neural tissues due to its high lipid solubility. This decreases the chances of rostral spread leading to lesser side effects like respiratory depression. Clonidine, a selective partial α2-agonist when given intrathecally easily penetrates the blood brain barrier due to its moderate lipid solubility leading to spinal and supraspinal receptor binding. It has also shown to increase acetylcholine levels in lumbar cerebrospinal fluid. Thus it provides antinociceptive effect on both visceral and somatic pain which is free of opioid related side effects.[15] A wide range of doses have been described in the literature for intrathecal buprenorphine and clonidine.[16] We decided to investigate the low doses of buprenorphine (60µg) and clonidine (30µg) keeping in mind the dose related side effects. When compared to intrathecal buprenorphine, we found intrathecal clonidine to provide prolonged duration of postoperative analgesia and higher degree of abdominal muscular relaxation, but the incidence of hypotension was more with clonidine though it was easily manageable. Many studies have shown increased duration of postoperative analgesia after both intrathecal buprenorphine and clonidine.[5,13] In one study Arora *et al.*[17] reported prolonged duration of postoperative analgesia in buprenorphine group than in clonidine group. Dixit *et al.*[18] in their study have found prolongation of duration postoperative analgesia after intrathecal administration of buprenorphine. Van Tuijl *et al.*[19] have stated that the addition of intrathecal clonidine to hyperbaric bupivacaine for caesarean section significantly prolongs the duration postoperative analgesia, reduces the VAS score and also reduces the morphine requirement in the recovery period. Khandelwal *et al.*[20] also found that the time for first analgesic request was prolonged by addition of intrathecal clonidine for abdominal hysterectomies. We compared degree of abdominal muscle relaxation by using rectus abdominis muscle (RAM) score. Some authors have used RAM scoring system in renal and lower abdominal surgeries and found it very useful to assess abdominal muscle relaxation.[6,8] Gautier P *et al*[21] used RAM score in caesarean section while Bajwa *et al.*[22] assessed abdominal relaxation in renal surgeries under epidural anaesthesia. We for the first time used this scoring system in abdominal hysterectomy and found it very useful for assessing abdominal relaxation. According to RAM score, we found better abdominal relaxation in clonidine group than in buprenorphine group. Clonidine blocks the conduction of C and Aδ fibres in the spinal cord, increases potassium conductance in isolated neurons *in vitro* and thus intensifies the conduction block of local anaesthetics. α2-agonists induce cellular modification in the ventral horn of spinal cord causing motor neuron hyperpolarization and hence facilitate the sensory and motor blocking property of the local anaesthetics.[17] Animal studies suggest that Tizanidine, a structural congener of clonidine, is a centrally acting antispastic agent. The rectus abdominis muscle relaxation caused by clonidine can be due to similar mechanism of action.[23] We found no significant difference in the onset time of sensory and motor blocks between two groups. These findings are also consistent with other studies.[5,24] In the present study, the time taken for two segment sensory regression was significantly prolonged in clonidine group than in buprenorphine group. Dobrydnjov *et al.*[25] and Sethi *et al.*[26] also reported similar results after intrathecal clonidine in their studies in gynecological patients. In our study we found significant prolongation of duration of sensory and motor blocks with intrathecal clonidine as compared to intrathecal buprenorphine. Fogarty DJ *et al.*[2] and Santos *et al.*[28] also reported prolonged sensory and motor duration with intrathecal clonidine when compared to other intrathecal adjuvants. Clonidine has agonistic action on hypothalamic α2-adrenoreceptors (which are inhibitory) causing decrease in outflow from the vasomotor and sympathetic centres. This leads to decreased peripheral vascular resistance, heart rate [HR] and blood pressure.[17] In our study HR was decreased in both the study groups but no patient had bradycardia [HR <50/min] in either group. Incidence of hypotension was significantly more in clonidine group than in buprenorphine group although it responded well to intravenous [IV] fluids and vasopressors. Elia *et al*[29] in a systematic review of 22 randomized trials concluded that addition of clonidine to various intrathecal local anesthetics, prolonged the duration of analgesia and increased the risk of hypotension in a linear, dose-dependent manner. However, Strebel *et al.*[16] studied effect of three different doses of Clonidine on eighty orthopedic patients and found relative haemodynamic stability even with 150 µg of clonidine. Figueroa XF *et al.*[30] described clonidine-induced nitric oxide-dependent vasorelaxation mediated by endothelial alpha- 2 adrenoceptor activation, as a mechanism of hypotension. Surgical condition was assessed by the surgeon (surgeon's satisfaction score) at the end of the surgery in terms of abdominal relaxation, bleeding, patient's response to surgical stimulus and patient's movement during the procedure. It was found to be excellent in clonidine group and good in buprenorphine group. Ramsay sedation score was low [<3] in all patients in our study and was comparable between the two groups. There was no respiratory depression in any patient in either group. In our study incidence of adverse effects noted was very low and was statistically insignificant in either groups. The confounding variables like co-administration of vasoactive, analgesic drugs were eliminated by

excluding the patients receiving them. Excluding patients with hypertension, cardiac and renal disease; doing optimisation of volume status by preloading with crystalloids and use of scoring systems avoided interpersonal variability in observations. In the present study we did not study the total analgesic consumption in a 24 hour period. We also did not include control group for comparison with the study groups. There is a need of further multicentric study in various age groups, both the genders and for various surgeries to find optimal dose of study adjuvants to achieve our study aims. There is also a need of use of multimodal analgesia along with intrathecal adjuvants for prolongation of postoperative analgesia.

CONCLUSION

Based on our study, we conclude that clonidine (30µg) is a better adjuvant to local anesthetic bupivacaine than buprenorphine (60µg) for abdominal hysterectomy under spinal anaesthesia. The duration of postoperative analgesia and the degree of abdominal muscle relaxation provided by clonidine was better compared to buprenorphine in given doses. However incidence of hypotension was more with clonidine which could be reverted back with appropriate treatment. Further studies are required to optimize the dose of clonidine which can have maximum effectiveness without causing significant hypotension.

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