Original Article

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Comparison of Low Dose Intrathecal Buprenorphine and Clonidine as an Adjuvant to Bupivacaine in Spinal Anesthesia for Post-Operative Analgesia in Lower Limb and Lower Abdominal Surgeries

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Abstract

Background: Management of postoperative pain is an important part of post-operative care. Spinal anesthesia when used with adjuvants can prolong analgesia well into the early postoperative period and is one of the commonly used methods in most lower abdominal and lower limb surgeries. Various studies have been done using higher doses of adjuvants. However, relatively fewer studies have been done using lower doses of these drugs. In this study, low doses of intrathecal buprenorphine and clonidine used as an adjuvant in spinal anaesthesia were compared in providing effective postoperative analgesia. **Subjects & Methods:** 100 ASA 1 and 2 patients who were planned for lower abdominal and lower limb surgeries were enrolled in our study and were randomly divided into 2 groups of 50 each- Group X and Y. Patients with a known allergy, on β blockers, α2 agonists, basal heart rate $\leq$50/min, pregnant and lactating women, obesity- BMI $\geq$ 30 were excluded from the study. The patients in group X received 15mg (3 ml) of 0.5% hyperbaric bupivacaine with 45μg (0.15 ml) of buprenorphine and patients in group Y received 15 mg (3 ml) of 0.5% hyperbaric bupivacaine with 22.5μg (0.15 ml) of clonidine. The duration of analgesia- the time to request for first rescue analgesic and the number of doses of systemic analgesics in the first 24 hrs postoperatively was noted. **Results:** The time to request for the first rescue analgesic was significantly longer in group X(buprenorphine) when compared to group Y(clonidine) with a p-value <0.001. Also, the mean requirement of the total number of analgesics was less in group X when compared to group Y and was statistically significant with a p-value <0.001. **Conclusion:** We conclude that intrathecal adjuvants buprenorphine and clonidine, even in low doses, provide effective postoperative analgesia and buprenorphine has a longer analgesic effect when compared to clonidine.

Keywords: Buprenorphine, Clonidine, Spinal Anesthesia, Lower Limb Surgeries, Post-Operative Analgesia.

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Introduction

Acute postoperative pain is due to the complex physiologic reaction to tissue injury manifested by autonomic, behavioral and psychological responses that result in unpleasant sensory and emotional experience. The various modalities for treatment of post-operative pain include the use of systemic analgesics, neuraxial techniques, and regional nerve blocks. Among these, spinal anaesthesia is the most commonly used neuraxial technique for various types of lower abdominal and lower limb surgeries.

Conventional local anaesthetics like bupivacaine when used intrathecally as the sole agent, have been unable to provide anaesthesia for long-duration surgeries and adequate postoperative analgesia. Hence various adjuvants have been used. Buprenorphine, a synthetic opioid, acts on the μ opioid receptors situated in the substantia gelatinosa of the dorsal horn of the spinal cord. When used intrathecally, it has improved both the duration and quality of postoperative analgesia. However, the use of higher doses of intrathecal opioids has been associated with dose-related side effects like pruritis, nausea, vomiting and respiratory depression as reported in previous studies. [1–3]

Clonidine, an α2 agonist is another agent that has been extensively studied as an adjuvant to intrathecal bupivacaine for postoperative analgesia and is a potent analgesic. The analgesic effect at the spinal level is mediated by postsynaptically situated α2 adrenoceptors in the dorsal horn of the spinal cord. However, intrathecal clonidine has again known to cause dose-related side effects like bradycardia, hypotension, dryness of

mouth and somnolence.[4] This study was thus undertaken to compare lower doses of intrathecal buprenorphine to intrathecal clonidine as an adjuvant in spinal anaesthesia effective enough to provide postoperative analgesia while minimizing side effects.

Subjects and Methods

After obtaining the approval for the study from the Institutional Ethics Committee and written informed consent was taken from all 100 patients (50 for each group- X and Y) based on computer-generated random block allocation. After the study (randomised double-blinded) was completed, drug X was revealed to be buprenorphine and drug Y clonidine. ASA Grade I and II patients, aged between 18 – 55 years, height range of 150-175 cm, scheduled to undergo elective lower abdominal and lower limb surgeries under spinal anaesthesia were included. Patients with a history of allergy to the medications used, patients on β blockers, $\alpha 2$ agonists, basal heart rate $\leq$50/min, pregnant and lactating women, obesity-BMI $\geq$ 30 were excluded from the study.

- The patients belonging to the buprenorphine group were given 15mg (3 ml) of 0.5% hyperbaric bupivacaine with 45μg (0.15 ml) of buprenorphine and patients belonging to the clonidine group were given 15 mg (3 ml) of 0.5% hyperbaric bupivacaine with 22.5μg (0.15 ml) of clonidine.

All patients followed the standard fasting guidelines before surgery and were given metoclopramide 10mg and ranitidine 150mg orally two hours before the surgery. After the anaesthesia machine and other equipment check, emergency drugs- atropine and ephedrine were loaded and kept ready. In the operating room, standard monitoring like an electrocardiogram, non-invasive blood pressure and pulse oximetry were connected and basal pulse rate, blood pressure and SpO_2 were recorded. Appropriate size cannula was secured for intravenous access and all patients were given 10 ml/kg of Lactated Ringer solution as preloading. Lumbar punctures were performed with the patient in the lateral position using a spinal (BD Spinal Needle, 26 G Quincke) needle in the L_{3-4} or L_{4-5} space. After obtaining a free backflow of CSF, the drugs were given over 15-20 seconds. Immediately after the administration of the drugs, patients were turned to the supine position and the hemodynamic and respiratory parameters were recorded. All patients were given supplemental oxygen with a face mask at 5L/min throughout the surgery.

- **The following hemodynamic parameters were monitored throughout the surgery:**

1. Heart rate (HR)- recorded every 5 min and continuously monitored
2. Blood pressure- Mean (MAP)- recorded every 5 min

- The following respiratory parameters were monitored continuously throughout the surgery and recorded every 5 min:

1. Saturation (SpO_2)
2. Respiratory rate (RR)

The duration of analgesia- a time of onset of the block to time to request for first rescue analgesic was noted and statistically analysed.

The following criteria were used for determining the characteristics of sensory blockade:

(Tested by using the pinprick method)

a) The onset of the sensory blockade- loss of sensation to pinprick at T10 [checked every 30 sec after turning the patient supine at T10 level].

b) Highest level of sensory block checked 20 min after administration of subarachnoid block.

c) Time to regression of sensory block to T10 [assessed after 2 hrs- every half an hr].

The following criteria were used for the assessment of postoperative analgesia

Assessment of pain intensity was done by the Visual Analogue Scale (VAS) starting in the recovery room, checked every second hrly till 24 hrs after surgery.

[VAS score includes a score from 0 to 10, 0 being no pain and 10 being the worst pain]

VAS SCALE

0—1—2—3—4—5—6—7—8—9—10

0 = no pain 10 = very severe pain SCALE: 0-2: no pain

4: little pain but is happy with analgesia

6: quite more pain

8– 10: severe to worst pain.

The first rescue analgesic was given when VAS $\geq$4 on checking second hrly or when the patient complained of pain and VAS was $\geq$4.

a) The duration of analgesia is the time of onset of sensory block to T10 till the time of request of first rescue analgesic for VAS $\geq$4 postoperatively.

As per the WHO step ladder for pain, paracetamol 1g intravenously was the first rescue analgesic up to a maximum of four doses in 24 hrs.

Diclofenac 75 mg intravenously in 100ml normal saline was given as the second rescue analgesic if the pain was not

controlled (VAS ≥4) within 30 min of giving paracetamol or if VAS ≥4 within six hrs of the last dose of paracetamol. It was given up to a maximum of two doses in 24 hrs

b) The number of doses of analgesics required (paracetamol and diclofenac) during the first 24 hrs postoperatively were noted.

If pain was not controlled with the above two NSAID's, opioids like tramadol 1-2 mg/kg intravenously were given for control of pain as the third rescue analgesic.

After a duration of 24 hrs, the routine protocol for post-operative analgesia in our hospital was followed.

Statistical methods

- Student t-test (two-tailed, independent) was used to find the significance of study parameters on a continuous scale between the two groups (intergroup analysis) on metric parameters. Chi-square/Fischer exact test was used to find the significance of study parameters on a categorical scale between two or more groups. $p<0.05$ was considered to be significant.
- The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

Results

We conducted a prospective, randomized, comparative and double-blinded clinical study. The study was done to study the efficacy of the two drugs buprenorphine and clonidine used as an adjuvant in spinal anaesthesia in terms of the sensory effects and postoperative pain relief in patients undergoing lower abdominal and lower limb surgeries. 100 patients ASA I and II were involved in the study.

Following observations were made in the study:

The demographic parameters like age, sex distribution, height, weight, BMI, ASA Physical Status and type of surgery- all were comparable in the two groups

Study variables

The time of onset of the sensory block to T10 (min) was comparable among the two groups and was not statistically significant with a p-value =0.727.

The time to regression of the sensory block to T10 was more in group Y when compared to group X which does not suggest clinical significance- p-value =0.066.

The distribution of the highest level of sensory block achieved at 20 min was statistically similar in the two groups with a p-value =0.680. Most of the patients achieved the highest level of the block between T4-T6 which was adequate for lower abdominal surgeries.

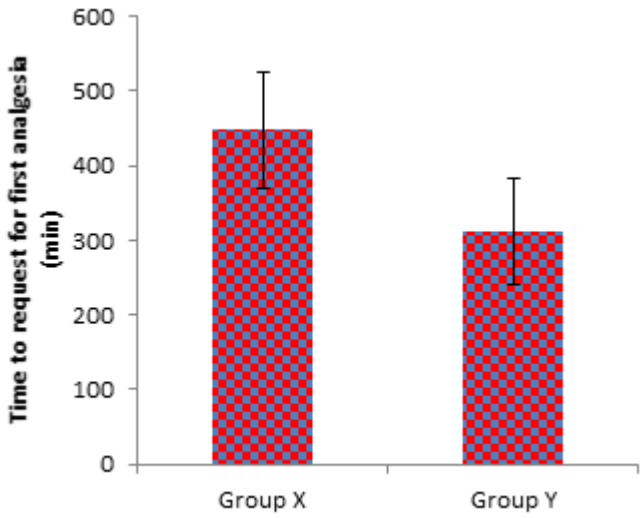

Figure 1: Comparison of the time to request for first rescue analgesic in the two groups studied

The time to request for the first rescue analgesic was significantly longer in group X when compared to group Y with a p-value <0.001.

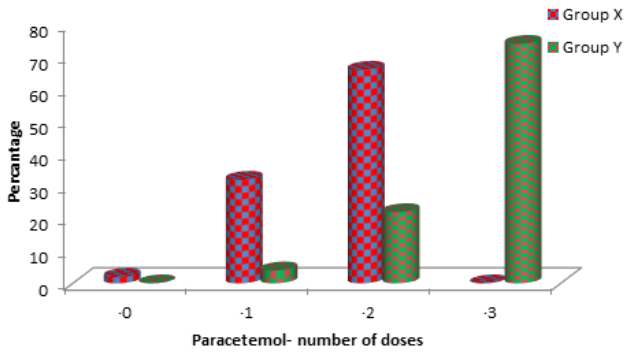

Figure 2: Comparison of treatment with the number of doses of paracetamol

The requirement of paracetamol was significantly less in group X when compared to group Y with a p-value <0.001.

The requirement of diclofenac was significantly less in group X when compared to group Y with a p-value <0.001.

92% of the patients in group X did not require the second rescue analgesic-diclofenac. None of the patients in group X

Table 1: 1 : Sensory variables: Comparison of the two groups studied

	Group X	Group Y	P-value
The onset of sensory block to T10 (sec)	138.30±60.10	142.80±68.18	0.727
Regression of the sensory block to T10 (min)	181.50±43.63	196.80±38.41	0.066+

Table 2: Comparison of the highest level of sensory block in the two groups studied

Highest level of sensory block	Group X (n=50)	Group Y (n=50)
T8	1 (2.0%)	2 (4.0%)
T6	20 (40.0%)	15 (30.0%)
T5	8 (16.0%)	7 (14.0%)
T4	21 (42.0%)	25 (50.0%)
T3	0 (0.0%)	1 (2.0%)

Table 3: Postoperative analgesia: Comparison of the two groups studied

	Group X	Group Y	P-value
Time to request for first analgesia (min)	448.47±78.08	311.70±71.92	<0.001**

Table 4: Comparison of treatment with the number of doses of paracetamol

Paracetamol	Group X (n=50)		Group Y (n=50)		P-value
	No	%	No	%	
• 0	1	2.0	0	0.0	<0.001**
• 1	16	32.0	2	4.0	
• 2	33	66.0	11	22.0	
• 3	0	0.0	37	74.0	

Table 5: Comparison of treatment with the second rescue analgesic -diclofenac

Diclofenac	Group X (n=50)		Group Y (n=50)		P-value
	No	%	No	%	
• 0	46	92.0	8	16.0	<0.001**
• 1	4	8.0	29	58.0	
• 2	0	0.0	13	26.0	

Table 6: Comparison of treatment with a total number of rescue analgesics

Total number of	Group X (n=50)		Group Y (n=50)		P-value
	No	%	No	%	
• 0	1	2.0	0	0.0	<0.001**
• 1-2	47	94.0	4	8.0	
• 3-5	2	4.0	46	92.0	

required both the doses of diclofenac as compared to 26% of patients in group Y.

• The total number of analgesics required postoperatively was significantly less in group X when compared to group Y with a p-value <0.001.

• 94% of patients in group X required 1 or 2 rescue analgesics postoperatively. Only 4% required more than 3 doses of analgesics.

• 8% of patients in group Y required 1 or 2 analgesics while 92% of patients required more than 3 doses of analgesics

• 1 patient in group X (2%) did not require any rescue analgesic in the first 24 hrs postoperatively.

The mean requirement of the total number of analgesics was significantly less in group X when compared to group Y with a p-value <0.001.

Hemodynamic and respiratory parameters:

These included heart rate, mean arterial pressure, SpO2 and respiratory rate recorded at definite time intervals. The basal parameters were recorded followed by recordings at 5, 15, 30 and every 30 minutes for the next 2 hrs.

There was no statistically significant difference in the mean heart rate, SpO2 and respiratory rate at any time between the two groups.

The fall in mean arterial pressure was statistically significant in group Y when compared to group X at 60, 90, 120 and 150 min with p values <0.05.

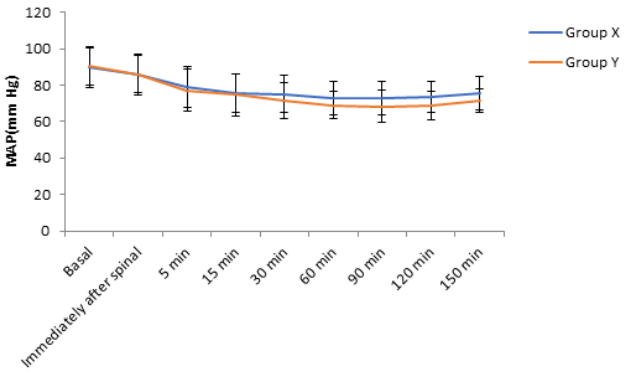

Figure 3: Comparison of mean arterial pressure in both the groups

Discussion

Spinal anaesthesia is one of the most commonly used technique for lower abdominal and lowers limb surgeries requiring a block up to T_6. Post-operative analgesia is another major advantage of regional anesthesia. Various adjuvants have been used for this purpose. Among them the most commonly used are opioids. Another class of drugs- $\alpha 2$ agonists like clonidine are also in use.

In our study, we compared a low dose of buprenorphine- 45μg with clonidine- 22.5μg when used as an adjuvant to bupivacaine intrathecally in spinal anaesthesia.

In a study conducted by Shaikh SI et al,[5] on patients who underwent lower abdominal and lower limb surgeries, 3 ml of 0.5% hyperbaric bupivacaine was used and the effect of the addition of buprenorphine-1μg/ kg intrathecally (max 50μg) was observed. In another study conducted by Pravin SS et al,[6] intrathecal clonidine and intrathecal buprenorphine were compared when added to 3ml of 0.5% hyperbaric bupivacaine in lower limb orthopedic surgeries. Based on these studies we chose the dose of 0.5% hyperbaric bupivacaine to be 15mg or 3ml for lower abdominal and lower limb surgeries which were expected to last for 2-3 hrs considering the duration of action of intrathecal bupivacaine to be 60-240 min.[7]

Ipe S et al used 150 μg buprenorphine intrathecally with bupivacaine in a combined spinal-epidural technique for caesarean section. It was observed that buprenorphine provided a longer duration of analgesia but was associated with side effects like nausea, vomiting (20%) and pruritis (20%). Shaikh SI et al used 1μg/kg (max 50 μg) in lower abdominal and lower limb surgeries and found that there was effective postoperative analgesia with little side effects. Therefore in our study, to reduce the incidence of side effects, we chose a low dose of buprenorphine of 45μg which was 0.15ml and when added to 3 ml of 0.5% hyperbaric bupivacaine would make a total volume of 3.15ml to be injected intrathecally.

In a study by Sethi BS et al, 70μg of clonidine was added to bupivacaine intrathecally in patients who underwent gynaecological surgeries. The duration of analgesia was prolonged but with clinically significant hypotension and sedation. Gecaj-Gashi A et al,[8] suggested that the addition of 25μg of clonidine to intrathecal bupivacaine improved the quality and duration of spinal anaesthesia and also provided a prolonged duration of postoperative analgesia without significant side effects. Hence in our study we used 22.5μg of clonidine which was again 0.15ml and when added to bupivacaine made a total volume of 3.15ml. Thus both the study drugs were equal in volume and the total volume injected intrathecally was 3.15ml in both the groups.

Duration of analgesia

In our study, we found that the duration of analgesia, that is the time of onset of sensory block to T10 till the time to request for first rescue analgesic was 448.47±78.08 min with 45μg of buprenorphine. This was comparable to the study conducted by Shaikh SI et al in which 1μg/kg (maximum 50μg) of buprenorphine was reported to provide a duration of analgesia of 475.6±93.7 min. Dixit S also showed that the duration of analgesia was 491.26±153.97 min when 60μg of buprenorphine was added to intrathecal bupivacaine.

Table 7: Mean arterial pressure- MAP (mm Hg): A comparison in the two groups studied

MAP (mm Hg)	Group X	Group Y	P-value
Basal	89.70±10.90	90.36±10.56	0.759
Immediately after spinal	85.82±11.35	86.16±10.17	0.875
5 min	78.82±11.18	77.28±11.42	0.497
15 min	75.64±10.82	74.66±11.46	0.661
30 min	75.28±10.41	71.48±9.62	0.061+
60 min	72.84±9.19	68.92±7.42	0.021*
90 min	72.98±9.31	68.22±8.88	0.010**
120 min	73.46±8.67	68.66±7.85	0.005**
150 min	75.64±8.98	71.48±6.59	0.010**

The duration of analgesia with 22.5μg of clonidine was found to be 311.7±71.92 min in our study which was also comparable to the study conducted by Thakur A et al.[9] They had used two doses of clonidine 15μg and 30μg as an adjuvant along with 12mg of bupivacaine and reported the duration of analgesia in the two groups to be 214± 46 min and 223±31 min respectively. In the study conducted by Sethi BS et al, it was observed that the duration of analgesia was 614 min (mean) which was longer when compared to our study. This finding could be attributed to the higher dose of clonidine used in their study which was 1μg/kg (max 70μg) along with 12.5mg of bupivacaine when compared to the dose of 22.5μg used in our study along with 15mg of 0.5% bupivacaine.

The duration of analgesia provided by intrathecal buprenorphine and clonidine when used intrathecally as adjuvants have been compared in previous studies.

Pravin SS et al used intrathecal clonidine 60 μg and intrathecal buprenorphine 60 μg along with 15mg bupivacaine and noted that buprenorphine provided longer postoperative analgesia when compared to clonidine (818.9±135 min vs. 686.5±41.9 min). Agarwal K et al,[10] also compared buprenorphine 75μg and clonidine 37.5μg and reported that the duration of analgesia was significantly longer in patients who received buprenorphine (690 min) when compared to clonidine (590 min). Similarly in our study, the group which received 45μg of buprenorphine was found to have a longer duration of analgesia (448.47±78.08 min) when compared to the group which received 22.5μg of clonidine (311.70±71.92 min) which was statistically significant with a p-value <0.001.

Opioids have been proved as good analgesics when used by various routes. Similarly in our study, we found that low dose buprenorphine when used intrathecally as an adjuvant is a very effective drug for postoperative analgesia when compared to clonidine.

The requirement of supplemental analgesics

In a study conducted by Sethi BS et al, it was shown that the number of doses of supplemental diclofenac injections was less with the use of adjuvants like clonidine (1μg/kg) when compared to the control group. The mean requirement of diclofenac injections in the control group was 2.66 (2-3) when compared to the clonidine group 1.16 (1-2). In another study by Agarwal K et al, it was reported that the requirement of diclofenac injections was less in the buprenorphine group when compared to the clonidine group. 18.42% of patients in the buprenorphine group required supplemental diclofenac injections when compared to 26.93% of patients in the clonidine group and 73% of patients in the control group who received bupivacaine alone. The mean number of diclofenac injections required was also less in the buprenorphine group 0.18 (0-1) when compared to 0.3 (0-2) in the clonidine group and 1.35 (1-3) in the control group.

Similarly in our study, the total requirement of analgesics postoperatively was significantly less in the buprenorphine group when compared to the clonidine group with a p-value <0.001. 94% of patients in the buprenorphine group required only 1 or 2 doses of total rescue analgesics postoperatively and only 4% required more than 3 doses. Whereas, 92% of patients in the clonidine group required more than 3 doses of analgesics and 8% of patients required 1 or 2 doses (p <0.001). One patient who underwent a vaginal hysterectomy and pelvic floor repair (lower abdominal surgery) in the buprenorphine group did not require any rescue analgesic in the first 24 hrs postoperatively. Hence we infer that intrathecal buprenorphine provides effective analgesia postoperatively and decreases the total requirement of supplemental systemic analgesics better than clonidine.

Another finding in our study was that all patients in the buprenorphine group required only 1 or 2 doses of the first rescue analgesic paracetamol and none of them required all 3 doses while 74% of patients in the clonidine group required all 3 doses (p <0.001). Only 8% of patients in the buprenorphine group required the second rescue analgesic diclofenac when

compared to 84% of patients in the clonidine group ($p < 0.001$). This shows that intrathecal buprenorphine provides adequate postoperative analgesia that can be managed with just one rescue analgesic in most of the patients.

Based on the above results in our study, we infer that buprenorphine provides effective postoperative analgesia better than clonidine in terms of requirement of the number of rescue analgesics and a total number of doses of analgesics.

None of the patients in both groups required the third rescue analgesic tramadol. This suggests that the addition of intrathecal adjuvants is very effective for acute postoperative pain avoiding the use of systemic opioids and their associated side effects.

Conclusion

Intrathecal adjuvants buprenorphine and clonidine, even in low doses, have been shown to provide effective post-operative analgesia with a lesser requirement of systemic analgesics in the postoperative period. But in comparison, a low dose of buprenorphine has better efficacy in terms of longer analgesic effect and decreased requirement of supplemental analgesics than a low dose of clonidine.

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