Original Article

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Minimal Side-effects and Adequate Analgesia in Spinal Anaesthesia: A Randomised Double Blinded Study Comparing Buprenorphine and Clonidine

Anaesthesia Section

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ABSTRACT

Introduction: Postoperative patient management includes managing the acute postoperative pain as well as the side-effects associated with the use of various medications in pain management. Opioids like buprenorphine are excellent in providing analgesia but causes nausea and vomiting among other side-effects. Clonidine is another class of drugs used as an adjuvant but the dose related sympatholytic effect is troublesome to handle.

Aim: To evaluate the efficacy buprenorphine (45 µg) and clonidine (22.5 µg) when used in low doses as an adjuvant in spinal anaesthesia and to study the incidence of the most common side-effects.

Materials and Methods: The double-blinded randomised clinical study was conducted in Bangalore Baptist Hospital, Hebbal, Bengaluru, karnataka, India, from January 2014 to October 2014. Hundred patients, aged between 18-55 years, American Society of Anaesthesiologists (ASA) grade I and II, scheduled for lower limb and lower abdominal surgeries were studied. They were divided randomly into two groups i.e, group X and group Y of 50 each. All patients were given 15 mg (3 mL) of 0.5% hyperbaric bupivacaine and along with that the patients in the group X (buprenorphine group) were given 45 µg (0.15 mL) of buprenorphine and the patients in group Y (clonidine group) were given 22.5 µg (0.15 mL) of clonidine. The duration of analgesia, requirement of supplemental analgesics and incidence of side-effects were noted.

Results: The duration of analgesia was found to be longer in the buprenorphine group (448.47±78.08 min) as compared to the clonidine group (311.70±71.92 min). The requirement of supplemental analgesics were, 94% in buprenorphine group required 1-2 doses and 92% in the clonidine group required 3-5 doses of analgesics in the first 24 hours, postoperatively. Among the side-effects, 4% of the patients in the buprenorphine group had bradycardia and hypotension, while 6% had nausea and vomiting. In comparison, 18% of patients in the clonidine group had hypotension, nausea (14%), vomiting (12%) and bradycardia (6%).

Conclusion: Both buprenorphine and clonidine, in low doses, provide effective postoperative analgesia with minimal side-effects; while in comparison, buprenorphine has been found to fair better.

Keywords: Incidence of side-effects, Opioids, Postoperative analgesia, Supplemental analgesics, Sympatholytic effect

INTRODUCTION

Spinal anaesthesia is one of the most favoured techniques of anaesthesia as it provides adequate analgesia, especially when used with various adjuvants like opioids and alpha-2 agonists [1,2]. But the accompanying adverse effects due to use of these adjuvants is the limiting factor in using these agents liberally. Higher doses are effective in providing excellent analgesia but both efficacy and adverse effects are dose related precluding use of such higher doses [3,4].

Buprenorphine, a commonly used opioid, has been associated with side-effects like nausea, vomiting, pruritus and respiratory depression [5,6]. Clonidine, an alpha-2 agonist, has also been associated with bradycardia, hypotension, dryness of mouth and somnolence [7]. Previous studies, using various doses of buprenorphine and clonidine as an adjuvant in spinal anaesthesia have been done [8-10]. Their effect on duration of analgesia and the various side-effects have been noted at different doses in separate studies. These two commonly used drugs have been compared when used in higher doses [11,12]. But there are not many studies comparing their least effective doses which minimises their dose related side-effects yet provides adequate analgesia.

This study was undertaken to compare the efficacy of low dose intrathecal buprenorphine (45 µg) to low dose intrathecal clonidine (22.5 µg) as adjuvant in spinal anaesthesia, in providing effective postoperative analgesia along with lesser incidence of side-effects. The primary objective was to compare the postoperative analgesia. The secondary objectives were to study the requirement of systemic opioids in postoperative period and to study the incidence of side-effects.

MATERIALS AND METHODS

The double-blinded randomised clinical study was conducted in Bangalore Baptist Hospital, Hebbal, Bengaluru, Karnataka, India, from January 2014 to October 2014. Approval for the study was obtained from the Institutional Ethics Committee (Ref no. ANA/40/2014) and written informed consent was obtained from all patients.

Sample size calculation: Proportion of patients requiring three or more rescue analgesics within 24 hours of surgery [Table/Fig-1].

Sample size: Randomised clinical trials	
Two-sided significance level (1-alpha)	95
Power (1-beta, percentage chance of detecting)	80
Ratio of sample size, Unexposed/Exposed	1
Proportion of patients requiring three or more rescue analgesics in clonidine group	60
Proportion of patients requiring three or more rescue analgesics in buprenorphine group	30
Odds ratio	0.29
Risk/Prevalence ratio	0.5
Risk/Prevalence difference	-30

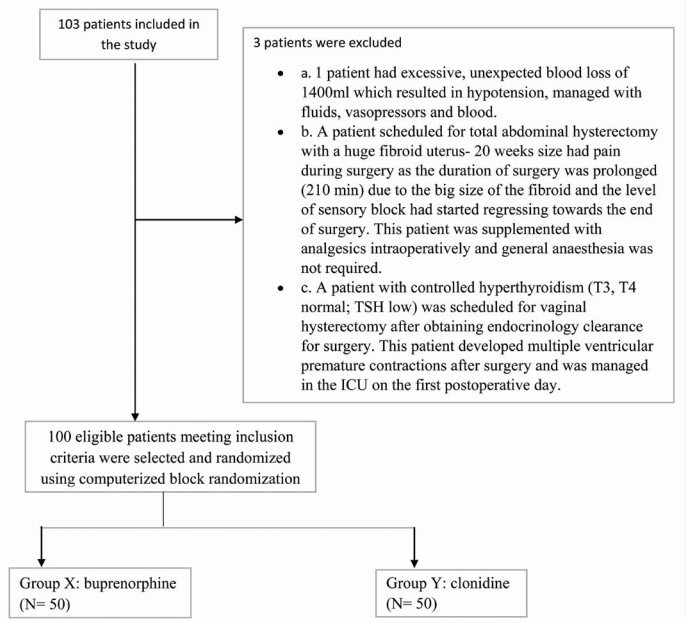
Fleiss with continuity correction	
Sample size-exposed	50
Sample size- non exposed	50
Total sample size	100

[Table/Fig-1]: Sample size calculation.
Results were rounded up to the nearest integer. Therefore, the total sample size needed for the study was calculated as 100 (50 for each group)

Inclusion criteria: All American Society of Anaesthesiologists (ASA) grade I and II patients, aged between 18-55 years, scheduled for lower limb and lower abdominal surgeries were included in the study.

Exclusion criteria: Patients on α2 agonists, β-blockers or with a basal heart rate ≤50/min, obese with Body Mass Index (BMI) ≥30 kg/m^2, pregnant and lactating women or patients with known allergy to medications used were excluded from the study.

Total 103 patients were enrolled for the study. Three patients were excluded due to various unexpected occurrences. Hence, 100 patients were included and were divided into 2 groups: X and Y of 50 subjects in each group, based on computer generated random block allocation method. After the study was completed, drug X was revealed to be buprenorphine and drug Y clonidine [Table/Fig-2].



[Table/Fig-2]: Consolidated Standards of Reporting Trials (CONSORT) diagram.

All patients were given 15 mg (3 mL) of 0.5% hyperbaric bupivacaine and along with that-

- Group X (buprenorphine group) were given 45 μg (0.15 mL) of buprenorphine,
- Group Y (clonidine group) were given 22.5 μg (0.15 mL) of clonidine.

Procedure

Standard fasting guidelines were followed by all patients and oral ranitidine 150 mg along with metoclopramide 10 mg were given as premedication 2 hours prior to surgery. Patients were connected to standard monitoring in the operation theatre and preloaded with 10 mL/kg of fluids. A patient was positioned laterally for lumbar puncture in the lateral position, and a spinal (Quincke) needle was pierced in the L3-L4 or L4-L5. space. After obtaining a free backflow of Cerebrospinal Fluid (CSF), the drugs were given over 15-20 seconds. Patients were immediately put to supine position and the vitals were noted. All patients were administered supplemental oxygen with a simple face mask at 5 L/min throughout the surgery. Vitals which included Heart Rate (HR), Systolic Blood Pressure (SBP), Respiratory Rate (RR) and Saturation (SpO_2) were monitored continuously and recorded throughout the surgery.

The sensory components analysed for determining adequate intraoperative anaesthesia and effective postoperative analgesia were the duration of analgesia and the number of doses of systemic analgesics required in the postoperative period till 24 hours after surgery. The duration of analgesia was defined as time of onset of block to time to request for first rescue analgesic. The onset of sensory blockade was the loss of sensation to pinprick at T10 after spinal anaesthesia which was tested by using the pin prick method. Assessment of pain intensity was done by the Visual Analogue Scale (VAS) (0-10) starting in the recovery room, checked every second hourly till 24 hours after surgery (0 being no pain and 10 being the worst pain).

Rescue analgesic:

- The first rescue analgesic was given when VAS was ≥4 on checking second hourly or when the patient complained of pain and VAS was ≥4. Paracetamol 1 gm intravenously was the first rescue analgesic given upto a maximum of four doses in 24 hours.
- If pain was not controlled (VAS ≥4) within 30 min of giving paracetamol, diclofenac 75 mg intravenously was given as the second rescue analgesic. Diclofenac was also used if VAS was ≥4 within six hours of the last dose of paracetamol to a maximum of two doses in 24 hours.
- If pain was not controlled with the above two NSAIDs, opioids like tramadol 50 mg intravenously was planned to be used as the third rescue analgesic.
- The total number of all the additional analgesics required during the first 24 hours postoperatively was noted. After a duration of 24 hours, the routine protocol for postoperative analgesia in our hospital was followed.

Side-effects: Patients were also monitored for the following adverse effects during and after surgery and treated accordingly. The following side-effects were looked for-

a) Bradycardia- Heart Rate (HR) <50/min was treated with atropine 0.6 mg intravenously.

b) Hypotension- Fall in the systolic blood pressure more than 20% of the baseline or less than 90 mmHg whichever was lower, was treated with ephedrine boluses of 6 mg intravenously.

c) Nausea

d) Vomiting- treated with ondansetron 4 mg intravenously.

e) Respiratory depression- was considered to be present if respiratory rate ≤10 or if SpO_2 <92%. Treated by increasing Fraction of Inspired Oxygen (FiO_2) of oxygen- which increases oxygen flow.

f) Sedation- assessed by sedation score by Campbell DC et al., [13]

- 0: Wide awake
- 1: Awake and comfortable
- 2: Drowsy and difficult to arouse
- 3: Not arousable

g) Dryness of mouth

h) Pruritus

STATISTICAL ANALYSIS

Descriptive and inferential statistical analysis was carried out. Results on continuous measurements are presented as mean±SD (min-max) and results on categorical measurements are presented in number and percentages. Significance was assessed at 5% level of significance. Student's t-test (two-tailed, Independent test) was used to find the significance of study parameters on continuous scale

between the two groups (intergroup analysis) on metric parameters. Chi-square/Fisher's-exact test was used to find the significance of study parameters on categorical scale between two or more groups. For the analysis of the data Statistical Analysis System (SAS) 9.2, Statistical Package for Social Sciences (SPSS) version 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment version 2.11.1 were used.

RESULTS

All demographic parameters like gender distribution, age, Body Mass Index (BMI), and ASA physical status in the two groups were comparable [Table/Fig-3].

Parameters	Group X	Group Y	p-value
Age (years, Mean±SD)	41.50±10.93	40.46±9.96	0.620
Body mass index (kg/m^2, Mean±SD)	24.03±2.67	24.96±2.96	0.101
Gender			
Male (%)	40	44	0.0685
Female (%)	60	56	
American Society of Anesthesiologists (ASA)			
Grade I (n)	29	32	0.539
Grade II (n)	21	18	

[Table/Fig-3]: Demographic parameters of both groups.
p-value ≤0.05 was considered as statistically significant

The time to request for first rescue analgesic i.e, the duration of intraoperative and postoperative analgesia, was significantly longer in the buprenorphine group when compared to the clonidine group [Table/Fig-4]. Total 94% of patients in the buprenorphine group required just 1 or 2 rescue analgesics and 92% of patients in the clonidine group required 3-5 doses of analgesics. Also, one patient in the buprenorphine group did not require any rescue analgesic [Table/Fig-4].

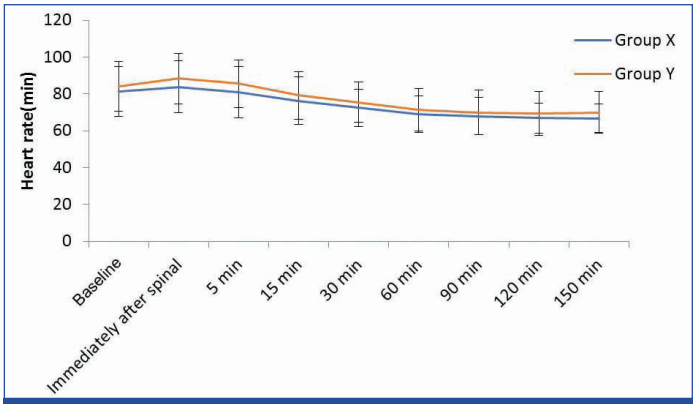
Variables	Group X (n, %)	Group Y (n, %)	p-value
Total number of rescue analgesics			
0	1 (2)	0	**<0.001**
1-2	47 (94)	4 (8)	
3-5	2 (4)	46 (92)	
Time to request for first analgesia (min) (mean±SD)	448.47±78.08	311.70±71.92	**<0.001**

[Table/Fig-4]: Comparison of treatment with the number of rescue analgesics required and comparison of intraoperative anaesthesia and effective postoperative analgesia.
p-value ≤0.05 was considered as statistically significant

Haemodynamic and respiratory parameters: These included heart rate, systolic blood pressure, SpO_2 and respiratory rate recorded at definite time intervals. There was no statistically significant difference in the mean heart rate, SpO_2 at any time between the two groups. There was no statistically significant difference in the mean heart rate at anytime between the two groups. There was no statistically significant difference in the oxygen saturation between the two groups at any point of time during the study. The fall in systolic blood pressure was statistically significant in group Y when compared to group X at 90, 120 and150 min with p-values <0.05 [Table/Fig-5-7].

The respiratory rate at 30 min and at 60 min showed statistically significant difference between the two groups. But it did not have any clinical significance as respiratory depression defined in the present study to be respiratory rate <10 was not present in any of the patients [Table/Fig-8].

Among all the side-effects looked for, incidence of hypotension was the only side-effect which was statistically significant between the 2 groups. Respiratory depression and pruritus were not present in any of the patients in both the groups [Table/Fig-9].



[Table/Fig-5]: Comparison of mean heart rate in both the groups (beats/minute).

SpO_2 (%)	Group X	Group Y	p-value
Baseline	100.00±0.00	100.00±0.00	-
Immediately after spinal	100.00±0.00	100.00±0.00	-
5 min	100.00±0.00	100.00±0.00	-
15 min	100.00±0.00	100.00±0.00	-
30 min	100.00±0.00	100.00±0.00	-
60 min	100.00±0.00	99.94±0.42	0.320
90 min	100.00±0.00	100.00±0.00	-
120 min	100.00±0.00	100.00±0.00	-
150 min	100.00±0.00	100.00±0.00	-

[Table/Fig-6]: Comparison of SpO_2 in both the groups.
p-value ≤0.05 was considered as statistically significant

Systolic blood pressure (mmHg)	Group X	Group Y	p-value
Baseline	130.58±16.79	129.46±11.62	0.699
Immediately after spinal	124.42±13.11	125.38±12.24	0.706
5 min	115.24±13.55	113.88±15.04	0.636
15 min	109.12±13.45	109.82±14.54	0.803
30 min	109.26±12.70	106.10±12.06	0.205
60 min	106.74±11.91	103.30±10.43	0.128
90 min	106.16±11.59	101.46±10.71	**0.038**
120 min	107.18±11.24	101.92±10.84	**0.019**
150 min	110.32±10.67	105.82±8.78	**0.023**

[Table/Fig-7]: Comparison of systolic blood pressure (mmHg).
p-value ≤0.05 was considered as statistically significant

Respiratory rate (per minute)	Group X	Group Y	p-value
Baseline	21.26±1.34	21.38±1.54	0.678
Immediately after spinal	22.40±1.21	22.02±1.39	0.149
5 min	18.56±1.09	18.38±1.21	0.437
15 min	16.58±1.25	16.58±1.42	1
30 min	15.56±1.16	16.00±0.99	**0.044**
60 min	15.84±1.27	15.32±1.17	**0.035**
90 min	15.98±1.00	16.00±0.86	0.915
120 min	15.92±1.19	15.84±1.13	0.731
150 min	15.60±1.23	15.58±1.18	0.934

[Table/Fig-8]: Comparison of respiratory rate (per minute).
p-value ≤0.05 was considered as statistically significant

The sedation scores of patients in both the groups were similar with a p-value=0.766, and none of the patients had scores of 2 or 3 [Table/Fig-10].

DISCUSSION

Among techniques of anaesthesia, spinal anaesthesia has several advantages especially in lower abdominal and lower limb surgeries which requires a block upto Thoracic segment (T) [6]. Various

Side-effects	Group X (n=50)		Group Y (n=50)		p-value
	no	%	no	%	
Bradycardia	2	4.0	3	6.0	1
Hypotension	2	4.0	9	18.0	**0.050**
Nausea	3	6.0	7	14.0	0.318
Vomiting	3	6.0	6	12.0	0.487
Respiratory depression	0	0.0	0	0.0	-
Pruritus	0	0.0	0	0.0	-
Dryness of mouth	0	0.0	1	2.0	1

[Table/Fig-9]: Comparison of side-effects.
Respiratory depression=Respiratory rate <10 or fall in SpO_2 <92%; p-value ≤0.05 was considered as statistically significant

Sedation score	Group X (n, %)	Group Y (n, %)	p-value
0	6 (12)	7 (14)	0.766
1	44 (88)	43 (86)	
2	0 (0)	0 (0)	
3	0 (0)	0 (0)	

[Table/Fig-10]: Sedation score.
p-value ≤0.05 was considered as statistically significant

adjuvants are combined with local anaesthetic and ideally expected to provide adequate intraoperative anaesthesia, good extended postoperative analgesia without causing adverse effects.

In the present study, buprenorphine (45 µg -0.15 mL) and clonidine (22.5 µg-0.15 mL) in low doses were used and their efficacy in providing analgesia and incidence of side-effects were compared. Buprenorphine proved to be better in terms of analgesia when compared to clonidine and even side-effects were seen to be lower with it.

Duration of analgesia: The duration of analgesia in this study is comparable to the studies of Shaikh SI and Kiran M, (50 µg buprenorphine) and Thakur A et al., (15 µg and 30 µg of clonidine) who used similar doses [1,4]. In a study by Agarwal K buprenorphine 75 µg and clonidine 37.5 µg were used and it was reported that the duration of analgesia was longer with buprenorphine (690 min) when compared to clonidine (590 min) [11]. Similarly, in the present study, it was found that the duration of analgesia with buprenorphine (448.47 min) was longer than that with clonidine (311.70 min).

Both the drugs, even when used in lower doses provided adequate and effective intraoperative and postoperative analgesia while in comparison, buprenorphine provided longer duration of analgesia.

Requirement of supplemental analgesics: In a study conducted by Sethi BS et al., it was shown that the number of doses of supplemental analgesics were less with the use of adjuvants like clonidine (1 µg/kg) when compared to the control group) [7]. In another study by Agarwal K, it was reported that the requirement of supplemental analgesics was less in buprenorphine group (18.42% of patients) when compared to clonidine group (26.93%) and the control group (73%). In the present study, 94% of patients in the buprenorphine group required only 1 or 2 doses of total rescue analgesics postoperatively and 92% of patients in the clonidine group required 3-5 doses of analgesics. One patient who underwent vaginal hysterectomy and pelvic floor repair (lower abdominal surgery) in the buprenorphine group did not require any rescue analgesic in the first 24 hours postoperatively.

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

Side-effects: Among the side-effects, in a study conducted by Kothari N et al., bradycardia was noted in 22.85% patients who received 50 µg of clonidine. In the present study, with the lower doses of adjuvants used, it was noted, a lesser incidence of bradycardia in 6% with 22.5 µg of clonidine and 4% with 45 µg of buprenorphine.

Hypotension occurred in significantly higher number of patients in clonidine (18% vs 4%) group. This was comparable with the study by Thakur A et al., which reported an incidence of 28% with 30 µg clonidine and much lesser when compared to the study by Kothari N et al., which reported higher incidences of hypotension (57.14%) with higher doses of clonidine (50 µg) [14]. Sethi BS et al., reported a significant fall in mean arterial pressure at and after 45 min [7]. The same was noted in this study too that the fall in systolic pressures were statistically significant after 60 min. This could be due to the peak effect of the drug clonidine which is 60-90 min [15]. The pressures gradually normalised before the patient was shifted back to ward requiring no interventions in the recovery due to the low doses used.

The incidence of nausea was found to be 6% in the buprenorphine group and 14% in the clonidine group. This incidence, with the low dose used in our study, is lesser than the incidence reported by Dixit S [6] which was 20% in patients who received 60 µg of buprenorphine. Pravin SS et al., [12]. also reported an incidence of 17.5% with 60 µg of buprenorphine and 7.5% with 60 µg of clonidine. The incidence of vomiting was found to be 6% in the buprenorphine group and 12% in the clonidine group in this study. This was less than the incidence of 10% with 60 µg buprenorphine as reported in the study conducted by Dixit S [6]. emphasising the reduction in incidence with reduced doses.

Nausea and vomiting are a well-known side effect of opioids. Hence, the incidence was expected to be more in the buprenorphine group. But in the study, the incidence of nausea and vomiting was found to be more in the clonidine group when compared to the buprenorphine group although this was not statistically significant. These episodes in the clonidine group occurred when hypotension was present. One patient in the clonidine group had nausea when there was hypotension which resolved after the hypotension was treated with ephedrine and did not require injectable ondansetron as the rescue antiemetic intraoperatively or postoperatively. The observed higher incidence of nausea and vomiting in the clonidine group when compared to the buprenorphine group as in contrast to the study by Pravin SS et al., [12]. Hypotension itself can cause nausea and vomiting and this could be a possible explanation for the observed results. Respiratory depression was not present in any of the patients in both the groups. In the study conducted by Ipe S et al., [3]. About 20% incidence of pruritus has been reported with 150 µg of buprenorphine. However, none of the patients in our study complained of pruritus which was comparable to the studies conducted by Dixit S [6]. and Khan FA and Hamdani GA [5]. who have also reported nil incidence using low doses of adjuvants.

Sethi BS et al., [7] reported an incidence of dryness of mouth to be 36.66% with 70 µg clonidine and Pravin SS et al., [12] reported an incidence of 10% with 60 µg of clonidine. In our study only one patient (2%) in the clonidine group complained of dryness of mouth.

The sedation score of patients in both the groups were comparable and all patients were either wide awake (score 0) or awake and comfortable (score 1). This degree of sedation keeps the patient comfortable during regional anaesthesia and avoids the use of systemic sedatives and their associated side-effects.

Limitation(s)

Low doses of adjuvants such as the ones used in the current study are not preferred in lower abdominal surgeries, which are expected to last longer than 2 hours as the sensory effect starts regressing and may result in abdominal pain and discomfort, nausea during peritoneal handling.

CONCLUSION(S)

Intrathecal adjuvants buprenorphine and clonidine, in low doses, have been shown to provide effective postoperative analgesia with a lesser requirement of analgesics in the postoperative period and also the incidence of side-effects have been found to be minimal. Buprenorphine may be considered as a good alternative to clonidine in hypertensive patients and patients on beta-blockers in whom we can expect an exaggerated fall in blood pressure or bradycardia.

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