

Original Research Article

A comparative study between intrathecal fentanyl and intrathecal buprenorphine as adjuvants to 0.5% hyperbaric bupivacaine in females undergoing lower segment caesarean section under spinal anesthesia: a randomized and double blinded study

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ABSTRACT

Background: Double blinded study involving intrathecal hyperbaric bupivacaine (1.5 ml) with adjuvants as Fentanyl and Buprenorphine

Methods: Sixty-six females posted for lower segment caesarean section under spinal anesthesia were randomized into two groups-A and B. Group A received 1.5 ml of hyperbaric Bupivacaine and 0.5 ml (75 µg) of Buprenorphine. Group B received 1.5 ml of hyperbaric Bupivacaine and 0.5 ml (25µg) of Fentanyl. Sensory blockade, motor blockade and duration of analgesia were evaluated. Randomization was done using randomization.com program with GraphPad Quick Cals. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) statistics version 28 software.

Results: There is no statistical difference in the demographic profiles of both groups. Duration of analgesia(minutes) in group A=255.37±34.63 and in group B=175.43±23.58 with p<0.001.

Conclusions: A significant drop in mean arterial pressure in both groups from preoperative values throughout surgery, (p<0.05) with the exception of MAP at 50 minutes in B (p=0.139). A significant increase in heart rate at 2 and 4 minutes in group A when compared with baseline HR (p<0.05). In group B, a significant increase only at 2 minutes post spinal anesthesia, p=0.002. Forty-three patients had hypotension (28 vs. 15), p=0.008. Nausea is higher in Group A than B (26 vs. 4). The difference in sensory level of blockade is statistically insignificant, p=0.62. The difference in time of onset of motor blockade of Bromage score 1 was statistically insignificant, p=0.093. Duration of analgesia (minutes) in group A=255.37±34.63 and in group B=175.43±23.58 with p<0.001.

Keywords: Buprenorphine, Fentanyl, Hyperbaric bupivacaine, Intrathecal, Spinal anesthesia

INTRODUCTION

LSCS under spinal anesthesia is one of the most commonly performed surgeries. Obtaining effective and rapid pain relief is challenging but necessary for patients' well-being, recovery and alleviating nociception.¹ Spinal anesthesia is the most commonly performed regional

anesthesia. It is inexpensive, has rapid onset of action and provides complete muscle relaxation.² Narcotic analgesics when used as adjuncts to local anesthetics, prolongs the duration of the block. Adjuncts also have profound dose sparing effects on the local anesthetics.³ Neuraxial anesthetics are used in abundance for intraoperative and postoperative analgesia without motor and sensory block

prolongation.⁴ The principal objective of the study is to evaluate the effects of 25 mcg Fentanyl and 75 mcg of Buprenorphine as adjuvants with 0.5% hyperbaric Bupivacaine on the time taken to achieve T10 level of sensory blockade (tested with pinprick), motor blockade assessed by onset of Bromage scale 3 and duration of postoperative analgesia.

METHODS

This randomised, double-blinded study was conducted in Regional Institute of Medical Sciences, Imphal, Manipur, between January 2021 to October 2022 on females undergoing elective LSCS under spinal anesthesia. Written informed consent was obtained from all the participants to use their data for research and educational purposes. Females aged 18-40 years belonging to American Society of Anesthesiologists (ASA) II were included in the study. Patients having contraindications to regional anaesthesia due to a history of allergy to local anaesthetics, procedure site infection, coagulation disorder or mental health issues were excluded. Randomization was done using computer generated table using randomization.com program with the help of GraphPad QuickCalcs. Group A (N=33) received 1.5 ml of hyperbaric Bupivacaine+0.5 ml (75 mcg) of Buprenorphine. Group B (N=33) received 1.5 ml of hyperbaric Bupivacaine+0.5 ml (25 mcg) of Fentanyl. Blinding done by anaesthesiologist not involved in the study. Initially the sample size was calculated to be 35 with a 5% dropout, the sample size is rounded to 33 Total 66 patients belonging to ASA II, posted for elective lower section caesarean section were included in the study. The study population was randomly divided into 2 groups of 33 patients each.⁵ Hollmen scale (sensory block): Scale 1-Normal sensation of pin prick; Scale 2-Weaker sensation of pin prick; Scale 3-Pin prick recognized as touch with blunt object; Scale 4-No perception of pin prick. Motor blockade was tested using Bromage Scale. Bromage 3 (complete)-unable to move feet or knees; Bromage 2 (almost complete)-able to move feet only; Bromage 1 (partial)-just able to move knees; Bromage 0 (none)- full flexion of knees and feet. Postoperatively, pain was assessed using visual analog scale (VAS) every 15 minutes in postanesthetic care unit during first 2 hours and then regularly at an interval of 4 hours till the next 24 hours in the ward. Whenever VAS score reached >6, rescue analgesia was given in the form of intramuscular diclofenac (75 mg). Time to the first dose of diclofenac and the total dose required for postoperative analgesia were recorded. They were informed that they will be blinded to the group assigned. Preoperative assessment was done a day prior to the scheduled day of surgery and a good rapport was established with the patients. Injection metoclopramide was given 2 hours before the operative procedure.

A routine pre-anesthetic check-up was done prior to surgery. Detailed history, general appearance and nutrition, electrocardiography (ECG), blood sugar,

bleeding, clotting time/international normalized ratio (INR), airway and spinal examination were documented. Prior to scheduled operation the study was explained to the patient, their relatives and informed consent was taken. Intravenous (IV) access was secured after wheeling the patient into the theatre and standard monitors were attached. Strict aseptic precautions were followed. All the blocks were performed by a single operator. Spinal anesthesia was performed using 25 G Quinke's needle, antiseptic solution, 2 sterile gauges, sponge holding forceps, sterile drape, stop watch and multiparameter monitor; HR, Non-invasive blood pressure (NIBP)-systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), arterial oxygen saturation (SpO₂), electrocardiography (ECG) through Nihon Kohden, Model SVM-7503, Shanghai Kohden electronics. Maintaining asepsis, lumbar puncture was done at L3-L4 interspace in left lateral position. After injection, patient was immediately placed in supine position and assessed for onset of block, onset of analgesia by loss of sensation to cold and pinprick. Respiratory rate, oxygen saturation, blood pressure (systolic, diastolic and MAP), quality and duration of post-operative analgesia were also monitored. Changes in hemodynamic status was closely noted. Post operatively, they were recorded 2 hourly till 12 hours and then 4 hourly for 1 day. Side effects like fatigue, drowsiness, nausea, vomiting, respiratory distress, urinary retention, itchiness, headache, perspiration were recorded.

Duration of analgesia was assessed by noting the time when the drug was injected till the patient complained of pain. Efficacy was assessed using VAS score. Visual analogue scale (VAS) was used with 2 end points as: 0- no pain and 10- worst pain. The above labels and its use were explained to the patients. Sensory blockade was assessed using cold spirit swabs along the midclavicular line bilaterally. In case of failure to respond to cold sensation, a 22-gauge needle (pin-prick sensation) was used. Onset of sensory block: The findings will be recorded at an interval of 2 min till a complete sensory block is achieved i.e. Hollmen Score=4. The onset time of sensory block (OTSB) will be taken as a minimum of scale 3 and complete block as scale 4 (Duration of sensory block will be the time interval between Hollmen scale 3 to onset of pain in postoperative period). Motor blockade was tested using Bromage Scale. Measurement of blood pressure, respiratory rate and oxygen saturation were obtained at every minute until BP stabilized and then was obtained every 5 minutes. Intraoperative complications like hypotension and bradycardia were treated with mephentermine (3 mg increment doses) and atropine (0.6 mg/ml) respectively. Patient was administered 6L/min of oxygen when saturation fell <90%. In the postoperative period, the mother was assessed for analgesia using VAS, regression of sensory blockade, motor block and any side effects such as nausea, vomiting, rigor, respiratory distress. Neonate was assessed using APGAR (appearance, pulse, grimace, activity and respiration)

Score at 1 and 5 minutes. If APGAR score was low, the neonate was immediately assessed by Pediatrician.

Independent variables

Independent variables were; Age (years), Weight (kg), Height (m), Duration of surgery, Outcome Variable, Maximal sensory level, Maximal motor block, Duration of analgesia, Study definitions, Onset of sensory blockade: from the time of injection of drug until the patient feels no cold/pin-prick sensation at T10 level. Time for maximum sensory block: it is the time taken to reach a state when patient fails perceive any pin-prick sensation after full dose of drug has been administered. Onset of motor block: when the patient develops modified Bromage grade 1 motor block. Time for maximum motor block: it is the time taken to achieve maximum block after full dose of drug has been administered. Duration of motor blockade: calculated from the moment of drug injection till the patient recovers complete motor function (Bromage scale-0). Duration of analgesia: time from drug injection till patient complains of pain (VAS score Hypotension is defined as 20% fall of systolic blood pressure from that of baseline values.

Statistical analysis

The completed questionnaires is checked for consistency. Data was entered in the Statistical Package for the Social Sciences (SPSS) version 26.0 for windows (Armonk, New York: International Business Machines Corporation; NY: IBM Corp; 2020 for analysis. Chi-square test assessed the association between categorical variables, t-test was done to analyse data and p value was determined, $p > 0.05$ was not significant, $p \leq 0.05$ was significant and $p \leq 0.01$ was highly significant.

RESULTS

Among 65 patients 33 patients (50.77%) were administered Buprenorphine 75 and remaining 32 patients (49.23%) were administered Fentanyl 25. Among 65 patients of 2 groups, time for maximum sensory block was ≤ 6 minutes in majority of patients (in 96.92% of patients).

Table 1: Overall distribution of all patients.

Groups	N	%
Buprenorphine 75	33	50.77
Fentanyl 25	32	49.23

Among 65 patients of 2 groups, maximum level of sensory block was T4 in 7 patients (10.77%). Maximum level of sensory block was T5 in 24 patients (36.92%). Maximum level of sensory block was T6 in 27 patients (41.53%). Maximum level of sensory block was T7 in 6 patients (9.23%). Maximum level of sensory block was T8 in only 1 patient (1.55%). So overall, maximum level

of sensory block was T6 (in 41.53% patients) followed by T5 (in 36.92% of patients).

Table 2: Association of age among patients of 2 groups.

Groups	Age (years)		P value**
	Mean	SD	
Buprenorphine 75 (n=33)	29.15	2.97	0.7527
Fentanyl 25 (n=32)	28.94	2.45	

**p value obtained by unpaired t test, so, there was no significant difference between the two groups in terms of age since $p > 0.05$.

Table 3: Distribution of weights among patients of 2 groups.

Groups	Weight (kg)		P value**
	Mean	SD	
Buprenorphine 75 (n=33)	65.15	3.54	0.0243
Fentanyl 25 (n=32)	67.00	2.87	

**p value obtained by unpaired t test, so, there was no significant difference between the two groups in terms of weight since $p > 0.05$.

Table 4: Time for maximum sensory block in all the patients.

Time for maximum sensory block (minutes)	N	%
≤ 6	63	96.92
> 6	02	3.08

Among 33 patients administered Buprenorphine 75, maximum level of sensory block was T4 in 6 patients (18.18%), T5 in 14 patients (42.42%), T6 in 11 patients (33.33%), T7 in remaining 2 patients (6.07%). So, in majority of the patients administered Buprenorphine 75, maximum level of sensory block was T5 (in 42.42% of patients), followed by T6 (in 33.33% of patients).

Table 5: Overall distribution of all patients according to level of maximum sensory block.

Maximum sensory levels	N	%
T4	7	10.77
T5	24	36.92
T6	27	41.53
T7	6	9.23
T8	1	1.55

Among 32 patients administered Fentanyl 25, maximum level of sensory block was T4 in only 1 patient (3.125%), T5 in 10 patients (31.25%), T6 in 16 patients (50.00%), T7 in 4 patients (12.50%) and T8 in only 1 patient (3.125%). So, in majority of the patients administered Fentanyl 75, maximum level of sensory block either T6

(in 50.00% of patients), followed by T5 (in 31.25% of patients).

Table 6: Distribution of time for onset of motor bromage1 among patients of 2 groups (n=65).

Groups	Time for onset of motor bromage 1 (minutes)		P value**
	Mean	SD	
Buprenorphine 75 (n=33)	6.55	0.55	0.7163
Fentanyl 25 (n=32)	6.59	0.53	

**p value obtained by unpaired t test, so, there was no significant difference between the two groups in terms of time of onset of motor bromage 1 since $p > 0.05$.

Table 7: Distribution of duration of total analgesia among patients of 2 groups (n=65).

Groups	Duration of total analgesia (minutes)		P value**
	Mean	SD	
Buprenorphine 75 (n=33)	500.61	14.56	0.0001
Fentanyl 25 (n=32)	278.48	24.24	

**p value obtained by unpaired t test, so, there was no significant difference between the two groups in terms of duration of analgesia since $p > 0.05$.

Time for onset of motor bromage 1 was $>6-6.5$ mins in only 4 patients (6.14 %) and also time for onset of motor bromage 1 was >7 mins in only 4 patients (6.14%). So overall, in majority of patients time for onset of motor bromage 1 was $>6.5-7$ mins (in 44.62% patients) or ≤ 6 minutes (in 43.10% patients).

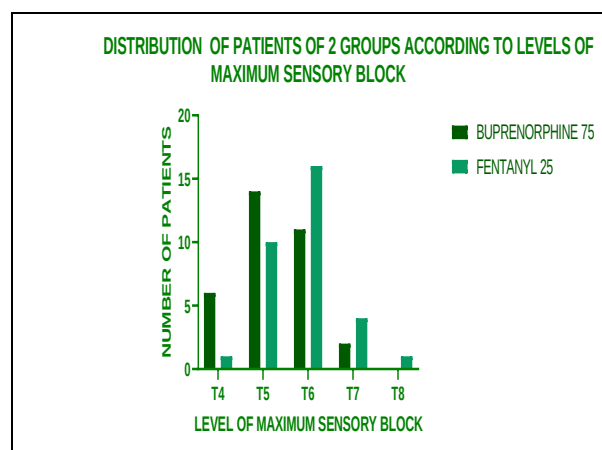


Figure 1: Distribution of patients of 2 groups according to level of maximum sensory block (n=65).

Among patients administered Buprenorphine 75 (N=33), mean time for onset of motor bromage 1 was 6.55 minutes (SD=0.55 minutes).

Among patients administered Fentanyl 25 (N=32), mean time for onset of motor bromage 1 was 6.59 minutes (SD=0.53 minutes). Table 8 shows that patients receiving bupre-75 had significantly lower VAS score of <6 at 2 hours, 6 hours and 14 hours compared to those receiving fentanyl ($p < 0.05$). Table 9 shows that occurrence of side effects was significantly higher among patients given buprenorphine 75 (since $p < 0.05$).

DISCUSSION

Fentanyl- a pure agonist and Buprenorphine- a partial agonist, both lipophilic but belonging to different classes were injected intrathecally with 0.5% hyperbaric bupivacaine. A dose of only 100 micrograms can produce equivalent analgesia to approximately 10 mg of morphine. Buprenorphine is a lipid soluble drug. Rapid absorption into the spinal venous plexus allows minimal increase in spinal fluid concentration with decreased risk of respiratory depression associated with rostral spread. Buprenorphine has a high affinity for narcotics receptors and therefore produces longer duration of analgesia compared to other agents. The demographic characteristics such as age, weight and height (Table 1-3). We compared the time of onset, level and duration of sensory as well as motor blockade and duration of analgesia. We also noted the occurrence of side effects such as hypotension, bradycardia, nausea, vomiting, shivering and pruritus. The recent developments in spinal anaesthesia have led to greater patient satisfaction and faster functional recovery. Currently, new methods of decreasing post-operative analgesic requirements are of high interest. The use of local anaesthetics like bupivacaine has been unable to provide analgesia for a longer duration. Most patients require further analgesia during the post-operative period. Various adjuvants are added to the intrathecal local anaesthetics for this purpose. Camorcia et al reported a potency ratio of 0.83 for Fentanyl/Buprenorphine.⁵ In this study we found it to be 0.33. According to Sia et al Fentanyl is 3 times more potent than Buprenorphine.⁶ We have also seen a similar result with Fentanyl. Coppejans et al proposed that Buprenorphine requires at least a 50% larger dose compared to Fentanyl.⁷ Here also we have used larger amount of buprenorphine than fentanyl. Parpaglioni et al suggested a potency ratio of 1.34 between intrathecal Buprenorphine and Fentanyl.⁸ We have noticed the potency ratio 0.33. However, the dose of Buprenorphine decided based on the study by D'Souza et al. The mean time of onset of maximum motor block, i.e., a Bromage score 3 in both the groups (Table 6) was similar with 7.07 ± 4.258 minutes in Fentanyl group and 8.83 ± 4.526 minutes in group Buprenorphine ($p = 0.125$). The mean duration of analgesia in Group B= 255.37 ± 34.63 and in Group F= 175.43 ± 23.58 with $p < 0.001$ (Table 7). The hemodynamic parameters such as pulse rate and blood pressure were comparable in the two groups.

Table 8: Distribution of patients of 2 groups according to vas scores at different times.

Time since beginning (hours)	VAS score*	Frequency (%) of patients given Buprenorphine 75 (N=33)	Frequency (%) of patients given Fentanyl 25 (N=32)	P value**
0.25	≤6	30 (90.9)	31 (96.9)	0.3170
	>6	3 (9.1)	1 (3.1)	
0.5	≤6	30 (90.9)	31 (96.9)	0.3170
	>6	3 (9.1)	1 (3.1)	
1	≤6	23 (69.7)	15 (46.9)	0.0619
	>6	10 (30.3)	17 (53.1)	
2	≤6	12 (36.4)	2 (6.3)	0.0032
	>6	21 (63.6)	30 (93.7)	
6	≤6	27 (81.8)	12 (37.5)	0.0003
	>6	6 (18.2)	20 (62.5)	
10	≤6	31 (93.9)	30 (93.8)	0.9747
	>6	2 (6.1)	2 (6.2)	
14	≤6	25 (75.8)	15 (46.9)	0.0167
	>6	8 (24.2)	17 (53.1)	
20	≤6	30 (90.9)	31 (96.9)	0.3170
	>6	3 (9.1)	1 (3.1)	
24	≤6	30 (90.9)	31 (96.9)	0.3170
	>6	3 (9.1)	1 (3.1)	

**p values obtained by Chi-square tests

Table 9: Distribution of occurrence of side effects among patients of 2 groups (n=65).

Side effects	Frequency (%) of patients given Buprenorphine 75 (N=33)	Frequency (%) of patients given Fentanyl 25 (N=32)	P value**
Present	10	2	0.0124
Absent	23	30	

**p values obtained by Chi-square tests

The incidence of side effects such as nausea, vomiting, shivering, hypotension and bradycardia were mild and comparable but not significant, presuming a Buprenorphine dose 3 times as that of Fentanyl. So we have used the dose of Buprenorphine and Fentanyl in the ratio of 0.3 (Table 9). Casati and colleagues compared hyperbaric solutions of the two drugs for unilateral spinal anesthesia.⁹ They also found no significant. Chung et al showed that adding a small dose of fentanyl (10 µg) to 0.5% hyperbaric bupivacaine increased the duration of analgesia to a mean duration of 207 min.¹⁰ Biswas et al found in their study that addition of 12.5 µg fentanyl to hyperbaric bupivacaine 0.5% increased the duration from time to subarachnoid injection to administration of first rescue analgesia to a mean of 248 min,¹¹ Similar results have been shown in study conducted by Thomas et al and Chan et al.^{12,13} Fentanyl 25 µg and buprenorphine 75 µg when used as adjuvants to 0.5% hyperbaric bupivacaine intrathecally produces significantly longer duration and better quality of postoperative analgesia than bupivacaine alone. However, on comparing the two drugs buprenorphine appears to be superior in prolonging the duration of sensory blockade (Table 6) and has better outcome in terms of pain relief postoperatively. There was difference in the onset time of sensory block in the two groups. Time to regression of sensory block to L1

was not observed in our study. In fact, the duration of analgesia was longer with Buprenorphine than Fentanyl in our study though, no statistically significant difference could be proved.

Limitations

A bigger sample size could have been taken which would have resulted in lesser sampling bias. Postoperative opioid consumption was not compared between the groups. VAS scores in the late postoperative period (more than 8 hours) couldn't be compared.

CONCLUSION

The detailed comparison of the narcotics with 0.5% hyperbaric bupivacaine for females undergoing lower segment caesarean sections under spinal anesthesia was done. Our findings were noted, discussed with the findings of previous authors. Our study concluded that Buprenorphine 75 µg provides better post-operative analgesia in comparison to Fentanyl 25 µg. Like other studies buprenorphine had better quality and longer duration of analgesia. Both the groups responded similarly after rescue analgesia. Rescue analgesia was required earlier in fentanyl 25 group. Hence,

Buprenorphine 75 is the better adjuvant providing longer duration of postoperative analgesia with bupivacaine for spinal anesthesia in females undergoing LSCS.

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