Original Research Article

Indian Journal of Anesthesia and Analgesia
2018; 5(7): 1232-1238
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.5718.23

A Comparative Evaluation of Intrathecal Administration of Hyperbaric Bupivacaine alone and in Combination of Different Low Doses of Hyperbaric Bupivacaine with Fentanyl in Cesarean Section

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Abstract

Background: This randomized study was conducted to compare the synergistic effect of intrathecally administered fentanyl and hyperbaric bupivacaine on hemodynamic, sensory and motor block characteristics alongwith their side effects. *Context:* This randomized study was done on pregnant women undergoing caesarean section under spinal anaesthesia. *Aims:* To compare and determine the efficacy of spinal anaesthesia with bupivacaine alone and in combination of different low doses of bupivacaine with additive fentanyl. *Settings and Design:* This study included 75 pregnant women scheduled for caesarean section who were then randomized into three groups of twenty five each. Group 1 (B group) received 12.5 mg (2.5 ml) of 0.5% of hyperbaric bupivacaine intrathecally, Group 2 (BF1 group) received 10 mg (2 ml) of 0.5% of hyperbaric bupivacaine + 12.5µg (0.5ml) fentanyl intrathecally, Group 3 (BF2group) received 8 mg (1.6ml of 0.5%) of hyperbaric bupivacaine + 12.5µg (0.5ml) fentanyl + 0.4 ml normal saline intrathecally. *Statistical analysis used:* The data of the study were recorded in the record chart and results were evaluated using statistical tests (ANOVA, student t-test, chi-square test and post hoc test, F-test whichever was applicable *Results:* Onset of sensory block to T10 dermatome occurred faster with increasing bupivacaine doses. Onset of motor block and duration of motor block was also longer in group B as compared to BF1 and BF2. The addition of Fentanyl to Bupivacaine significantly delayed the postoperative pain and sensory recovery. *Conclusions:* Spinal anaesthesia for cesarean delivery using low dose hyperbaric bupivacaine in combination with fentanyl is associated with significantly less hypotension, vasopressor requirement and nausea.

Keywords: Bupivacaine; Caesarean Section; Fentanyl; Spinal Anesthesia.

How to cite this article:

Dogra Ravikant, Kumar Ramesh, Verma Anjana. A Comparative Evaluation of Intrathecal Administration of Hyperbaric Bupivacaine alone and in Combination of Different Low Doses of Hyperbaric Bupivacaine with Fentanyl in Cesarean Section. Indian J Anesth Analg. 2018;5(7):1232-38.

Introduction

Spinal anaesthesia is most commonly used for patients who require surgical anaesthesia for procedures that involve the lower abdomen, lower extremities, perineum and pelvic girdle.

In the past, general anaesthesia was considered to be the technique of choice. But now the number of caesarean sections performed under general anaesthesia has dropped significantly because of airway problems in pregnancy due to anatomical and physiological changes causing airway oedema, breast enlargement and excessive weight gain and risk of pulmonary aspiration in general anaesthesia in obstetric patients [1].

Spinal anaesthesia has many advantages over general anaesthesia like minimum physiological disturbance resulting in minimum stress response, rapid onset of action, superior blockade, cost

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Received on 01.04.2018, **Accepted on** 23.04.2018

effectiveness and less chances of postoperative morbidity [2], avoidance of multiple drugs required for general anaesthesia, less neonatal exposure to highly depressant drugs, decreased risk of pulmonary aspiration and awake mother at the birth of her child [3]. Local anaesthetic agents have always been the drugs of choice for spinal anaesthesia. Intrathecal bupivacaine alone may be insufficient to provide complete analgesia despite high sensory block. But large doses of bupivacaine are associated with hypotension and delayed recovery of motor block. Hence adjuvants are added to decrease the dose of LA required. Opioids are the commonest adjuvant drugs added to the local anaesthetics for improved intra-operative and postoperative analgesia.

Fentanyl is one of the most commonly used opioid for caesarean section as it improves intraoperative and postoperative analgesia [8]. It has been found to be safe and effective both in terms of neonatal and maternal outcome [17]. Because of high lipid solubility, it undergoes rapid uptake by the spinal cord and hence the chances of respiratory depression are less.

Many studies were done to know synergistic effect of intrathecal fentanyl with bupivacaine in spinal anaesthesia for caesarean section. The combination of low dose bupivacaine with fentanyl makes it possible to achieve adequate spinal anaesthesia with minimal haemodynamic changes. Hence this study was undertaken to investigate whether this synergistic phenomenon could be used to provide less frequent hypotension and side effects without compromising spinal anaesthesia for caesarean section.

Materials and Methods

A comparative clinical study of subarachnoid block with 0.5% hyperbaric bupivacaine alone and 0.5% hyperbaric bupivacaine used in different doses with fixed dose of 12.5 µg fentanyl was conducted in ASA grade I-II patients with age between 20-35 years and weight 50-70kg at IGMC Shimla, after obtaining permission from ethical committee. 75 patients who had to undergo caesarean section were enrolled for this study and they were divided into three groups with 25 patients in each group. Every patient received total 2.5 ml of drug intrathecally as described below: Group 1 (B group) received 12.5 mg (2.5 ml) of 0.5% of hyperbaric bupivacaine intrathecally, Group 2 (BF1 group) received 10 mg (2 ml) of 0.5% of hyperbaric bupivacaine + 12.5µg (0.5ml) fentanyl intrathecally, Group 3 (BF2group) received 8 mg (1.6ml of 0.5%) of hyperbaric bupivacaine + 12.5µg (0.5ml) fentanyl + 0.4 ml normal saline intrathecally.

Inclusion Criteria

ASA physical status I or II with normal coagulation profile, age between 18 to 30 years, weight between 45 and 70 kg.

Exclusion Criteria

Twin pregnancy, severe anaemia, pregnancy induced hypertension, history of allergy to local anaesthetics, fentanyl, patients with a history of diabetes, respiratory, liver, renal, cardiovascular diseases, uncooperative patients, neurological disorder, musculoskeletal deformity.

Study Plan

Preanaesthetic examination was carried out in detail including detailed history regarding coexisting medical problems, current medications, allergies, previous anaesthetic and surgical experience. General physical examination, vital parameters (pulse rate, blood pressure), systemic examination, airway assessment and spine examination was done in every patient. Routine preoperative investigations including haemogram, blood sugar (Fasting /Random); electrocardiography were also done. Study protocol was explained to all the patients during preanaesthetic evaluation after taking written informed consent. The participants were made familiar with a 10 point visual analogue scale (where 0 is no pain and 10 is the worst imaginable pain).

After shifting patient on the operating table, nil by mouth was confirmed and monitors like pulse oximeter, non-invasive blood pressure, electrocardiographic electrodes were applied. Baseline heart rate, blood pressure and arterial oxygen saturation (SpO_2) were noted. Intravenous access was secured using 18G venous cannula and intravenous infusion was started with crystalloids fluid. The patients were placed in right lateral position on a horizontal table. After drapping the area with sterile towel, L3/L4 space was selected and by using 26G spinal needle subarachnoid block was performed under all aseptic precautions. Immediately after procedure patient was shifted to supine position, in 15-30 degree head down position. Oxygen was given through ventimask at the rate of 4 l/min. All patients received Inj. oxytocin 10 units in drip after delivery of baby. Neonatal outcome was assessed using APGAR score at 1 and 5

min. Incidence of APGAR score <7 was recorded and if respiratory depression occurred it was reversed by inj. naloxone in a dose of 0.1mg/kg intramuscularly. Intraoperatively pulse, non invasive blood pressure and SpO_2 were measured every 3 min for the first 15 min then every 5 min for next 15 min and thereafter every 10 min till 90 min.

Sensory Block Assessment

Onset of action was noted from the time of injecting the drug into subarachnoid space till complete analgesia at the level of T 10. Level of sensory block was checked bilaterally by loss of pinprick sensation to 23G hypodermic blunt needle and dermatomal level was tested every 2 min until the highest level was stabilized for four consecutive tests. Maximum level achieved was noted. After that, sensory level assessment was continued every 10 min till there was two segment regression of the block. Onset of two segment regression of the block was taken as the time from the onset of sensory block to the time taken for sensory regression to two segments below T6 level achieved. Complete sensory recovery was noted and was defined as the return of sensation of great toe.

Motor block assessment

The onset of motor block was defined as the time from the injection of drug in subarachnoid space till the patient was unable to raise the extended legs (grade 1). The degree of motor block was assessed with Bromage scale. Duration of motor blockade was calculated from the time of injecting the drug into subarachnoid space to the recovery of motor blockade (Bromage grade 0). Intraoperative side effects such as hypotension, nausea, vomiting, pruritus, maternal respiratory depression were noted till the end of surgery. Hypotension was defined as a decrease in systolic blood pressure of less than 90 mm of Hg. Hypotension was treated with Inj. Mephentermine 6mg intravenous bolus as needed.

Continuous monitoring of oxygen saturation was done. If bradycardia (heart rate less than 60 beats per min) occurred, it was treated with i.v. injection of atropine 0.6mg. Respiratory depression was defined as respiratory rate less than 10 per min. Inj. Ondansetron 4mg intravenous was given for nausea & vomiting.

Assessment of analgesia

This was taken as the time interval between injection of the spinal drug to first report of pain. Postoperatively the patients were evaluated for pain at the operation site with visual analogue scale (0 = No pain, 10 = Worst pain). On complaining of pain (VAS-3), inj. tramadol intramuscularly was given as rescue analgesia.

Statistical Analysis

Statistical analysis of data among groups was performed by using appropriate tests (ANOVA, Student t test, post hoc test).

Results

There were 25 patients in each group of total 75 patients, and there were no significant differences between three groups with respect to age and weight (p>0.05) (Table 1).

Mean time of onset of sensory block in group B was 1.60±0.50 min, in group BF1 was 1.88±0.52 min and in group BF2 was 2.16±0.59 min which was statistically significant (p<0.05) (Table 2).

Maximum patients in group B attained the highest sensory level of T4 (76%) and in group BF1 maximum patients achieved highest sensory level of T5 (52%) and also in group BF2 maximum patients attained highest sensory level T5 (68%) and this difference

Table 1: Demographic Data

Parameter	Group B Mean ±S.D	Group BF1 Mean ±S.D	Group BF2 Mean ±S.D	P value
Age (years)	28.48±2.57	27.36±2.93	28.24±3.77	0.579
Weight(Kg)	65.76±4.21	62.36±3.75	63.36±4.64	0.645

p > 0.05= not significant, p <0.05=significant (*), p< 0.001=highly significant (**)

The baseline parameters in all three groups were found to be comparable and the differences were statistically insignificant (p>0.05) [Table 2].

Abbreviations: Group 1 (B group) received 12.5 mg (2.5 ml) of 0.5% of hyperbaric bupivacaine intrathecally, Group 2 (BF1 group) received 10 mg (2 ml) of 0.5% of hyperbaric bupivacaine + 12.5µg (0.5ml) fentanyl intrathecally, Group 3 (BF2group) received 8 mg (1.6ml of 0.5%) of hyperbaric bupivacaine + 12.5µg (0.5ml) fentanyl + 0.4 ml normal saline intrathecally.

was found statistically significant ($p<0.05$) (Table 3).

Mean time taken for two segment sensory regression in group B was 91.08±5.27 min, in group BF1 was 91.78±8.07 min, and in group BF2 was 88.08± 5.23 min, this difference between the different groups was not statistically significant ($p>0.05$) (Table 3).

The mean time for effective analgesia in group B was 226.01±7.04 min, in group BF1 was 339.85± 10.28 min, and in group BF2 was 327.28±12.90 min, which was statistically significant ($p<0.05$) (Table 3).

The mean time for effective analgesia in group B was 199.80±11.08 min, in group BF1 was 208.56±5.26 min, and in group BF2 was 203.96±5.97 min, which was statistically significant ($p<0.05$) (Table 3).

The mean time of onset of motor block in group B was 2.56±0.51 min, in group BF1 was 2.68±0.48 min and in group BF2 was 2.76±0.60 min, this difference was not statistically significant among the groups even on intergroup comparison ($p>0.05$) (Table 3).

The mean time for complete recovery of motor blockade in group B was 184.24±7.61 min, in group BF1 was 171.00±8.46 min, and in group BF2 was 163.28±7.11 min, which was statistically significant among all the groups ($p<0.05$) (Table 3).

The apgar score was calculated at 1 min and 5 min interval and it was found comparable in all the three groups ($p>0.05$) (Table 4).

Amongst the side effects, on comparing the different groups hypotension was present in 40% of patients in group B, 20% of patients in group BF1 and none of patients in group BF2, which was statistically significant ($p<0.05$) (Table 5). None of the patient among the different groups had any pruritus or respiratory depression.

Discussion

General anaesthesia is associated with higher mortality rate in comparison to regional anaesthesia. This is one of the most important reason for increased use of regional anaesthesia, but regional anaesthesia is not without risk. Deaths in regional anaesthesia are primarily related to

Table 2: Baseline Parameters of the patients in three groups

Parameter	Groups			P value
	Group B Mean ± S.D	Group BF1 Mean ± S.D	Group BF2 Mean ± S.D	
HR (bpm)	86.64±9.84	87.60±8.12	90.00±8.31	0.385
SBP (mmHg)	119.28±9.31	116.12±5.63	120.92±7.56	0.077
DBP(mmHg)	68.88±7.40	70.12±8.08	71.64±7.67	0.453
MAP(mmHg)	86.56±6.96	85.36±5.65	88.04±6.63	0.342
SpO2	98.40±1.19	98.88±0.60	99.08±0.40	0.084

p > 0.05= not significant, p <0.05=significant (*), p< 0.001=highly significant (**)

Abbreviations: HR- Heart rate, SBP- systolic blood pressure, DBP- diastolic blood pressure, MAP- mean arterial pressure, SpO_2- saturation of oxygen

Table 3: Time related parameters of sensory and motor blocks in the groups

Variables	Group B Mean ± SD	Group BF1 Mean ± SD	Group BF2 Mean ± SD	P value
Onset of sensory block	1.60 ± 0.50	1.88 ± 0.52	2.16 ± 0.59	0.003*
Maximum sensory level	T4	T5	T6	0.003*
Time for two segment regression	91.08 ± 5.27	91.78 ± 8.07	88.08 ± 5.23	0.150
Complete sensory recovery	199.80 ±11.08	208.56 ± 5.26	203.96 ± 5.97	0.001**
Onset of motor block	2..56 ± 0.51	2.68 ± 0.48	2.76 ± 0.60	0.409
Duration of Motor Block	184.24 ± 7.61	171.00 ± 8.46	163.28 ± 7.11	0.010*
Total duration of effective analgesia	226.01 ± 7.04	339.85 ± 10.28	327.28 ± 12.90	0.001**

Table 4: APGAR score

APGAR score	Group B	Group BF1	Group BF2	P value
1 min	7-8	7-8	7-8	0.987
5 min	9-10	9-10	9-10	0.879

p > 0.05= not significant, p <0.05=significant (*), p< 0.001=highly significant (**)

Table 5: Side effects

Variables	Group B N=25	Group BF1 N=25	Group BF2 N=25
Hypotension	10 (40%)	5 (20%)	0 (0%)
Bradycardia	1 (4%)	0 (0%)	0 (0%)
Nausea	5 (20%)	1 (4%)	0 (0.0%)
Pruritus	0 (0.0%)	0 (0%)	0 (0%)
Respiratory depression	0 (0.0%)	0 (0.0%)	0 (0.0%)

excessive high regional blocks and toxicity of local anaesthetics. Opioids are well known to improve the analgesic potency of local anesthetics, if administered intrathecally a short acting lipophilic opioid is known to augment the quality of subarachnoid block. Fentanyl is a lipophilic opioid and is preferred for having a rapid onset and short duration of action with lesser incidence of respiratory depressions. Therefore in this study fentanyl was added to bupivacaine with the aim of providing adequate depth of anaesthesia with lesser doses of bupivacaine, thereby reducing chances of high block. The dose of fentanyl 12.5 microgram had been chosen in ourstudy, because it was mid range for doses quoted inthe literature [3,7].

In our study time of onset of sensory block was comparable in group B and BF1 and group BF1 and BF2. Whereas it was significantly lower in group B in comparison to group BF2, hence it can be concluded that time of onset of sensory block goes on increasing with decreasing the dose of bupivacaine and further addition of fentanyl to bupivacaine leads to dilution of bupivacaine concentration resulting in increase in the duration of onset of sensory block.

Our result are in accordance with the result observed by Bogra et al. [12], who observed that the onset of sensory block to T6 occurred faster with increasing bupivacaine doses in bupivacaine only groups. Therefore addition of fentanyl to bupivacaine did not alter the onset of sensory block. This finding is consistent with the findings of study conducted by Biswas et al. [11] and Harsoor et al. [13] Similar observations were made by Hunt et al. [13] and Shende et al. [5]

In the present study on comparing the highest sensory level, difference was found statistically significant between group B and BF2, whereas the difference was comparable between group B and BF1, group BF1 and BF2. Thus we concluded that on increasing the dose of bupivacaine significantly more number of patients attained highest sensory level. As the highest sensory level attained was more in group B than in group BF1 and BF2 which means that addition of fentanyl to bupivacaine did not change the height of block as the analgesia of opioid is not associated with sympathetic nervous system denervation. Our findings are consistent with the result of Biswas et al. [11], Harsoor et al. [13], and Choi et al. [17] Choi et al. [17] in their study observed a significant difference in attainment of higher sensory level in bupivacaine 12mg group and the difference between 8mg and 10mg bupivacaine groups was comparable as in our study. Similar results were observed in Biswas et al. [11] using 10mg Bupivacaine and Harsoor et al. [13] using 8mg of bupivacaine.

The mean time taken for two segment sensory regression was comparable among all the three groups. Our results were in agreement with the study done by Kotwani et al. [14], where time for two segment sensory regression in group B was 91 min and in group BF was 73 min, which was statistically not significant. Similar results were obtained in the study by Ben David et al. [10], in their study the time to two segment regression was 53 and 67 min in bupivacaine and bupivacaine plus fentanyl groups respectively, which was not significant. Similar results were also obtained in the study by Belzarena et al. [6].

In the present study mean time for effective analgesia in group B was 226.01±7.04 min, in group BF1 was 339.85±10.28 min and in group BF2 was 327.28±12.90 min, which was statistically significant, however this difference was statistically significant between group B and BF1, group B and BF2, whereas the time of effective analgesia between group BF1 and BF2 was comparable. This difference between group B, BF1 and BF2 was explained on the basis of synergistic effect of addition of fentanyl to bupivacaine. Hence we concluded that addition of fentanyl to bupivacaine significantly increased the time of effective analgesia among the bupivacaine plus fentanyl groups. This finding is consistent with the results of the study done by Hunt et al. [3], Biswas et al. [11], Bogra et al. [12] and Harsoor et al. [13]. Results of the studies done by Belzarena et al. [6] and Singh et al. [9] also in line with the results of our study.

In the present study, the time for complete sensory recovery in group BF1 was maximum followed by group BF2 and then Group B, although this difference was significant only between group B and BF1. This difference between group B, BF1 can be explained on the basis of synergistic effect of addition of fentanyl to bupivacaine. This finding is consistent with the results of the study done by Belzarena et al. [6], Harbhej Singh et al. [9] and Biswas et al. [11].

The onset of motor blockade was clinically earlier in group B than in group BF1 followed by group BF2, but was statistically non significant. Hence it can be concluded that fentanyl has no effect on motor blockade. This finding is consistent with Study done by Bogra et al .[12], Gajbhare et al. [15] and Ahmed NU et al. [16].

In our study as we increased the dose of bupivacaine, the total duration of motor blockade also increased among different groups and this finding is consistent with study done by Bogra J et al. [12] and Choi DH et al. [17] where they observed that increase in bupivacaine dose prolongs the motor recovery. The study done by Hunt CO et al. [3], Singh H et al. [9] and Biswas BN et al. [11] concluded that addition of fentanyl does not alter the duration of motor block which was consistent with the results of our study.

Apgar score was normal in all three groups and there were no significant difference in neonatal apgar score among the groups at 1 and 5 min, thus we conclude that there was no effect on neonatal respiration, which were similar with observations of study conducted by Hunt et al. [3] and Shinde et al. [5].

Systolic blood pressure decreased from the baseline value in all the three groups and fall in blood pressure was maximum in group B then group BF1 followed by group BF2. Thus decrease in systolic blood pressure can be explained on the basis of higher dose of bupivacaine significantly decreased SBP mostly due to more sympathetic blockade by higher doses of bupivacaine. Diastolic blood pressure decreased from the baseline value in all the three groups but the difference was not statistically significant between the groups.

Mean arterial pressure decreased from the baseline value in all the three groups but the difference was not statistically significant. This finding is consistent with the study done by Bogra et al. [12], Seyedhejazi Gandam et al. [18] and Madarek et al. [19].

Oxygen saturation was recorded during the procedure at regular intervals; the saturation was comparable in all the three groups with no evidence of respiratory distress any time during the procedure.

In this study different side effects of the drug were recorded and compared among the different groups. In the present study hypotension was present in 40% of patients in group B, 20% of patients in group BF1 and none of patients in group BF2. This difference was statistically significant among these groups. Thus we concluded that incidence of hypotension increases with increasing the dose of bupivacaine. Our study results are comparable to the study done by Bogra et al.[12], Gandam et al. [18], Seyedhejazi and Madarek et al. [19].

Nausea was seen in 20% patients in group B, 4% patients in group BF1 and none in group BF2. The higher incidence of nausea may be due to high dose of bupivacaine in group B. This suggests that the addition of fentanyl does not increase the incidence of nausea. Various studies by Ben David et al. [10], Biswas et al. [11] and Bogra et al. [12] also correlate with our findings.

Bradycardia was observed only in 4% of patients in group B and none in the other groups and this difference was not statistically significant among different groups ($p>0.05$). This result concurs with Hunt et al. [3], Singh et al. [9] and Biswas et al. [11], and Choi DH et al. [17].

In the present study we did not notice any incidence of pruritus, maternal or neonatal respiratory depression among different groups. This finding is consistent with study done by Hunt et al. [3], Singh et al. [9] and Biswas et al. [11].

Conclusion

In our study, we observed that spinal anaesthesia for cesarean delivery using low dose hyperbaric bupivacaine in combination with fentanyl is associated with significantly less hypotension, vasopressor requirement and nausea than spinal anaesthesia with conventional dose of hyperbaric bupivacaine and without any untoward effects. This combination has been shown to improve quality of spinal anaesthesia for cesarean delivery. Therefore, low dose bupivacaine with fentanyl gives adequate intraoperative analgesia and thus making it a reliable alternative. Even then more studies are required to verify a reliable minimum dose of bupivacaine with fentanyl for spinal anaesthesia in cesarean delivery.

Acknowledgement

None

Conflict of Interest: Nil

Key Messages

Spinal anaesthesia for cesarean delivery using low dose hyperbaric bupivacaine in combination with fentanyl is associated with significantly less hypotension,

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