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Effect of Low Dose Bupivacaine and Fentanyl during Elective Cesarean Section under Spinal Anesthesia

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Abstract

Background: Intrathecal opioids have gained popularity in recent years as they augment the analgesia produced by local anesthetic agents. The purpose of this research is to study the effect of adding Fentanyl to low dose hyperbaric Bupivacaine for spinal anesthesia during cesarean delivery in terms of sensory blockade, hemodynamics and side effect profile.

Study design: Prospective randomized double blind study.

Method: Sixty, American Society of Anesthesiologist Physical Status (ASA PS) I and II parturients undergoing cesarean section under subarachnoid block were randomly divided into two groups; Group B received 2 ml (10 mg) hyperbaric 0.5% bupivacaine and 0.25 ml inj Normal Saline intrathecally and BF group received 2 ml (10 mg) 0.5% hyperbaric bupivacaine and 0.25 ml (12.5 µg) injection fentanyl intrathecally. Onset and extent of sensory and motor block, maternal hemodynamics, neonatal APGAR score and occurrence of maternal side effects were compared.

Results: The patients' demographic data were comparable. The mean time to peak sensory level in B and BF groups were 7.92 minutes and 9 minutes (p=0.354) respectively. The mean duration of effective analgesia was 49.17 minutes and 64.73 minutes respectively in-group B and group BF (p=0.002). The mean time duration to two-segment regression was 76.30 minutes in-group Bupivacaine and 95.17 minutes in-group BF (p=0.001). Eleven patients in-group B (36%) required intraoperative rescue analgesia whereas only six patients (20%) in-group BF required intraoperative rescue analgesia (p=0.15). The incidence of hypotension in group B was 50% and in group BF was 23.33% (p=0.032). Thirteen patients in group B required inj Phenylephrine and only 4 patients required inj phenylephrine in group BF (p value 0.01). Neonatal APGAR score at 1 minute and 5 minutes of birth was similar in two groups.

Conclusion: From this double blind, randomized, prospective study, it was concluded that low dose Bupivacaine with Fentanyl provides prolonged period of sensory blockade with stable maternal hemodynamics and without maternal and neonatal side effects in elective cesarean section.

Keywords: Bupivacaine; Cesarean section; Fentanyl; Spinal anesthesia

Introduction

Spinal blocks are major regional techniques with a long history of effective use for a variety of surgical procedures and pain relief. It produces sympathetic block, sensory analgesia, and motor block depending on dose, concentration, or volume of local anesthetic [1]. Subarachnoid block is widely used for cesarean section due to the rapid induction, complete analgesia, low failure rate and the prevention of aspiration pneumonia [2,3]. A larger dose of local anesthetics within a clinical range is required to obliterate the visceral pain caused due to traction on peritoneum and intraparitoneal organs during cesarean deliveries [2]. Dosages of local anesthetics used for spinal anesthesia vary with height of the patient, desired segmental level, the specific gravity of the drug and use of adjuvants. Different additives like opioids, clonidine, neostigmine, ketamine, midazolam are used in order to improve the quality of anesthesia, duration of spinal anesthesia, postoperative analgesia, to minimize the dose of local anesthesia, and to reduce the extent and effects of sympathetic blockade.

Among the various adjuvants, opioids are more popular. Intrathecal administration of combined opioids and local anesthetics has a potent synergistic analgesic effect. Intrathecal opioids potentially act as ligands on opioid receptors in three different areas to produce analgesia [4]. They have direct access to the dorsal horn of the spinal cord (their main site of action). Also, they are transported supra-spinally by bulk CSF flow where they modulate descending inhibitory pain pathways. Similarly, a small amount of opioid diffuses into the epidural space with subsequent systemic absorption resulting in centrally mediated analgesia (minor effect). Intrathecal opioids undergo minimal metabolism within the CSF. The onset and duration of analgesia and the degree of cephalad spread are dependent on lipid solubility. Highly lipid soluble (lipophilic) opioids such as fentanyl and sufentanil diffuse into the spinal cord and bind dorsal horn receptors rapidly. This produces a rapid onset of analgesia with minimal cephalad spread and subsequently a low risk of delayed respiratory depression. Intrathecal opioids enhance analgesia from subtherapeutic

doses of local anesthetics and make it possible to achieve successful spinal anesthetic using otherwise inadequate doses of local anesthetic. It is possible to enhance the sensory blockade without altering the degree of sympathetic blockade.

The explanation of this differential synergism likely draws from the drug's separate mechanism of action; where in inhibition of nociceptive transmission occurs at sequential stages of that signal transmission. Intrathecal opioids inhibit nociceptive afferent synaptic transmission via A delta and C fibres by opening presynaptic potassium channels to inhibit transmitter release and thus reduce calcium influx. There is also a direct postsynaptic effect with hyperpolarisation and reduced neuronal activity. On the other hand, local anesthetics work primarily by causing blockade of voltage-gated sodium channels in the axonal membrane and possibly a further effect on pre-synaptic inhibition of calcium channels [4]. This study hypothesized that intrathecal fentanyl with low dose bupivacaine prolongs the sensory blockade in patients undergoing cesarean section with stable maternal hemodynamics and without causing neonatal side effects. General objective of the study was to compare intrathecal fentanyl and low dose hyperbaric bupivacaine, with hyperbaric bupivacaine alone, for the duration of sensory blockade along with maternal hemodynamics and neonatal side effects after spinal anesthesia in elective cesarean section. Specific objective were finding out time to achieve peak sensory level in each group, to determine two-segment regression time, to compare duration of effective analgesia, to compare the hemodynamic (MAP and HR), and to compare the APGAR score at 1 minute and 5 minutes between two groups.

Methods

Institutional review board (IRB) at Tribhuvan University Teaching Hospital (TUTH) approved this prospective, randomized, double blind controlled study. Oral and written informed consent was obtained from each patient to enroll in the study. The sample size was based on the number during the previous year where pregnant lady underwent lower segment cesarean section under spinal anesthesia in the Department of Anesthesiology at TUTH. A size of 30 patients per group was required to attain a power of 80% and type I error of 0.05. The inclusion criteria were parturient aged between 16 to 45 years scheduled for elective cesarean section with American Society of Anesthesiologist physical status Physical Status (ASA PS) I–II. Patients with any contraindication to spinal anesthesia, patients having problem with communication, non-reassuring fetal status, fetal maturity less than 36 week's period of gestation and parturient weight >90 kg or BMI >40 were excluded from the study. After pre-anesthetic evaluation patients were randomized to one of the two groups, using a computer generated random number table, to receive either 2 ml (10 mg) of 0.5% hyperbaric bupivacaine plus 0.25 ml NS (Group B) or 2 ml (10 mg) of 0.5% hyperbaric bupivacaine plus 0.25 ml of Fentanyl (12.5 μg) (Group BF) intrathecally. All drugs were made in a volume of 2.25 ml in a similar looking syringe. Numerical rating scale (NRS) was explained to each patient during per operative evaluation. Primary investigator and the patients were blinded to the study drugs. The blinded primary investigator did assessment of the patient prior to, during and after the operation. Patients were premedicated with inj. ranitidine 50 mg and inj. metoclopromide 10 mg, half an hour before surgery. In the pre-anesthetic preparation room, each patient was preloaded with normal saline (NS) 10 ml/kg 20 minutes before the induction of spinal anesthesia. In operating room, patient was monitored for heart rate, non-invasive blood pressure, arterial oxygen saturation and electrocardiogram until the completion of surgery. Subarachnoid block was performed at the L3-L4 space with 2.25 ml hyperbaric bupivacaine alone (Group B) or hyperbaric bupivacine with fentanyl (Group BF) as per group allocation with the patient in the sitting position, and then the patient was immediately placed in the supine with 15 degrees leftward tilt of the operating table. Each patient was catheterized with 16 French size Foley's urinary catheter. Pulse and NIBP were recorded every 2.5 minutes until baby delivery and every 5 minutes thereafter till the end of surgery. SpO_2 and ECG were monitored continuously throughout the study period. Hypotension (defined as a decrease in systolic blood pressure of more than 20% from the baseline or to less than 90 mmHg) was promptly treated with intravenous fluid bolus (200 ml) and/or 50 μg of phenylephrine boluses, which was repeated if necessary. Bradycardia (defined as heart rate less than 60 beats per minute or decrease in heart rate by at least 20% from the base line heart rate) was treated with inj. atropine 0.6 mg.

The level of sensory block was assessed by cold spirit swab bilaterally along the midclavicular line at 2, 5, 10, 15, 20, 25, and 30 minutes after intrathecal injection, and every 15 minutes thereafter until regression of the block by two segments. Surgery was allowed to proceed after achieving the level of sensory dermatome T6. If T6 sensory dermatome could not achieve even in 20 minutes, then case would have been excluded and case converted to general anesthesia. Time taken to achieve peak sensory level and time till two-segment regression of the block were noted. Duration of sensory block was taken from the time of intrathecal injection till the demand of first rescue analgesic dose. Time taken for onset, and time taken to achieve maximum motor block (grade IV in modified bromage scale) were also noted. During surgery, Inj. fentanyl 50 μg was given i.v, if pain on NRS scale was ≥ 3. The time of rescue analgesic medication (NRS ≥ 3) and duration of effective analgesia (from the time of intrathecal drug administration to the first supplementation with a rescue analgesic) were noted. Neonatal APGAR scores at one and five minutes of birth were assessed as shown in the table below and were recorded accordingly. The occurrences of adverse events like hypotension, bradycardia, shivering, pruritus, urinary retention, nausea and vomiting, dizziness, neurological deficits or any other side effects were monitored intraoperative. Adverse effects, if any, were treated with the respective drugs and recorded.

Results

Data of the study were entered into MS-excel 2007 and SPSS 17. Independent T test and chi square tests were used for analysis according to suitability of data. P value <0.05 was considered statistically significant. All sixty patients enrolled completed the study. Demographic data (Age, Weight, Height, BMI and duration of surgery) in the both groups were comparable as shown in Table 1.

	Group B (n=30)	Group BF (n=30)	p
Mean Age (yrs)	26.9 ± 3.79	27.43 ± 4.34	0.614
Mean Height (cm)	155.67 ± 6.05	157.21 ± 6.02	0.331
Mean Weight (kg)	62.17 ± 6.38	64.6 ± 7.99	0.198
Duration of surgery (min)	45.27 ± 7.15	42.13 ± 7.21	0.096

Data described as Mean ± SD, *p<0.0: Statistically Significant

Table 1: Demographic parameters.

In both group, there was no difference in time to achieve the peak sensory level (p=0.354), peak sensory level, and grade of motor blockade and the need of the rescue analgesia. However, the two-segment regression time of sensory blockade (p=0.001) and duration of effective analgesia (0.002) was significantly high in fentanyl group compared to bupivacaine alone group (Table 2).

Parameters	Group B (n=30)	Group BF (n=30)	p Value
Peak Sensory Level			
T2 dermatome	1 (3.3%)	1 (3.3%)	1
T4 dermatome	27 (90%)	28 (93.3%)	0.605
T6 dermatome	2 (6.6%)	1 (3.3%)	0.712
Time to peak sensory level (min)	7.92 ± 4.0	9.00 ± 4.9	0.354
Two sensory segment regression time (min)	76.3 ± 22.9	95.17 ± 16.5	0.001*
Motor block Grade III	4	2	0.667
Motor block Grade IV	26	28	0.572
Patients requiring rescue analgesia	11 (36%)	6 (20%)	0.15
Duration of effective analgesia (min)	49.17 ± 12.5	64.73 ± 22.4	0.002*
Data described as mean ± SD or number (percentage); *p<0.05 considered statistically significant; T: Thoracic			

Table 2: Sensory and motor blockade due to spinal anesthesia.

Baseline hemodynamic parameter (heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure) (Table 3) and respiratory parameter (arterial oxygen saturation and respiratory rate) were comparable (Table 4) in both group were comparable. Over the time, intraoperative hemodynamics and respiratory parameter did not change significantly in both groups and they were comparable.

Variables	Group B (n=30)	Group BF (n=30)	p Value
Baseline HR	101.6 ± 11.4	102.2 ± 12.1	0.4
Baseline SBP	124.4 ± 12.0	119.4 ± 13.5	0.1
Baseline MAP	91.1 ± 12.3	86.8 ± 11.3	0.163
Baseline DBP	75.3 ± 13.2	72.5 ± 11.4	0.9
Intraoperative mean HR	97.9 ± 10.8	96.7 ± 11.4	0.681
Intraoperative Mean SBP	109.0 ± 11.5	111.7 ± 13.3	0.403
Intraoperative Mean MAP	82.9 ± 17.1	84.1 ± 16.2	0.774
Intraoperative Mean DBP	64.1 ± 11.3	66.2 ± 8.6	0.429
Data described as mean ± SD; p<0.05 considered statistically significant; HR: Heart Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure			

Table 3: Hemodynamic parameters.

Variable	Group B	Group BF	p Value
Base line SpO_2 (%)	97.8 ± 2	97.2 ± 1.8	0.226
Baseline RR (breath/minute)	18.9 ± 6	17.8 ± 6.2	0.42

Intraoperative RR (breath/minute)	18 ± 2.9	18.2 ± 2.6	0.689
Intraoperative SpO_2 (%)	97 ± 2	97 ± 1.4	0.51
Data described as mean ± SD; p<0.05 considered statistically significant; SpO_2: Arterial Oxygen Saturation; RR: Respiratory Rate			

Table 4: Maternal oxygenation and respiratory parameter.

Neonatal cardiorespiratory and neurological status as described by APGAR score were also comparable in both group (Table 5) indicating that the use of intrathecal fentanyl in mother didn't hamper those parameter in neonate.

APGAR score (median)	Group B	Group BF	p Value
At 1 minutes	7	7	0.321
At 5 minutes	8	8	0.305
Data described as median; p<0.05 considered statistically significant			

Table 5: Neonatal APGAR score.

Although the intraoperative mean blood pressure (SBP, MAP and DBP) were comparable in both group, the incidence of hypotension (p=0.032) and use the use of phenylephrine for the treatment of hypotension were significantly high (p=0.01) in in bupivacaine alone group than Group BF (Table 6).

Parameters	Group B (n=30)	Group BF (n=30)	p Value
Intraoperative hypotension	15 (50%)	7 (23.3%)	0.032*
Phenylephrine required	13 (43%)	4 (13%)	0.01*
Data described number (percentage); *p<0.05 considered statistically significant			

Table 6: Intraoperative events and treatment required.

Discussion

In our study, the addition of intrathecal fentanyl to hyperbaric bupivacaine prolonged the duration of sensory block, with favorable hemodynamics and no significant adverse events. Also the neonatal outcome was not affected. There are two general categories of anesthesia for cesarean section: general anesthesia and regional anesthesia. Regional anesthesia is the preferred anesthetic technique for cesarean section because of its ability to reduce the risks of aspiration pneumonia and fetal respiratory suppression induced by the systemic administration of anesthetics in general anesthesia. Spinal block is more commonly used over epidural block in clinical practice because it is technically less complicated, faster onset of action, suffices for intra-operative analgesia, provides adequate muscle relaxation and requires small dosage of local anesthetics [5]. Intrathecal opioids are quite commonly used these days to improve the duration and quality of spinal anesthesia for cesarean section. Fentanyl is shown to produce many of its clinical effects very early after intrathecal administration [2]. In the intraoperative period, it enhances surgical analgesia and prolongs duration of anesthetic block without influence on the clinical condition of the neonate [2,6,7]. Moreover, when used in combination, reduces the doses requirement of intrathecal hyperbaric bupivacaine required to produce adequate intraoperative anesthesia and analgesia [8].

Present study aim to find the effects of lowering the dose of intrathecal bupivacaine with addition of fentanyl 12.5 μg on sensory and motor blockade, maternal hemodynamics, neonatal outcome and maternal side effects as well. To study the characteristics of sensory blockade, parameters like time to peak sensory block, time till two-segment regression of sensory block, and duration of effective analgesia were chosen. Similarly, to study the characteristics of motor blockade, time to onset of motor block and extent of maximum motor block were recorded. Intraoperative maternal hemodynamics and APGAR scores also studied to detect maternal and neonatal adverse effect during and after operation. In this study, the two groups were well matched for comparison. There were no significant difference between the groups in terms of age, weight, height, duration of surgery and ASA physical status. The mean time to achieve peak sensory level in both groups was comparable (p=0.354). Similar observations were made by the study done by Biswas et al. [2] Shende et al., [9] Hunt et al. [10] and Lee et al. [11] which implied the addition of intrathecal fentanyl with bupivacaine didn't prolong the time to achieve peak sensory level. Contrary to the findings, Sarvela et al. [12] had compared of intrathecal hyperbaric bupivacaine (9 mg) with plain bupivacaine plus Fentanyl (20 μg) on sensory and motor block characteristics. They reported the time to maximum sensory block was prolonged in fentanyl group (19 min). In another study, Siddik-Sayyid et al. [13] had compared two groups regarding characteristics of sensory blockade [intrathecal hyperbaric bupivacaine (12.5 mg) + Fentanyl (12.5 μg) versus intrathecal hyperbaric bupivacaine (12.5 mg) + intravenous Fentanyl (12.5 μg)]. In both group, time to achieve the peak sensory level were comparable.

The mean time duration of effective analgesia (time from the intrathecal drug administration to the first supplementation with a rescue analgesic was 49.17 ± 12.46 minutes and 64.73 ± 22.42 minutes respectively in group B and group BF, which was statistically significant. Similar results was noted in the study by Harsoor et al. [1] they showed the total duration of analgesia and time for first request of analgesics was prolonged to 184 minutes in fentanyl compared to 103 minutes in B group bupivacaine only group. Similarly, the study of Biswas et al. [2] found the duration of effective analgesia was increased with the dose of intrathecal fentanyl 12.5 μg in addition to intrathecal bupivacaine (248 ± 11.76 minutes).

In our study, peak level of sensory block achieved was similar in both groups (Table 2). In-group B T4 dermatome was obtained in 90% cases and in BF group level was T4 dermatome in 93% of cases. Jain et al. [7] studied varying doses of fentanyl with low dose intrathecal bupivacaine for cesarean delivery in patients with pregnancy-induced hypertension. In the study forty-five parturients were randomly allocated to receive 7.5 mg bupivacaine with either saline 1 ml, or fentanyl 10 μg or Fentanyl 20 μg intrathecally. An adequate surgical block level T4 dermatome was observed in all the patients and they

found that there was no significant difference on maximum sensory block height among the three groups. Hence, the addition of intrathecal fentanyl didn't change the sensory block height. The mean time duration to two-segment regression was 76.3 ± 22.95 minutes in-group B and 95.17 ± 16.51 minutes in-group BF, which was statistically significant (p=0.001). Similar was the finding in a recent study done by Dhumal et al. [14] where they found Group BF [(intrathecal 5 mg of 0.5% heavy Bupivacaine (1 ml) with 25 μg preservative free fentanyl (0.5 ml)] had significantly longer two segment regression time (84.83 ± 10.7 min) compared to Group B [intrathecal 7.5 mg of 0.5% heavy Bupivacaine (1.5 ml)] (64.0 ± 12.06 min). Sergio DB [15] concluded that time to regression below T12 dermatome was longer in fentanyl group and increased with increasing dose of fentanyl. The prolonged sensory block suggests synergism between fentanyl and bupivacaine as seen with other opioids and local anesthetics.

There was no significant difference between two groups regarding motor block (modified Bromage scale) in 5 minutes of spinal anesthesia in both the groups. In a study by Roussel et al., [16] maximum motor blocks was bromage scale grade III in fentanyl group and bromage scale grade II in only bupivacaine group. However, Talwar et al. [17] studied the characteristics of motor blockade with fentanyl added to bupivacaine in patients undergoing lower limb surgeries. They found longer times to onset of motor block, time to maximum motor block and duration of motor block. In our study, eleven patients in-group B (36%) required intraoperative rescue analgesia whereas only six patients (20%) in-group BF required intraoperative rescue analgesia, which showed decrease need of rescue analgesia in BF group, however there was no statistically significant difference. These findings were similar to the findings of Shende et al. [12] and Chu et al. [18] In a recent study, using 20 μg of fentanyl with bupivacaine dose adjusted to height and weight, Lee et al. [14] found better intraoperative analgesia as compared to bupivacaine alone. Also in the study conducted by Harsoor et al. [1] the rescue analgesia requirement was nil in patient receiving intrathecal fentanyl and bupivacaine whereas 14% patients received rescue analgesia in intrathecal only bupivacaine group ($p < 0.05$).

The incidence of hypotension in-group B and group BF was 50% and 23.33% respectively, which is statistically significant (p=0.032). Similar to our study, hypotension was shown to be the most common intraoperative adverse event in the study by Talwar et al. [17]. In their study, incidence of hypotension was 24.14% in fentanyl group and 20.69% in midazolam group. They randomly divided 58 patients between the ages of 18-60 years scheduled to undergo elective lower limb surgery into two groups: first Midazolam group (2.6 ml of 0.5% hyperbaric bupivacaine 13 mg with 1 mg preservative free midazolam) or second fentanyl group (2.6 ml of 0.5% hyperbaric bupivacaine 13 mg with 20 μg Fentanyl). The higher incidence seen in our patients might be due to the fact that they had used intrathecal adjunct in both groups and we had used intrathecal inj NS in group B. There was significant statistical difference regarding the requirement of inj phenylephrine between the two groups (p=0.01) in the present study. Similarly, in a study conducted by Dhumal et al. [10], Group B (16%) and Group BF (3%) required vasopressor (mephentermine).

In the present study, three patients in group B (10%) and one in BF group (3%) developed bradycardia. Similarly, in a study by Harsoor et al., bradycardia was observed in 5% patients in group B and 7% patients in group BF. These results were statistically not significant. The other well-known adverse effect of intrathecal opioids including fentanyl is pruritus. Pruritus after intrathecal fentanyl is related to direct central effect on brainstem opiate receptors [2]. In the present study, none of the patients complained of pruritus during intraoperative period. Various studies have shown that intrathecal injection of fentanyl as an adjuvant to hyperbaric bupivacaine attenuates the incidence of nausea and vomiting [7,19]. Like those findings, in the present study none of the patients in BF group complained of nausea during intraoperative period whereas three patients in B group complained of nausea but none of the patients vomited. Less incidence of hypotension in group BF could explain less incidence of nausea in comparison to group B. We could not study the propensity of intrathecal fentanyl to cause urinary retention because all of our patients were routinely catheterized as part of preparation for surgery.

Regarding APGAR score, we did not find any difference between the groups. This is in agreement with other study [12]. In our study all the newborns had an APGAR score of 6 or more at one minute and 8 or more at five minutes. Similarly in study by Harsoor et al., [1] there was no difference in the neonatal outcome in both groups; with one min APGAR score six being seen in 2 and 3 patients in group B and BF respectively and there was no statistical significance. But the APGAR score at 5 min was above 7 in all newborns of both groups.

Limitations

- Baricity of the solution between two groups is not compared.
- Fetal blood pH was not measured.
- Neonates were not followed up beyond immediate postnatal period for possible adverse events.
- Postoperative analgesia and side effects was not assessed.

Conclusion

From this double blind, randomized, prospective study, it was concluded that intrathecal low dose bupivacaine with fentanyl provides prolonged period of effective analgesia, decreases incidence of intraoperative maternal hypotension and use of vasopressor without maternal and neonatal side effects in elective cesarean section.

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