Comparative Study of Intrathecal Bupivacaine versus Bupivacaine with Fentanyl for Cesarean Section

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Abstract

Background: Spinal anaesthesia for cesarean section has been the preferred technique for majority of anaesthesiologist. Maternal hypotension following spinal anaesthesia remains common place in cesarean delivery. The combination of reduced dose of local anaesthetics with intrathecal opioids makes it possible to achieve adequate spinal anaesthesia with minimum hypotension.

Objectives: The aim of our study was to compare the effectiveness of plain bupivacaine with low dose bupivacaine plus fentanyl with respect to sensory and motor blockade, hemodynamic changes, side effect profile and post-operative analgesia after spinal anaesthesia.

Material and methods: 60 patients undergoing elective cesarean section under spinal anaesthesia were randomly allocated to two equal groups; Group B patients received 10 mg (2 mL) of 0.5% hyperbaric bupivacaine and Group B + F received 8mg (1.6 mL) of 0.5% hyperbaric bupivacaine plus 20 ug (0.4 mL) preservative free fentanyl. The clinical profile of subarachnoid block in two groups and its effect on maternal and neonatal outcome was studied.

Results: The mean time required to reach peak sensory level was earlier in Group B + F. Mean time of two segment regression of sensory analgesia and complete sensory recovery was significantly earlier in Group B. Duration of motor recovery was earlier in Group B +F. Mean maximal heart rate was significantly more in Group B. Mean minimal systolic arterial pressure was significantly less in Group B compared to Group B + F. The duration of effective analgesia was significantly more in Group B + F (235.33$\pm$29.15) compared to Group B (120.33$\pm$10.98). The incidence of side effects was less in Group B + F than Group B.

Conclusion: We can conclude that the addition of low dose fentanyl to 0.5% hyperbaric bupivacaine for spinal anaesthesia in cesarean section provides satisfactory sensory and motor blockade, better hemodynamic stability, less side effects and effective post-operative analgesia.

Key words: Bupivacaine, Fentanyl, Cesarean section, Spinal anaesthesia

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Introduction

Regional anaesthetic techniques present the most flexible, effective and least depressant option when compared with parenteral and inhalation techniques. When it comes to anaesthetising a gravida for cesarean section, spinal anaesthesia appears to be the preferred technique nationwide. It allows the mother to remain awake, minimizes or completely avoids the problem with airway management and avoids possible neonatal drug induced depression from general anaesthetics. Also the rapid onset of sensory analgesia and profound motor blockade compared to epidural anaesthesia shortens the surgical time. Moreover, the technique is simple to perform with appearance of cerebrospinal fluid as the definitive end point, thus has a higher degree of success than epidural anaesthesia. One important disadvantage of the technique is the finite duration of anaesthesia and a higher incidence of hypotension.

Bupivacaine, an amino-amide has been the local anaesthetic of choice for spinal anaesthesia in parturient. The use of lignocaine for spinal anaesthesia has become controversial due to concerns related to transient radicular irritation. The incidence is greater with lignocaine than with bupivacaine.[1]

Addition of opioids to local anaesthetic for spinal anaesthesia was first introduced in 1979 with intrathecal morphine. They act on opioid receptors present in the substantia gelatinosa of dorsal horn of spinal cord. They are synergistic with local anaesthetics and intensify the sensory block without increasing the sympathetic block. They are commonly used as additive with local anaesthetics for potentiating their effects, thus offering hemodynamic stability by reducing the dose and side effects of local anaesthetics. They also prolong the duration of post-operative analgesia.[2]

Fentanyl, a lipophilic opioid, has rapid onset and offset of action. Given intrathecally it improves quality of anaesthesia, improves postoperative analgesia and offers hemodynamic stability.

The aim of our work was to compare and determine the efficacy of intrathecal fentanyl as an adjuvant to bupivacaine in cesarean section.

Material and Methods

After approval of the institutional Ethics Committee and patients informed, written consent, 60 female patients posted for elective cesarean deliveries under spinal anaesthesia were enrolled in the study.

Inclusion criteria: ASA physical status I or II with normal coagulation profile, age between 18 to 30 years, weight between 45 and 70 kg and height between 145 and 160 cm were enrolled in the study.

Exclusion criteria: ASA III or IV, patient refusal, infection at the site of injection, coagulopathy, anticoagulant medications, pre-existing neurological disease, cardiac or respiratory system failure, musculoskeletal deformity, uncooperative patient, allergy to local anaesthetics, complicated pregnancy such as multiple pregnancies, placenta praevia, pregnancy induced hypertension, foetal distress.

Study plan: The patients were divided randomly using computer generated number and concealed using sequentially numbered, sealed opaque envelope technique into two equal groups; 30 patients each: Group B and Group B+F. All patients were assessed clinically by general and systemic examination, airway assessment, spine examination. Routine preoperative investigations were done which included complete blood count, blood sugar, kidney function test, coagulation profile, urine routine and microscopy and electrocardiogram. On arrival to the operating room nil-by-mouth status was confirmed. The monitors (non-invasive blood pressure, electrocardiogram, pulse-oximeter) were applied. Baseline systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation and electrocardiogram were recorded. Emergency drugs and equipments for resuscitation were kept ready. A suitable peripheral vein was cannulated and I.V. Ringer solution 10ml/kg (preload) was given to all patients before the procedure. Inj.Ranitidine 50 mg IV and Inj.Metoclopramide 10 mg IV was given. The position of table was kept horizontal. All patients were put in left lateral position. Sterilization was done. Dural puncture was performed at L3-4 or L4-5 interspace with 25 gauge Quincke spinal needle.

Group B (n=30): Received intrathecal injection of 0.5% hyperbaric bupivacaine 2 mL (10 mg).

Group B + F (n=30): Received intrathecal injection of 1.6 ml (8 mg) of 0.5% hyperbaric bupivacaine plus 0.4 ml (20 ug) fentanyl.

Immediately after intrathecal injection the patients were placed in supine position with a wedge under the right hip to maintain left uterine displacement. Oxygen supplementation was done by face mask at 5 L/min. Spinal anaesthesia was given by anaesthesiologist who did not participate in recording patients data. Both patients and observers were blinded to the drugs given. All patients received Inj. Pitocin 10 units in drip after delivery of baby.

Parameters recorded intra-operatively

- Continuous monitoring of the patients conscious level and oxygen saturation.
- Level of sensory block:

Sensory level was assessed by pin prick method using a hypodermic needle. The 'onset of analgesia' was defined as the time interval from completion of subarachnoid injection ('0' time) to the loss of pin prick sensation at the knee joint (L_4). Peak sensory dermatome level was tested by pin prick in midline every minute until the level stabilized for two consecutive tests. Afterwards sensory level was tested every 15 minutes until complete sensory recovery. Surgery began when the block height reached T5 dermatome. 'Two segment regression' and 'complete sensory recovery' were recorded. Complete sensory recovery was defined as the return of sensation of great toe (L5). Time taken to achieve peak sensory level, two segment regression and complete sensory recovery was noted. Duration of anaesthesia was recorded from onset of analgesia to complete sensory recovery.

- 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. The degree of motor block was assessed with Bromage scale.

Grade 0 – No motor block

Grade I – Inability to raise the extended leg

Grade II – Inability to flex the knee, able to flex the ankle

Grade III – Inability to flex the ankle (complete motor block)

Recovery from motor blockade was recorded every 15 minutes. Duration of motor blockade was calculated from the time '0' to the recovery of motor blockade.

- Heart rate and blood pressure measured every 2 min for first 20 min, then at 15 min interval till the end of surgery and thereafter at 30 min interval until the patient complained of pain.
- Visual analogue scale (VAS) was recorded. It ranges from 0 indicating no pain and 10 indicating severe intolerable pain with variable degrees of ascending pain in between. If VAS $\geq$ 4, general anaesthesia was given and the patient was excluded from the study.
- The Neonatal APGAR score at 1 min and 5 min after baby delivery was calculated by an attending paediatrician.

Assessment of additional analgesia: Need for additional analgesia was noted using Bromage scale as degree of analgesia.

I: Required general anaesthesia for completion of surgery.
II: Pain that required addition of analgesic drug.
III: Mild discomfort but did not required systemic analgesic.
IV: No discomfort at all during the procedure.

Parameters recorded post-operatively

- Continuous monitoring of the conscious level, respiratory rate and oxygen saturation every 15 min till complete recovery.
- Sensory level and motor block every 15 min till complete recovery.
- Heart rate and non-invasive blood pressure every 30 min till complete recovery.
- Intra-operative patients comfort was assessed in recovery room 30 min after surgery with visual linear analogue scale.
- 'Duration of effective analgesia' (time taken from the administration of subarachnoid block to the time patients first dose of rescue analgesic). Non-steroidal anti-inflammatory drugs were given to all patients with VAS $\geq$ 4.

Monitoring and treatment of side effects: Intra-operative and postoperative side effects such as hypotension, bradycardia, respiratory depression, nausea, vomiting, shivering and sedation were noted till complete recovery.

- Hypotension was defined as a decrease in systolic blood pressure of more than 20% of baseline value or < 100 mm Hg. It was treated with leg elevation, IV fluids, oxygen supplementation or Inj.Mephenteramine 3mg intravenous as needed.
- Bradycardia was defined as fall in heart rate < 60 beats per minute. Inj.Atropine 0.01 mg/kg was kept ready.
- Respiratory depression was defined as respiratory rate less than 10 per minute and hypoxia was defined as an oxygen saturation of < 95%. Inj. Naloxone was kept ready for respiratory depression.
- Inj.Ondansetron 4mg intravenous was given for nausea and vomiting.
- Inj.Pheniramine maleate 45.5 mg intravenous for pruritis.

Statistical analysis: Results were expressed as mean±standard deviation of the means (SD) or number (%). Comparison between different parameters in the two studied groups was performed using unpaired t test. Comparison between categorical data was performed using Chi square test using Open Epi software. The data was considered significant if p value $\leq$ 0.05 and highly significant if p value < 0.01.

Results

Demographic data: There was no statistical difference among groups as far as age, weight, height and duration of surgery (Table 1).

Table 1: Demographic Data and duration of surgery among the two groups

Parameters	Group B Mean±SD	Group B + F Mean±SD	p value
Age (Years)	24±3.14	24.40±3.66	> 0.05
Weight (Kg)	53.06±4.85	51.3±5.80	> 0.05
Height (Cm)	150.83±4.06	149.36±5.20	> 0.05
Duration of surgery (min)	54.60±8.14	55.67±7.63	> 0.05

Sensory blockade: Time required for the 'onset of sensory analgesia' was comparable in both the groups. Peak level of sensory analgesia was comparable in both the groups (p > 0.05). Thus the addition of fentanyl to 0.5% hyperbaric bupivacaine did not change the height of block. The mean time required to reach 'peak sensory level' was earlier in Group B + F than Group B and this was statistically significant (p < 0.001). Mean time of 'two segment regression' of sensory analgesia and duration of 'complete sensory recovery' was statistically significant.

The 'duration of effective analgesia' was prolonged in Group B + F as compared to Group B (p < 0.05) and was statistically significant. The above parameters are shown in Table 2.

Table 2: Comparison of sensory blockade between two groups

Parameter	Group B Mean±SD	Group B + F Mean±SD	p value
Time for onset of sensory blockade (sec)	69±9.22	66 ± 8.55	> 0.05
Time to reach peak sensory level (min)	6.36±1.32	5.03 ± 1.44	<0.001
Time for two segment regression (min)	69.0±17.63	89.66 ± 18.84	< 0.05
Time for complete sensory recovery (min)	112.66±9.07	131.4 ± 11.36	< 0.05
Duration of effective analgesia	120.33±10.98	235.33 ± 29.15	< 0.05

Motor blockade: The 'onset of motor blockade' was clinically earlier in Group B than Group B + F but statistically was not significant. All patients in both the groups had complete motor blockade. The mean 'duration of motor recovery' was shorter in Group B + F than Group B and was statistically significant ($p < 0.05$). The above parameters are shown in Table 3.

Table 3: Comparison of motor blockade between two groups

Parameter	Group B Mean±SD	Group B + F Mean±SD	p value
Onset of motor blockade (sec)	70.5±11.77	76.33±12.65	> 0.05
Time required for motor recovery (min)	108.80±8.91	87.16±14.72	< 0.05

Maternal and foetal outcome: Mean uterine incision to delivery time and neonatal APGAR score at 1 and 5 minute was statistically not significant (Table 4)

Table 4: Comparison of maternal and foetal outcome

Parameter	Group B Mean±SD	Group B + F Mean±SD	p value
Uterine incision to delivery time (sec)	87±15.84	81.83±16.05	> 0.05
APGAR score at 1 min	9.46±0.81	9.9±0.30	> 0.05
APGAR score at 5 min	9.8±0.55	9.53±0.73	> 0.05

Hemodynamic variables: The mean maximum heart rate was significantly more in Group B than Group B + F ($p < 0.05$). The decrease in systolic blood pressure in Group B was significantly more than in Group B + F ($p < 0.05$). More patients in Group B required additional fluid and vasopressors as compared to patients in Group B + F (table 5).

Table 5: Comparison of Hemodynamic variables between both groups

Parameters	Group B Mean±SD	Group B + F Mean±SD	P value
Basal Heart Rate (min)	94.6±6.34	97.2±5.08	>0.05
Minimal Heart Rate (min)	95.33±5.86	95.27±4.22	>0.05
Maximal Heart rate (min)	107.73±5.65	101.53±4.35	<0.05
Basal systolic arterial blood pressure (mm Hg)	123.73±6.92	122.53±6.62	>0.05
Minimal systolic arterial blood pressure (mm Hg)	96.66±9.69	105.8±8.50	<0.05
No. of patients additional crystalloid	4	1	<0.05
No. of patients requiring vasopressor (Mephenteramine)	5	1	<0.05

The difference in respiratory rate and SpO_2 was not significant in both the groups.

Adverse effects

Table 6: The incidence of adverse effects

Adverse effects	No. of patients (%)	
	Group B	Group B + F
Nausea	3(10%)	-
Vomiting	2(6.66%)	-
Bradycardia	0	-
Hypotension requiring treatment	9(30%)	2(6.66%)
Pruritus	0	3(10%)
Shivering	4(13.33%)	0(0%)
Respiratory depression	0	0

Discussion

Anaesthesia related complications accounted for 5.2% of maternal deaths.[3] The relative risk of fatality during general anaesthesia is 16 times more than that for regional anaesthesia.[4] Hence in absence of any contraindications spinal anaesthesia is preferred for cesarean section. The goals for decreasing mortality associated with regional anaesthesia are reduction in the dose of local anaesthetics, the use of new techniques to avoid higher blocks and better management of local anaesthetic toxicity.[5]

In this prospective randomized double blind study the effect of addition of intrathecal fentanyl to 0.5% hyperbaric bupivacaine was studied. Both the groups were comparable with respect to age, weight, height and duration of surgery.

Intrathecal fentanyl acts on mu receptors present in substantia gelatinosa of spinal cord. Analgesic effects of opioids arise from the ability of these drugs to inhibit the ascending transmission of nociceptive information from the spinal cord dorsal horn and to activate the descending inhibitory pathway.

Sensory blockade: The mean 'time of onset' of sensory blockade was comparable in both the groups. Onset of sensory analgesia was defined as loss of pin prick sensation at the knee joint. The 'peak level of sensory analgesia' was comparable in both the groups. It varied between T_4 –T_6. The addition of fentanyl to hyperbaric 0.5% bupivacaine did not change the height block as the analgesia of opioids is not associated with sympathetic nervous system denervation. Bogra J et al [5] and Tolia G et al [6] found similar results in their study.

The time required to reach 'peak level of sensory analgesia' was earlier in Group B + F than Group B. Wang et al[7] in their study on dogs concluded that intrathecal bupivacaine has no selectivity for the afferent and efferent pathways and intrathecal fentanyl acts synergistically to enhance the effect of bupivacaine on the afferent pathway without a measurable effect on the sympathetic outflow. The 'quality of sensory analgesia' was superior in Group B + F. No patient in Group B + F complained of any intra-operative discomfort (grade IV) while 3 patients in Group B complained of minimal discomfort for which no analgesic was required (grade III). 1 patient in Group B required supplementation with Inj.ketamine 0.25 mg / kg (grade II). This can be explained by the fact that analgesia by opioids is specific for visceral rather than somatic pain. Similar result was noted by Agarwal A et al.[8]

Time for 'two dermatome regression' (onset of sensory recovery) and time for 'complete sensory recovery' (return of pin prick sensation at great toe) was longer in Group B + F compared to Group B and was statistically significant. Agarwal et al[8] and Dahlgren et al [9] found similar results.

The 'duration of effective analgesia' was prolonged in Group B + F than Group B. Bano F[10], Tolia G[6] and Agarwal A[8] also found similar results. Fentanyl due to its synergistic effect with bupivacaine prolongs the duration of analgesia thus decreasing the analgesic requirement post operatively. This contributes to patients comfort and satisfaction.

Motor Blockade: The onset of motor blockade was earlier in Group B in comparison with Group B + F, but was not statistically significant. In both the groups, majority of patients had motor onset between 50-70 seconds. Fentanyl has no effect on motor blockade.[7] Patients in Group B received 10 mg bupivacaine while those in Group B + F received 8 mg of the drug. All patients had grade III motor blockade.

Maternal and foetal outcome: While adding any additive to intrathecal bupivacaine for cesarean section foetal safety and outcome is equally important to maternal outcome. There was no neonatal depression in our study. Mean APGAR score at 1 min and 5 min was similar in both the groups. Mean uterine incision to delivery time in both the groups was similar. Bogra J et al[5], Agarwal A et al[8] and Dahlgren G et al[9], all reported good neonatal outcome with intrathecal fentanyl.

Hemodynamic variables: Baseline heart rate and minimal heart rate was comparable in both groups. Fentanyl induced bradycardia is due to stimulation of central vagal nucleus. None of the patients in either group experienced bradycardia. This may be due to low dose of intrathecal fentanyl. Seyedheazi M et al [11] found no significant change in heart rate in their study. There was a significant difference in maximum heart rate. The less increase in maximum heart rate in Group B + F may be due to efficacy of fentanyl in abolishing visceral pain, better quality of surgical analgesia and less incidence of hypotension.

Maintenance of normal maternal blood pressure during cesarean section under spinal anaesthesia is key factor for adequate neonatal outcome. The mature placenta has no autoregulatory ability, so uteroplacental perfusion pressure is dependent on systemic blood pressure. Maintenance of adequate blood pressure results in better neonatal blood gas and acid-base measurements at cesarean delivery.

Basal systolic arterial blood pressure was comparable in both the groups. The fall in systolic blood pressure in Group B was statistically significant compared to Group B. Bogra J et al[5] studied the efficacy of 12.5 mcg fentanyl with increasing doses of bupivacaine and found that the incidence of hypotension was more with increasing concentration of bupivacaine. In Group B, 10 mg bupivacaine was used while in Group B + F only 8 mg bupivacaine was used in combination with 20 ug fentanyl to make a total volume of 2 mL.

Two patients in Group B + F had hypotension, out of which one patient required additional intravenous fluids while other required additional inj.mephenteramine 3 mg IV along with intravenous fluids. On the other hand, in Group B nine patients had hypotension out of which four patients required additional fluids and five patients required inj.mephenteramine 3 mg in addition with intravenous fluids.

Adverse effects: Nausea caused by opioids is due to direct stimulation of the chemoreceptor trigger zone for emesis in the area postrema of the medulla. Intraoperative nausea and vomiting occurs in 66% of cesarean deliveries performed under regional anaesthesia mainly related to peritoneal traction, exteriorization and reposition of the uterus.[12] Thus despite adequate level of $T_4 – T_6$, 3 patients complained of nausea and 2 patients complained of vomiting in Group B. It may be secondary to increased incidence of hypotension, as it was relieved after correction of hypotension after mephenteramine administration. No patient in Group B + F complained of nausea and vomiting. In Group B + F, the quality of surgical analgesia of bupivacaine is improved by fentanyl due to its synergistic effect. Also due to better hemodynamic stability there was no nausea and vomiting.

Shivering during spinal anaesthesia occurs due to decrease in core body temperature secondary to heat loss due to peripheral vasodilatation resulting from sympathetic blockade, use of cold intravenous fluids, decrease in shivering threshold. No patient in Group B + F had shivering compared to 4 patients in Group B. Opioids stimulate cAMP formation which increases the thermo-sensitivity in warm sensitive and moderate slope temperature insensitive neurons.[13] Anchalee et al[14] studied the effect of intrathecal fentanyl for prevention of shivering in cesarean section. They reported the incidence of shivering to be less in fentanyl group.

In Group B + F, 3 patients complained of pruritis but did not require any treatment. An encephalinergic mechanism is proposed for pruritis, with an itch centre in the central nervous system and activation of the medullary dorsal horn, in addition to possible antagonism of inhibitory transmitters.[15] Similar results were noted by Agarwal A et al[8] and Dahlgren et al[9].

Respiratory rate and SpO_2 was comparable in both the groups. Respiratory rate varied between 16–23 per min and SpO_2 between 95-97%. All patients received oxygen supplementation by face mask at 5 L/min. Opioids primarily cause respiratory depression by reducing brainstem respiratory centre responsiveness to carbon dioxide. They also depress the respiratory centres in pons and medulla, which are involved in regulating respiratory rhythmicity. Fentanyl is highly lipid soluble with rapid offset of action by redistribution to fat and skeletal muscle. The risk of delayed respiratory depression by rostral spread to medullary respiratory centres with single dose is less likely. Belzarena SD[16] found that no patient developed respiratory depression. They suggested that larger doses of fentanyl will be associated with respiratory depression.

Conclusion

Thus, we conclude that intrathecal fentanyl helps in reducing the dose of 0.5% hyperbaric bupivacaine for spinal anaesthesia in cesarean section thus reducing the incidence of side effects associated with it. By its synergistic effect with 0.5% hyperbaric bupivacine it provides better intra-operative and post-operative analgesia, good hemodynamic stability, less incidence of complications like nausea, vomiting and shivering without compromising the safety of mother and the foetus.

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