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Original Research Article

A Comparative Study between Two Adjuvants Nalbuphine and Fentanyl to Hyperbaric Local Anesthetic Bupivacaine for the Control of Post-Operative Pain in Cesarean Section under Spinal Anesthesia

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Abstract:

Background: Spinal anaesthesia for caesarean section has always gained popularity because of its simplicity, rapid onset, dependability and avoidance of complications of general anaesthesia. However, postoperative pain control is a concern because spinal anaesthesia using only local anaesthetics is associated with relatively short duration of action. Adjuvant drugs added to bupivacaine intrathecally improve the duration and quality of the blockade and prolong the postoperative analgesia. Nalbuphine is a synthetic opioid with mixed agonist antagonist effect, at both mu- and kappa receptors while Fentanyl is pure agonist at mu, kappa and delta receptors.

Material and Methods: A randomized study of 100 patients, divided in 2 equal groups, with adjuvant drug added to local anesthetic Bupivacaine for intrathecally use:

Group BN- Nalbuphine 0.8 milligram (0.5 milliliter) + 0.5% 2 milliliter Heavy Bupivacaine.

Group BF- Fentanyl 25 microgram (0.5 milliliter) + 0.5% 2 milliliter Heavy Bupivacaine.

Patients with ASA Physical status I, II, normal spine examination, stable vitals were selected prior to the procedure. Spinal Anesthesia given and intraoperative vitals, sensory and motor blockade characteristics, duration of analgesia were recorded. Postoperative Pain Score and vitals were recorded up to 12 hours and development of complication, if any was noted.

Results: Mean duration of Analgesia, in Group N: 249.98±8.71 minutes and in Group F: 225.24±3.27 minutes and it is statistically significant *P*=<0.0001. Visual Analogue Scale <4 after 1hr to 12hr in Group N was in 60% of patients while 40% in Group F and is statistically significant *P*=<0.0001. In group N; 4% reported nausea, 2% reported shivering, while in group F; 12% reported nausea, 4% reported pruritis and 10% reported shivering.

Conclusion: Intrathecal Nalbuphine is an effective alternative to Fentanyl for providing postoperative analgesia in patients undergoing cesarean section under spinal Anaesthesia.

Keywords: Cesarean Section, Spinal Anesthesia, Fentanyl, Nalbuphine, Analgesia.

Introduction

Spinal anesthesia is a commonly used anesthetic technique for cesarean section because of its rapid onset, simplicity, reliability and overall cost of administration. Also, it avoids various complication of general anaesthesia like difficult endotracheal intubation, pulmonary aspiration and respiratory depression in newborns. However, spinal anesthesia alone with local anesthetic like bupivacaine is associated with relatively short duration of action, and thus need for early analgesic intervention for postoperative pain control.[1]

Adjuvants drugs added to bupivacaine intrathecally, improve the duration and quality of the blockade and prolong the postoperative analgesia.[2,3]

Nalbuphine is a synthetic opioid with mixed agonist antagonist effect. It binds with kappa receptors and produces agonist effect and produces analgesia through the receptors present in brain and spinal cord,[4] while binding at mu receptors, it displaces other mu agonists, decreasing the mu agonist side effects such as nausea, vomiting, respiratory depression, urinary retention, pruritis and prolonged sedation.[5] Addition of fentanyl to intrathecal bupivacaine produces adequate intraoperative visceral analgesia, this reduces the requirement of intraoperative analgesics and

prolong postoperative analgesia.[6] It improves the quality of subarachnoid block in intraoperative and early postoperative period.[7]

Our study involves comparison of two adjuvants nalbuphine and fentanyl with local anesthetic bupivacaine, when administered intrathecally in cesarean section performed under spinal anaesthesia with aim, to estimate mean duration of analgesia provided by both adjuvants as primary end point and to study the sensory and motor characteristics, hemodynamic parameters and side effects if any, as secondary end points.

Materials and Methods

After obtaining ethical committee approval (B.J. Medical College & Civil Hospital, Ahmedabad, Dated 15/02/2021, Ref No. EC/Approval/37/2021), written and informed consent was obtained from patient and relatives. This prospective study was carried out in the Obstetric surgical operation theatre in civil hospital, B.J. Medical college, Ahmedabad from February 2021 to September 2021. Patients in the age group 19-35 years, weight within 50-100kg, height of 160-180 cm, having normal blood coagulation profile and belonging to ASA-PS I, II were enrolled in the study. Patients having any local site infection, pre-existing neurological disease, severe cardio-respiratory compromise, known allergy to local anesthetic agents, intrauterine fetal compromise and patients belonging to ASA-PS III, VI were excluded from the study. All patients underwent preanesthetic evaluation with general, systemic examination, review of all blood investigation, were explained about the anesthetic technique, perioperative course and were familiarized with the visual analogue scale. Total 100 patients were allocated into two equal groups (n=50 in each group) using random number, the allocation ratio 1:1, syringes labelled BF and BN. At the end of the study these labels were removed showing, BF stands for Bupivacaine (2 ml of 0.5% hyperbaric) + Fentanyl (25 microgram(0.5ml)) and BN for Bupivacaine (2 ml of 0.5% hyperbaric) + Nalbuphine (0.8 milligram(0.5ml)).

Preparation in OT: On arrival to operative room, NBM status was asked, baseline vitals, ECG, pulse, blood pressure, spo2 was recorded. 18G/20G intravenous cannula secured and ringer lactate 10 ml/kg/15 min administered before spinal anaesthesia.

Spinal Anaesthesia:

All patients in sitting position with leaning forward, local site sterilization was done. Dural puncture performed at L3-L4 Interspace or L4-L5 with a 23 G Quincke's spinal needle, free flow of clear CSF confirmed, drug given intrathecally. Immediately patients made placed in supine position with wedge over right hip. Elevation of the head by a pillow and oxygen mask 5L/min was applied.

Monitoring: Continuous monitoring of pulse, bp, spo2, consciousness state of patient was done. The level of sensory block was assessed by pin-prick in caudo-cephalic manner, onset of sensory block (no sensation at T10 dermatome), highest level of sensory block achieved, time to achieve highest level and total duration of sensory block was recorded and level of motor block done by Modified Bromage scale done until skin incision. Onset and total duration of motor block was recorded. The surgery started until block reached T6 dermatome.

Vital monitoring was done every 2 min till 10 min, every 5 min till 30 min, every 10 min till the end of procedure intraoperatively and every 30 min up to 24 hours postoperatively.

VAS score was recorded intraoperatively and at 1,2,4,8 and 12 hours postoperatively.

The duration of analgesia (from intrathecal injection to VAS greater than 0) was recorded. The time of first analgesic dose was recorded (effective analgesic time: from intrathecal injection to VAS >= 4). NSAIDS (injection diclofenac 75 mg intravenous) was given for analgesia to all patients scoring >= 4. The total number of rescue analgesic required and the time of their use was noted in the postoperative period.

Atropine (0.01 mg/kg) was given if bradycardia (HR <60/ min) develops. Ephedrine 10 mg iv was given, if the systolic arterial blood pressure decreased by more than 20% below preanesthetic level or less than 100 mmHg.

For vomiting metoclopramide 10 mg iv was given, for pruritis pheniramine 45.5 mg iv was given. For shivering pethidine 20 mg iv was given. Respiratory depression was defined as respiratory rate <10 breaths/min and was treated with supplemental oxygen using face mask.

Data Analysis: All observations were recorded and results were analyzed statistically. Data was entered in Microsoft Excel and analyzed using student's'‘t' test. Numerical data was expressed as mean +/-SD.

Categorial data was expressed as percentage and frequencies and were analyzed using chi-square test. P value <0.05 was interpreted as clinically significant.

Study endpoint: The study involves observation and comparing the post-operative analgesic effect of fentanyl and Nalbuphine as an adjuvant to hyperbaric intrathecal bupivacaine.

The end points were to assess the VAS score at 1, 2, 4, 8, 12 hours after caesarean section, the timing

and dosage of rescue analgesic required to control post-operative pain and any effects of intrathecal adjuvants on fetal APGAR Score.

Results

Table 1: Demographic Parameters and Duration of Surgery in studied groups

Parameter	BF(n=50)	BN(n=50)	p value
Age(years)	25.40 ±3.97	24.96 ±3.17	0.11
ASA-PS (I: II)	22:28	26:24	0.72
Duration of Surgery(min)	75.92±5.83	77.04±5.27	0.31

Table 1 shows that both the study groups, group BF and BN, were comparable with respect to age, ASA-PS and total duration of surgery time taken and the difference is statistically not significant (p>0.05)

Table 2: Characteristics of Subarachnoid Block in studied groups

Parameter(min)	BF(n=50)	BN(n=50)	p value
Time of onset of sensory block	1.79±0.18	3.34±0.49	0.0001
Time of onset of motor block	4.49±0.34	5.43±0.31	0.0001
Total duration of sensory block	131.32±4.87	189.28±6.04	0.0001
Total duration of motor block	186.52±4.08	188.32±5.52	0.06
Duration of Effective Analgesia	225.24±3.27	249.98±8.71	0.0001

Table 2 shows characteristics of spinal block produced by both study drugs. For onset of sensory block, mean time in Group F patients was 1.79±0.18 minutes and in Group N patient were 3.34±0.49 minutes, which is shorter on Group F as compared to Group N.

The mean duration of Sensory block in Group N patient was 189.28±6.04 minutes and in Group F patient was 131.32±4.87 minutes, which is shorter in Group F as compared to Group N and the difference is statistically significant (p<0.001) as per as unpaired t test. For onset of motor block, mean time in Group N patient was 5.43±0.31 minutes and Group F patient was 4.49±0.34 minutes, which was shorter in Group F than Group N and the difference is statistically significant (p<0.001) as per unpaired t test.

The mean duration of Motor block in Group N patient was 188.32±5.52 minutes and in Group F patient was 186.52±4.08 minutes and the difference are statistically not significant (p>0.05) as per unpaired t test. In Group N, the mean duration of Analgesia was 249.98±8.71 minutes. Whereas in Group F, the mean duration of Analgesia was 225.24±3.27 minutes. The duration of Analgesia was shorter in patients Group F than patients Group N which is statistically significant (p<0.001) as per unpaired t test.

Table 3: Comparison of vitals in studied groups

Parameter	BF	BN	p value
Intraoperative			
HR	76.87±8.48	77.29±8.48	0.80
SBP	113.47±9.07	114.18±8.91	0.69
DBP	72.84±6.67	73.66±6.74	0.54
RR	12.78±1.03	12.77±1.02	0.96
SPO2	98.10±0.68	98.10±0.64	1.00
Postoperative			
HR	82.96±7.36	83.11±7.27	0.92
SBP	120.42±7.98	121.11±7.51	0.66
DBP	77.07±6.96	77.49±7.01	0.61
RR	12.45±0.83	12.41±0.81	0.81
SPO2	98.11±0.68	98.11±0.57	1.00

Table 3 shows, hemodynamic and vital monitoring in Group F and Group N. Intraoperative up to 80 minutes and postoperative up to 24 hours heart rate, systolic and diastolic blood pressure, respiratory rate and saturation of oxygen did not differ in both the groups during course of anaesthesia, p (>0.05), statistically insignificant as per unpaired t test.

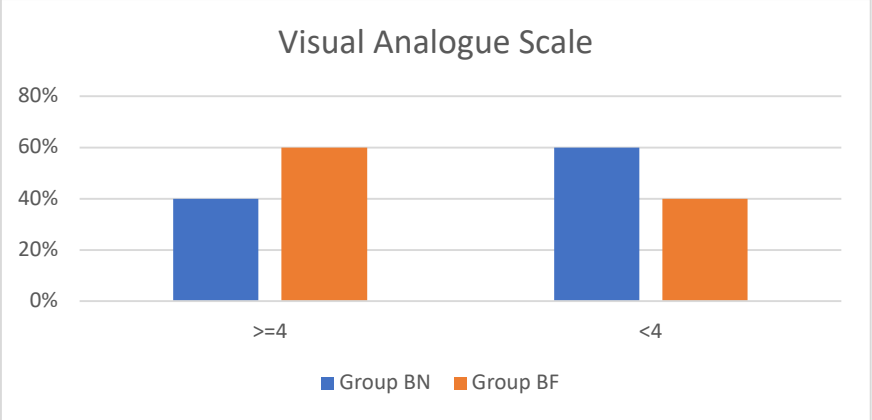

Figure 1: Visual Analogue Scale in studied groups

Figure 1 shows, Visual Analogue Scale <4 after 1hr to 12hr in Group N patient was in 60% of patients while 40% in Group F patients which is statistically significant (p<0.001) as per chi square test.

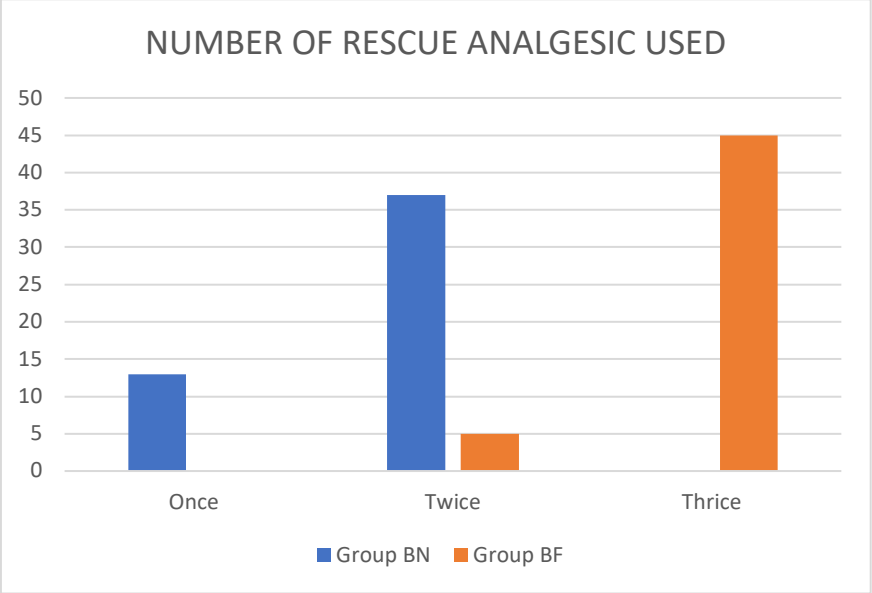

Figure 2: Rescue Analgesic required in studied groups

Figure 2 shows, requirement for Rescue Analgesia in Group N patient was once for 13 patients & twice for 37 patients. While in Group F patient was twice for 5 patients and thrice for 45 patients.

Table 4: Side effects in studied group

Parameter	BF(n=50)	BN(n=50)
PONV	6(12%)	2(4%)
Pruritis	2(4%)	0(0%)
Sedation	0(0%)	0(0%)
Shivering	5(10%)	1(2%)
Respiratory Depression	0(0%)	0(0%)

Table 4 shows side effects in both groups in which, in group N; 4% reported nausea, 2% reported shivering, while in group F; 12% reported nausea, 4% reported pruritis and 10% reported shivering.

Table 5: APGAR Score

Time(min)	BF	BN	p value
1	8.28±0.67	8.04±0.73	0.09
5	8.92±0.40	8.72±0.45	0.02

Table 5 shows, in both the groups, as per as Apgar Score, no newborn encountered respiratory depression and the Apgar score was >8 at 5 min after birth.

Discussion

Cesarean section can be carried out under various modes of anaesthesia, but one of the most promising methods is to perform under spinal anaesthesia. Spinal anaesthesia because of its early onset, ease of administration, predictability and lesser uses of resources is preferred over general anaesthesia but has limitation of shorter duration of block and postoperative analgesia [8]. Most of the patients experience moderate to severe pain with in first 24 hours post-surgery and alleviation of these symptoms results in faster ambulation, lesser incidence of chronic pain and early discharge from recovery room [9]. Various adjuvants are used intrathecally to provide prolonged post-operative analgesia. Neuraxial opioids are widely used as adjuvant as they shorten the onset and reduces total dose and dose related side effects of local anesthetic drugs, provide intraoperative and postoperative analgesia [10]. Fentanyl is a synthetic opioid, pure μ agonist, which provides high potency analgesia with rapid onset, shorter duration of action and lesser chance of respiratory depression while nalbuphine is a mixed agonist-antagonist which provides analgesia by agonism on k-receptors and by antagonism at μ receptors reduces side effects of opioid like nausea, vomiting, itching, sedation, respiratory depression, tolerance and dependence [11]. In our study, we have used 25 mcg of fentanyl and 0.8 mg of nalbuphine [12,13]. There have been no documented studies of nalbuphine neurotoxicity [14,15,16].

Table 1 shows that in our study demographic variables are comparable in each group in form of age, ASA-PS grade and duration of surgery. ($p > 0.05$). Gupta et al., 2021 [17], Shah et al., 2022 [18] also have comparable demographics. ($p > 0.05$)

Table 2 shows various characteristics of spinal blockade in each group. In our study, Time of sensory onset is 3.34 ± 0.49 min in group N and 1.79 ± 0.18 min in group F which is statistically significant. ($p < 0.05$), and Time to onset of motor blockage in our study is 5.43 ± 0.31 min in group N and 4.49 ± 0.34 min. in group F, which is statistically significant. ($p < 0.05$) which can be due to higher lipid solubility of fentanyl as compared to nalbuphine. Gurunath et al., 2018[19] also had similar findings in their study. Duration of motor blockage in our study is 188.32 ± 5.52 min in group N and 186.52 ± 4.08 min. in group F, which is statistically not significant. ($p > 0.05$). Prabhakaraiah UN et al., 2017 [20] also had similar findings in their study. Table 3 shows HR, SBP, DBP, RR, Spo2 changes in each group respectively. In all groups hemodynamic variables were stable in intraoperative period. ($p > 0.05$) Decrease in SBP in each group was observed less than 30 % of baseline which is physiological change of spinal anaesthesia. No pharmacological intervention required ($p > 0.05$). Sharma et al., 2019[21] also have shown statistically non-significant both groups comparable hemodynamic stability. ($p > 0.05$). In the study conducted by Shagufta Naaz et al., 2017[22], six patients in Group F, three patients in NL Group and none of the patients in NH Group reported hypotension, which can be due to use 12.5 mg dose of bupivacaine, while in our study we used 10 mg of bupivacaine.

As per as Table 2 in our study, duration of effective analgesia in our study is 249.98 ± 8.71 min in group N and 225.24 ± 3.27 min. in group F, which is statistically significant. ($p < 0.05$). Total duration of sensory block in Group F is 131.32±4.87 min and in Group N is 189.28±6.04 min, which is statistically significant. ($p < 0.05$). Fentanyl being higher lipophilic drug as compared to nalbuphine, causing rapid onset and rapid offset of block, thus nalbuphine showing prolonged duration of sensory block and effective analgesia.

As per as, Tripat Kaur Bindra et al. 2018 [23]. The mean duration of effective analgesia was 259.20 ± 23.23 min in Nalbuphine Group I, 232.70 ± 13.15 min in fentanyl Group. The mean number of rescue analgesics required was significantly lower ($P < 0.001$) in Nalbuphine Group as compared to Fentanyl Group, supporting findings of our study.

As per as, Farahat I. Ahmed et al. 2019 [24] . Duration of postoperative complete and effective analgesia were highly significantly longer in BN group than the corresponding durations in BF group ($P<0.001$ and 0.002, respectively). The postoperative 24-h analgesic doses of ketorolac and pethidine were less in BN group than in BF group ($P=0.03$, 0.005, respectively), above findings are supporting our study.

VAS score measured in our study were lower in nalbuphine group, with lesser requirement of rescue diclofenac drug as compared to fentanyl group. Similar findings were found in study by Mehdi et al., 2021[25]

Studying various characteristics of both the adjuvants for neuraxial block, nalbuphine can be considered an effective alternative to fentanyl for control of post-operative pain for cesarean section under spinal anaesthesia. Findings of H.M. Gomaa et al., 2014 [26] Mohamed et al., 2021 [27] are supportive of our study

As per as Table 4, side effects were more in fentanyl as compared to nalbuphine group in terms of PONV, pruritis and shivering. No serious side effects like respiratory depression were encountered in any of the patients in our study. Satapathy et al., 2023[28] also have similar findings as in our study. Raghuraman M.S.,

2017[29] also explained in his study's similar outcomes of nalbuphine.

As per as Table 5, APGAR score at 1 min there is no statistical difference between two groups (p value > 0.05), at 5 min in both the groups the APGAR score where more than 8 in both age groups and according to Neonatal Resuscitation Program, these scores are reassuring [30] and no new born encountered respiratory depression post-delivery. As according to American Academy of Pediatrics, administration of spinal anaesthesia for cesarean section can be a factor for a good APGAR score of more than or equal to 8 in new born [31].

Strength and Limitations of study:

Nalbuphine is a cost-effective alternative of fentanyl, which does not require prescription for its procurement and use.

Our study involves pregnant patients of ASA-PS I and II posted for cesarean section. Further studies are required for wider age group patients, of different ASA profile, posted for different surgeries for wider conclusions.

Conclusion

From the data of our study, it can be concluded that, nalbuphine prolongs the total duration of sensory block, total duration of analgesia resulting in lesser requirement of rescue analgesics when added intrathecally to bupivacaine for caesarean section, with lesser maternal side effects as compared to intrathecal addition of fentanyl to bupivacaine.

However, time of onset of Sensory and Motor Block is earlier in fentanyl group as compared to nalbuphine. Hemodynamic stability was maintained throughout the intraoperative and postoperative period in both groups and no any serious side effects like respiratory depression, deterioration in neonatal Apgar score was observed in both groups.

Therefore, intrathecal Nalbuphine is safe and effective alternative to intrathecal Fentanyl for control of post-operative pain in obstetric patients posted for caesarean section under spinal anaesthesia.

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