

Evaluation of the Efficacy of Intrathecal Fentanyl Versus Intrathecal Nalbuphine as Adjuvants to 0.75% Ropivacaine for Post-operative Pain Relief in Cesarean Section: A Double-blind Randomized Comparative Study

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Abstract

Background: Spinal anesthesia is safe, simple to perform, and also has many advantages such as intense analgesia and awake mother to permit bondage between mother and the newborn. Nalbuphine is a mixed agonist-antagonist opioid and has a potential to attenuate the μ -opioid effects and to enhance the kappa-opioid effects. It produces desirable analgesia without causing the undesirable side effects of a mu agonist. Hence, the aim of this study is to compare the efficacy of intrathecal fentanyl versus intrathecal nalbuphine when added to isobaric ropivacaine for spinal anesthesia in cesarean section patients.

Aim: The aim of the study is to evaluate the efficacy of intrathecal fentanyl versus intrathecal nalbuphine as adjuvants to ropivacaine for post-operative pain relief in cesarean section patients.

Materials and Methods: After Institutional Ethics Committee approval and written informed consent, 50 pregnant females of ASA Grade II presented to Rangaraya Medical College for elective cesarean section were enrolled for this randomized, double-blinded comparative study. Group RF ($n = 25$) was given intrathecal injection of 2 ml isobaric 0.75% ropivacaine + 25 mg (0.5 ml) fentanyl (fentanyl 1 cc = 50 mg). Total volume made up to 2.5 ml. Group RN ($n = 25$) was given intrathecal injection of 2 ml of 0.75% isobaric bupivacaine + 1 mg (0.1 ml + 0.4cc NS) nalbuphine (nalbuphine 1 cc = 10 mg, 0.1 cc = 1 mg is made to 0.5 ml with normal saline) total volume made up to 2.5 ml. After performing the spinal injections, the following parameters were (noted) recorded. The onset times of sensory block to T_8 and motor block (MBO) to MB_2 using pinprick and modified Bromage scale, respectively. Time to first request of analgesia, i.e., time from administering intrathecal drug to time at which the patient demands rescue analgesia for post-operative pain is defined as the duration of analgesia. Post-operative hemodynamics were recorded continuously. Level of consciousness, respiratory depression, and pulse oximetry were continuously monitored up to initial 24 hours post-operative period. The data were analyzed statistically.

Results: (1) Duration of sensory blockade was also significantly prolonged in RN group (RF vs. RN 180.75 ± 34.27 vs. 263.63 ± 44.88); $P < 0.0186$ was considered statistically significant, (2) the duration of motor blockade was significantly higher in nalbuphine group (RF vs. RN 148.13 ± 23.09 vs. 220 ± 34.59) $P < 0.0002$, (3) the time to first request of analgesia was significantly prolonged in nalbuphine group (RF vs. RN: 233.88 ± 36.82 vs. 312.38 ± 65.48); $P < 0.01$ was considered statistically significant.

Keywords: Fentanyl, Nalbuphine, Sensory blockade, Spinal anaesthesia

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INTRODUCTION

Regional anesthesia is the anesthesia of choice which is being traditionally administered for cesarean section patients.¹ Spinal anesthesia is safe, simple to perform, and also has many advantages such as intense analgesia, awake mother to permit bondage between mother and

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the newborn, allows early breastfeeding, early ambulation to the mother, and minimizes the incidence of deep vein thrombosis while avoiding all the complications of general anesthesia.² Several adjuvants have been added to prolong the duration of single shot spinal anesthesia such as fentanyl, morphine, clonidine, dexmedetomidine, and adrenaline.³ Fentanyl is a lipophilic opioid with a rapid onset of action following intrathecal injection.⁴ It has been added to local anesthetics to improve the quality of blockade and also to prolong the duration of post-operative analgesia, which has been proved in many randomized clinical trials.

Nalbuphine is a mixed agonist–antagonist opioid and has a potential to attenuate the μ -opioid effects and to enhance the kappa-opioid effects.⁵ It produces desirable analgesia without causing the undesirable side effects of a μ agonist. It was used as an adjuvant to local anesthetics in many randomized clinical studies, especially in orthopedic procedures of lower limbs in doses between 0.2 and 2.4 mg in various studies.^{6,7} There are few studies, in which nalbuphine has been used as an adjuvant in cesarean section.⁸

Hence, the aim of this study is to compare the efficacy of intrathecal fentanyl versus intrathecal nalbuphine when added to isobaric ropivacaine for spinal anesthesia in cesarean section patients.

MATERIALS AND METHODS

After Institutional Ethics Committee approval and written informed consent, 50 pregnant females of ASA Grade II presented to Rangaraya Medical College for elective cesarean section were enrolled for this randomized, double-blinded comparative study.

Inclusion Criteria

1. Age: 18-25 years
2. Weight: 50-80 kg
3. Height: 150-170 cm
4. ASA: II.

Exclusion Criteria

1. Patient refusal
2. History of any contraindication to spinal anesthesia
3. History of allergy to study drugs
4. Systemic disease complicating pregnancy
5. Pregnancy-induced hypertension or eclampsia.

The patients were divided into two groups of 25 each into group RF and RN; randomization was done using computer-generated random number table, three anesthesiologists were involved in the study. The anesthesiologist (b) who performed the spinal injections was unaware of the study

drugs as the drugs were given to him or her in sealed envelope which were prepared by the principal investigator anesthesiologist (a). Monitoring and collection of data were done by another anesthesiologist (c).

Routine pre-operative investigations were performed in all patients including complete blood count, BT, CT, kidney function test, fasting blood sugar and random blood sugar, and electrocardiographic (ECG). Injection ranitidine 50 mg IM and injection metoclopramide 10 mg IV were administered to all patients 1 h before surgery.

Baseline parameters such as PR, noninvasive blood pressure (NIBP), RR, and SPO₂ were noted.

An 18G cannula was secured in the non-dominant hand. The patients were shifted to operating room in left lateral position. All the monitoring devices such as NIBP, pulse oximetry, and ECG were applied to the patients. Spinal injection is performed in the left lateral position under strict aseptic conditions with 25G Quincke Babcock needle at L₂/L₃ or L₃/L₄ interspace.

Group RF (*n* = 25) was given intrathecal injection of 2 ml 0.75% isobaric bupivacaine + 25 μ g (0.5 ml) fentanyl (fentanyl 1 cc = 50 μ g). Total volume made up to 2.5 ml.

Group RN (*n* = 25) was given intrathecal injection of 2 ml of 0.75% isobaric bupivacaine + 1 mg (0.1 ml + 0.4 cc NS) nalbuphine (nalbuphine 1 cc = 10 mg, 0.1 cc = 1 mg is made to 0.5 ml with normal saline) total volume made up to 2.5 ml.

After performing the spinal injections, the following parameters were (noted) recorded.

The onset times of sensory block to T₈ and motor block (MBO) to MB₂ using pinprick and modified Bromage scale, respectively. Maximum height (level) of sensory blockade and two-segment regression time were noted. Duration of sensory (T₁₁) and MBO were recorded. PR and blood pressures are monitored with non-invasive monitoring. PR and NIBP were monitored continuously every minute for initial 30 min after spinal anesthesia. Later PR and NIBP were monitored every 5 min until the end of surgery. Injection atropine 0.01 mg/kg iv was administered if PR <60/min. Injection ephedrine was administered in increments of 5 mg IV for hypotension (defined as >20% fall of BP from baseline).

Neonatal APGAR scores at 1 min and 5 min, respectively, were recorded.

Intraoperative complications such as hypotension, bradycardia, shivering, nausea, vomiting, and pruritus were recorded and appropriately managed.

Urinary retention was not a problem in these patients as urinary catheter was left *in situ* for 24 h.

Postoperatively, all these patients were assessed for pain using visual analog scale (VAS) until the first 24 post-operative hours. If VAS >4 rescue analgesia was administered in the post-operative period with injection diclofenac 75 mg IM and tramadol 1 mg/kg slow iv. Injection ondansetron 0.1 mg/kg IV was administered for nausea and vomiting. Injection chlorpheniramine maleate slow iv was administered for shivering.

Time to first request of analgesia, i.e., time from administering intrathecal drug to time at which the patient demands rescue analgesia for post-operative pain is defined as the duration of analgesia. Post-operative hemodynamics were recorded continuously. Level of consciousness, respiratory depression, and pulse oximetry were continuously monitored up to initial 24 h post-operative period. The data were analyzed statistically.

Statistical Analysis

Statistical analysis was done using the software GraphPad.com. Demographic data were analyzed using Fisher’s exact test. Comparison between sensory and motor blockade characteristics and duration of analgesia between the two groups was done using unpaired *t*-test. Categorical data were analyzed using Chi-square test. Data were expressed as a mean ± standard deviation, absolute numbers, and percentage. The data were considered statistically significant if *P* < 0.05.

RESULTS

- 50 ASA 1 and 2 pregnant parturients were included in this study.
- All the patients completed the study.
- All pregnant women were comparable with respect to demographic characters such as age, weight, height, gestational age, and duration of surgery. *P* > 0.005 was considered statistically not significant (Table 1).
- The onset time of sensory blockade was significantly earlier in fentanyl group (RF vs. RN: 2.50 ± 0.76 vs. 4.63 ± 1.19). *P* < 0.005 was considered statistically significant (Table 2).
- Two-segment regression time was prolonged in nalbuphine group (RF vs. RN: 120.88 ± 7.81 vs. 136.31 ± 6.15) *P* < 0.0007 was considered statistically highly significant (Table 2).
- Duration of sensory blockade was also significantly prolonged in RN group (RF vs. RN 180.75 ± 34.27 vs. 263.63 ± 44.88) *P* < 0.0186 was statistically significant (Table 3).

- The duration of motor blockade was significantly higher in nalbuphine group (RF vs. RN 148.13 ± 23.09 vs. 220 ± 34.59) *P* < 0.0002 was statistically highly significant (Table 3).
- The time to first request of analgesia was significantly prolonged in nalbuphine group. (RF vs. RN: 233.88 ± 36.82 vs. 312.38 ± 65.48) *P* < 0.01 was considered statistically significant (Table 4).
- Apgar scores were comparable between two groups at 1 and 5 min (Table 5).
- Side effects such as hypotension, nausea, vomiting,

Table 1: Demographic data

Variable	Group RF (n=25)	Group RN (n=25)	P value
Age (years)	22.25±2.38	22.00±3.12	0.859
Height (cm)	160.38±5.63	155.50±5.66	0.1060
Weight (kg)	66.13±6.40	62.88±4.39	0.2560
Gestational age (weeks)	37.75±0.71	37.63±0.52	0.6927
Duration of surgery	49.63±5.66	51.50±6.78	0.557

Data expressed as mean±SD, absolute numbers and ratio, *P*>0.05, not significant, Fisher’s Exact test

Table 2: Sensory block characteristics

Time in min	Group RF (n=25)	Group RN (n=25)	P value
Sensory onset (min) to T10	2.50±0.76	4.63±1.19	0.0008**
Maximum height of block	5.50±0.76	5.50±1.07	1.000
2-segment regression time	120.88±7.81	136.31±6.15	0.0007
Duration of sensory blockade	180.75±34.27	263.63±44.88	0.0010**

Data expressed as mean±SD, absolute numbers and ratio. **P*<0.05, statistically significant, **extremely statistically significant, *statistically significant, unpaired *t*-test

Table 3: MBO characteristics

Time in min	Group RF (n=25)	Group RN (n=25)	P value
Motor onset (min) [MB ₂]	4.50±0.76	6.13±1.55	0.0186
Duration of motor blockade	148.13±23.09	220±34.59	0.0002

Data expressed as mean±SD, absolute numbers and ratio, **P*<0.05, statistically significant, Unpaired *t*-test, MBO: Motor block

Table 4: Mean duration of analgesia

Time (min)	Group RF (n=25)	Group RN (n=25)	P value
Time to 1 st request of analgesia	233.88±36.82	312.38±65.48	0.0104*

Data expressed as mean±SD, absolute numbers and ratio, **P*<0.05, statistically significant, Unpaired *t*-test

Table 5: Apgar scores

Group	1 min median (range)	5 min median (range)
Group RN	8 (8-10)	10 (10-10)
Group RF	8 (8-10)	10 (10-10)

and bradycardia were comparable between two groups. ($P > 0.005$, statistically not significant) (Tables 5 and 6).

- The incidences of pruritus and shivering were higher in fentanyl group than nalbuphine group, but statistically not significant ($P > 0.005$) (Table 5).
- Intraoperative hemodynamics (systolic blood pressure) were comparable between two groups (Figure 1).

DISCUSSION

Neuraxial anesthesia is the choice of anesthesia in cesarean patients. The limitations of single shot spinal anesthesia are its short duration of action and the need to supplement with parental analgesics in the immediate post-operative period.⁹ Several intrathecal adjuvants have been used to improve the quality as well as prolong the duration of post-operative analgesia, of which opioids have been the gold standard agents.¹⁰ Morphine and fentanyl are the common agents used in several clinical trials because of their potency and other advantages. Emesis and pruritus have been the common side effects of neuraxial morphine.¹¹ The intrathecal use of fentanyl is limited by its brief prolongation of post-operative analgesia, i.e., between 2 and 4 h.¹² Hence, the search for alternative opioid has led to the use of intrathecal nalbuphine as adjuvant to local

anesthetics in various studies.¹³ Till date, there are very few studies which used nalbuphine as an intrathecal adjuvant.

In this study, intrathecal nalbuphine was compared with intrathecal fentanyl with isobaric bupivacaine as local anesthetic.

Nalbuphine is a synthetic agonist–antagonist opioid belonging to phenanthrene group. It is structurally related to naloxone, an antagonist of the opiate receptors and to oxymorphone, an analgesic agonist of opiate receptors.¹⁴ Nalbuphine has been used as additive for spinal anesthesia in several clinical settings in doses ranging from 200 to 2100 mg. It is highly lipid-soluble opioid with agonist at kappa and antagonist at mu receptors. Hence, it provides potent analgesia at spinal level.¹⁵ The analgesic effects of spinal nalbuphine can be reverted by naloxone.

The onset times of sensory and MBO were earlier with fentanyl group when compared with nalbuphine group, in this study.

Intraoperative hemodynamics, quality of subarachnoid block, and oxygen saturation were comparable between both the groups.

The duration of sensory blockade was significantly higher in nalbuphine group as compared to fentanyl group. $P < 0.05$ was considered highly significant (RF vs. RN: 180.75 ± 34.27 vs. 263.63 ± 44.88).

The duration of post-operative analgesia was significantly prolonged in the nalbuphine group when compared to fentanyl group. (RF vs. RN 233.88 ± 36.82 vs. 312.38 ± 65.48), $P < 0.005$ was considered statistically significant.

Regarding side effects, there were no significant differences in the incidence of side effects such as nausea, vomiting, hypotension, and bradycardia.

Intraoperative shivering was significantly higher in the fentanyl group when compared to nalbuphine group. (RF vs. RN: 20% vs. 4%).

None of the patients in both the groups had respiratory depression and decreased oxygen saturation in the intra- and post-operative periods.

The mean fetal APGAR scores at 1 and 5 min intervals were between 8 and 10 in both the groups. The delivered fetuses are healthy and vigorous.

None of the patients had pruritus as a side effect in nalbuphine group.

Table 6: Side effects

Side effect	Group RF (n=25)	Group RN (n=25)	P value
Hypotension	4	3	1.00
Nausea	3	1	1.00
Vomiting	1	-	1.00
Shivering	5	1	0.189
Pruritus	1	-	1.00
Respiratory depression	-	-	1.00
Bradycardia	2	3	1.00
Sedation	-	-	1.00

$P > 0.05$ not significant, Chi-square test

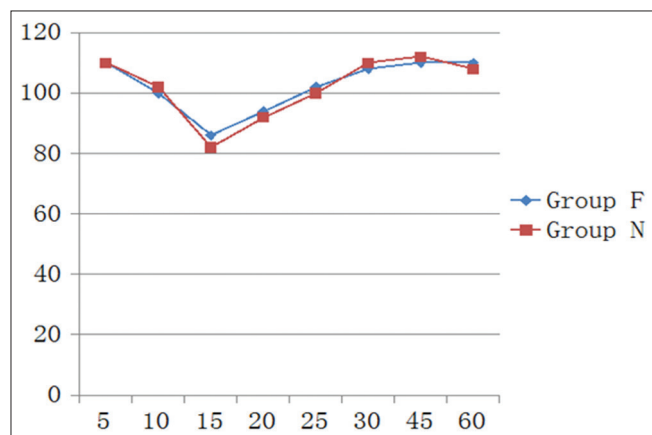


Figure 1: Mean systolic blood pressure. On x-axis – time in minutes, Y axis means systolic blood pressure

The first study with intrathecal nalbuphine in obstetric patients was conducted by Culebras *et al.*, in which they injected 200 µg, 800 µg, and 1600 µg mixed with hyperbaric 0.5% bupivacaine versus morphine 200 µg with bupivacaine in cesarean patients and concluded that 0.8 mg of nalbuphine produced analgesic duration comparable with 1.6 mg of nalbuphine without producing maternal or newborn respiratory depression. Overall, the duration of analgesia was significantly prolonged with 200 mg of intrathecal morphine in their study.¹⁶ Itching and post-operative nausea and vomiting were significantly greater with morphine in this study.

Yoon *et al.* found that an intrathecal mixture of nalbuphine 1000 µg, morphine 100 µg, and hyperbaric bupivacaine 10 mg for cesarean delivery intensified intraoperative analgesia compared to morphine alone. The combination of nalbuphine with morphine failed to prolong duration of post-operative analgesia significantly compared to morphine alone though there was no pruritus in the combination group.¹⁷

Obara *et al.* evaluated the effects of intrathecal fentanyl added to hyperbaric bupivacaine for cesarean section and concluded that addition of intrathecal fentanyl to hyperbaric bupivacaine improved the quality without side effects.¹⁸

Gomma *et al.* compared the effects of intrathecal nalbuphine and fentanyl when added to intrathecal bupivacaine for cesarean section. They concluded that the onset of times for sensory and MBO was significantly earlier in fentanyl group than in nalbuphine group.¹⁹ The duration of post-operative analgesia was more prolonged in nalbuphine group, but the difference was insignificant statistically. There was no significant difference between two groups with respect to sensory and MBO duration, hemodynamics, and adverse effects. The dose of nalbuphine used was 0.8 mg.

Mukherjee *et al.* evaluated intrathecal nalbuphine as an adjuvant to subarachnoid block with 0.5% hyperbaric bupivacaine in lower limb orthopedic surgeries and concluded that nalbuphine in a dose of 0.4 mg is a useful adjuvant for spinal anesthesia without increased side effects.²⁰

Ahluwalia *et al.* evaluated the effects of intrathecal nalbuphine in patients underwent lower abdominal surgeries under spinal anesthesia and concluded that the duration of analgesia was about 298.43 ± 30.92 min in nabuphine + bupivacaine group compared to 201.31 ± 34.31 in the normal saline + bupivacaine group ($P < 0.05$) which was statistically significant.²¹ The dose of nalbuphine

used in this study is 0.8 mg. The observations of our study correlated with the above studies. The difference was isobaric bupivacaine was used instead of hyperbaric bupivacaine. 0.75% ropivacaine was used in our study, whereas 0.5% bupivacaine was in our studies. Our study did not differ from the above studies with respect to quality of MBO though we have used isobaric bupivacaine as the local anesthetic. Surgeons' satisfaction was adequate for all the cases regarding the quality of spinal blockade.

Yaksh and Bisbaeh in their editorial titled as "intrathecal nalbuphine after caesarean delivery: Are we ready?" mentioned that the general trend of human studies on neuraxial nalbuphine is that epidural or intrathecal delivery of nalbuphine produces a significant analgesia accompanied by minimal pruritus and respiratory depression.²²

There are few studies with ropivacaine and nalbuphine, especially in pregnant women. The issue with intrathecal nalbuphine is regarding its neurotoxicity. None of the studies in humans done until now reported signs of neurotoxicity. None of the patients in this study also had reports of neurotoxicity in the perioperative period. Jyothi *et al.* have used intrathecal nalbuphine in doses of 0.8, 1.6, and 2.5 mg for lower abdomen and orthopedic surgeries also did not report any neurotoxicity signs.²³ The duration of analgesia in this study was well correlated with our study. The difference is they did a controlled study and ours is a comparative study with fentanyl. Further research with this opioid is necessary to validate the results of the previous clinical trials.

We conclude that addition of intrathecal nalbuphine 1mg to isobaric 0.75% ropivacaine significantly prolonged the duration of post-operative analgesia when compared to intrathecal fentanyl 25 µg with minimal side effects. Intraoperative hemodynamics and quality of spinal blockade were comparable between the groups.

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