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Comparative study of intrathecal preservative-free midazolam versus nalbuphine as an adjuvant to intrathecal bupivacaine (0.5%) in patients undergoing elective lower-segment caesarean section

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Abstract

Background: Intrathecal anesthesia is common for parturients undergoing lower-segment caesarean section. Various adjuvants are added to intrathecal bupivacaine for potentiating pharmacological effects, improving quality of sensorimotor block and postoperative analgesia, and preventing adverse effects. The study period was from November 2017 to September 2018, and it was a randomized double-blinded observational study. The sample size calculation was done according to results of our pilot study (done with 5 patients in each group) and discussion with the institutional review board. Also, in this study, we aim to assess nalbuphine/midazolam as adjuvant to intrathecal bupivacaine for LSCS in terms of quality of sensorimotor block, postoperative analgesia, adverse effects, hemodynamic stability, and Apgar scores of baby at 1 and 5 min. One hundred full-term parturients between 20 and 35 years of ASA grade I/II scheduled for elective lower-segment caesarean section after approval from the institutional review board, and written informed consent were allocated into 2 groups. Randomization was done at the time of giving intrathecal anesthesia by odd and even numbers in an opaque sealed envelope.
Group A (n = 50): Bupivacaine heavy (0.5%) 2.0 ml (10 mg) + 0.2 ml Preservative-free inj. midazolam 1 mg
Group B (n = 50): Bupivacaine heavy (0.5 %) 2.0 ml (10 mg) + 0.2 ml (0.75 mg) Preservative-free inj. nalbuphine
The primary outcome was to assess the perioperative hemodynamic stability, Apgar score, and postoperative analgesia, and the secondary outcome was to assess the complications and adverse effects during the study period.

Results: The onset of sensory and motor block was earlier in group A than in group B. Total duration of effective postoperative analgesia was more in the midazolam group as compared with the nalbuphine group. The incidence of complications (nausea, vomiting, and pruritus) were more in group B as compared with group A.

Conclusion: Nalbuphine and midazolam both are good adjuvants to hyperbaric bupivacaine for LSCS in terms of hemodynamic stability and good Apgar scores at 1 and 5 min. Intrathecal midazolam provides better postoperative analgesia and less adverse effects.

Keywords: Intrathecal anesthesia, Midazolam, Nalbuphine

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Background

Intrathecal anesthesia is the preferred technique for lower-segment caesarean sections (LSCS).

Effective postoperative analgesia reduces the incidence of respiratory and cardiac complications.

Adjuvant drugs used for intrathecal anesthesia to improve the analgesia of local anesthetics and prevent the effects of their toxic doses. Nalbuphine, an opioid with mixed μ antagonist and κ agonist properties, is related chemically to oxymorphone and is highly lipid soluble. The side effects of nalbuphine are nausea, vomiting, pruritus, and urinary retention. It has been used for 10 years, but no evidence of neurotoxicity has been found (Culebras et al. 2000).

Midazolam is a potent short-acting, water-soluble benzodiazepine. Intrathecal analgesic effect of midazolam is mediated through benzodiazepine–gamma aminobutyric acid (GABA) receptor complex within the intrathecal cord. Its antinociceptive effect is mediated via intrathecal delta opiate receptors (Edwards et al. 1990).

The present study was undertaken to evaluate and compare analgesic efficacy, hemodynamic stability, and side effects of intrathecally administered nalbuphine and midazolam as an adjuvant to bupivacaine heavy (0.5%) for elective lower-segment caesarean section surgery.

Methods

After approval from the institutional review board on 23rd October 2017, we carried out this study on 100 full-term parturients of ASA grades I & II, between 20 and 35 years of age and mean weight of 52.5 kg, mean height of 163 cm, and the mean BMI of 19.81 kg/m^2, presenting for elective lower-segment caesarean section under intrathecal anesthesia at a tertiary health care center.

Patient exclusion criteria

The following are excluded from the study:

- Patient refusal; patients with psychiatric disorders, chronic pain or any condition that precludes intrathecal anesthesia, known case of alcohol or drug abuse; patients with any gross congenital anomaly, coagulopathy, known allergy to the local anesthetic, skin infection at the site of anesthesia, neurological disorder, and deformity of spine; and patients who are hemodynamically unstable
- Patients diagnosed with preeclampsia or diabetes mellitus or having twin pregnancy/multiple pregnancy and emergency surgeries like fetal distress and cord prolapse
- Patients taking sympathomimetics/sympatholytic drugs
- Patients belonging to ASA grades III, IV, and V

Preanesthetic evaluation

Preoperative evaluation was carried out in all patients with detailed history and general physical examination including height and weight on the day before surgery. Vital parameters were noted (pulse, BP, RR, SPO_2), and systemic examination was performed. Fetal cardiotocography was done by the obstetrician in each patient to assess fetal well-being.

All patients were fasted overnight. Vital signs were noted in the preoperative room and considered as baseline values.

Preoperatively, a peripheral venous access was secured with 18-gauge cannula, and preloading with lactated Ringer's solution was initiated at the rate of 10 ml/kg over 30 min.

On entering the OT, noninvasive monitoring was initiated including pulse oximeter, ECG, and non-invasive blood pressure (NIBP). Premedication was given in the form of inj. glyocopyrrolate 0.2 mg i.v., inj. ondansetron 4 mg i.v., and inj. ranitidine 40 mg i.v. as per the institutional protocol.

Study groups

It was a double-blinded study. Group allocation was done by randomization through odd & even numbering in an opaque sealed envelope. Execution of randomization was at the time of giving intrathecal anesthesia to patients. The study drugs were prepared by an anesthetist who was not a part of the study.

Patients were divided into two groups with 50 patients in each according to the drugs they received.

Group A (midazolam group): 0.5% bupivacaine heavy 2.0 ml (10 mg) (Danelli et al. 2001) + 1 mg (0.2 ml) preservative-free midazolam (Prakash et al. 2006; Tucker et al. 2004; Goodchild et al. 1996) (Neon laboratories)

Group B (nalbuphine group): 0.5% bupivacaine heavy 2.0 ml (10 mg) + 0.2 ml (0.75 mg) of preservative-free injection nalbuphine (Culebras et al. 2000). {We have used 1 ml of 10 mg nalbuphine in insulin syringe and 3 markings of it (0.75 mg) are taken, and injection normal saline is added to it to make the solution 0.2 ml.} (Neon laboratories)

All patients received a total volume 2.2 ml intrathecally.

Under strict aseptic and antiseptic precautions, subarachnoid block was performed in lateral position, between L_3 and L_4 intervertebral space, with 25 Gauge Quincke needle via midline approach. After free flow of CSF, the test drug was injected. Patients were positioned supine with left uterine displacement and 100% oxygen was given by Magill's circuit. Then afterwards, no change in patient's position was done.

Sensory block was assessed by the loss of sensation of cold to spirit swab. Time to achieve maximum sensory level of T4 was noted. Motor block was assessed by

modified Bromage scale. Surgery was allowed when motor block reaches Bromage grade III, and sensory block was achieved up to T4 dermatomal level.

Intraoperative hemodynamic monitoring was done at 1, 2, 4, 6, 8, 10, 15, 20, 25, and 30 min and then every 30 min till 120 min. Postoperatively, hemodynamic monitoring was done at half, 1, 2, 3, 4, 6, 12, and 24 hrs.

The level of sedation was recorded every 15 min intraoperatively and postoperatively for 6 hrs by OAA (Observer's Assessment of Alertness/Sedation scale).

Time interval from skin incision to delivery of baby and time from uterine incision to delivery of baby were noted, and Apgar score of baby was assessed by the pediatrician who was not involved in the study, noted at 1 min and at 5 min after delivery. Intraoperative fluid loss and blood loss were assessed. Intraoperative urine output was also assessed.

Postoperative pain was assessed by the Visual analogue scale (VAS) (Revill et al. 1976). When VAS was > 3 analgesia was repeated by inj. tramadol 50 mg i.v.. Time to first recue analgesia was noted and total number of analgesic request in 24 hrs were noted.

Postoperative monitoring

Patients were observed for 24 hrs postoperatively for any complications. After completion of surgery, patients were shifted to postoperative ward. Postoperatively, hemodynamic monitoring and respiratory monitoring and VAS score assessment were done periodically at every half hour for 2 hrs then at 1-h interval up to 6 hrs and then at 12 and 24 hrs. OAA score was assessed postoperatively up to 6 hrs in similar periodic intervals.

Evaluation of sensorimotor characteristics

- Measurement of sensory blockade (sensory blockade was assessed by the pin prick method)
- Time of onset of sensory analgesia (time from injection of study drug to complete loss of cold sensation to the spirit swab)
- Effective analgesia (time between complete sensory block to return of pain sensation which is tolerable)
- Total duration of sensory analgesia
- Measurement of motor blockade (motor blockade was assessed by the Modified Bromage scale) (Bromage 1965)
- Time of onset of motor blockade (time from injection of study drug to time to achieve bromage scale III)
- Degree of motor blockade
- Total duration of motor blockade (time of onset of complete motor block to the restoration of normal musculature force)

For the present study, various terms were defined as follows:

- During the surgery, bradycardia was defined as fall in pulse rate more than 20% of the baseline or less than 60/min and treated with injection atropine 0.6 mg i.v..
- Hypotension was defined as fall in blood pressure more than 30% of baseline value and was treated with i.v. fluids, manual uterine displacement to left, and injection ephedrine 6 mg alliquots i.v. given if required.
- Respiratory depression was defined as SPO_2 < 90%.
- Sedation was assessed by OAA (Observer's Assessment of Alertness/Sedation scale) (Chernik et al. 1990) (Table 1).
- Neonatal assessment was done by Apgar score by the pediatrician.
- Nausea was assessed using a 5-point scale: No, mild, moderate, severe, and intractable nausea labelled as 0, 1, 2, 3, and 4 points. IV inj. ondansetron hydrochloride 4 mg stat was given when nausea score was $\geq$ 3.
- Grading of shivering was done as per Wrench (Wrench and Singh n.d.). Treatment of shivering was carried out with warm fluids, covering of patient, and decreasing cooling of OT. No antihistaminics or opioids causing sedation were administered.
- Pruritus: In any patient who began to scratch or who complained of itching, intensity was assessed as
  Mild: Itching was only a minor concern.
  Moderate: Itching was a primary concern, although bearable, and the patient said that he/she would itch rather than hurt.
  Severe: Unbearable; patient requested treatment. In the severe form of pruritus, antihistaminic (inj. pheniramine maleate) was kept ready.
- Post dural puncture headache (PDPH): Headache was classified as PDPH if it was aggravated by erect or sitting position, relieved on lying flat, mainly occipital or frontal, and increased on coughing, sneezing, or straining.

Table 1 Sedation scale

Content	Score
Responds readily to name spoken in normal tone	5
Responds lethargically to name spoken in normal tone	4
Responds only after name is called loudly, repeatedly or both	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

- Transient neurological symptoms (TNS): It was defined as pain and/or dysesthenia in the back, buttocks, and legs or pain radiating to lower extremities after initial recovery from intrathecal anesthesia and resolved within 72 hrs. Patients were followed up to 7 days to check for any other neurological symptoms.
- Patients were assessed for delay in voiding.

Statistical analysis

The data were statistically analyzed using Microsoft Excel 2013. Data were expressed as mean and standard deviation and was compared using unpaired *t* test. *P* value > 0.05 was considered statistically not significant (NS), *P* value < 0.05 was considered significant, and *P* < 0.001 was considered highly significant (HS).

Results

Patient characteristics (Table 2)

The table below shows that there was no significant difference in relation to age, height, weight, and duration of surgery in both the groups (P > 0.05).

Sensorimotor characteristics (Table 3)

The table below shows the comparison of sensorimotor characteristics and their statistical values in the two groups.

Heart rate (per minute) (Fig. 1)

The graph shows that there was no significant intraoperative variation in the heart rate and it was comparable in both the groups.

Systolic blood pressure (mmHg) (Fig. 2)

The graph shows that there was no significant intraoperative variation in the systolic blood pressure, and it was comparable in both the groups.

Diastolic blood pressure (mmHg) (Fig. 3)

The graph shows the diastolic blood pressure comparison of the two groups up to 120 min, and it was comparable in both the groups.

Table 2 Patient characteristics

Parameters	Group A (*n* = 50)	Group B (*n* = 50)
Age (years)	26 ± 3.57	27.34 ± 3.86
Height (cm)	156.88 ± 3.53	155.86 ± 3.16
Weight (kg)	53 ± 2.14	53.3 ± 2.10
Duration of surgery (min)	74.10 ± 21.59	75.5 ± 21.88

Skin incision to baby delivery time (*P* > 0.05) (Table 4)

The table below shows the comparison of baby delivery time in the two groups in form of skin incision to delivery time and uterine incision to delivery time.

Apgar score (*P* > 0.05) (Table 5)

The table below shows the neonatal Apgar scores at 1 min and 5 min after delivery in the two groups.

Adverse effects (Table 6)

The table below shows the comparison of the adverse effects in the two groups.

- All patients were monitored for sedation through OAA score till 6 hrs, and it was 5 in each group (*P* > 0.05).
- Shivering was mild in nature in each group. No pharmacological intervention was required.
- Nausea and vomiting were comparatively more in patients of group B but were of low score (mild) which were treated accordingly.
- Pruritus was present in 12% of the patients of the nalbuphine group and treated with inj. pheniramine maleate.
- Oxygen saturation and respiratory rate were stable and comparable in both the groups (*P* > 0.05).
- Mean blood loss during surgery was 550 ± 50 ml.
- Mean urine output intraoperatively was 75 ± 20 ml.

Postoperative monitoring

- We have monitored vitals of all patients till 24 hrs.
- OAA score was monitored up to 6 hrs, and it was 5 in each group.
- Hemodynamic parameters were within normal limits.
- Rescue analgesics were repeated when VAS > 3.
- All patients were conscious and cooperative.
- No adverse effects were noted during postoperative period.
- Patients were inquired for TNS within 72 hrs postoperatively and at the time of discharge.
- No patient had PDPH or TNS.

Discussion

Intrathecal midazolam has shown to potentiate effect of local anesthetic by BZD–GABA receptor complex at intrathecal cord level leading to segmental analgesia without any neurotoxic effects (Edwards et al. 1990).

Intrathecal opioids (nalbuphine) cause segmental analgesia by binding to the opioid receptors in the dorsal horn of the intrathecal cord. They prolong the duration

Table 3 Sensorimotor characteristics

Parameter (mean ± SD)	Group A (n = 50)	Group B (n = 50)	P value	Inference
Onset of sensory analgesia (sec)	73.1 ± 10.97	74.4 ± 9.98	0.537	NS
Time to highest sensory level (min)	3.77 ± 0.50	3.69 ± 0.49	0.421	NS
Onset of motor blockage (sec)	101.7 ± 7.40	102.1 ± 6.32	0.772	NS
Time to highest motor level (Bromage grade 4) (min)	4.82 ± 0.53	4.67 ± 0.49	0.146	NS
Two-segment regression time (min)	154 ± 4.95	125.2 ± 5.44	< 0.001	HS
Time for motor grade to 0 (min)	186.6 ±5.93	173 ± 8.63	< 0.001	HS
Time to S2 segment regression (hrs)	5.59 ± 0.41	4.12 ± 0.19	< 0.001	HS
Time of first analgesic request (hrs)	6.5 ± 0.44	5.02 ± 0.40	< 0.001	HS
Total analgesic request in 24 hrs (no.)	1.5 ± 0.51	1.7 ± 0.46	0.042	S

of analgesia without affecting motor or autonomic nervous function.

Patient characteristics (Table 2)

The study shows that patient characteristics like age, height, weight, duration of surgery, and ASA status were comparable in both groups ($P > 0.05$).

Drug and dosage

In our study in group A, we had taken 1 mg of preservative-free midazolam as adjuvant to 10 mg of 0.5% bupivacaine. In group B, we had taken 0.75 mg of nalbuphine as adjuvant to 10 mg of 0.5% bupivacaine.

*Danelli et al (*Danelli et al. 2001*)*, .in their study, demonstrated that the minimum effective dose of intrathecal bupivacaine effective for producing intrathecal block in 95% of women undergoing elective caesarean section was 0.06 mg/cm of height.

*Prakash et al. (*Prakash et al. 2006*)* have also used 10 mg hyperbaric bupivacaine 0.5% and 1 mg preservative-free midazolam in their study.

*Tucker et al. (*Tucker et al. 2004*)* have also used intrathecal midazolam and concluded that when it is given 0.03 mg/kg, it is safe in human.

C.S.Goodchild et al. (Goodchild et al. 1996) concluded that intrathecal midazolam causes intrathecal mediated antinociception by involving the delta opioid receptors. This effect is reversible with naloxone.

*Culebras et al. (*Culebras et al. 2000*)* have used different doses of nalbuphine with bupivacaine for caesarean section and suggested that 0.8 mg of intrathecal nalbuphine is the most appropriate dosage for a parturient

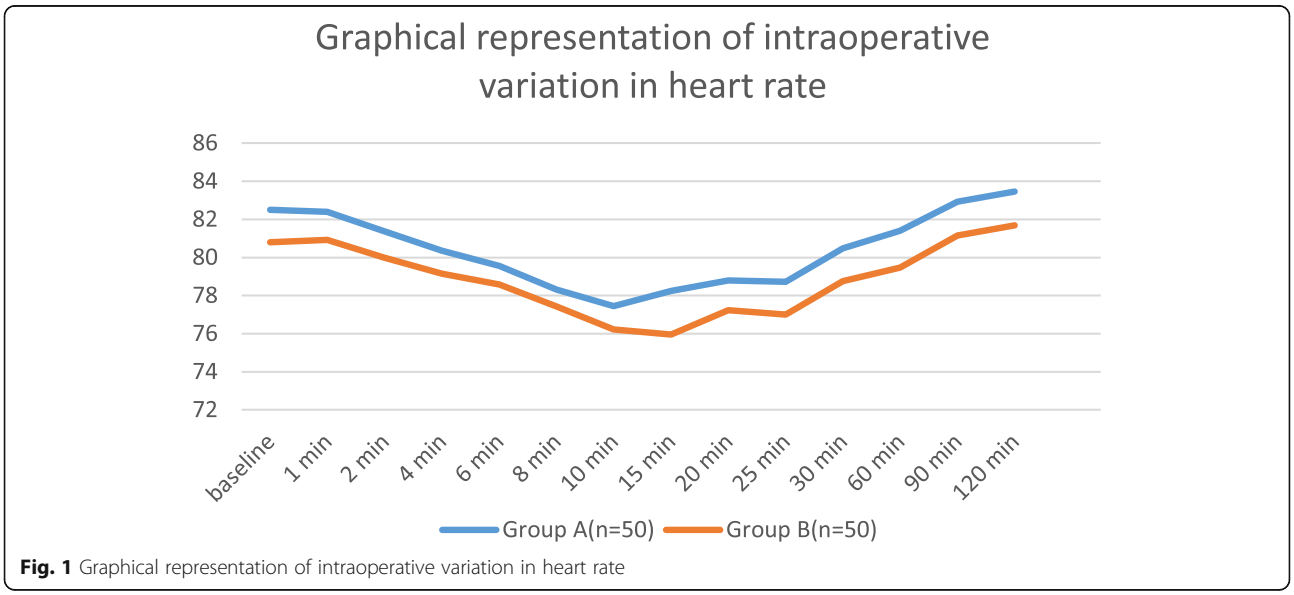

Fig. 1 Graphical representation of intraoperative variation in heart rate

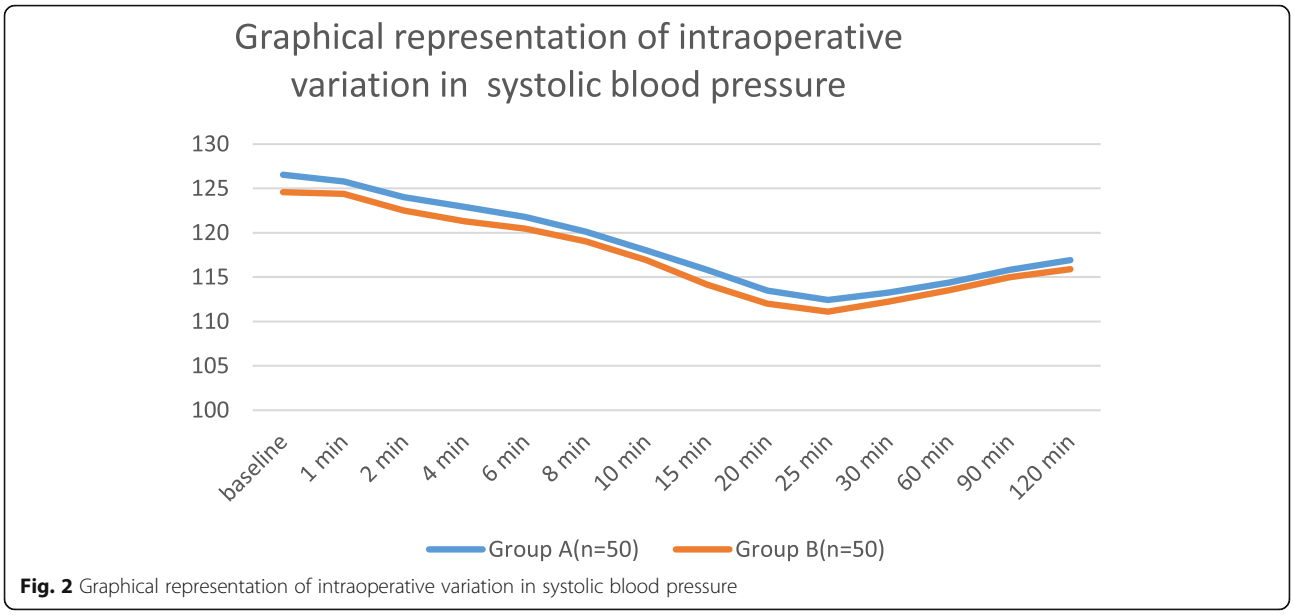

Fig. 2 Graphical representation of intraoperative variation in systolic blood pressure

and has no maternal or newborn respiratory depression and neonatal complication (Apgar score and arterial blood analysis). Dose more than 0.8 mg has a ceiling effect. So in the present study, we have taken 0.75 mg of nalbuphine.

Regarding neurotoxicity concerns

*Tucker et al. (*Tucker et al. 2004*)* evaluated 574 patients who received intrathecal midazolam and observed the patients for 1 month for a wide range of neurotoxicity and conclude that up to 2 mg of intrathecal midazolam did not increase the occurrence of neurological symptoms. We have 1 mg preservative-free midazolam along with 2 ml of 10 mg bupivacaine (0.5%).

*Mukherjee et al. (*Mukherjee et al. 2011*)* have concluded that intrathecal nalbuphine is used in modern practice for more than 10 years without any neurotoxicity.

Characteristics of sensorimotor blockage (Table 3)

- *Time to onset of sensory analgesia* was comparable in both the groups.

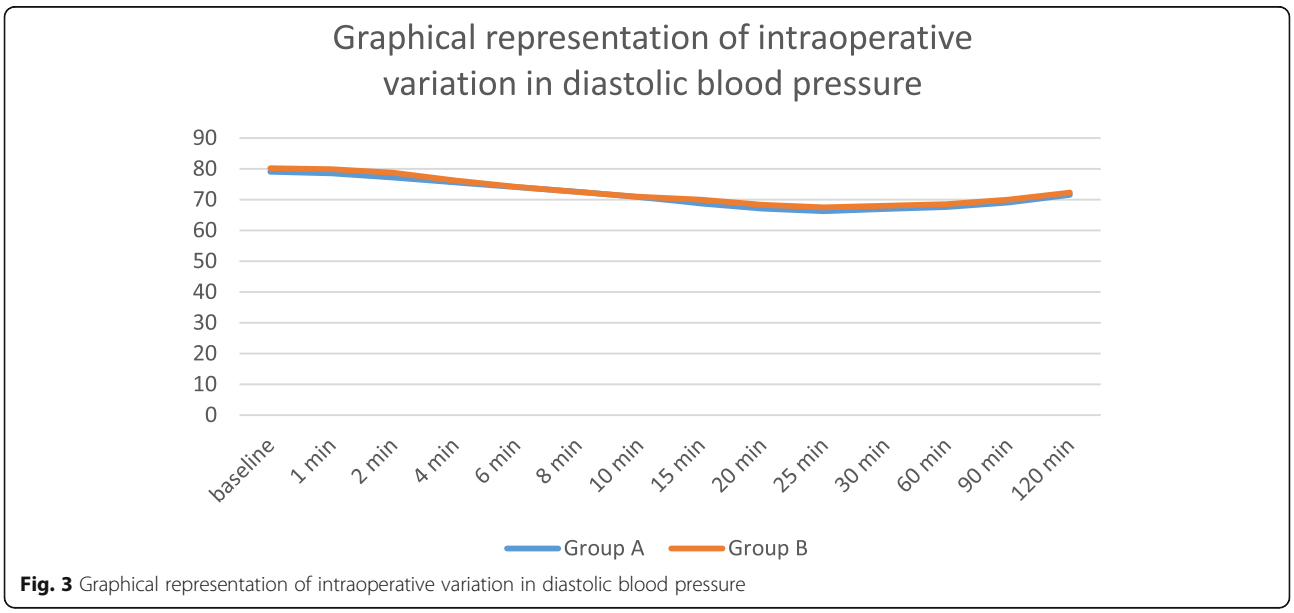

Fig. 3 Graphical representation of intraoperative variation in diastolic blood pressure

Table 4 Baby delivery time in Groups A and B

	Group A (n = 50)	Group B (n = 50)
Skin incision to delivery time (min)	4.5 ± 0.61	4.48 ± 0.84
Uterine incision to delivery time (sec)	150.20 ± 6.77	152 ± 6.14

*Tucker et al. (*Tucker et al. 2004*)* has studied and concluded that intrathecal midazolam improves sensory and motor onset.
*Gomaa et al. (*Gomaa et al. 2014*)* have sensory onset of 1.60 ± 0.10 min in the nalbuphine group.

- *The time to achieve highest sensory level* was comparable in both the groups.
- *Time to onset of motor blockage* was comparable in both the groups.
  *B K Shadangi (*Shadangi et al. 2011*)* concluded that the onset of motor block was comparable between the 2 groups (control group and midazolam group) (Onset of motor block in midazolam group: 6 ± 0.8 min)
  *Suwalka et al. (*Suwalka et al. 2012*)* have concluded that addition of intrathecal midazolam causes faster sensorimotor onset than the lignocaine group (control).
- *Time to achieve highest motor block* was comparable in both the groups.
  *Gomaa et al. (*Gomaa et al. 2014*)* have complete motor blockage in 5.72 ± 0.17 min in the nalbuphine group.
  *Gomaa et al (*Gomaa et al. 2014*)*, in their study, have significantly prolonged time to complete motor block while using intrathecal nalbuphine.
- *Time to 2-segment regression* was 154 ± 4.95 min in group A and 125.2 ± 5.44 min in group B which is highly significant (< 0.001).
  B K Shadangi et al. (Shadangi et al. 2011), in his study, concluded that the time to 2-segment regression was prolonged in the midazolam group (115.8 ± 8.1 min).
  Prakash et al. (Prakash et al. 2006) concluded that two-segment regression in midazolam 1 mg group was 152 ± 32 min which was prolonged than bupivacaine group 126 ± 20 min (P < 0.001).
  *Gomaa et al. (*Gomaa et al. 2014*)* had a 2-segment regression time of 123 ± 5.66 min in the intrathecal nalbuphine group.

Table 5 Apgar scores

	Group A (n = 50)	Group B (n = 50)
1 min after delivery	8.4 ± 0.99	8.5 ± 0.86
5 min after delivery	8.9 ± 0.74	9.02 ± 0.74

- *Time for motor grade to 0* was 186.6 ± 5.93 in group A and 173 ± 8.63 in group B which is highly significant (P < 0.001).
- *The time to S2 segment regression* between the two groups was highly significant (P < 0.001).
- *Time for first analgesic request* was 6.5 ± 0.44 hrs in group A and 5.02 ± 0.40 hrs in group B which is highly significant (P < 0.001).
  Nanjegowda et al. (Nanjegowda et al. 2011) have noticed prolonged duration of analgesia in the midazolam group with total duration of analgesia being 399.40 ± 88.11 min.
  *Nidhi Agrawal et al. (*Agrawal et al. 2005*)* have noticed prolonged postoperative analgesia and time to first rescue analgesic request in the midazolam group (17.56 ± 8.87 hrs).
  Gomaa H M et al. (Gomaa et al. 2014) have duration of analgesia 231.83 ± 15.73 min in the nalbuphine group.
- *Total analgesic request in 24 hrs* was 1.5 ± 0.51 in group A and 1.7 ± 0.46 in group B which is significant (P < 0.05).
  Prakash et al. (Prakash et al. 2006) have suggested that addition of midazolam in different doses with bupivacaine curtail supplemental analgesic requirement.
  *Tripat Kaur Bindra et al. (*Bindra et al. 2018*)* have 1.54 ± 0.705 number of analgesic requests in 24 hrs in the nalbuphine group.

Hemodynamic monitoring (graphs 1 to 3)

In the present study, there was no significant hypotension and bradycardia in both the groups.

Table 6 Adverse effects

Adverse effect	Group A (n = 50)	Group B (n = 50)
Nausea	3 (6%)	5 (10%)
Vomiting	Nil	5 (10%)
Shivering	5 (10%)	5 (10%)
Pruritus	Nil	3 (6%)
Sedation	Nil	Nil
Bradycardia	Nil	Nil
Hypotension	Nil	Nil
Respiratory depression	Nil	Nil

Gomaa et al. (Gomaa et al. 2014) in their study showed that 20% of patients have hypotension in the nalbuphine group.

Goodchild et al. (Goodchild et al. 1996) found no added hemodynamic changes (such as hypotension, bradycardia) when preservative-free midazolam was added to intrathecal bupivacaine.

Skin incision to delivery time (Table 4)

In the present study, the skin incision to delivery time was comparable in both the groups.

Uterine incision to delivery time (Table 4)

In the present study, the uterine incision to delivery time was comparable in both the groups.

Kamat et al. (Kamat et al. 1991) in their study have shown that prolonged uterine–delivery interval has definite effect on the Apgar scoring of the newborn.

Apgar score (Table 5)

In present study, Apgar scores monitored at 1 and 5 min after the delivery of the baby were comparable in both the groups.

Gomaa et al. (Gomaa et al. 2014) have studied the effect of intrathecal nalbuphine and concluded that fetal Apgar score was 8.83 ± 0.38.

Culebras et al. (Culebras et al. 2000) studied different doses of intrathecal nalbuphine and compared with intrathecal morphine and concluded that 0.8 mg of intrathecal nalbuphine is safe for maternal and newborn outcome (Apgar scores at 1 and 5 min and arterial blood gas analysis values).

Suwalka et al. (Suwalka et al. 2012) had observed that addition of intrathecal midazolam had prolonged the postoperative analgesia without adversely affecting the mother and the baby (Apgar scores at 1 and 5 min after delivery of baby).

Adverse effects (Table 6)

Nausea and vomiting

In the present study, the incidence of nausea was 6% in group A and 10% in group B. The incidence of vomiting was nil in group A and 10% in group B.

Nidhi Agrawal et al. (Agrawal et al. 2005) have studied the effect of intrathecal midazolam and concluded that addition of midazolam reduces incidence of nausea and vomiting, and no other side effects were observed.

*Vijay Jalaki and Pawan Havaldar (*Jalaki et al. 2015*)* have studied the effect of intrathecal midazolam on nausea vomiting in parturients undergoing LSCS and have shown that midazolam decreases the incidence of nausea and vomiting.

Bharti et al. (Bharti et al. 2003) concluded that addition of midazolam to intrathecal bupivacaine have no increase in the side effects.

*Gomaa et al. (*Gomaa et al. 2014*)* conducted study of intrathecal nalbuphine in LSCS and have reported incidence of 3.3% of nausea and vomiting.

Mukherjee and Pal et al. (Mukherjee et al. 2011) stated that 0.4 mg of intrathecal nalbuphine has no increase in the side effects.

Tiwari et al. (Tiwari et al. 2013) 0.2 mg and 0.4 mg nalbuphine added to bupivacaine and suggested that 0.4 mg nalbuphine has no adverse reaction.

Shivering

In the present study, the incidence of shivering was comparable in both the groups.

Eslam Nada et al. (Nada and Ezz 2017) in their study concluded that adding a small dose of nalbuphine (400 μg) to intrathecal bupivacaine reduces the incidence and severity of shivering in patients.

- In the present study, the incidence of pruritus was 6% in group B.
  *Prakash et al. (*Prakash et al. 2006*)* had nil incidence of pruritus in his study in the midazolam group.
  *Gomaa et al. (*Gomaa et al. 2014*)* had zero incidence of pruritus in his study in the nalbuphine group.
- In the present study, there was no significant sedation or respiratory depression in both the groups.
  *Goodchild et al. (*Goodchild et al. 1996*)* found no shivering, respiratory depression, pruritus when preservative-free midazolam was added to intrathecal bupivacaine.

No patient had PDPH or TNS complains.

Conclusion

In nutshell intrathecal midazolam and nalbuphine both are good adjuvants to hyperbaric bupivacaine 0.5% for caesarean section, as in both groups stable maternal hemodynamic profile and normal neonatal Apgar score were noticed.

Intrathecal midazolam provides prolonged postoperative analgesia with minimum adverse effects than intrathecal nalbuphine.

Abbreviations

25 G: 25 Gauge; ASA: American Society of Anesthesiology; BP: Blood pressure; cm: Centimeter; CSF: Cerebro intrathecal fluid; DBP: Diastolic blood pressure; ECG: Electrocardiogram; et al.: (et alibi); GABA: Gamma-aminobutyric acid; Hg: Mercury; h/hrs: Hour/s; HR: Heart rate; HS: Highly significant; i.v.: Intravenous; inj.: Injection; IT: Intrathecal; kg: Kilogram; LA: Local anesthetics; LSCS: Lower-segment caesarean section; MAP: Mean arterial pressure; mg: Milligrams; min: Minutes; ml: Milliliters; n/No: Number; NBM: Nil by mouth; NIBP: Non-invasive blood pressure; NS: Not significant;

OAA: Observer's Assessment of Awareness; RR: Respiratory rate; RS: Respiratory system; S: Significant; SBP: Systolic blood pressure; SD: Standard deviation; sec: Seconds; SPO_2: Partial pressure of oxygen saturation; TNS: Transient neurological symptoms; VAS: Visual analogue scale; %: Percentage

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Authors' contributions
SD analyzed, observed, and interpreted the patient data, and MK performed spinal anesthesia in the patients and was a major contributor in writing the manuscript. The authors have read and approved the final manuscript.

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Availability of data and materials
The data sets used/analyzed during this study are available from corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate
The above study was presented in front of the NHL institutional review board (NHLIRB) on the 14th September 2017 and was approved by the same (approval letter received on the 23rd October 2017). Written and informed consent was taken from all the patients involved in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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