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Research Article

A comparison between post-operative analgesia after intrathecal nalbuphine with bupivacaine and intrathecal fentanyl with bupivacaine after cesarean section

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KEYWORDS

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Abstract *Background:* Adding intrathecal opioids to intrathecal local anesthetics to decrease their doses and provide hemodynamic stability are major goals during spinal anesthesia in cesarean section. Different opioids were used to select the one with the longest duration of analgesia and the least side effects. In this study, intrathecal nalbuphine was compared with intrathecal fentanyl as an adjuvant to hyperbaric bupivacaine in cesarean section.

Patients and methods: Sixty female patients of ASA grades I and II presented for elective cesarean deliveries with spinal anesthesia were randomly allocated to 2 equal groups; Group F: 30 patients received intrathecal injection of 2 ml of 0.5% hyperbaric bupivacaine plus 0.5 ml fentanyl (25 μg); Group N: 30 patients received intrathecal injection of 2 ml of 0.5% hyperbaric bupivacaine plus 0.5 ml nalbuphine (0.8 mg). The onset of sensory and complete motor blockade, time of sensory blockade, duration of analgesia and motor blockade, fetal Apgar score, visual analog scale score, oxygen saturation, adverse effects and hemodynamic parameters were recorded intra-operatively and up to 4 h post-operatively. The effective analgesic time was recorded.

Results: The onset of complete motor block was significantly more rapid in fentanyl group than in nalbuphine group. The duration of post-operative analgesia was more prolonged in nalbuphine group but the difference was insignificant. No significant difference was found between both groups as regards the duration of sensory block, motor block, duration of analgesia, fetal Apgar score, visual analog scale score, hemodynamic parameters and oxygen saturation. Adverse effects were less common in nalbuphine group but the difference was insignificant.

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Conclusion: Either intrathecal nalbuphine 0.8 mg or intrathecal fentanyl 25 μg combined with 10 mg bupivacaine provides good intra-operative and early post-operative analgesia in cesarean section.

1. Introduction

Spinal anesthesia for cesarean delivery is the best anesthetic technique as it is simple to perform with rapid onset of anesthesia and complete muscle relaxation. Lower incidence of failed block, less drug doses, minimal neonatal depression and decreased incidence of aspiration pneumonitis are added advantages of spinal anesthesia [1,2].

Intrathecal opioids are synergistic with local anesthetics and intensify the sensory block without increasing the sympathetic block. They are commonly added to local anesthetics for potentiating their effects, reducing their doses, and thereby reducing their complications and side effects and offer hemodynamic stability. They also prolong the duration of post-operative analgesia [3].

Fentanyl is a lipophilic opioid with a rapid onset following intrathecal injection. It does not migrate to the 4th ventricle in sufficient concentration to cause respiratory depression. It is commonly added to intrathecal bupivacaine in cesarean delivery by many anesthesiologists [2,4–8]. It improves quality of anesthesia without producing significant side effects and improves post-operative analgesia and hemodynamic stability [9].

Nalbuphine, a mixed agonist–antagonist opioid, has a potential to attenuate the mu-opioid effects and to enhance the kappa-opioid effects. It was synthesized in an attempt to produce analgesia without the undesirable side effects of a μ agonist. Also, its combination with μ agonist opioids was tried by many researchers [10–12] to decrease the incidence and severity of the common μ-agonist side effects (respiratory depression, undesirable sedation, pruritus, nausea, vomiting and urinary retention). Meanwhile, the benefits of both κ and μ analgesia can be obtained.

Few studies had investigated intrathecal nalbuphine with hyperbaric bupivacaine [13,14], and as far as we know, no study had compared it with intrathecal fentanyl which is the opioid in common practice added to hyperbaric bupivacaine in cesarean section.

The aim of the work was to compare the intra-operative and post-operative analgesic effect of intrathecal nalbuphine and intrathecal fentanyl as an adjuvant to bupivacaine during cesarean delivery.

2. Patients and methods

After approval of the Local Ethics Committee and patients' informed written consent, sixty female patients presented to Kasr Al-Ainy Hospital for elective cesarean deliveries with spinal anesthesia were enrolled in the study.

2.1. Inclusion criteria

ASA physical status I or II with normal coagulation profile, age between 20 and 45 years, weight between 60 and 90 kg and height between 160 and 180 cm were enrolled in the study.

2.2. Exclusion criteria

ASA III or IV, patient refusal, infection at the site of injection, coagulopathy, anticoagulant medications, pre-existing neurological disease, uncooperative patients, cardiac or respiratory system failure, allergy to local anesthetics.

The patients were divided randomly using computer generated number and concealed using sequentially numbered, sealed opaque envelope technique into two equal groups (each 30 patients): Group F and Group N.

All patients were clinically assessed and routine preoperative investigations were done: CBC, PT, PTT, INR, liver function tests, kidney function tests, fasting blood sugar and ECG. Ranitidine 150 mg was administered orally before surgery.

The monitors (electrocardiography, non-invasive blood pressure and pulse oximetry) were applied to the patient on arrival to the operating room. A suitable peripheral vein was cannulated and I.V. Ringer solution 10 ml/kg/15 min (preload) was given to all patients before the procedure.

All patients were put in the sitting position with leaning forward. Sterilization was done. Dural puncture was performed at L4–L5 interspace or L3–L4 with a 25 gauge Quincke spinal needle.

The patients were divided equally into two groups according to the additive (fentanyl or nalbuphine), and all patients were received the same amount of local anesthetic (2 ml 0.5% heavy bupivacaine).

2.3. Group F (fentanyl) n = 30

Thirty patients received intrathecal injection of 2 ml of 0.5% hyperbaric bupivacaine plus 0.5 ml fentanyl (25 μg).

2.4. Group N (nalbuphine) n = 30

Thirty patients received intrathecal injection of 2 ml of 0.5% hyperbaric bupivacaine plus 0.5 ml nalbuphine hydrochloride (0.8 mg) (nalufin 20 mg in 1 ml ampoule, Amoun Pharmaceutical Co., Cairo, Egypt).

Spinal injections were done by anesthesiologists who did not participate in recording patients' data. Both patients and observers were blinded to the drugs given.

Then, the patients were placed in the supine position with a wedge under the right hip to maintain left uterine displacement. Elevation of the head by a pillow and oxygen mask 5 l/min was applied.

2.5. The following parameters were recorded intra-operatively

Continuous monitoring to the conscious level and oxygen saturation. The level of sensory block (assessed by pin prick) and motor block (assessed by Bromage scale; 0 = none, 1 = just able to move the knee but not the hip, 2 = able to move the foot only, 3 = unable to move the knee or foot) [15] were continuously recorded until skin incision. Surgery began when the

block reached T_5 dermatome. Heart rate and blood pressure were measured noninvasively every 5 min. Atropine (0.01 mg/kg) was given if H.R. decreased below 60/min. Intermittent doses of ephedrine 10 mg I.V. if the systolic arterial blood pressure decreased by more than 20% below pre-anesthetic level or less than 100 mmHg.

Visual analog scale (VAS) was recorded [it ranges from 0 indicating no pain till 10 indicating severe intolerable pain with variable degrees of ascending pain in between]. If VAS $\geqslant 4$, general anesthesia was given and the patient was excluded.

The neonatal Apgar score at 1 min after delivery was calculated by an attending pediatrician. Complications related to spinal block or drug allergy (hypotension, bradycardia, pruritus, nausea, vomiting, shivering, rash and bronchospasm) were recorded and managed.

A urinary catheter was left in situ and removed 24 h later.

2.6. The following parameters were recorded post-operatively up to the time of the first analgesic dose

Continuous monitoring to the conscious level, respiratory rate and oxygen saturation, sensory level and motor block were assessed every 15 min till complete recovery. Heart rate and noninvasive blood pressure were recorded after 2 and 4 h. The duration of analgesia (from intrathecal injections to VAS greater than 0) was recorded. The time of the first analgesic dose was recorded (effective analgesic time: from intrathecal injection to VAS $\geqslant 4$). NSAIDs (non-steroidal anti-inflammatory drugs) were given for analgesia to all patients scoring $\geqslant 4$.

Any complication was recorded and managed as before. In addition: for vomiting; metoclopramide 10 mg I.V. was given, for pruritus; pheniramine maleate 45.5 mg I.V. was given. For shivering; pethidine 20 mg I.V. Respiratory depression was defined as a respiratory rate of <10 breaths/min and hypoxia was defined as an oxygen saturation of $<95\%$.

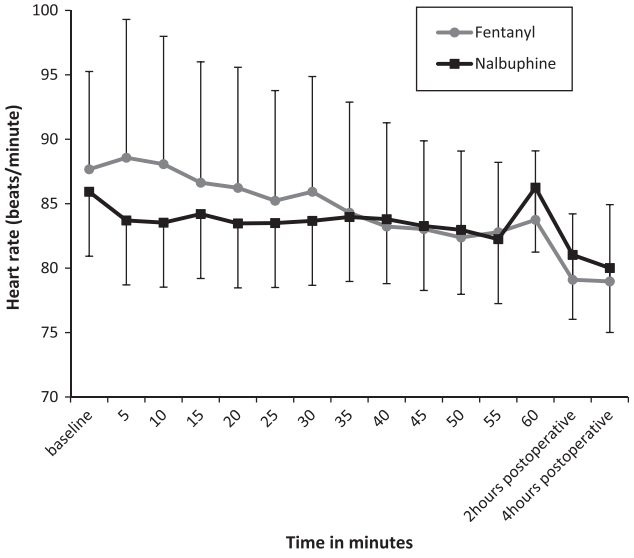

Figure 1 Heart rate (beats/min) of the two studied groups. There was no significant difference in the heart rate between group F and group N.

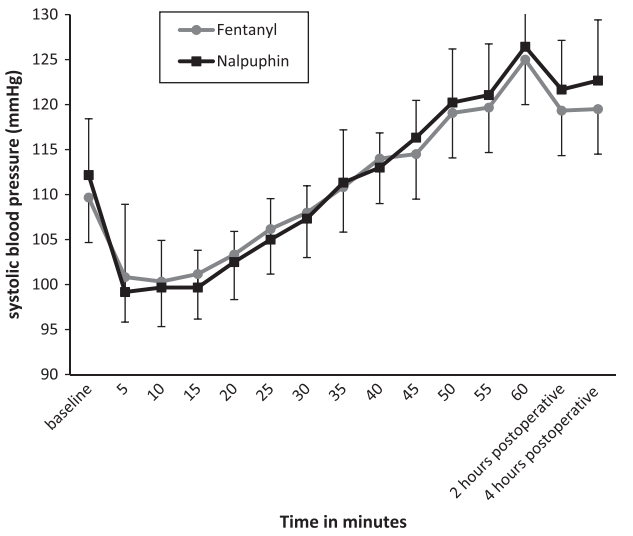

Figure 2 SBP (mmHg) of the two studied groups. There was no significant difference in systolic blood pressure between group F and group N.

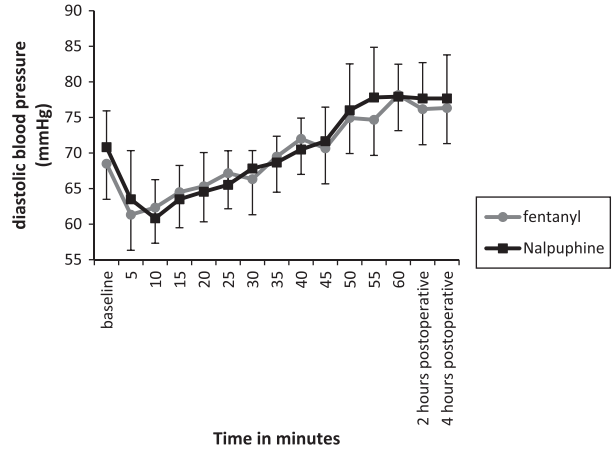

Figure 3 DBP (mmHg) of the two studied groups. There was no significant difference in diastolic blood pressure between group F and group N.

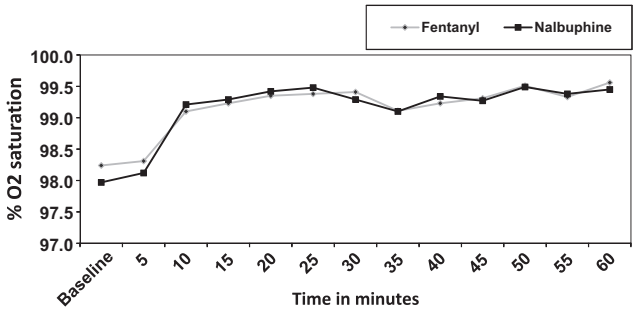

Figure 4 SPO_2 (%) of the two studied groups. No significant difference was found in oxygen saturation between group F and group N.

2.7. Power analysis

Being the primary outcome, power analysis was based on the difference in duration of analgesia between fentanyl and nalbuphine groups provided that we studied 30 cases in each arm. Our results showed that the mean ± SD of duration of analgesia was 155.8 ± 31 min in fentanyl group, while it was 166.7 ± 14 min in Nalbuphine group. If the true mean difference in duration of analgesia between the 2 drugs was similar to our calculated difference (11 min), we will be able to reject the null hypothesis with 89.9% power. Student's *t* test was used in the analysis with type I error probability equals 0.05. Calculations were done using PS Power and Sample Size Calculations Software, version 3.0.11 for MS Windows (William D. Dupont and Walton D. Vanderbilt, USA).

2.8. Statistical analysis

Results were expressed as means ± 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. The data were considered significant if p value was equal to or less than 0.05 and highly significant if p value < 0.01. Statistical analysis was performed with the aid of the SPSS computer program (version 12 windows).

3. Results

Sixty patients completed the study.

3.1. Group F (n = 30)

Fentanyl is the additive to bupivacaine.

3.2. Group N (n = 30)

Nalbuphine is the additive to bupivacaine (see Figs. 1–4; Tables 1–3).

4. Discussion

Regional anesthesia is now more popular than general anesthesia during cesarean delivery because of the increased mortality rate associated with general anesthesia [16]. Excessive high regional blocks and local anesthetics toxicity are the commonest causes of mortality associated with regional blocks. So, reduction in the doses of local anesthetics, the use of new techniques to avoid higher blocks and better management of local anesthetic toxicity are the new goals for decreasing mortality associated with regional anesthesia [2].

Intrathecal opioids cause segmental analgesia by binding to opioid receptors in the dorsal horn of the spinal cord. They prolong the duration of analgesia without affecting motor or autonomic nervous function. Their combination with intrathecal local anesthetics limits the regression of the sensory block seen with local anesthetics alone. Respiratory depression is the most serious side effect of intrathecal opioids while pruritus is the commonest. Others include nausea, vomiting, urine retention and sedation [17,18].

In this prospective randomized double blind study, the post-operative analgesic requirements and the spinally mediated analgesic effects of bupivacaine (hyperbaric) 0.5% in combination with fentanyl (25 μg) or nalbuphine (0.8 mg) in patients undergoing elective cesarean section were observed and recorded.

As regards the onset and duration of sensory block, there was no statistically significant difference between group F and group N.

The onset of complete motor block was more rapid with fentanyl than nalbuphine and this was statistically significant. This may be explained by the high lipid solubility and rapid tissue uptake of fentanyl more than nalbuphine, and this needs further studies.

Also in the present study, no statistically significant difference was found between both groups as regards the duration of motor block, hemodynamics and oxygen saturation. Neither bradycardia nor oxygen desaturation was recorded.

The duration of post-operative analgesia and the effective analgesic time were more prolonged in nalbuphine group than in fentanyl group with no statistically significant difference.

As regards the side effects, they were less in nalbuphine group than the fentanyl group with no statistically significant difference. The fetal Apgar score showed no statistically significant difference between both groups.

Intrathecal fentanyl is used commonly with heavy bupivacaine 0.5% for spinal and epidural anesthesia by many researchers [2,4–7]. Kang et al. [7] combined it with heavy bupivacaine during cesarean section to provide adequate depth of anesthesia. The duration of complete analgesia was longer in (bupivacaine and fentanyl) group 146 ± 47 min versus bupivacaine alone 104 ± 44 min. The incidence of pruritus was higher with fentanyl but shivering was less. This comparison was also done by Biswas et al. [5] in cesarean section and concluded the same results.

Sivevski [19] had studied the combination of reduced dose of local anesthetics (9 mg of isobaric bupivacaine) with

Table 1 Demographic data and duration of surgery of the two studied groups.

Characteristics	Fentanyl (*n* = 30)	Nalbuphine (*n* = 30)	*p* Value
Age (yrs)	26.33 ± 6.08	26.97 ± 5.40	0.671 (NS)
Height (cm)	168.97 ± 5.22	170.30 ± 6.94	0.404 (NS)
Weight (kg)	78.83 ± 8.26	81.53 ± 9.85	0.255 (NS)
Duration of surgery (min)	53.00 ± 5.19	53.17 ± 4.82	0.898 (NS)

Data are expressed as means ± standard deviation.
NS = $p > 0.05$ = not significant.
There was no statistically significant difference among the two groups as regards: age, height, weight and duration of surgery.

Table 2 Sensory block, motor block and duration of analgesia of the two studied groups.

Characteristics	Fentanyl (n = 30)	Nalbuphine (n = 30)	p Value
Onset of sensory block (min)	1.64 ± 0.09	1.60 ± 0.10	0.131 (NS)
Onset of complete motor block (min)	5.57 ± 0.23	5.72 ± 0.17	0.008**
2 Segment regression time of sensory block (min)	122.33 ± 5.21	123.00 ± 5.66	0.637 (NS)
Duration of motor block (min)	125.87 ± 20.17	125.33 ± 5.71	0.890 (NS)
Duration of analgesia (min)	155.83 ± 30.96	166.33 ± 14.02	0.096 (NS)
Effective analgesic time (min)	222.5 ± 28.46	231.83 ± 15.73	0.1215(NS)

Data are expressed as means ± standard deviation.
NS = $p > 0.05$ = not significant.
No statistically significant difference was found between both groups as regards the onset of sensory block, 2 segment regression time of sensory block and duration of motor block.
There was statistically significant more rapid onset of complete motor block in group F than in group N.
The duration of analgesia and the effective analgesic time were more prolonged in group N than in group F but this was not statistically significant.
** $p < 0.01$ = highly significant.

Table 3 Adverse effects and fetal Apgar score in the two studied groups.

Characteristics	Fentanyl (n = 30)	Nalbuphine (n = 30)	p Value
Hypotension	8 (26.7%)	6 (20%)	0.542 (NS)
Neusea and vomiting	3 (10%)	1 (3.3%)	0.301 (NS)
Pruritus	1 (3.3%)	0 (0%)	0.313 (NS)
Shivering	2 (6.7%)	1 (3.3%)	0.554 (NS)
Fetal Apgar score	8.83 ± 0.46	8.83 ± 0.38	1.000 (NS)

Data are expressed as means ± standard deviation or number (%).
NS = $p > 0.05$ = not significant.
The adverse effects were less in group N than group F but there was no significant difference between both groups.
Respiratory rates were similar for both groups. Maternal oxygen saturation to < 95% was not observed.

intrathecal opioids (fentanyl 20 μg) in comparison with higher doses of local anesthetics alone (13.5 mg of isobaric bupivacaine) during cesarean delivery. He concluded that adding intrathecal opioids to reduced dose of local anesthetics can produce adequate spinal anesthesia with minimum hypotension and decreased vasopressor requirements. Also, the increased incidence of emesis with the use of bupivacaine alone may be secondary to increased incidence of hypotension because the emetic effects are relieved after the administration of ephedrine and elevation of blood pressure.

Obara et al. [8] and Chavada et al. [9]agreed with these results. They concluded that the addition of intrathecal fentanyl to hyperbaric bupivacaine decreased the required amount of intra-operative analgesics and improved quality of anesthesia without producing significant side effects.

The first study which used intrathecal nalbuphine was conducted by Culebras et al. [14] who compared intrathecal morphine (0.2 mg) added to hyperbaric bupivacaine with different doses of intrathecal nalbuphine (0.2 mg), (0.8 mg) and (1.6 mg) added to hyperbaric bupivacaine in cesarean section and their study concluded that intrathecal nalbuphine 0.8 mg provides good intra-operative and early post-operative analgesia without side effects (no PONV or pruritus). Nalbuphine 1.6 mg did not increase efficacy but increased the incidence of complications. So, the dose 0.8 mg was chosen in this study. They also reported that the post-operative analgesia lasted significantly longer in the morphine group. There was no maternal or newborn respiratory depression and the neonatal conditions (Apgar scores and arterial blood gas values) were similar for all groups.

Regarding the appropriate dose of intrathecal nalbuphine, Lin [20] had compared intrathecal nalbuphine 400 μg added to hyperbaric tetracaine with intrathecal morphine 400 μg and concluded that intrathecal nalbuphine in a dose of 400 μg prolongs intra-operative and post-operative analgesia with fewer side effects. Culebras et al. [14] recommended the dose of 0.8 mg nalbuphine to be injected intrathecally after cesarean delivery and explained their difference with Lin [20] by the fact that they used a different patient population (non-pregnant patients) and different local anesthetic (hyperbaric tetracaine).

Mukherjee et al. [21] had studied 100 patients undergoing lower limb orthopedic surgery using subarachnoid block. They used different doses of nalbuphine intrathecally (200, 400 and 800) μg added to 0.5% hyperbaric bupivacaine. They concluded that the duration of sensory block and the duration of effective analgesia were prolonged with the doses 400 μg and 800 μg but the side effects were higher with the dose 800 μg.

Fournier et al. [22] compared between intrathecal nalbuphine 400 μg and intrathecal morphine 160 mcg in old patients undergoing total hip replacement using continuous spinal anesthesia. They concluded that intrathecal nalbuphine produces faster onset of pain relief but the duration of analgesia is shorter than intrathecal morphine.

Yoon et al. [23] compared between intrathecal (morphine 0.1 mg), (nalbuphine 1 mg) and (morphine 0.1 mg with nalbuphine 1 mg) in addition to 0.5% bupivacaine 10 mg in 60 obstetric patients undergoing cesarean section. They concluded that the duration of effective analgesia was longer with

morphine alone and morphine added to nalbuphine than in nalbuphine group alone. The incidence of pruritus was significantly higher in morphine groups while nausea and vomiting were the same in all groups.

Tiwari et al. [13] had compared intrathecal nalbuphine 200 μg and 400 μg added to hyperbaric bupivacaine with bupivacaine alone. They concluded that the duration of sensory block and duration of analgesia was maximally prolonged with nalbuphine 400 μg without complications.

In a randomized, double blind, controlled study done by Sapate et al. [24] on adding intrathecal nalbuphine to bupivacaine for patients undergoing infraumbilical surgeries, they concluded that intrathecal nalbuphine added to bupivacaine provides better quality of block and longer post-operative analgesia (8–9) hours than bupivacaine alone without any significant adverse effects. This long duration can be explained by doing the study in age group (50–70) years and by using higher volume of heavy bupivacaine (3 ml).

As regards the neurotoxicity of intrathecal nalbuphine, it has been used in modern practice for more than 10 years without any reports of neurotoxicity [21].

5. Conclusion

We concluded that either intrathecal nalbuphine (0.8 mg) combined with (10 mg) bupivacaine or intrathecal fentanyl (25 μg) combined with (10 mg) bupivacaine improves intra-operative analgesia and prolongs early post-operative analgesia in cesarean section.

Conflict of interest

None declared.

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