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ORIGINAL INVESTIGATION

Comparison of the effect of adding midazolam versus fentanyl to intrathecal levobupivacaine in patients undergoing cesarean section: double-blind, randomized clinical trial

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Abstract

Background: Many adjuvants are added to prolong the effects of spinal analgesia. We investigated the postoperative analgesic efficacy of the addition of midazolam or fentanyl to intrathecal levobupivacaine in women undergoing cesarean delivery.

Methods: Eighty patients were randomly assigned to two groups (n = 40). Group M received 10 mg of 0.5% levobupivacaine plus 2 mg of midazolam. Group F received 10 mg of 0.5% levobupivacaine plus 25 μg of fentanyl. Assessments included motor and sensory block, APGAR score, time to first request for analgesia, postoperative pain score, total consumption of rescue analgesics, and adverse effects.

Results: Sensory blockade was prolonged in Group M compared with Group F (215.58 $\pm$ 27.94 vs. 199.43 $\pm$ 19.77 min; p = 0.004), with no differences in other characteristics of the spinal block in intraoperative hemodynamics or APGAR score. The mean time to first request for rescue analgesia was longer in Group M (351.45 $\pm$ 11.05 min) than in Group F (268.83 $\pm$ 10.35 min; p = 0.000). The median total consumption of rescue analgesics in the first 24 hours postoperatively was 30 mg in Group M vs. 60 mg in Group F (p = 0.003). The median Visual Analog Scale (VAS) scores were lower in Group Ethan in Group F from the 8th to the 12th hour postoperatively, with no differences between the groups at other time points. The incidence of adverse effects was higher in Group F than in Group M.

Conclusion: Intrathecal midazolam (2 mg) was superior to intrathecal fentanyl (25 μg) in increasing the duration of the sensory blockade and postoperative analgesia with lower postoperative pain scores and decreasing the incidence of adverse effects.

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Introduction

Cesarean section is performed with the patient under general anesthesia or regional anesthesia. The subarachnoid blockade is the preferred technique. It avoids the depressant effect of general anesthesia on the neonate and the risk of aspiration with satisfactory postoperative analgesia. [1] Its main disadvantage is that it does not offer prolonged postoperative analgesia if only a local anesthetic is administered.[2]

Levobupivacaine, the S enantiomer of bupivacaine, which has been recently introduced for obstetric spinal and epidural anesthesia, has been found to afford a more selective neuraxial blockade than racemic bupivacaine.[3] Levobupivacaine is a high-potency, long-acting local anesthetic with a moderately slow onset of action. [4] Levobupivacaine has less attraction for cardiac sodium channels and better plasma protein-binding affinity than the dextranomer, which decreases the risk of cardiotoxicity. Plain levobupivacaine is isobaric concerning cerebrospinal fluid, resulting in the more predictable spread of the drug and thus reducing the incidence of hypotension and bradycardia. Levobupivacaine also results in earlier motor recovery linked with racemic bupivacaine. These advantages make levobupivacaine an attractive substitute for racemic bupivacaine for spinal anesthesia.[5]

Various intrathecal additives are added to local anesthetics to increase the speed of onset, improve the quality, and prolong the influence of spinal anesthesia. There are numerous choices of neuraxial additives, such as opioids (morphine, fentanyl, buprenorphine, nalbuphine), N-methyl-d-aspartate antagonists (ketamine), alpha 2 adrenoceptor agonists (clonidine and dexmedetomidine), vasoconstrictors (adrenaline), Gamma-Aminobutyric Acid (GABA) receptor agonists (midazolam), cholinergic agonists (neostigmine), and sodium bicarbonate, but no drug inhibits nociception without its associated side effects. [6]

Opioids such as morphine and fentanyl are extensively used as an adjunct to local anesthetics in neuraxial blockade to enhance the duration of postoperative analgesia.[7] However, worrisome adverse effects, such as pruritus, urinary retention, postoperative vomiting, and respiratory depression, limit the use of opioids in such procedures.[8]

Midazolam has a synergistic effect on postoperative analgesia when administered intrathecally with bupivacaine.[9] Previous studies did not report any major side effects in patients receiving intrathecal midazolam. A large cohort study examining the adverse neurologic effects of intrathecal midazolam also found no association between intrathecal midazolam and neurologic symptoms.[8]

In the current study, we compared the analgesic efficacy of midazolam and fentanyl added to intrathecal levobupivacaine in women undergoing cesarean delivery.

Methods

This prospective, randomized, comparative, controlled, double-blind study was conducted at Assiut University Hospital (Egypt). We enrolled and treated our patients with complete adherence to the most recent declaration of Helsinki. Approval from the local institutional ethics committee was first obtained (17100665). The study was then registered on clinical trials.gov under the number NCT03824314.

This study enrolled eight pregnant women with the American Society of Anesthesiologists (ASA) physical status I or II scheduled for elective cesarean sections. Written informed consent was obtained from all patients. Women with eclampsia or a history of preeclampsia, heart disease, uncontrolled diabetes mellitus, morbid obesity, coagulation abnormalities, vertebral deformities, contraindications to spinal anesthesia, height less than 150 cm or more than 170 cm, or who refused regional anesthesia were excluded from the study.

Randomization and blinding

According to a computer−generated randomized number table, patients were allocated randomly to two groups. Group M received 10 mg of 0.5% isobaric levobupivacaine (2 mL) plus 2 mg of midazolam (0.5 mL), and Group F received 10 mg of 0.5% isobaric levobupivacaine (2 mL) plus 25 μg of fentanyl (0.5 mL) intrathecally. To avoid bias during drug administration, the total drug volume was kept constant at 2.5 mL in both groups.

The syringes of drugs were prepared by well-trained investigators who were not involved in data collection. The surgeon, the patients, the anesthesiologist, and the investigators who collected the data and interpreted the results were unaware of the intervention assignments. The codes of the syringes were stored in opaque envelopes numbered from 1 to 80. Access to the codes was available only to one anesthesiologist who packed the envelopes.

Anesthesia and monitoring

The patients were examined preoperatively, and a full medical history and the examination results were recorded. The patients fasted for 6 h before the scheduled time of surgery. They were premedicated with ranitidine tablets 150 mg the night before surgery, ranitidine tablets 150 mg, and metoclopramide tablets 10 mg orally 2 h before surgery.

Monitoring was established in the operating theater, including Noninvasive Blood Pressure (NIBP), Electrocardiography (ECG), and Pulse Oximetry (SpO_2). Baseline interpretations of vital parameters were noted; intravenous (IV) lines were secured with suitable-sized IV cannulas. Lactated Ringer's 10 $mL.kg^{-1}$ solution was rapidly infused in all patients. Spinal anesthesia was administered under sterile and universal precautions at the L3-L4 interspace with a 25G Quincke spinal needle. At the same time, the patient was

sitting, and the study drug was injected according to the group assignment. Subsequently, the patient was put in a 15° to 20° left lateral supine position. Oxygen 4 L.min^{-1} was administered via a face mask. Heart rate, NIBP, and SpO_2were monitored 0, 3 and 5 min after the block, then every 5 min up to 30 min, and then every 15 min until the end of surgery. Hypotension and bradycardia were recorded when Mean Arterial blood Pressure (MAP) was < 60 mmHg and heart rate was < 60 beats/min and were treated with IV boluses of ephedrine 6 mg and atropine 0.6 mg, respectively. Nausea and vomiting, if occurred, were treated with ondansetron 4 mg IV. When the sensory block reached the level of the T4 dermatome, the surgical procedure was commenced. The block was considered to fail if a complete motor and sensory blockade was not achieved even after 15 minutes. Patients with fallen blocks were transferred to general anesthesia and were excluded from the study.

Assessment parameters

Patients' clinical characteristics included age, weight, ASA physical status, and duration of surgery. The intraoperative data (considering the time of intrathecal drug administration as time 0) were as follows: vital signs including heart rate, NIBP, and SpO_2. Sensory block level was measured by the loss of sharp sensation from a pinprick test and was noted at the midclavicular line bilaterally. Sensory block level was measured every minute for 10 min after administration of the study drug, then at 20 min, and at the end of the operation. The time of onset and the duration of sensory blockade (regression to the S1 dermatome) were recorded. The degree of motor block was evaluated using the Modified Bromage Score (MBS).[10] Motor block was assessed at the same time as a sensory block. The time to the start of the motor block, the time to reach MBS3, and the time of complete disappearance of the motor block were recorded. The duration of the block (the interval from intrathecal administration of the drug to the point at which the MBS was back to zero) was also recorded, and the APGAR scores of the newborn babies were also compared between the two groups at 1 and 5 min after delivery.[3]

During the postoperative period, the patients in both groups were monitored for hemodynamic parameters and pain using the Visual Analog Scale (VAS) scores (ranging from 0 = no pain to 10 = the worst pain imaginable) on arrival at the PostAnesthesia Care Unit (PACU) (time 0) and then every 30 min for 120 min, then hourly for 8 h postoperatively, then every 4 h up to 24 h postoperatively. Rescue analgesia in ketorolac 30 mg IV was administered at the patient's request or when VAS ≥ 4. The time until the first dose of rescue analgesia was requested was recorded. The patients were observed for side effects, such as pruritus, nausea, vomiting, hypotension, bradycardia, headache, and neurologic changes for 24 postoperatively. At the end of the study, a patient satisfaction score was obtained by asking the patients about their experience of anesthesia and analgesia during the intraoperative and postoperative periods. The answers were recorded as 1 (very dissatisfied), 2 (dissatisfied), 3 (neutral), 4 (satisfied), and 5 (very satisfied). Another anesthesiologist in the PACU who did a postoperative assessment was not aware of the drug administered, and a nurse in the ward was also blinded to the drug administered. The patients were discharged home when pain-free with no residual motor or sensory block, and were followed up for 7 days. They were called every day by telephone and examined after 7 days for any neurologic complications.

Outcomes

The primary outcome was the first postoperative request for analgesia after surgery, i.e., the period from intrathecal injection to the administration of the first rescue analgesia. The secondary outcomes were the time taken to achieve adequate motor and sensory block, the total duration of motor and sensory blockade, the incidence of intraoperative hemodynamic changes, the period of effective analgesia, the total amount of analgesia required, and side effects such as pruritus, hypotension, nausea, and vomiting.

Statistical analysis

Using the G-Power calculator 3.1.9.7 for sample size determination, a total sample size of 34 patients in each group would be sufficient for statistical testing based on a priori analysis with *t*-tests. Means: difference between two independent means (two groups) with a two-tailed type I error of 0.05, a power of 0.8, and an effect size of 0.7. Forty patients were enrolled in each group to account for patient dropout. The Shapiro-Wilk test assessed the distribution of baseline variables. Continuous variables were described as mean ± SD) and analyzed by Student's *t*-test and one-way analysis of variance with post hoc multiple comparisons. Nonparametric data were presented as median (range) and analyzed by the Mann-Whitney U−test. Categorical data were reported as numbers and percentages and were analyzed by the Chi-Square test or Fisher's exact test. A *p*-value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed with IBM SPSS statistics version 20 (SPSS Inc, Chicago, IL, USA).

Results

Among the 90 patients who were screened for eligibility, 80 were recruited for the study; each group contained 40 patients (Fig. 1). The two groups were similar in age, height, weight, and duration of surgery; there were no significant differences between the groups regarding demographic data (Table 1).

Hemodynamic vitals

No significant differences were recorded between the groups in MAP, mean heart rate, or SpO_2 at any studied time point (data not presented). NIBP and HR were stable during the whole procedure.

Sensory and motor block

The onset of sensory block was comparable in the two groups ($p = 0.710$). The time to reach the motor block and the duration of the motor block were comparable, with no significant differences between the two groups ($p > 0.05$) (Table 2).

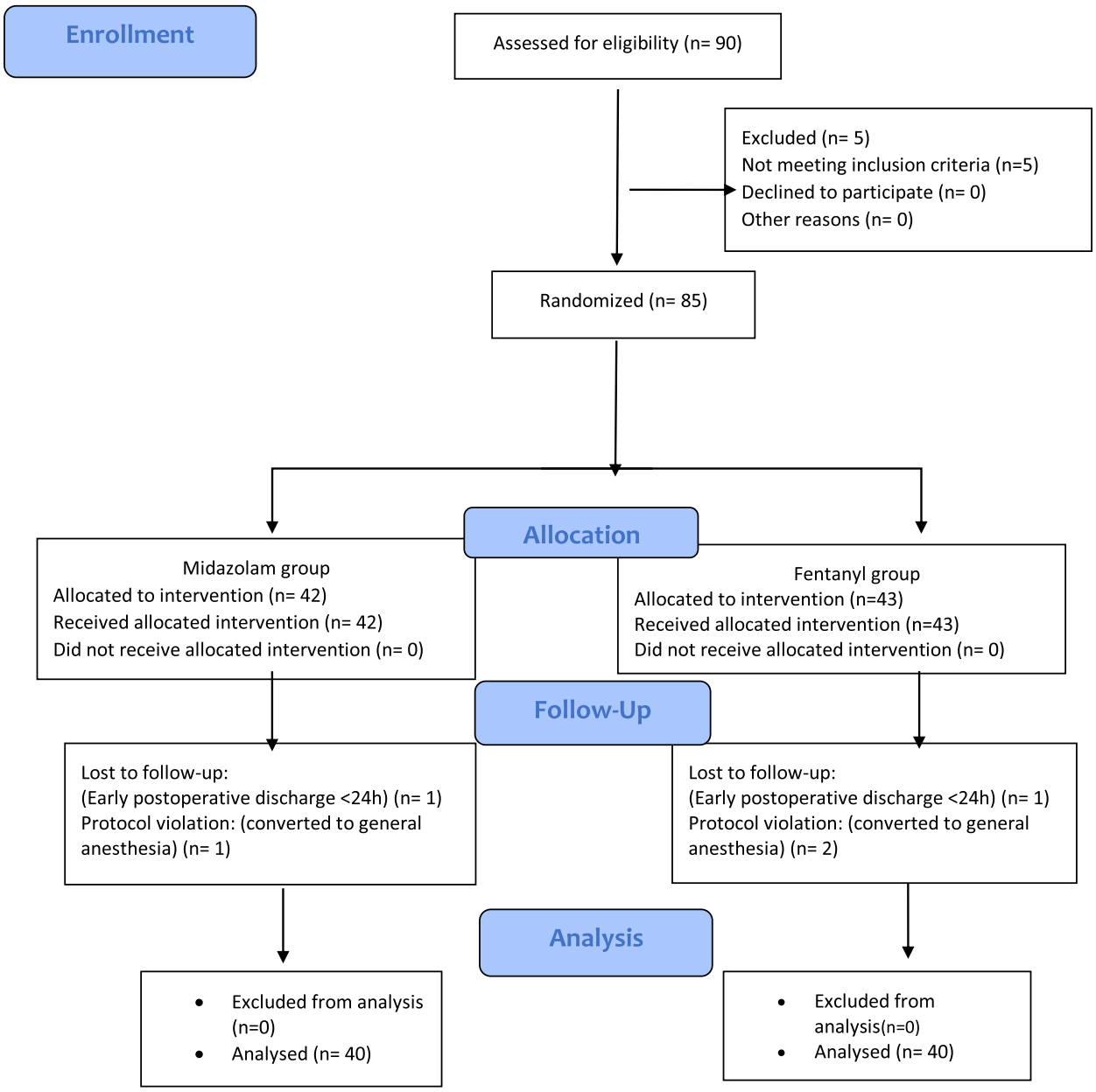

Figure 1 Participants flow diagram.

Table 1 Demographic data, neonatal APGAR score, and duration of surgery.

Variable	Group M (n = 40)	Group F (n = 40)	*p*-value
Age (y)	28.05 ± 6.18	28.82 ± 6.00	0.571
Height (cm)	162.75 ± 5.64	161.18 ± 5.86	0.224
Weight (kg)	75.00 ± 8.58	76.85 ± 8.11	0.325
ASA I/II	40/0	40/0	
Duration of surgery (min)	45.38 ± 2.86	44.38 ± 2.58	0.105
Neonatal APGAR score			
At 1 min: 8/9/10	9/24/7	10/22/8	0.902
At 5 min: 8/9/10	0/20/20	0/18/22	0.654

Data are presented as means ± SD or numbers. Group M, Levobupivacaine Plus Midazolam; Group F, Levobupivacaine Plus Fentanyl; ASA, American Society of Anesthesiologists physical status.

Table 2 Characteristics of the motor and sensory blocks.

Characteristic	Group M (n = 40)	Group F (n = 40)	*p*-value
Time to maximum motor block (min)	3.70 ± 1.11	3.87 ± 1.04	0.470
The total duration of motor block (time to motor recovery) (min)	189.48 ± 22.48	182.68 ± 16.27	0.125
The onset of sensory block (min)	2.65 ± 0.83	2.72 ± 0.96	0.710
The total duration of sensory block (regression to S1 dermatome) (time to sensory recovery) (min)	215.58 ± 27.94	199.43 ± 19.77	0.004[a]

Data are presented as means ± SD. Group M, Levobupivacaine Plus Midazolam; Group F, Levobupivacaine Plus Fentanyl.
[a] $p < 0.05$.

The time to regression to S1 dermatome was significantly shorter in Group F than in Group M ($p = 0.004$).

APGAR score

The neonatal APGAR scores were comparable between the two groups. All neonates scored 9 or 10 at 5 min after delivery (Table 1).

Postoperative pain profile

The mean time to first request for IV ketorolac rescue analgesia was significantly longer in Group M (351.45 ± 11.05 min) than in Group F (268.83 ± 10.35 min; $p = 0.000$). The median total consumption of rescue analgesia in the first 24 h postoperatively was 30 mg in Group M and 60 mg in Group F ($p = 0.003$) (Table 3). The median VAS scores were significantly lower in Group A than in Group F from the 8^{th} to the 12^{th} hour postoperatively, with no significant differences between the groups at other studied timepoints (Fig. 2).

Side effects

In Group M, 31 patients did not experience any side effects, compared with 12 patients in Group F ($p = 0.000$). Nausea, vomiting, and pruritus were significantly more frequent in Group F than in Group M. However, no significant differences were detected between the two groups in other side effects (hypotension, bradycardia, and headache). None of the patients complained of any neurologic deficits.

Patient satisfaction

Assessed by the Likert scale was adequate (very satisfied, satisfied, or neutral) in 90% of the patients in Group M and 82.5% in Group F, with no significant difference between the groups ($p = 0.106$).

Discussion

This study showed that 2 mg of midazolam added to 10 mg of 0.5% levobupivacaine increased the duration of sensory blockade, provided adequate postoperative analgesia, and had fewer side effects than that obtained from 25 μg of fentanyl added to 10 mg of 0.5% levobupivacaine intrathecally for cesarean section, without any major complications.

Bremerich et al. found that, compared with 7.5 mg of levobupivacaine, 10 and 12.5 mg of levobupivacaine prolonged the duration of effective analgesia postoperatively (45 vs. 81 and 96 min, respectively).[11] These authors recommended 10 mg of levobupivacaine for patients undergoing elective cesarean delivery with spinal anesthesia.

In agreement with the present study, Shadangi et al. showed that the addition of preservative-free midazolam to bupivacaine in spinal anesthesia resulted in prolonged postoperative analgesia without an increase in the duration of motor block.[12] In another study, Isazadehfar et al. showed that intrathecal midazolam (2 mg), when used as an additive to bupivacaine, could provide an adequate prolongation of postoperative analgesia with reduced incidence of postoperative nausea and vomiting,[13] a result that was comparable to our study. Other investigators observed that intrathecal midazolam produced significant postoperative analgesia in patients undergoing lower abdominal and perineal operations.[14]

Valentine et al. examined the influence of intrathecal midazolam and hyperbaric bupivacaine for cesarean section under spinal anesthesia and found that no side effects attributable to midazolam were recognized. Intrathecal midazolam appears to be safe and has clinically obvious analgesic properties.[15] In the same year, Borg and Krijnendescribed long-term intrathecal administration of midazolam and clonidine in patients with refractory musculoskeletal pain continuing for more than 2.5 years. They found promising results using intrathecal midazolam up to 6 mg/day. They concluded that

Table 3 Time to the first request and total consumption of postoperative intravenous ketorolac rescue analgesia.

Variable	Group M (n = 40)	Group F (n = 40)	*p*-value
Total analgesic consumption (mg) median (range)	30 (60)	60 (60)	0.003[a]
Number of doses			
1	23	10	
2	15	23	
3	2	7	
Time to first rescue analgesia (min) (mean ± SD)	351.45 ± 11.05	268.83 ± 10.35	0.000[a]

Data are presented as means ± SD. Group M, Levobupivacaine Plus Midazolam; Group F, Levobupivacaine Plus Fentanyl.
[a] $p < 0.05$.

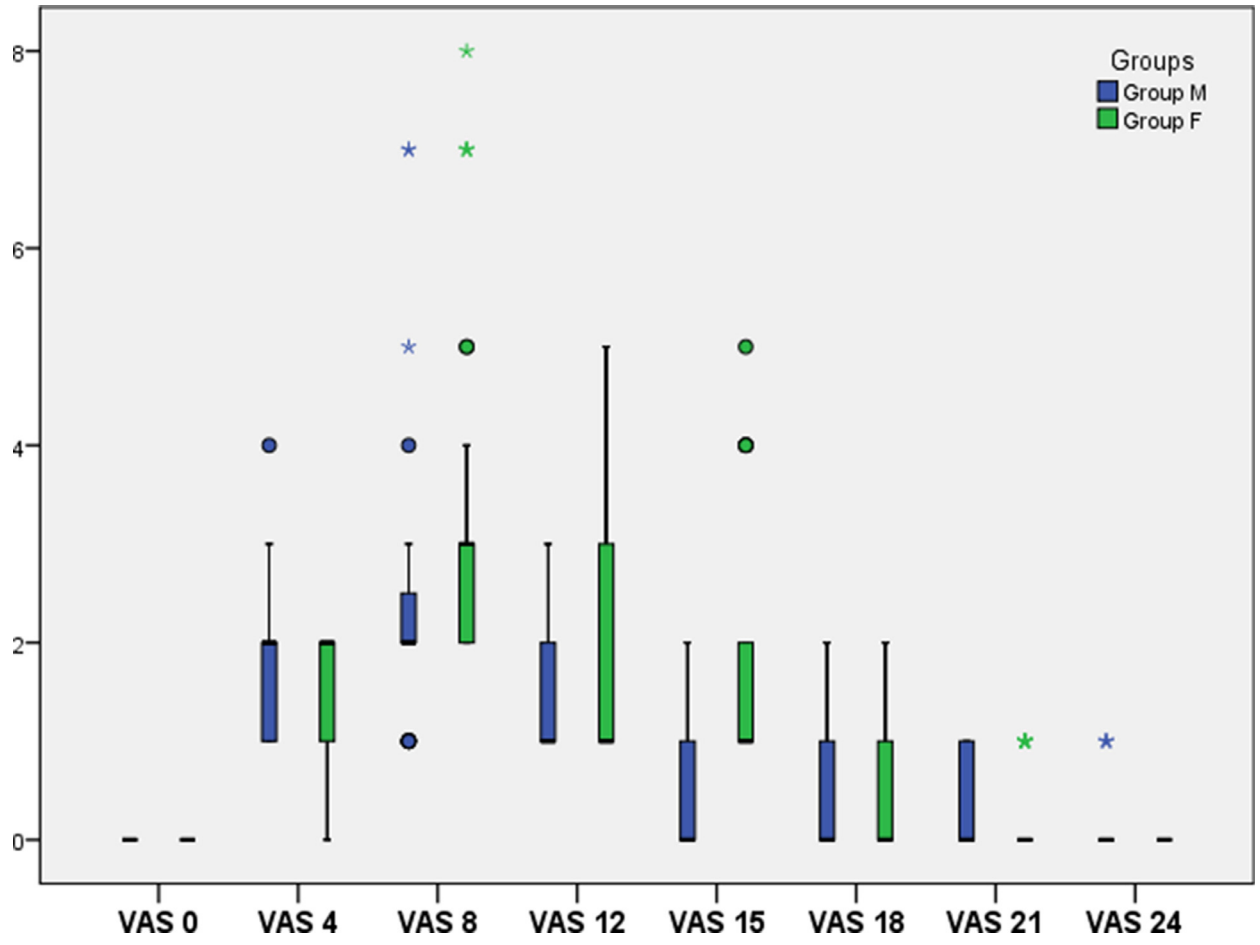

Figure 2 Postoperative Visual Analog Scale (VAS) scores in the two study groups.

this high dose did not cause any adverse neurologic effects in patients suffering from chronic refractory musculoskeletal pain.[16]

Contrary to our findings, Francis et al. reported no significant difference in the duration of effective analgesia between 2 mg of adjuvant intrathecal midazolam and 20 μg of intrathecal fentanyl in patients undergoing lower limb orthopedic surgery.[17]

Midazolam provides spinal analgesia through GABA receptors densely present in lamina 2 of the dorsal horn ganglia. This region plays a prominent role in nociceptive and thermoceptive stimulation processing. Midazolam also acts by activation of spinal opioid receptors.[18]

A study on the influence of 1 mg of adjuvant midazolam compared with 25 μg of fentanyl on the duration of spinal anesthesia with 0.5% bupivacaine in opium addicts established that midazolam is more effective than fentanyl in such cases.[19] Our study corroborates these findings.

In the present study, nausea and vomiting occurred intraoperatively and postoperatively and were less frequent in the Group M. These results were comparable to those of Ho et al. Their meta-analysis of the use of intrathecal midazolam to increase postoperative analgesia reported that midazolam increased perioperative analgesia and decreased nausea and vomiting in patients undergoing cesarean delivery.[20]

In concordance with the results of this study, Gupta et al. measured the start times of motor block and sensory nerve block in patients. They observed a very slight difference between the groups, which was not statistically significant.[21]

Contrary to our findings, Sawhney et al. reported that adding fentanyl to intrathecal bupivacaine in spinal anesthesia for lower limb surgical procedures led to a better quality of postoperative analgesia than in patients receiving midazolam.[22]

Bogra et al.[23] reported that the administration of adjuvant intrathecal midazolam or fentanyl did not cause any additional adverse effects in neonates, as demonstrated by the APGAR score.

Limitations

The limitations of this study include the small number of patients, the absence of the use of intrathecal morphine as an adjuvant in both groups, and the absence of an adequate protocol for postoperative analgesia. Further studies should be done with longer postoperative follow-

up periods, testing other doses of midazolam, and comparison with other drugs.

Conclusion

Intrathecal midazolam (2 mg) was superior to intrathecal fentanyl (25 μg) in enhancing the duration of sensory block by levobupivacaine, improving postoperative analgesia and the time of postoperative pain relief, and decreasing the incidence of adverse effects. The neonatal outcomes were comparable with the use of midazolam and fentanyl.

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Conflicts of interest

The authors declare no conflicts of interest.

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