



Fentanyl versus midazolam added to bupivacaine for spinal analgesia in children undergoing infraumbilical abdominal surgery: A randomized clinical trial

Marwa Mahmoud AbdelRady^a, Khaled Abdelbaky Abdelrahman^b, Wesam Nashat Ali^a, Ahmed Mohammed Ali^c and Ghada Mohammad AboElfadl^b

^aLecturer in Anesthesia and Intensive Care Department, Faculty of Medicine, Assiut University, Assiut, Egypt; ^bAnesthesia and Intensive Care Department, Faculty of Medicine, Assiut University, Assiut, Egypt; ^cLecturer in General Surgery Department, Faculty of Medicine, Assiut University, Assiut, Egypt

ABSTRACT

Background: The addition of fentanyl or midazolam to intrathecal bupivacaine was tested to reduce the occurrence and pain degree in children undergoing infraumbilical surgery under sevoflurane anesthesia with intrathecal analgesia.

Methodology: Children (6–8 years) were randomized into three groups of 30 patients each with consent from parents. Groups C, F, and M received 0.3 mg/kg of 0.5% bupivacaine + 0.9% NaCl (placebo), 0.3 mg/kg of 0.5% bupivacaine + 0.2 µg/kg of fentanyl, and 0.3 mg/kg of 0.5% bupivacaine + 0.5 mg of midazolam, respectively. Assessments included time to first analgesic request, postoperative pain score, the total amount of rescue analgesics, motor and sensory blocks, sedation, family satisfaction, and adverse effects.

Results: The Children's Hospital of Eastern Ontario score was higher in the control than in the midazolam and fentanyl groups. The mean time to the first request for rescue analgesia was longer in group M (297.1 ± 10.7 min) than in groups F (219.9 ± 25.4 min) and C (162.7 ± 37.5; P = 0.000). The total analgesic consumption was higher in both control and fentanyl groups (P = 0.044). Family satisfaction was significantly higher in group M (P = 0.013) with no adverse effects.

Conclusion: In the present study, intrathecal midazolam (0.5 mg) was superior to intrathecal fentanyl (0.2 µg/kg) in increasing the duration of postoperative pain relief with lower postoperative pain scores and less incidences of adverse effects. Consequently, intrathecal midazolam can be used as an adjuvant to local anesthetics if fentanyl is not accessible or contraindicated.

ARTICLE HISTORY

Received 15 November 2021

Revised 12 January 2022

Accepted 18 January 2022

KEYWORDS

Spinal anesthesia; fentanyl; midazolam; postoperative pain

1. Introduction

Subarachnoid block (SAB) was first defined in children in 1909 but did not become part of routine practice until the 1980s when regional anesthesia increased in popularity. The specific advantage suggested for subarachnoid in children was general anesthesia (GA) avoidance in those at risk for postoperative apnea development [1]. However, in the previous three decades, intrathecal anesthesia has gained popularity in newborns, infants, and children, especially for surgeries involving the lower extremities, urogenital, perineal, and lower abdominal [2].

The SAB produces intense and evenly distributed sensory blockade with rapid and proper muscle relaxation and negligible physiological changes. Intrathecal anesthesia has been specifically suggested in circumstances associated with respiratory tract infection, intestinal obstruction, and patients with a full stomach.

Furthermore, postdural puncture headache has been revealed to occur less frequently in children than in adults [2].

Neuraxial anesthesia is increasing in popularity because of its rapid onset and the intense, evenly distributed motor and sensory blockade with a high success rate [3]. Moreover, bupivacaine is considered the most common local intrathecal anesthesia for children. Various adjuvants were combined with the local anesthetic to increase intrathecal block quality and extend analgesia duration [4]. The frequently used adjuvants contain α2 stimulants (e.g., clonidine [4] and dexmedetomidine [5]), opioids (e.g., Fentanyl [6] and nalbuphine [7]), midazolam (e.g., gamma-aminobutyric acid (GABA) receptor agonists [8]), and N-methyl-D-aspartate receptor antagonist (e.g., Ketamine [9]).

Fentanyl is the most commonly utilized short-acting opioid in intrathecal injections with local anesthetics. It improves the status of intraoperative and postoperative analgesia by acting synergistically with local

anesthetics [10]. However, intrathecal opioids can produce itchiness, urine retention, nausea, vomiting, and respiratory depression [11].

Intrathecal midazolam was first used for analgesia after the discovery of benzodiazepine receptors in the spinal cord [12]. Moreover, midazolam has a synergistic effect on postoperative analgesia when combined with intrathecal bupivacaine [13]. Previous studies have shown that combining intrathecal midazolam with local anesthetics prolongs intrathecal anesthesia and postoperative analgesia following abdominal and perianal operations [14].

This study was conducted to investigate the analgesic efficacy regarding hemodynamic stability and sedation produced by intrathecal fentanyl or midazolam when used as an adjunct to intrathecal bupivacaine in pediatric patients undergoing infraumbilical surgery.

2. Methods

The Medical Research Ethics Committee, Faculty of Medicine, Assiut University, Assiut, Egypt, approved this prospective, randomized, double-blind comparative study (approval no: 17,100,485). This study follows the Helsinki Declaration and was registered at ClinicalTrials.gov (NCT03592537). The study was conducted from 15 August 2018 to 14 May 2021. All the guardians of the participants provided written informed consent.

Inclusion criteria: This study enrolled 90 children aged 6–8 years old with the American Society of Anesthesiologists (ASA) physical status I or II who were undergoing elective infraumbilical abdominal surgery.

Exclusion criteria: Children with a known history of heart disease, local anesthetic allergy, body mass index of ≥ 95 th percentile for age, vertebral malformations, bleeding diathesis, pre-existing neurological, or spinal disease, and patients who had any contraindications to intrathecal anesthesia, analgesia failure, or inadequate analgesia (received intravenous paracetamol, 15 mg/kg) were excluded from the study.

Randomization was conducted following a computer-generated randomized table of numbers. The patients were randomly assigned into three groups (each group has 30 participants).

Group B received 0.3 mg/kg 0.5% intrathecal bupivacaine (1.5 mL) (in a dose of 0.5 mg/kg for children <5 kg, 0.4 mg/kg for children 5–15 kg, 0.3 mg/kg for children >15 kg) [3] plus 0.9% NaCl (0.3 mL; placebo; the placebo volume corresponded to the calculated midazolam and fentanyl dose for each child).

Group M received 0.3 mg/kg of 0.5% intrathecal bupivacaine (1.5 mL) + 0.5 mg of preservative-free midazolam (dormicum 5 mg/mL; F. Hoffmann-La Roche Ltd, Basel, Switzerland) (0.3 mL). In agreement

with previous research in adult studies [15], the bupivacaine-midazolam combination resulted in prolonged postoperative analgesia without prolonged discharge from the recovery room or significant side effects. They use intrathecal midazolam at a dose of 1 mg in the age group 18–60 years. Accordingly, we have calculated the midazolam dose for children to be 0.5 mg.

Group F received 0.3 mg/kg of 0.5% intrathecal bupivacaine (1.5 mL) + 0.2 μ g/kg (25 μ g) fentanyl (0.3 mL) intrathecally. The corresponding intrathecal fentanyl dose was designed for children built on adult studies using 10–25 μ g fentanyl in patients with an average weight of 65–75 kg (0.15–0.33 μ g/kg) with 0.2 μ g/kg of fentanyl [16].

Fentanyl and midazolam were made in a separate syringe by mixing midazolam or fentanyl with 0.9% NaCl. Bupivacaine and midazolam or fentanyl solutions were mixed into a single syringe before administration. The drug volume was kept constant at 1.8 mL in all groups to avoid bias during drug administration. The preparation of syringes with drugs was conducted by a well-trained physician excluded from data collection. The surgeon, parent or guardian, anesthesiologist, and investigators who collected the data and interpreted the results were unaware of the intervention assignments.

All patients studied were subjected to a detailed pre-anesthetic assessment. Moreover, all routine examinations were conducted. Standard preoperative fasting strategies were followed before the elective anesthesia procedure. No premedication was given, and all patients were pre-oxygenated for 3 min through a face mask with 100% oxygen. Standard Association of Anesthetists of Great Britain and Ireland monitoring was applied, and baseline vitals were recorded. Inhalation induction was conducted with sevoflurane (8%) and oxygen. The airway was secured with a laryngeal mask with spontaneous ventilation. Post-induction intravenous line was established to infuse ringer lactate at a dose of 10 mL/kg. Anesthesia was maintained with sevoflurane at approximately 2.5% and 50% air and oxygen, respectively. Moreover, blood pressure was maintained between 80% and 70% of the baseline record.

Intrathecal anesthesia was administered at the L3–L4 space with full asepsis (gown, glove, and mask), and the study drug was injected following the group assignment using a 25 G Quincke spinal needle while the patients were in the lateral decubitus posture.

The SpO₂ and heart rate (HR) were continuously monitored, and noninvasive blood pressure (NIBP) was monitored every 5 min until the end of surgery. No sedatives or opioids were administered during the operation. A lack of tachycardia or a rise in mean arterial pressure (MAP) compared with baseline vitals was considered. A rise in HR or MAP (>15%) in

response to surgery 15 min after intrathecal anesthetic injection was regarded as an analgesic failure. However, an increase in HR and MAP during surgery was considered failed analgesia. Bradycardia and hypotension were treated with atropine and ephedrine-titrated boluses.

Patients with analgesia failure or inadequate analgesia received intravenous (IV) paracetamol (15 mg/kg). Moreover, those patients were excluded from the study.

At the end of the operation, the laryngeal mask airway was removed, and the child was moved to the post anesthesia unit (PACU). Pain intensity and Aldrete–Krolik recovery score [17] were noted every 10 min until an Aldrete score of >9 was attained. Consequently, the patients were transferred to the ward.

2.1. Assessment parameters

The patient's demographic and clinical characteristics, including age, weight, ASA classification, and surgical time, were noted.

Intraoperative data: *Vital signs* include HR, NIBP, and peripheral oxygen saturation.

In the postoperative period, patients were observed for hemodynamic parameters and pain using the Children's Hospital of Eastern Ontario score (CHEOPS) [18] at 0 (upon PACU arrival), 1, 2, 6, 12, and 24 h after recovery from anesthesia. Paracetamol (15 mg/kg) was administered IV for rescue analgesia when two paired observations separated by a waiting period of 5 min showed CHEOPS of >6.

The time when the patient was given the first dose of rescue analgesia was recorded. Moreover, the number of doses of rescue analgesia needed in the postoperative period (first 24 h) was also recorded.

Motor block: The motor block grade was evaluated using the Modified Bromage Score [19]. The time of complete disappearance and block duration was noted (interval from intrathecal drug administration to the point where the Bromage Score returned to zero). The significant remaining motor blockade was defined as a motor block grade of ≥ 1 point. Motor recovery was evaluated until the hip flexion returned that reflected SAB. Consequently, the patients are discharged from PACU when fully conscious and with stable hemodynamics including respiratory parameters and full hip flexion. The time of discharge from PACU was recorded.

Sedation scores were recorded at 0, 1, 2, 4, 8, 12, and 24 h after the operation using a modified Ramsay sedation score [20]. Moreover, the patients were observed for any complications or side effects (e.g., nausea, vomiting, urinary retention, pruritus, hypotension, bradycardia, and neurological changes) for 24 h. A neurological examination was conducted to exclude any neurological deficits upon discharge.

At the end of the study, the parents were requested to express their overall satisfaction about the analgesic care of their children's patient satisfaction score using a 5-point Likert scale (1, very dissatisfied; 2, dissatisfied; 3, neutral; 4, satisfied; and 5, very satisfied). A postoperative assessment was conducted by another anesthesiologist in the PACU and a nurse on the unit who did not know the drug being administered.

All parents received a phone call from the same nurse the day after surgery and were asked if any side effects were noticed. Follow-ups were arranged 1 month after surgery to rule out any neurological complications.

The time to first postoperative analgesic request was the primary outcome, and secondary outcomes were the incidence of intraoperative hemodynamic changes, the total amount of analgesia required, and side effects (e.g., Hypotension, bradycardia, pruritus, nausea, and vomiting in patients).

3. Sample size

The postoperative analgesia duration measured from the first request for analgesics was the primary endpoint of this study. Moreover, a target sample size was calculated based on the results of a previous study [21]. Equal group number, two-tailed study, and 27 patients in each group should be included to be able to detect a difference of 60 min between groups with standard deviation (60 min), α error (0.05), and power of the study (0.8). Three patients were added to each group to compensate for dropouts. Thus, 90 individuals were included.

4. Statistics

The Shapiro–Wilk test was used to assess the baseline variables' distribution. Continuous variables were expressed as mean (\pm SD) with 95% confidence intervals and median (range). The one-way analysis of variance test with multiple post hoc comparisons was used to evaluate normally distributed continuous data.

Categorical data were reported as numbers and percentages, and adjusted *P* values were calculated using the chi-square test or Fisher's exact test with Bonferroni's correction. The Mann–Whitney *U* test was used to assess nonparametric data. Statistical significance was defined as a *p* value of <0.05. IBM SPSS Statistics (version 20; SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

5. Results

Of the 102 patients screened for eligibility, 90 patients were recruited for this study with each group having 30 patients. Figure 1 shows the participant recruitment and analysis.

Table 1. Comparison of demographic data and surgery type and duration.

	Group F	Group M	Group C	P-value
Age (year)	7 ± 0.8	7.1 ± 0.7	7.1 ± 0.7	0.918
Weight (kg)	26.2 ± 1.5	25.5 ± 1.2	25.6 ± 1.3	0.122
Height (cm)	119.2 ± 5.2	120 ± 5	121.2 ± 5	0.314
Duration of surgery	33.9 ± 3.1	33.1 ± 2.8	34.5 ± 2.6	0.177
Sex M/F	18/12	19/11	21/9	0.712
ASA (I/II)	26/4	28/2	25/5	0.484
Type of surgery				
*Inguinal hernia	15 (50%)	19 (63%)	17 (57%)	0.832
*Hydrocele	10 (33%)	6 (20%)	8 (27%)	
*Undescended testis	5 (17%)	5 (17%)	5 (17%)	

Data presented as mean ± SD, number of patients, and number (%).

ASA: American Society of Anesthesiologists.

P > 0.05 is considered statistically non-significant between the 3 groups.

The three groups were similar in age, height, weight, and surgery duration, and no significant inter-group differences were noted in these demographics (Table 1).

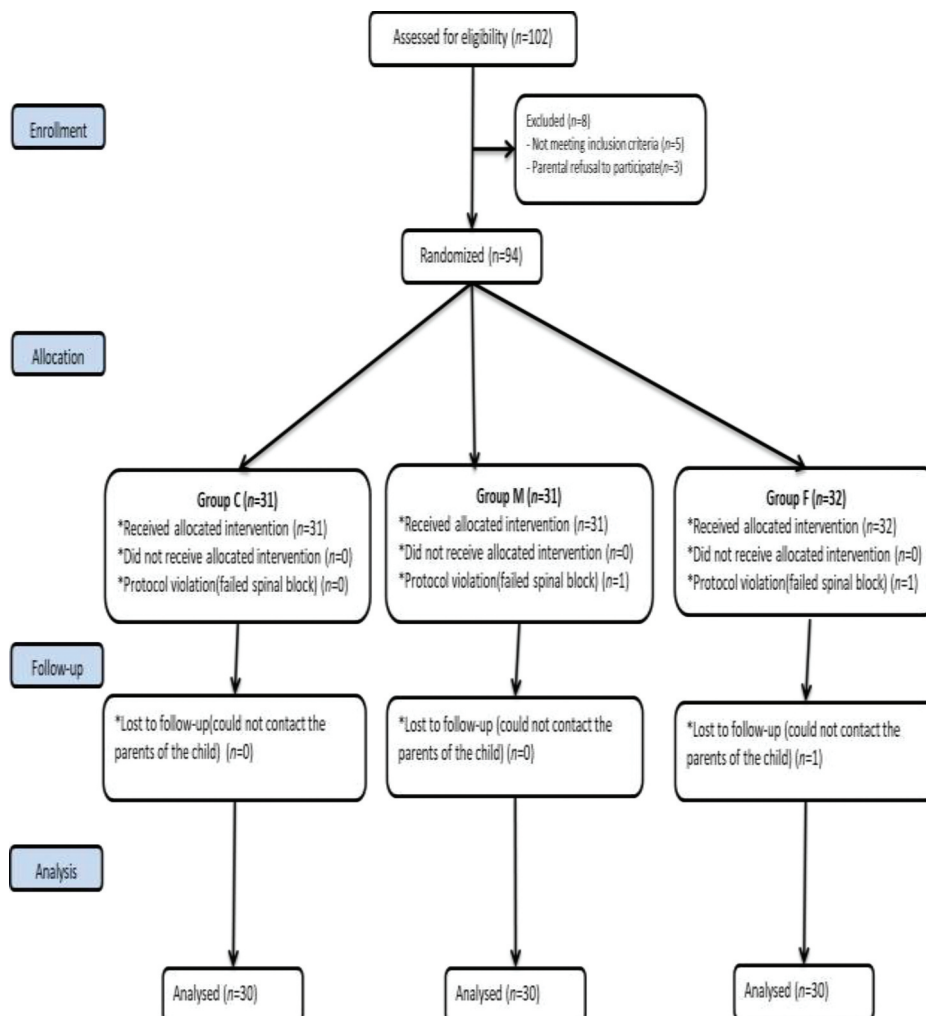
In the postoperative period, The CHEOPS scores were significantly lower in the midazolam group. Additionally, the three groups showed comparable CHEOPS scores ($P > 0.05$) from baseline to 90 min. The difference in CHEOPS scores of the three groups was statistically significant between the midazolam and the two other groups at 210 and 240 h with

$P < 0.05$. A statistically significant difference between the three groups was noted at 120, 240, and 18 h. The midazolam group had lower CHEOPS scores at nearly all-time intervals (Figure 2).

The rescue analgesia and analgesic consumption: CHEOPS score was higher in group B requiring rescue analgesia (162.7 ± 37.5), whereas the CHEOPS score started to increase and require rescue analgesia in the midazolam and fentanyl groups (297.1 ± 10.7 and 219.9 ± 25.4 min; Table 2).

Not only that the time needed for the first rescue analgesia (primary outcome) was significantly shorter in favor of the control and fentanyl groups ($P = 0.000$) but also the number of patients who required more than one rescue analgesic dose was higher in the control and fentanyl groups ($n = 12$ and 6 ; $P = 0.044$) than in the midazolam group ($n = 4$; Table 2). The postoperative rescue analgesia was administered with paracetamol injection bolus 15 mg IV as required or whenever the CHEOPS score was >6 for 24 h.

The time to full motor recovery was significantly longer in the fentanyl group (111.5 ± 12.3) than in the midazolam (106.2 ± 14.4) and control (98.3 ± 7.5 ; $P = 0.000$) groups (Table 2).

**Figure 1.** Consort flow chart of the participants.

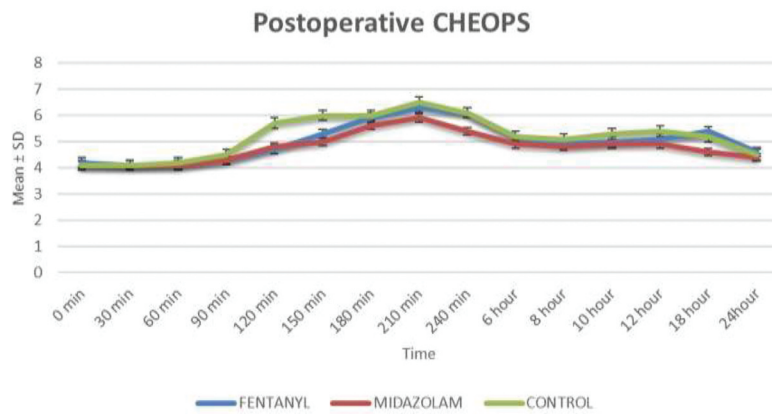


Figure 2. CHEOPS scores in the postoperative period.

Table 2. Time to first request, time to full recovery, total consumption of postoperative IV paracetamol rescue analgesia and Likert score.

	Group F	Group M	Group C	P-value
1st rescue analgesia. (min)	219.9 ± 25.4	297.1 ± 10.7	162.7 ± 37.5	0.000*
time to full recovery(min)	111.5 ± 12.3	106.2 ± 14.4	98.3 ± 7.5	0.000 +
Total analgesic consumption	24(80%)	26(86.7%)	18(60%)	0.044*
No. of doses:				
* one dose				
*two doses				
Likert score:				
very	1(3.3%)	0	2(6.7%)	0.013
*dissatisfied	2(6.7%)	1(3.3%)	4(13.3%)	
*dissatisfied	15(50%)	12(40%)	22(73.3%)	
*neutral	11(36.7%)	14(46.7%)	2(6.7%)	
*satisfied	1(3.3%)	3(10%)	0	
*very satisfied				

Data presented as mean ± SD, number of patients (%).

*: significant difference between the all groups using Tukey post- hoc test
+: significant difference between the control and other two groups using chi square test

Hemodynamics: No significant differences were recorded among groups regarding the mean arterial blood pressure, the mean HR, or SPO₂ in all-time points (data not presented).

Sedation and patients' satisfaction: Sedation was assessed using the *modified Ramsay sedation score* and was comparable in all the groups (data not presented).

Patients' satisfaction was assessed using the Likert scale; the satisfaction score was adequate (very satisfied, satisfied, and neutral) in 96% of the midazolam group compared with 90% and 80% in the fentanyl and control groups, respectively ($P = 0.013$; Table 2).

Side effects: The appearance of pruritus was noted in three children in the fentanyl group without requiring intervention because it was self-limiting. However, no child developed pruritus in the other groups. One child in the midazolam group and two children in the fentanyl and control groups had transient bradycardia that did not require medical treatment. Moreover, no episodes of hypoxia or respiratory depression were

Table 3. Comparison of side effects.

	Group F	Group M	Group C	P-value
Nausea & vomiting	4(13.3%)	1(3.3%)	2(6.7%)	0.338
pruritus	3(10%)	0 (0%)	0 (0%)	0.045 ‡
Headache	2(6.7%)	2(6.7%)	4(13.3%)	0.578
bradycardia	2(6.7%)	1(3.3%)	2(6.7%)	0.809
hypotension	3(10%)	2(6.7%)	3(10%)	0.872
Urinary retention	1 (3.3%)	0 (0%)	0 (0%)	0.364
shivering	6(20%)	8(26.7%)	7(23.3%)	0.830

Data presented as number (%)

‡ a significant difference was found between fentanyl group and the other two groups using chi square test

noted. Only one patient in the midazolam group suffered postoperative vomiting compared with two and four in the control and fentanyl groups without significant difference. Furthermore, no significant difference was noted between the three groups regarding other side effects (hypotension, urinary retention, and headache). None of the patients suffered from a neurological deficit (Table 3).

6. Discussion

This study shows that adding midazolam to bupivacaine, compared to placebo and fentanyl, decreased the frequency and intensity of pain and increased the time for first post-operative analgesic request in children undertaking infra-umbilical abdominal surgery with intrathecal analgesia in combination to general anesthesia.

This study is believed to be the first study to compare midazolam and fentanyl as neuraxial adjuvants with 0.5% hyperbaric bupivacaine in intrathecal analgesia in children. Moreover, very limited data are available on the use of intrathecal midazolam for post-operative pain relief in children. The appropriate intrathecal midazolam dose in children is still under investigation. The present study depended on previous studies in adults because of the lack of studies in intrathecal midazolam in children [15,22].

Consistent with previous studies on adults [15], the bupivacaine–midazolam combination produced extended postoperative analgesia without delaying the discharge from the recovery room or significant side effects. Moreover, intrathecal midazolam (1 mg dose) was used by Kulkarni et al. for adults. On the basis of this study, the midazolam dose for children was calculated as 0.5 mg.

Following the present study, previous studies have shown a dose-dependent effect of intrathecal midazolam on postoperative analgesia. However, these studies were conducted in adults. Kim et al. recorded that the addition of 1 or 2 mg of midazolam to intrathecal bupivacaine provides analgesia for approximately 2 and 4.5 h, respectively [23].

Intrathecal midazolam [24] and fentanyl [21] influence the properties of the spinal column block concerning the extension of sensory analgesia duration and the time to the first postoperative analgesic request in a dose-dependent manner with comparable hemodynamic stability. These doses of midazolam and fentanyl did not also cause clinically significant hemodynamic or respiratory changes. The discharge times from the PACU were also not significantly extended by any of them.

A significant elongation of the sensory block (the period from the sensory block after the surgical procedure, evaluated by the CHEOP value, to the patient's request for rescue analgesia or CHEOP value is >6) was noted. Patients who received midazolam or fentanyl as an adjuvant have a significantly higher rate of sensory block duration than the control group. This is because of the existence of benzodiazepine receptors in the spinal cord, which are activated when midazolam is injected intrathecally to prolong spinal anesthesia [25].

Midazolam produces intrathecal γ -mediated analgesia; the quality of which differs from that of the μ -opioid agonist fentanyl. Moreover, intrathecal midazolam's analgesic effects are due to its intrathecal interactions with intrathecal receptors that affect type A GABA receptors [26]. Intrathecal midazolam has also been proposed to be a cause of the release of an endogenous opioid that acts on the intrathecal delta receptors [27].

Niv et al. examined the histological and vascular lesions in spinal cord specimens from animals to determine the neurotoxic effects of intrathecal midazolam. Thus, they cautioned against using intrathecal midazolam in humans [28]. Subsequent studies in humans [29,30] found no adverse neurological symptoms in patients who received intrathecal midazolam. Consistent with these studies, the present study did not observe any significant adverse neurological effects in any patient until 1 month from the time of discharge. Thus, the use of low-dose preservative-free

midazolam (0.5 mg) thereby contributed to postoperative analgesia without leading to any neurotoxicity.

Different studies have found different sedation incidences after intrathecal midazolam. In the study by Talwar et al. [31], the incidence of sedation was higher in the IT fentanyl group than in the IT midazolam group. In the present study, no significant difference was noted in the incidence of sedation among the three groups. However, by contrast, Yegin et al. stated that prolonged analgesia with mild sedation in perianal cases may be the cause of sedation in their study because they used a higher dose of midazolam (5 mg) [32].

In addition to extending the analgesia duration, the quality of analgesia in the postoperative period was found to be better with midazolam (0.5 mg) and fentanyl (0.2 μ g/kg). This was also concomitant with a significantly increased postoperative pain-free period and a decreased need for rescue analgesics.

Evaluating blocking properties (i.e., the maximum level of the sensory block) and time to two dermatome analgesia regression are the main limitations of this study. In children, the pinprick method of assessing analgesia is problematic because it causes discomfort, pain, and restlessness. The second limitation is that the optimal dose of intrathecal midazolam in children has not been recognized. The present study uses 0.5 mg of midazolam consistent with previous studies in adults (1 mg). The third limitation is the assumption that both 0.2 μ g/kg of fentanyl and 0.5 mg of midazolam are equipotent and further studies are suggested to determine the equipotential dose ratio of fentanyl to midazolam. The last limitation may be the small sample size.

7. Conclusion

In the present study, intrathecal midazolam (0.5 mg) was superior to intrathecal fentanyl (0.2 μ g/kg) in increasing the duration of postoperative pain relief with lower postoperative pain scores and less incidences of adverse effects. Consequently, intrathecal midazolam can be used as an adjuvant to local anesthetics if fentanyl is not accessible or contraindicated.

Acknowledgments

The authors thank all pediatrician consultants, nurses, residents, and other personnel of the operative theater for their generous cooperation.

Disclosure statement

The authors declare that they have no conflicts of interest".

Funding

"The authors declare that they have never received any fund from any agency and the authors withstand the whole cost on their own expenses".

References

- [1] Abajian JC, Mellish RP, Browne AF, et al. Spinal anesthesia for surgery in the high-risk infant. *Anesthesia Analg.* 1984;63(3):359–362.
- [2] Parag K, Sharma M, Khandelwal H, et al. Intraoperative comparison and evaluation of intrathecal bupivacaine combined with clonidine versus fentanyl in children undergoing hernia repair or genital surgery: a prospective, randomized controlled trial. *Anesth Essays Res.* 2019;13(2):323.
- [3] Islam MA, Khanum E, Karim MR, et al. Effect of Spinal Anaesthesia in Children of 4-10 Years. *J Enam Med Col.* 2017;7(1):10–14.
- [4] Yallapragada SV, Vemuri NN, Shaik MS. Effect of adding clonidine to intrathecal bupivacaine on the quality of subarachnoid block: a prospective randomized double-blind study. *Anesth Essays Res.* 2016;10(3):451.
- [5] Gupta R, Verma R, Bogra J, et al. A comparative study of intrathecal dexmedetomidine and fentanyl as adjuvants to bupivacaine. *J Anaesthesiol Clin Pharmacol.* 2011;27(3):339.
- [6] Gupta K, Rastogi B, Gupta PK, et al. Intrathecal nalbuphine versus intrathecal fentanyl as adjuvant to 0.5% hyperbaric bupivacaine for orthopedic surgery of lower limbs under subarachnoid block: a comparative evaluation. *Indian J Pain.* 2016;30(2):90.
- [7] Vashishth T, Sharma G, Garg S, et al. A comparative study of nalbuphine and fentanyl with bupivacaine in spinal anaesthesia for lower abdomen and lower limb surgeries. *Nat J Med Dental Res.* 2016;4:93–100.
- [8] Bakshi U, Chatterjee S, Sengupta S, et al. Adjuvant Drugs In Central Neuraxial Analgesia-A Review. *Internet J Anesthesiol.* 2009;26(1).
- [9] Khezri MB, Ghasemi J, Mohammadi N. *Evaluation of the analgesic effect of ketamine as an additive to intrathecal bupivacaine in patients undergoing cesarean section.* *Acta Anaesthesiologica Taiwanica.* 2013;51(4):155–160.
- [10] Jain N, Mathur PR, Soni P, et al. A comparative clinical study of intrathecal bupivacaine 2.5 mg with dexmedetomidine 5 µg versus intrathecal bupivacaine 2.5 mg with fentanyl 25 µg on the duration of labor analgesia using combined spinal epidural technique. *J Obstetric Anaesth Crit Care.* 2019;9(1):24–29.
- [11] Jarineshin H, Fekrat F, Kargar Kermanshah A. Treatment of Postoperative Pain in Pediatric Operations: comparing the Efficiency of Bupivacaine, Bupivacaine-Dexmedetomidine and Bupivacaine-Fentanyl for Caudal Block. *Anesth Pain Med.* 2016;6(5):e39495.
- [12] Hasan SA. Effect of addition of intrathecal midazolam to 0.5% hyperbaric bupivacaine to prolong the post-operative analgesia in lower abdominal surgeries. *Int J Adv Med.* 2019;6(3):790.
- [13] Karbasfrushan A, Farhadi K, Amini-Saman J, et al. Effect of intrathecal midazolam in the severity of pain in cesarean section: a randomized controlled trail. *Iran Red Crescent Med J.* 2012;14(5):276.
- [14] Talebi H, Yazdi B, Alizadeh S, et al. Effects of combination of intrathecal lidocaine and two doses of intrathecal midazolam on post-operative pain in patients undergoing herniorrhaphy: a randomized controlled trial. *Pak J Biol Sci.* 2010;13(23):1156–1160.
- [15] Kulkarni M, Kurdi M, Itagimath S, et al. The role of intrathecal midazolam as an adjunct to bupivacaine in providing post-operative pain relief. *Int J Health Allied Sci.* 2012;1(4):231–234 10.4103/2278-344x.107852 10.4103/2278-344x.107852.
- [16] Fares KM, Mohamed SA, Abd El-Rahman AM, et al. Analgesic Effect of Intrathecal Fentanyl vs Dexmedetomidine as Adjuvants to Bupivacaine Following Abdominal Surgery for Cancer in Children, a Randomized Trial. *Pain Med.* 2020;21(11):2634–2641.
- [17] Aldrete JA, Kroulik D. A postanesthetic recovery score. *Anesthesia Analg.* 1970;49(6):924–934.
- [18] McGrath PJ. CHEOPS: a behavioral scale for rating post-operative pain in children. *Adv Pain Res Ther.* 1985;9:395.
- [19] Singh G, MA. Intrathecal block in caesarean section - Comparison between levobupivacaine-fentanyl and levobupivacaine. *Annals Int Medi Dental Res.* 2017;3:9–12.
- [20] Walsh TS, Ramsay P, Lapinlampi TP, et al. An assessment of the validity of spectral entropy as a measure of sedation state in mechanically ventilated critically ill patients. *Intensive Care Med.* 2008;34(2):308–315.
- [21] Duman A, Apiliogullari S, Duman, et al. Effects of intrathecal fentanyl on quality of spinal anesthesia in children undergoing inguinal hernia repair. *Pediatric Anesth.* 2010;20(6):530–536.
- [22] Shah VA, Contractor H. Efficacy and potency of intrathecally administered bupivacaine and bupivacaine with midazolam in lower limb surgery at Ahmadabad, India. *Indian J Clin Anaesthesia.* 2016;3(3):488–491.
- [23] Kim MH, Lee YM. *Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy.* *BJA. Br J Anaesth.* 2001;86(1):77–79.
- [24] Shadangi BK, Garg R, Pandey R, et al. Effects of intrathecal midazolam in spinal anaesthesia: a prospective randomised case control study. *Singapore Med J.* 2011;52(6):432–435.
- [25] Möhler H, Okada T. Benzodiazepine receptor: demonstration in the central nervous system. *Science.* 1977;198(4319):849–851.
- [26] Maeda A, Katafuchi T, Oba Y, et al. *Enhancement of GABAergic tonic currents by midazolam and noradrenaline in rat substantia gelatinosa neurons in vitro.* *Anesthesiology. J Am Soc Anesthesiologists.* 2010;113(2):429–437.
- [27] Goodchild C, Guo Z, Musgreave A, et al. Antinociception by intrathecal midazolam involves endogenous neurotransmitters acting at spinal cord delta opioid receptors. *Br J Anaesth.* 1996;77(6):758–763.
- [28] Niv D, Whitwam J, Loh L. Depression of nociceptive sympathetic reflexes by the intrathecal administration of midazolam. *Br J Anaesth.* 1983;55(6):541–547.
- [29] Tucker AP, Lai C, Nadeson R, et al. Intrathecal midazolam I: a cohort study investigating safety. *Anesthesia Analg.* 2004;98(6):1512–1520.
- [30] Valentine J, Lyons G, Bellamy M. The effect of intrathecal midazolam on post-operative pain. *Eur J Anaesthesiol.* 1996;13(6):589–593.

- [31] Talwar V, Rai A, Gandhi R, et al. Comparison of intrathecal midazolam and fentanyl added to bupivacaine for lower limb surgery. *J Anaesthesiol Clin Pharmacol*. 2008;24(4):447–450.
- [32] Yegin A, Sanli S, Dosemeci L, et al. The analgesic and sedative effects of intrathecal midazolam in perianal surgery. *Eur J Anaesthesiol*. 2004;21(8):658–662.