



2023

Section: Anesthesiology

Evaluation of Midazolam as an Adjuvant to Rectus Sheath Block for Postoperative Analgesia in Patients Undergoing Umbilical Hernia Repair

Ahmed Younes

Department of Anesthesiology, Intensive Care, and Pain Management, Faculty of Medicine, Al-Azhar University, Cairo, Egypt, ahmedyounes9664484@gmail.com

Ahmed Mahmoud M.M. Elgarhy

Department of Anesthesiology, Intensive Care, and Pain Management, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Emad Shaban

Department of Anesthesiology, Intensive Care, and Pain Management, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Follow this and additional works at: <https://aimj.researchcommons.org/journal>



Part of the [Medical Sciences Commons](#), [Obstetrics and Gynecology Commons](#), and the [Surgery Commons](#)

How to Cite This Article

Younes, Ahmed; Elgarhy, Ahmed Mahmoud M.M.; and Shaban, Emad (2023) "Evaluation of Midazolam as an Adjuvant to Rectus Sheath Block for Postoperative Analgesia in Patients Undergoing Umbilical Hernia Repair," *Al-Azhar International Medical Journal*: Vol. 4: Iss. 6, Article 28.

DOI: <https://doi.org/10.58675/2682-339X.1836>

This Original Article is brought to you for free and open access by Al-Azhar International Medical Journal. It has been accepted for inclusion in Al-Azhar International Medical Journal by an authorized editor of Al-Azhar International Medical Journal. For more information, please contact dryasserhelmy@gmail.com.

Evaluation of Midazolam as an Adjuvant to Rectus Sheath Block for Postoperative Analgesia in Patients Undergoing Umbilical Hernia Repair

Ahmed Younes*, Ahmed Mahmoud M.M. Elgarhy, Emad Shaban

Department of Anesthesiology, Intensive Care, and Pain Management, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Abstract

Background: Various adjuvants have been tried to improve quality and increase duration of local anesthetics during various nerve blocks. We aimed to evaluate the efficacy of midazolam as an adjunct for RS block to reduce the need for morphine, discomfort, nausea, and vomiting after surgery.

Patients and methods: 66 Cases undergoing umbilical hernia repair randomized into two groups Midazolam group 33 cases, received bilateral administration of bupivacaine 0.25% 20 ml, combined with 50 mcg/kg midazolam, and control group 33 cases, received the same anesthesia without addition of midazolam.

Results: Heart rate was comparable between groups and patients in the midazolam group exhibited lower MBP with no significant difference. The control group experienced higher morphine rescue analgesia than the midazolam. The 24-h morphine consumption was more declined among patients in the midazolam group. Static and dynamic VAS recordings were more declined in midazolam group against the control group. Cases in the midazolam group exhibited higher satisfaction score with lower Postoperative nausea and vomiting (PONV) ($P < 0.01$).

Conclusion: Midazolam administration as an adjunct to bupivacaine during rectus sheath block increased analgesic qualities, as demonstrated by lower VAS grades, lower postoperative morphine doses, and a longer time to first request of analgesia. Midazolam also showed antiemetic actions, and no major side effects were observed.

Keywords: Midazolam, Umbilical hernia repair, Analgesia, Rectus sheath block

1. Introduction

The sensory innervation to the central portion of the anterior abdominal wall is derived from the ventral rami of the last thoracic spinal nerves from T7 to T12. Anatomically, these sensory neurones travels anteriorly to traverse the rectus abdominis muscle and distribute between the muscle the posterior layer of the rectus sheath, where the local anaesthetic can be administered to obtain analgesia to the midline anterior abdominal wall. Anesthesia for these nerves is considered a plane block, therefore, a large volume of local anaesthetic is required to provide efficient pain control. Indeed, the inter-space between the rectus abdominis muscle and the posterior rectus sheath is

attributed to the non-fusion between the muscle insertion and the posterior sheath layer, allowing for cephalic spread of the local anaesthetic. Consequently, the supra- and infra-umbilical parts of the anterior abdominal wall are covered.

Regional nerve block for midline incision is deficient, whilst epidural blockade is optimal. Being an invasive procedure and associated with motor block, the application of epidural anaesthesia in midline incision is limited. Consequently, motor-sparing regional anesthesia techniques are recommended to take the advantages of early mobilization and enhanced recovery. Rectus sheath block is proposed as an optimal alternative to epidural anaesthesia in umbilical hernia surgery. Multiple adjuncts have been added to the local anaesthetic in regional

Accepted 27 December 2022.
Available online 20 November 2023

* Corresponding author at: Department of Anesthesiology, Intensive Care, and Pain Management, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.
E-mail address: ahmedyounes9664484@gmail.com (A. Younes).

<https://doi.org/10.58675/2682-339X.1836>

2682-339X/© 2023 The author. Published by Al-Azhar University, Faculty of Medicine. This is an open access article under the CC BY-SA 4.0 license (<https://creativecommons.org/licenses/by-sa/4.0/>).

nerve blocks, including opioids, and dexamethasone. Midazolam, when administered perineurally, may potentiate and prolong analgesia of the local anaesthetic. Indeed, GABA-A receptors is the site of action of midazolam, and found in the peripheral neurons. Nevertheless, little evidence is known on the outcome of perineural midazolam adjunct administration to the local anaesthetic. The current study designed to assess the effectiveness of midazolam as an adjunct in combination with the local anaesthetic in the treatment of RS block. We hypothesized that employing midazolam as an adjunct for RS block would reduce the need for morphine, discomfort, nausea, and vomiting after surgery (PONV).

2. Patients and methods

2.1. Ethical approval

66 Cases enrolled after receiving individual informed consent. Approval from Al-Azhar University ethics board is also obtained.

2.2. Study design and sampling

Sample size was calculated using MedCalc program version 11.3.0.0. According to *Kartalov et al., 2017*, who stated in his study that morphine intake in the 24 h following the procedure was reduced in group II (mean = 3.731.41) than in group I (mean = 8.8).¹ Adjusting the confidence interval to 95%; power 90% and ratio between groups to 1:1; a sample of 60 cases was found reliable. Estimating a dropout ratio of 5%, we finally included 66 patients (33 patients in each group). Patients were randomized using a computerized random number generator. Midazolam = 33 cases, received bilateral administration of bupivacaine 0.25% 20 ml, combined with 50 mcg/kg midazolam, and control group = 33 cases, received the same anesthesia without addition of midazolam.

2.3. Eligibility criteria

Patients of both sexes, aged 21–60 years, with ASA I-II and a BMI of 30 kg/m² enrolled. Patient refusal, local infection, coagulopathies, and a history of analgesic use were all exclusion factors.

2.4. Procedure

Prior to the intervention, all patients in this trial underwent clinical, laboratory, and imaging exams. When the patients came in the operating room, they

were exposed to basic monitoring before being sedated. 0.5 mg/kg Atracurium to allow for endotracheal intubation and artificial breathing. To relax the muscles, 0.1 mg/kg atracurium was administered during the surgery. To maintain anaesthesia, sevoflurane 2% inhalation anaesthesia and muscle relaxants were utilized.

2.5. Rectus sheath block

A linear ultrasound probe (Sonosite Nanomaxx) was considered for visualization of the sonoanatomy. The needle was then introduced between the posterior layer of the sheath and the muscle to infiltrate the local anaesthetic solution in this plane. The anesthetic mixture is composed of 20 ml of 0.25% bupivacaine hydrochloride (SUNNYPIVACAINE 100MG/20 ML, Sunny Pharmaceutical, Cairo, Egypt) with or without midazolam 50 mcg/kg, according to the patients' allocation.

2.6. Outcome assessment

The information was gathered by well-trained medical experts who were unaware of the research participants or group assignment. The outcome was evaluated at baseline, 2, 4, 8, 16, 20, and 24 h after surgery. Age, gender, BMI, and operation length were among the patient demographics. The pain amplitude was recorded using the visual analogue scale (VAS). The number of individuals who needed postoperative morphine, as well as the total amount of morphine taken within the first 24 h, were also recorded. The block's duration was determined. Satisfaction was measured using a four-point scale (1, excellent; 2, good; 3, fair; 4, poor).

2.7. Postoperative analgesic regimen

All trial participants received an intravenous infusion of paracetamol 15 mg/kg every 8 h. Patients with a VAS greater than 3 were given a titration of 2 mg intravenous morphine every 10 min until their VAS was equal to or less than 3, as long as their respiration rate was greater than 10 breaths per minute. Cases with a VAS score of 3 or above after three consecutive doses of IV morphine 2 mg are considered unsuccessful.

2.8. Statistical analysis

SPSS version 23.0 considered for analysis. Presentation was based on the type, normality and distribution of the variables. Kolmogorov test was

first applied. Normally distributed variables, explicated mean and standard deviation, whilst non-normal data explicated median and IQR. The Mann Whitney U test and the student-t test were mentioned in this study for inter-group analysis regarding the non-parametric and parametric numerical variables respectively. In addition, categorical variables were analysed using the Chi-square test. A point of 0.05 was set as the significant level.

3. Results

3.1. Patient demographics

This trial comprised 66 cases who were assigned to one of two equal groups at random: midazolam or control. Fig. 1 depicts a flow diagram of the design process (1). In terms of age, gender, and BMI, there were no significant distinctions between groups (Table 1).

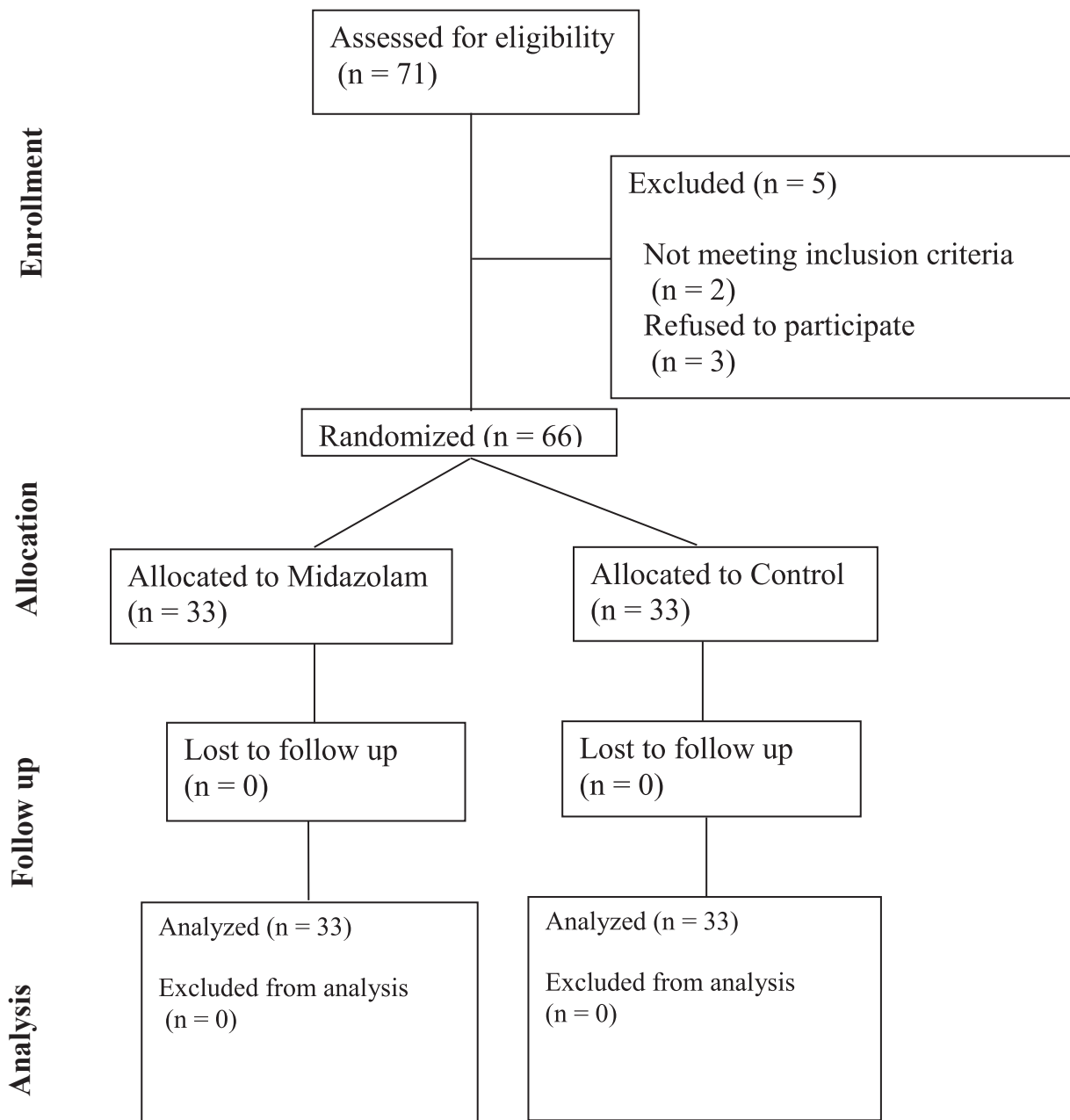


Fig. 1. CONSORT flow diagram.

Table 1. Comparison between both groups according to the baseline and demographic characteristics.

Demographic data	Midazolam (n = 33)	Control (n = 33)	P value
Age (years)	32.5 ± 8.46	31.28 ± 7.61	0.061
Sex n (%)			
Male	13 (39.4)	11 (33.3)	0.538
Female	20 (60.6)	22 (66.7)	
BMI (kg/m ²)	23.3 ± 2.67	24.8 ± 2.57	0.679
ASA physical status n (%)			
ASA I	12 (36.4)	14 (42.4)	0.278
ASA II	21 (63.6)	19 (57.6)	
Duration of surgery (min)	83.8 ± 13	79.2 ± 9.5	0.471

Abbreviations; (ASA, American Society of Anesthesiology; BMI, Body Mass Index).

3.2. Assessment of hemodynamic stability

No significant distinction in heart rate between the comparison arms at the beginning. After skin incision, the heart rate with midazolam was significantly declined more than the control arm. Furthermore, the heart rate was measured two, four, eight, sixteen, twenty, and 24 h after hernia, without significant distinctions reported in the comparison arms, as shown in Table 2. In addition, patients in the midazolam group exhibited lower MBP recordings, however this variation did not reach significance (Table 3).

Table 2. Comparison between studied groups according to the heart rate (beat/min).

HR (beat/min)	Midazolam (n = 33)	Control (n = 33)	P value
Baseline	74.77 ± 6.47	72.69 ± 6.15	0.03
After incision	76.30 ± 9.38	80.97 ± 7.91	<0.01
After 2 h	81.54 ± 11.67	83.20 ± 7.28	0.243
After 4 h	85.06 ± 10.93	87.37 ± 10.38	0.311
After 8 h	78.97 ± 9.96	73.03 ± 7.02	0.141
After 16 h	80.23 ± 11.27	81.67 ± 10.14	0.417
After 20 h	81.43 ± 10.13	83.94 ± 8.38	0.272
After 24 h	79.77 ± 11.36	79.86 ± 13.7	0.115

Abbreviations; (HR, heart rate).

Table 3. Comparison between studied groups according to mean blood pressure (MBP) (mm Hg).

MBP (mm Hg)	Midazolam (n = 33)	Control (n = 33)	P value
Baseline	78.24 ± 3.3	72.86 ± 5.2	0.31
After incision	81.41 ± 6.13	87.67 ± 3.8	0.811
After 2 h	75.48 ± 4.3	79.61 ± 5.81	0.072
After 4 h	79.10 ± 3.70	81.44 ± 4.14	0.192
After 8 h	84.19 ± 4.1	83.13 ± 6.42	0.272
After 16 h	80.71 ± 4.15	77.28 ± 7.45	0.153
After 20 h	80.71 ± 4.15	77.28 ± 7.45	0.351
After 24 h	71.48 ± 5.67	75.88 ± 4.97	0.139

Table 4. Comparison between the two groups according to the number of postoperative morphine rescue analgesia doses.

Number of Morphine doses (2 mg)	Midazolam (n = 11)	Control (n = 14)	P value
1 dose	8 (72.7)	9 (64.3)	0.006
2 doses	3 (27.3)	3 (21.4)	
3 doses	0 (0)	2 (14.3)	
The cumulative morphine consumption mg (24 h)	28	42	0.01

3.3. Assessment of the analgesic efficacy and requirements

The control arm experienced higher morphine rescue analgesia than the midazolam comparison arm (14 vs. 11, $P = 0.028$). In the midazolam group, 27.3% of the patients required more than one dose of morphine to keep VAS ≤ 3 , compared to 35.7% in control arm ($P = 0.006$). Moreover, the 24-h morphine consumption was more declined among patients in the midazolam group (Midazolam, 28 vs. Control, 42 mg, $P = 0.01$) (Table 4). When opposed to the control arm, the period from initial request for analgesia was considerably lengthier in the midazolam against control arms (455 vs. 346 min, $P = 0.02$) respectively. Moreover, static VAS recordings were more declined in midazolam arm, against the control arm at 4, 6, 8, and 12 h postoperatively (Fig. 2). The dynamic VAS score was significantly demoted in the midazolam group at 6, 8, and 12 h postoperatively (Fig. 3). Importantly, 63.6% reported excellent satisfaction in the midazolam arm, against 36.4% in control arm (Table 5).

3.4. Comparison of the complications in the study groups

No serious complications were reported in both groups, like respiratory depression, nerve injury, hematoma formation, systemic toxicity of local anesthetics, and intravascular injection. In terms of pruritus, there was no substantial distinction in the comparison arms ($P > 0.05$). Regarding Postoperative nausea and vomiting (PONV), it was less frequently encountered in midazolam arm, against the control arm (1 vs. 7, $P = 0.01$) (Fig. 4).

4. Discussion

According to this trial, the addition of midazolam to bupivacaine for RS block considerably reduced postoperative morphine dosages. The VAS pain levels in the midazolam arm were more declined after surgery, and the period to initial request of analgesia was correspondingly longer, indicating

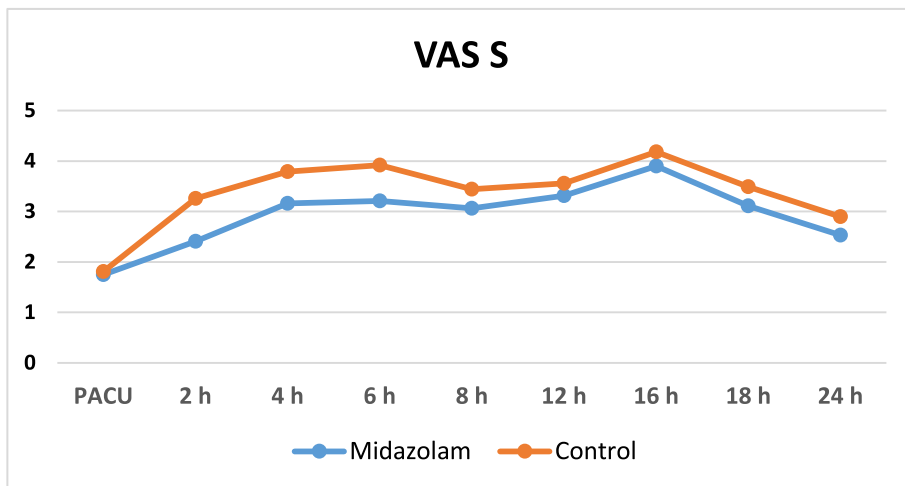


Fig. 2. Trends of static VAS score in both groups.

more effective analgesia. Furthermore, failure was more frequently seen in the bupivacaine-only group, despite the fact that cases in midazolam group reported higher levels of satisfaction.

Using midazolam in tandem with local anaesthesia during peripheral nerve block boosted analgesic properties, according to many investigations. Ammar et al. found that, in addition to bupivacaine, midazolam provided adjuvant analgesia, as demonstrated by fewer morphine usage, lengthier analgesia endurance and a reduced VAS grade. 7 According to Jarbo et al., experiment, in which 50 mcg/kg of midazolam was administered adjunct with bupivacaine in supraclavicular brachial block. The authors found that there was a faster induction of sensory and motor blocking, pain relief, and analgesia with no adverse effects.² After discovering advantages from intravenous supplementation, Xu

Table 5. Comparison between both groups according to patient satisfaction.

Parameters	Midazolam (n = 33)	Control (n = 33)	P value
Excellent	21 (63.6)	12 (36.4)	<0.001
Good	7 (21.2)	10 (30.3)	
Fair	5 (15.2)	7 (21.2)	
Poor	0	4 (12.1)	

et al., highly suggested midazolam auxiliary application in nerve block for upper extremity surgery.³

Desai et al., in contrast to our findings, considered midazolam effect as inconsistent, owing to conflicting data regarding its advantages over systemic distribution. Finally, the authors came to the conclusion that midazolam should not be administered intravenously. 3 Furthermore, in children with unilateral inguinal herniorrhaphy, Baris et al. discovered that adding midazolam (50 g/kg) to

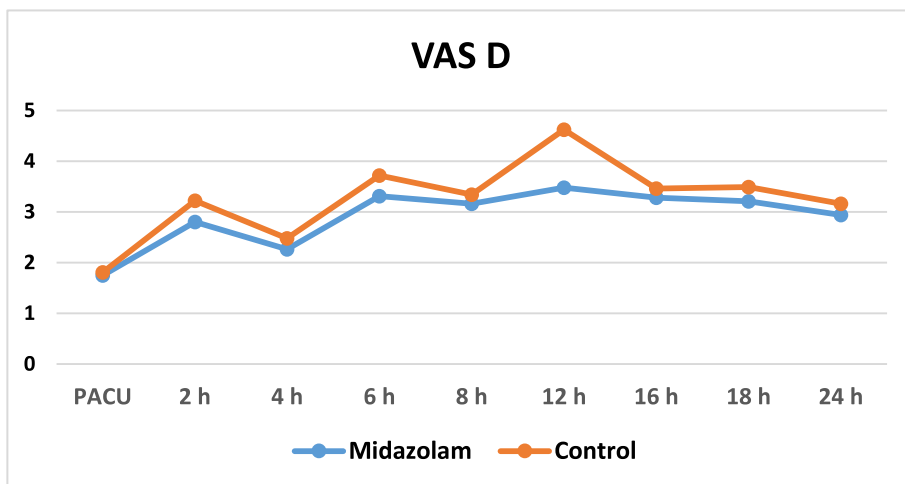


Fig. 3. Trends of dynamic VAS score in both groups.

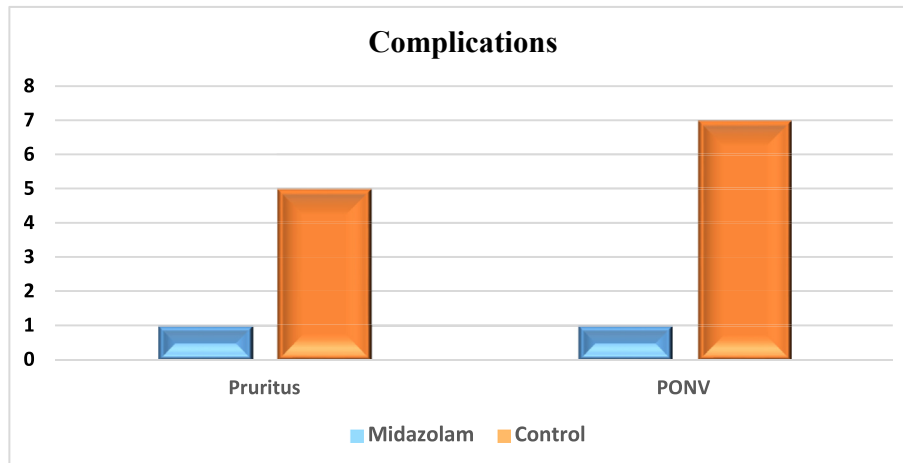


Fig. 4. Comparison between groups regarding complications.

bupivacaine in caudal block produced no further analgesic advantages over bupivacaine alone.⁴ This conflicting conclusion may be based on the argument that with such a less painful therapy, bupivacaine 0.25% alone may offer enough and sufficient pain control, concealing the action of the additives. Furthermore, Pain assessment in children might be problematic since caregivers could be unprepared to appropriately assess their child's discomfort.

Midazolam is a GABA agonist. GABA receptors can be found in peripheral neurons. The effect of midazolam on the translocator protein is hypothesised to produce nerve block (TPSO).⁵ Midazolam works on peripheral g-aminobutyric acid or GABA-A receptors, which are significant in midazolam's sedative action.³ Furthermore, its effect on the limbic system lessens unpleasant sensations like as concern and dread, which lowers the chance of cardiovascular and cerebrovascular events.³

4.1. PONV and complications associated with RSB

Nausea and vomiting after umbilical hernia surgery can be induced by a variety of factors, including inhalational anaesthesia, opioid analgesics, or surgical manipulations. The current investigation revealed that prevalence of PONV was considerably reduced in midazolam arm against the control arm. Furthermore, Ammar et al. investigated combining midazolam with RS block in cases of umbilical hernia surgery.⁶ They observed that the group given midazolam had considerably lower incidence of PONV and pruritus. Furthermore, El kenany et al. demonstrated that midazolam had equivalent antiemetic effects when paired with bupivacaine in transversus abdominis plane block.⁷ Midazolam's antiemetic function is not well

explored. Its anxiolytic impact, as well as its potential to boost adenosine action by limiting reuptake of adenosine in chemoreceptor trigger zone, may be connected to a lower occurrence of PONV. Because midazolam binds the GABA receptor, the antiemetic effect might be attributed to a reduction in 5-HT secretion.⁸ Preoperative anxiety, according to Van den Bosch et al., may impact the incidence rate of PONV.⁹ As a result, reducing anxiety may aid in the prevention of PONV.

4.2. Midazolam and neurotoxicity

Midazolam's potential neurotoxicity is the most significant concern of using it as an adjuvant in nerve block.⁷ Numerous animal studies indicate that intravenous midazolam administration is neurotoxic, and that midazolam significantly enhances neuronal cytotoxicity when combined with LA.¹⁰ Midazolam had no neurotoxicity in vitro or in vivo when used with a clonidine–buprenorphine–dexamethasone combination that does not contain any LA.¹¹ Furthermore, according to a 2015 study, midazolam-induced neurotoxicity may be distinguished, with particular activation of the translocator protein (TPSO) lowering the risk of neurotoxicity.⁵ Midazolam as an adjunct in nerve block is currently restricted to a set dosage with proven local anaesthetic until more research is completed.

4.3. Conclusion

This study found that midazolam administration as an adjunct to bupivacaine during rectus sheath block increased analgesic qualities, as demonstrated by lower VAS grades, lower postoperative morphine doses, and a longer time to first request of analgesia.

Midazolam also showed antiemetic actions, and no major side effects were observed. More research is required to evaluate the possible neurotoxicity of adding local anaesthesia to peripheral nerve blocks.

Authors' contribution

The authors equally contributed in this study.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

There are no conflicts of interest.

References

1. Kartalov A, Jankulovski N, Kuzmanovska B, Zdravkovska M, Shosholcheva M, Tolevska M, et al. The effect of Rectus Sheath block as a supplement of general anesthesia on postoperative analgesia in adult patient undergoing umbilical hernia repair. *Pril (Makedon Akad Nauk Umet Odd Med Nauki)*. 2017;38:135–142. <https://doi.org/10.2478/prilozi-2018-0014>.
2. Jarbo K, Batra YK, Panda NB. Brachial plexus block with midazolam and bupivacaine improves analgesia. *Can J Anaesth*. 2005;52:822–826. <https://doi.org/10.1007/BF03021776>.
3. Xu X, Hu X, Han Y, Zhuang X, Tang R, Xu Y. Application of Midazolam injection in patients with intraoperative nerve block anesthesia and sedation assisted by imaging guidance. *World Neurosurg*. 2021;149:453–460. <https://doi.org/10.1016/j.wneu.2020.11.101>.
4. Baris S, Karakaya D, Kelsaka E, Güldogus F, Arıturk E, Tür A. Comparison of fentanyl-bupivacaine or midazolam-bupivacaine mixtures with plain bupivacaine for caudal anaesthesia in children. *Paediatr Anaesth*. 2003;13:126–131. <https://doi.org/10.1046/j.1460-9592.2003.00979.x>.
5. Yılmaz E, Hough KA, Gebhart GF, Williams BA, Gold MS. Mechanisms underlying midazolam-induced peripheral nerve block and neurotoxicity. *Reg Anesth Pain Med*. 2014;39:525–533. <https://doi.org/10.1097/AAP.0000000000000176>.
6. Ammar A, Mahmoud K, Kasemy Z. Effect of adding midazolam to bupivacaine during rectus sheath block: a randomized controlled trial. *Acta Anaesthesiol Scand*. 2018;62:857–862. <https://doi.org/10.1111/aas.13090>.
7. El Kenany S, Elshehawi ME, Farid AM, Eid MI. Efficacy of adding midazolam to bupivacaine for transversus abdominis plane block on postoperative analgesia after hysterectomy: a randomized controlled study. *Anesth Essays Res*. 2019;13:522–527. https://doi.org/10.4103/aer.AER_95_19.
8. Kim DS, Koo GH, Kang H, Baek CW, Jung YH, Woo YC, et al. The antiemetic effect of midazolam or/and ondansetron added to intravenous patient controlled analgesia in patients of pelviscopic surgery. *Korean J Anesthesiol*. 2012;62:343–349. <https://doi.org/10.4097/kjae.2012.62.4.343>.
9. Van den Bosch JE, Moons KG, Bonsel GJ, Kalkman CJ. Does measurement of preoperative anxiety have added value for predicting postoperative nausea and vomiting? *Anesth Analg*. 2005;100:1525–1532. <https://doi.org/10.1213/01.ANE.0000149325.20542.D4>.
10. Kirksey MA, Haskins SC, Cheng J, Liu SS. Local anesthetic peripheral nerve block adjuvants for prolongation of analgesia: a systematic qualitative review. *PLoS One*. 2015;10:e0137312. <https://doi.org/10.1371/journal.pone.0137312>.
11. Knight JB, Schott NJ, Kentor ML, Williams BA. Neurotoxicity of common peripheral nerve block adjuvants. *Curr Opin Anaesthesiol*. 2015;28:598–604. <https://doi.org/10.1097/ACO.0000000000000222>.