Randomised Controlled Trial

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Comparison of the effect of use of preoperative mexiletine tablets and control on reducing postoperative pain in patients undergoing abdominal surgery

Masoud Saadat Fakhr, MD[a], Abolfazl Jadididavodabadi, MD[a], Kiana Rezvanfar, MD[a], Zahra Amini, MD[a], Koosha Amiri, MD[a], Mahnaz Narimani Zamanabadi, MD[b,*]

Objective: Postoperative pain is a major concern for patients and healthcare providers following abdominal surgery. This study aimed to compare the effectiveness of mexiletine in reducing postoperative pain in patients undergoing abdominal surgery.
Methods: In this double-blind randomized controlled trial, 34 patients were divided into two groups. One group received 600 mg of mexiletine tablets, while the other group received vitamin C tablets (control) two hours before surgery. Postoperative pain levels were assessed at 6, 12, and 24 h by using the Visual Analog Scale (VAS). Additionally, the amount of narcotics received within the first 24 h after surgery was recorded.
Results: The results showed that the average postoperative pain score in patients who received mexiletine was significantly lower than in those who received vitamin C tablets ($P < 0.001$). Furthermore, the average amount of narcotics received after surgery was significantly lower in the mexiletine group compared to the control group ($P = 0.03$). Pain scores at 6, 12, and 24 h after surgery were also significantly lower in the mexiletine group ($P < 0.001$).
Conclusion: Mexiletine was effective in reducing postoperative pain and the need for narcotics in patients undergoing abdominal surgery. This study highlights the potential of mexiletine as a valuable preoperative intervention for postoperative pain management.

Keywords: abdominal surgery, mexiletine, pain, surgery

Introduction

Postoperative pain is a common consequence of abdominal surgery, and it can result in both short- and long-term issues[1,2]. Furthermore, effective pain management is critical to accelerate recovery and reduce the risk of postoperative complications[3], whereas Inadequate pain management could lead to prolonged hospital stays, escalated healthcare costs, and compromised patient outcomes[4]. Thus, strategies to lessen postoperative pain could help patients recover faster initially and improve their long-term health outcomes[5]. Emerging evidence suggests that interventions introduced before surgery could have a substantial impact on postoperative pain[6]. Progressive approaches such as IV acetaminophen, NSAIDs, magnesium, ketamine, dexmedetomidine, and improved pain control techniques are replacing traditional opioid-focused postoperative pain management[7,8]. While opioids are effective, they bring with them concerns about tolerance, dependence, and adverse effects[9].

Respiratory depression, sedation, nausea, vomiting, drug interactions, allergic responses, cognitive impairment, and recovery delays are only a few of the side effects of opium use in postoperative surgery[10,11]. Mexiletine, an oral class IB antiarrhythmic drug, has demonstrated efficacy in the treatment of a variety of disorders beyond cardiac care[12]. Mexiletine can be effective in treating neuropathic pain, amyotrophic lateral sclerosis, and diabetic neuropathy[13,14]. The expansion of mexiletine's applications is noteworthy because its ability to block sodium channels could potentially be used to modulate pain perception[15,16]. Mexiletine

HIGHLIGHTS

- Postoperative pain is a major concern for patients and healthcare providers following abdominal surgery.
- Mexiletine were effective in reducing postoperative pain and the need for narcotics in patients undergoing abdominal surgery.
- -This study highlights the potential of mexiletine as a valuable preoperative intervention for postoperative pain management.

[a]Faculty of Medicine, Tehran Medical Sciences Branch, Islamic Azad University and [b]Department of Anesthesiology, Faculty of Medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

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*Corresponding author. Address: Shohada-e Hesarak Blvd., University Square, end of Shahid Sattari Highway (North), Central Organization of Islamic Azad University, Tehran 1477893780, Iran. Tel.: +98 214 735 202 30. E-mail: mahnaznarimani@yahoo.com (M. Narimani Zamanabadi).

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has the potential to be an effective preoperative intervention for postoperative pain management[17,18].

The mechanism of action through which Mexiletine exerts its analgesic effects involves its ability to block voltage-gated sodium channels: Sodium Channel Blockade, Reduction of Ectopic Discharges, Modulation of Central Sensitization and Anti-inflammatory Effects[19,20].

However, its role in pain management remains is still inadequate[21,22]. This study will compare mexiletine tablets to control the reduction of postoperative pain after abdominal surgery. The findings of this study will contribute to improving pain management strategies and patient outcomes.

Method

This randomized clinical trial was conducted in hospitals affiliated with Islamic Azad University, Tehran Medical Branch in the year 2021–2022. After obtaining written and informed consent to participate in the study from ASA I, and II patients who were candidates for elective abdominal surgery [Total Abdominal Hysterectomy (TAH)], patients were divided into two groups based on an online random number table. To ensure double blinding in this study, the medications used by the surgical ward nurse were divided into two groups, A/B, so that the researcher and participants were unaware of the type of medication received.

One group was administered a 600 mg mexiletine tablet, and the other group was given a vitamin C tablet along with 50 mg of water 2 h before entering the operating room.

After patients entered the operating room, they underwent general anesthesia with the same medications: propofol at a dose of 2 mg/kg of patient weight or sodium thiopental at a dose of 5 mg/kg of patient weight, midazolam at a dose of 0.01 mg/kg of patient weight, fentanyl at a dose of 2–3 mg/kg of patient weight, and atracurium at a dose of 0.5 mg/kg of patient weight for induction. For maintenance, isoflurane at a concentration of 1–2% and oxygen with nitrous oxide (50/50) were used.

During surgery, fentanyl at a dose of 1 μg/kg of patient weight per hour was repeated, and then at the end of the surgery, muscle relaxant reversal was performed using a mixture of neostigmine and atropine.

Then, after surgery and at 6, 12, and 24 h post-operation, the patient's pain levels were assessed based on the Visual Analog Scale (VAS), and if VAS was greater than 5, patients were injected with 30–50 mg of pethidine intravenously. At the end of the first day, the amount of analgesic consumed was recorded in a questionnaire by a trained nurse.

The sample size was calculated using the statistical software G-Power. Since a similar study was not found to determine the effect size, considering an effect size of 0.4, a Type I error rate of 0.05, and a power of %80, a total of 17 samples per group, totaling 34 samples, were included in the study.

Inclusion criteria for the study: abdominal surgery (such as hysterectomy, myomectomy, colectomy, vasectomy, laparoscopy, and ovarian cyst removal), age between 15 and 75 years, signing a personal consent form to participate in the study, ASA I–II, No history of drug abuse or alcohol consumption, and elective nature of the surgical procedure.

Criteria for exclusion: decreased level of consciousness, hemodynamic instability, unusual bleeding during surgery, duration of surgery exceeding 4 h, cardiopulmonary arrest, and patient withdrawal from further participation in the research.

The sampling method in this study was simple random sampling. Data collection in this study was conducted in the field.

Data collection tools: data collection form, patient records, VAS scale:

Data analysis

For data analysis in this study, SPSS version 26 software was utilized. Quantitative data results were presented as mean and standard deviation and visualized through charts and tables. Additionally, qualitative data results were presented in terms of frequency and percentage, also visualized through charts and tables. The Shapiro–Wilk test was employed to assess the normality of quantitative data. Based on its results, either the *t*-test or the Mann–Whitney U test was used. The Kruskal–Wallis test was utilized for the analysis of qualitative variables. To compare changes in the VAS scale after surgery, repeated measures ANOVA was employed. Moreover, for comparing quantitative data across more than two qualitative groups, the ANOVA test was utilized. A significant difference was defined as a P value less than 0.05.

This randomized controlled trial study was approved by the Ethics Committee of the Islamic Azad University, Tehran Medical Branch (IR.IAU.TMU.REC.1401.166) and registered in the Iranian Registry of Clinical Trials (IRCT20230405057824N1).

Research Registry UIN: 9448 research registry.

The work has been reported in line with the CONSORT flowchart and checklist criteria (Fig. 1)[23].

Result

The demographic characteristics of the 34 participants are summarized as follows: Patients' ages ranged from 18 to 67, with an average age of 46.7 ± 10.8 years.

The average duration of surgery was 119.1 ± 30.8 min, with a range of 60–180 min. Postoperative pain scores were recorded at various intervals: 1 h after surgery (7.5 ± 0.7), 6 h after surgery (6.4 ± 1.1), 12 h after surgery (5.6 ± 1.2), and 24 h after surgery (4.5 ± 0.9).

The average amount of narcotics received in the first 24 h post-surgery was 14 ± 36 mg. 5 (14.7%) male and 29 (85.3%) females made up the participants.

The average postoperative pain score in patients who received Mexiletine was significantly lower (7.1) compared to those who received the control (8 ± 0.1) ($P < 0.001$) (Table 1).

The Shapiro–Wilk test results in the table allow us to draw the following conclusion: The distribution of age-related data is likely normal because it is not statistically significant ($P > 0.05$).

The distributions of other quantitative data related to the amount of narcotics received after surgery, duration of surgery, VAS scores 1 h after surgery, 6 h after, 12 h after, and 24 h after surgery are significant ($P < 0.05$), indicating these data are likely not normally distributed (Table 2).

Using the precise Fisher's test, it was determined that in the group receiving Mexiletine, 3 individuals (17.7%) were male and 14 individuals (82.3%) were female, and in the group receiving Vitamin C, 2 individuals (17.8%) were male and 15 individuals (88.2%) were female ($P = 0.1$).

Using the independent *t*-test, it was determined that the mean age of patients who received Mexiletine was 47.2 ± 2.9 years, and

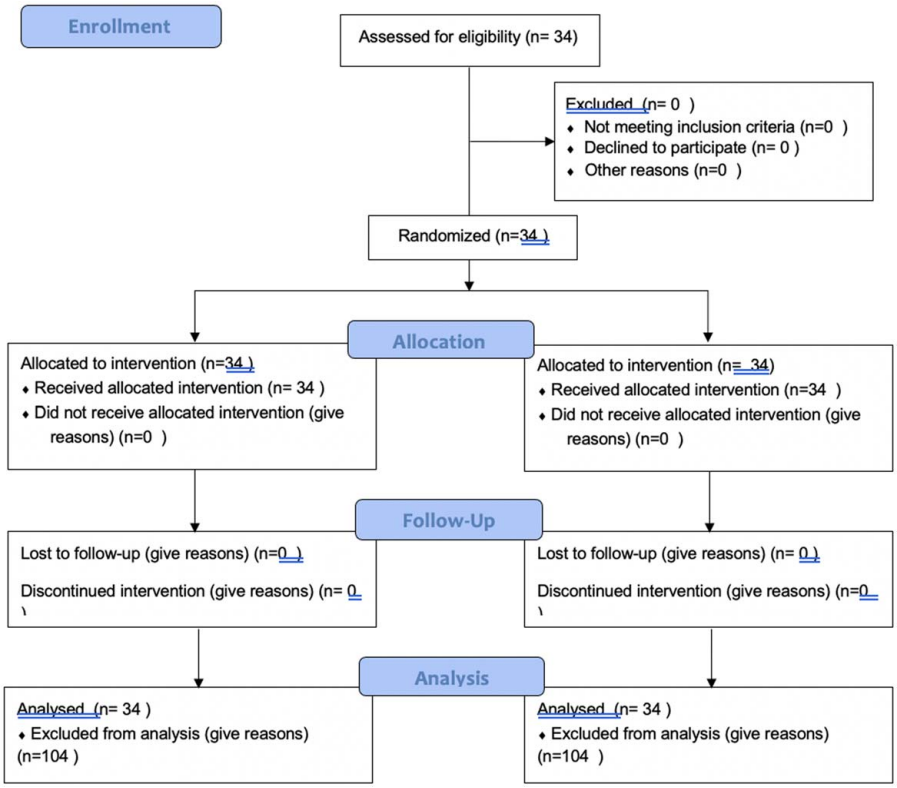

Figure 1. Consort flow diagram.

the patients who received vitamin C were 46.1 ± 2.2 years ($P = 0.78$).

Using the Mann–Whitney test, it was determined that the mean duration of surgical procedure for patients who received Mexiletine was 111.1 ± 7.6 min, and for patients who received vitamin C, it was 127 ± 7 min ($P = 0.08$).

Utilizing the Mann–Whitney test, we found that 6 h post-surgery, patients given Mexiletine had a mean pain score of 5.6 ± 0.1, whereas those given vitamin C had a score of 7.2 ± 0.2 ($P < 0.001$). At 12 h post-surgery, Mexiletine recipients had a mean pain score of 4.7 ± 0.1, while vitamin C recipients had a score of 6.6 ± 0.1 ($P < 0.001$). Additionally, at 24 h post-surgery, patients treated with Mexiletine had a mean pain score of 3.9 ± 0.2, whereas those given vitamin C had a score of 5.1 ± 0.1 ($P < 0.001$).

Furthermore, the Mann–Whitney test revealed that the average amount of narcotics received after the surgery was significantly lower in the Mexiletine group (30.8 ± 2.6 mg) compared to the control group (41.1 ± 3.6 mg) ($P = 0.03$) (Table 3).

At 6 and 12 h after surgery, the pain scores were significantly lower in the Mexiletine group compared to the control group ($P < 0.001$).

At 24 h post-surgery, the pain scores were also significantly lower in the Mexiletine group (3.9 ± 0.2) compared to the control group (5.1 ± 0.1) ($P < 0.001$).

Over the four examined periods, there was a significant change in the pain intensity scores (P 0.001).

Additionally, there was significant variation in the alterations in pain intensity evaluations between the Mexiletine and control groups ($P = 0.024$).

The graph in completing the above tables illustrates that the pain intensity score in the two groups has decreased over time in the four measured intervals (Fig. 2).

Initial post-surgery pain was higher in the vitamin C group than in the Mexiletine group.

At the 6-h post-surgery assessment, pain decreased in both groups.

By the 12-h assessment, pain had decreased in both Mexiletine and vitamin C groups.

Pain also decreased in both groups after 24 h.

Mexiletine group showed greater pain reduction after 24 h compared to the vitamin C group.

Table 1

Comparison of demographic and clinical characteristics between groups

Parameter	Mexiletine	Vitamin C	*P*
Sex, *N* (%)	Male: 3 (17.7) Female: 14 (82.3)	Male: 2 (17.8) Female: 15 (88.2)	0.1
Age (year)	47.2 ± 2.9	46.1 ± 2.2	0.78
Duration of surgery (min)	111.1 ± 7.6	127 ± 7	0.08
VAS score after surgery	7.1	8 ± 0.1	< 0.001

VAS, Visual Analog Scale.

Discussion

There is a growing emphasis on the use of pre-surgical interventions and non-opioid analgesics to improve outcomes after

Table 2

Quantitative data distribution

		Kolmogorov–Smirnova			Shapiro–Wilk		
Test	**Group**	**Statistic**	**df**	**Sig.**	**Statistic**	**df**	**Sig.**
Duration of surgery	Vitamin C	0.302	17	0.000	0.849	17	0.010
	Mexiletine	0.279	17	0.001	0.876	17	0.027
Narcotics amount	Vitamin C	0.426	17	0.000	0.630	17	0.000
	Mexiletine	0.469	17	0.000	0.533	17	0.000
Pain after surgery	Vitamin C	0.237	17	0.012	0.819	17	0.004
	Mexiletine	0.521	17	0.000	0.385	17	0.000
Pain 6 h after	Vitamin C	0.234	17	0.014	0.891	17	0.048
	Mexiletine	0.292	17	0.000	0.776	17	0.001
Pain 12 h after	Vitamin C	0.379	17	0.000	0.765	17	0.001
	Mexiletine	0.260	17	0.003	0.789	17	0.001
Pain 24 h after	Vitamin C	0.224	17	0.024	0.812	17	0.003
	Mexiletine	0.295	17	0.000	0.825	17	0.004
Age	Vitamin C	0.155	17	0.200*	0.960	17	0.635
	Mexiletine	0.134	17	0.200*	0.964	17	0.701

Sig., significance.

surgery[24,25]. This is in response to concerns about opioid tolerance, addiction, and side effects[5–7].

Researchers have been exploring alternative approaches to pain management that reduce the reliance on opioids and their associated drawbacks[26]. This study investigated the efficacy of administering mexiletine tablets to patients before abdominal surgery to alleviate postoperative pain and reduce the need for opioid-based pain relief medication.

The findings of the study provide clinically significant evidence that mexiletine has a clear advantage over control in reducing postoperative pain. Those who received Mexiletine exhibited significantly reduced postoperative pain scores compared to those who received a control. Furthermore, the Mexiletine group required substantially less pain relief medication, emphasizing the potential of Mexiletine to effectively manage postoperative pain and reduce the dependence on opioids for pain relief[26,27].

The line graph in Figure 2 shows changes in pain intensity scores over time for Mexiletine and control groups, indicating decreasing pain in both groups across four intervals. Initially, the control group had higher pain, but Mexiletine group exhibited a greater reduction in pain after 24 h post-surgery, suggesting Mexiletine's efficacy in reducing postoperative pain in abdominal surgery patients, evident through lower pain scores and reduced need for narcotics[28].

These results highlight the promising role of Mexiletine as a preoperative intervention to enhance postoperative comfort and minimize the use of narcotic pain relief medication. There are no similar studies available to directly compare the effectiveness of Mexiletine as explored in this study, however, a full comparison of the study's findings with previous research emphasizes Mexiletine's role in pain management. Fassoulaki *et al.*[29] demonstrated that Mexiletine and gabapentin reduced postoperative analgesic consumption, aligning with the reduced pain relief medication usage observed in this study. Niraj *et al.*[30] suggested that Mexiletine might affect reducing postoperative pain, similar to our study's findings, but emphasized the need for further research. Arsalani-Zadeh *et al.*[31] indicated that Mexiletine combined with local anesthetic provided acute analgesia but had limited impact on chronic post-mastectomy pain, reflecting the selective effectiveness of Mexiletine seen in our results. Ning *et al.*[32] further supported Mexiletine's efficacy in reducing postoperative pain and preventing chronic post-surgical pain, aligning with our findings. Furthermore, Dharma Naidu's study (2023) emphasized the potential of Mexiletine in opioid-sparing strategies, echoing our study's potential to diminish narcotic reliance[33]. Several factors should be noted as limitations of our study. The small sample size might restrict generalizability, emphasizing the need for larger multi-center studies. Conducting our research in a single center could introduce biases, underlining the importance of diversifying patient populations and healthcare settings. Additionally, our study's short 24-h follow-up period and focus on abdominal surgery limit the understanding of long-term effects and applicability to different surgeries[34,35]. Future research should include larger, diverse samples, longer follow-up, and exploration across various surgical contexts to accomplish these limitations.

Table 3

Comparison of postoperative pain scores and narcotic consumption between groups

	Mexiletine	**Vitamin C**	***P***
VAS score at 6 h	5.6 ± 0.1	7.2 ± 0.2	< 0.001
VAS score at 12 h	4.7 ± 0.1	6.6 ± 0.1	< 0.001
VAS score at 24 h	3.6 ± 0.1	4.7 ± 0.1	< 0.001
Total narcotic received (mg)	30.8 ± 2.6	41.1 ± 3.6	0.03

VAS, Visual Analog Scale.

Conclusion

This study contributes to the growing body of research exploring alternative approaches to postoperative pain management. The use of Mexiletine tablets before abdominal surgery demonstrated a significant reduction in postoperative pain scores and the requirement for pain relief medication. These findings highlight the potential of Mexiletine to enhance postoperative comfort and reduce narcotic reliance. By addressing the limitations identified, further research can build upon these results to establish

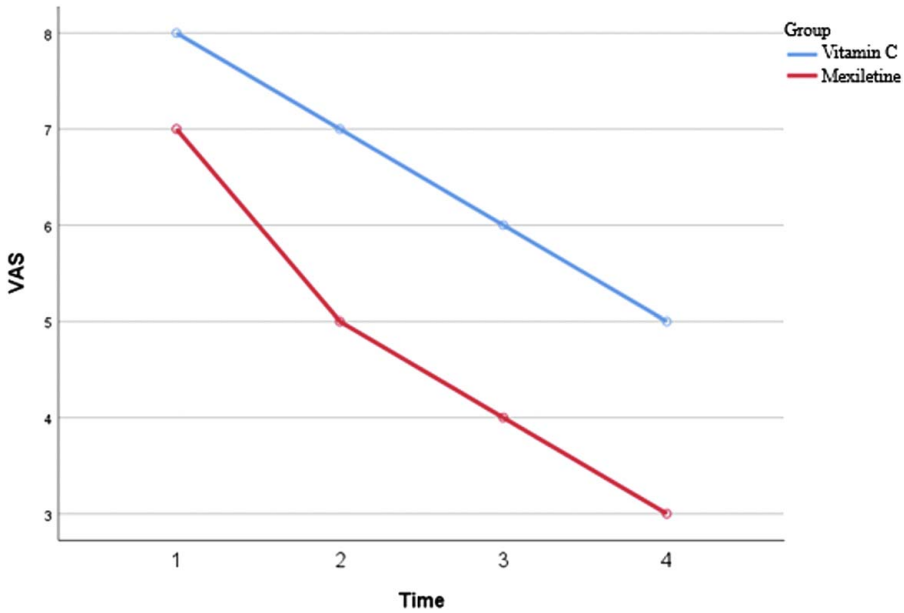

Figure 2. Pain intensity changes in 4 time intervals measured in two groups. VAS, Visual Analog Scale.

Mexiletine's role as a valuable preoperative intervention in postoperative pain management.

Research limitations

A small sample size is one of the limitations of this study. The duration of hospitalization after surgery was not evaluated. Patient satisfaction was not assessed. It is recommended that further studies, with a larger sample size, be conducted to confirm the findings of this study. Additional studies on the use of alternative analgesic drugs in surgical candidates should be conducted, and the results should be compared with this study.

Ethical approval

No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (Islamic Azad University, Tehran Medical Branch (IR.IAU.TMU.REC.1401.166), and with the Helsinki Declaration of 1975, as revised in 2013. This study was approved by the Research Ethics Board of Islamic Azad University.

Consent

Informed consent was obtained from each participant.

Source of funding

None.

Author contribution

M.S.F. and M.N.Z.: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. A.J. and K.R.: designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. Z.A., K.A.: coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Conflicts of interest disclosure

The authors deny any conflict of interest in any terms or by any means during the study.

Research registration unique identifying number (UIN)

Research Registry UIN: 9448 research registry.

Guarantor

Mahnaz Narimani Zamanabadi.

Data availability statement

All relevant data and materials are provided with in manuscript.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Human and animal rights

No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (Islamic Azad University, Tehran Medical Branch (IR.IAU.TMU.REC.1401.166), and with the Helsinki Declaration of 1975, as

revised in 2013. This study was approved by the Research Ethics Board of Islamic Azad University.

References

[1] Arefian N, Faresani HA, Tabashi S, *et al*. Postoperative pain management in obese patients undergoing gastric bypass surgery, Ketorolac and Morphine combination compared to Morphine administration effects: A Randomized Controlled Trial. 2023.

[2] Kehlet H. Postoperative pain, analgesia, and recovery—bedfellows that cannot be ignored. Pain 2018;159:S11–6.

[3] Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. Lancet 2003;362:1921–8.

[4] Chan EY, Blyth FM, Nairn L, *et al*. Acute postoperative pain following hospital discharge after total knee arthroplasty. Osteoarthritis Cartilage 2013;21:1257–63.

[5] Abeles A, Kwasnicki RM, Darzi A. Enhanced recovery after surgery: current research insights and future direction. World J Gastrointest Surg 2017;9:37.

[6] Glowacki D. Effective pain management and improvements in patients' outcomes and satisfaction. Crit Care Nurse 2015;35:33–41.

[7] Mitra S, Carlyle D, Kodumudi G, *et al*. New advances in acute postoperative pain management. Curr Pain Headache Rep 2018;22:35.

[8] Aldamluji N, Burgess A, Pogatzki-Zahn E, *et al*. PROSPECT guideline for tonsillectomy: systematic review and procedure-specific postoperative pain management recommendations. Anaesthesia 2021;76:947–61.

[9] Anne S, Mims JW, Tunkel DE, *et al*. Clinical practice guideline: opioid prescribing for analgesia after common otolaryngology operations. Otolaryngol–Head Neck Surg 2021;164:S1–42.

[10] Jin Z, Zhu M, Gupta A, *et al*. Evaluating oliceridine as a treatment option for moderate to severe acute post-operative pain in adults. Expert Opin Pharmacother 2022;23:9–17.

[11] Small C, Laycock H. Acute postoperative pain management. Jo Br Surg 2020;107:e70–80.

[12] Manolis AS, Deering TF, Cameron J, *et al*. Mexiletine: pharmacology and therapeutic use. Clin Cardiol 1990;13:349–59.

[13] Singh S, Kerndt CC, Chauhan S, *et al*. Mexiletine. StatPearls. StatPearls Publishing LLC; 2023. ineligible companies. Disclosure: Connor Kerndt declares no relevant financial relationships with ineligible companies. Disclosure: Shaylika Chauhan declares no relevant financial relationships with ineligible companies. Disclosure: Roman Zeltser declares no relevant financial relationships with ineligible companies.StatPearls Publishing. Copyright © 2023.

[14] Kushnarev M, Pirvulescu IP, Candido KD, *et al*. Neuropathic pain: preclinical and early clinical progress with voltage-gated sodium channel blockers. Expert Opin Investig Drugs 2020;29:259–71.

[15] Sloan P, Basta M, Storey P, *et al*. Mexiletine as an adjuvant analgesic for the management of neuropathic cancer pain. Anesth Analg 1999;89:760.

[16] Jarvis B, Coukell AJ. Mexiletine: a review of its therapeutic use in painful diabetic neuropathy. Drugs 1998;56:691–707.

[17] Kucuk N, Kizilkaya M, Tokdemir M. Preoperative epidural ketamine does not have a postoperative opioid sparing effect. Anesth Analg 1998; 87:103–6.

[18] Rivara M, Zuliani V. Novel sodium channel antagonists in the treatment of neuropathic pain. Expert Opin Investig Drugs 2016;25: 215–26.

[19] Desaphy JF, Dipalma A, De Bellis M, *et al*. Involvement of voltage-gated sodium channels blockade in the analgesic effects of orphenadrine. PAIN® 2009;142:225–35.

[20] Nakagawa H, Munakata T, Sunami A. Mexiletine block of voltage-gated sodium channels: isoform-and state-dependent drug–pore interactions. Mol Pharmacol 2019;95:236–44.

[21] Zhorov BS. Molecular modeling of cardiac sodium channel with mexiletine. Membranes 2022;12:1252.

[22] Stephens JM, Pashos CL, Haider S, *et al*. Making progress in the management of postoperative pain: a review of the cyclooxygenase 2-specific inhibitors. Pharmacotherapy 2004;24:1714–31.

[23] Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 2010;152:726–32.

[24] Jelodar AG, Makrani NF, Shafizad M, *et al*. Comparison of dexmedetomidine and ketamine in adjuvant with morphine for postoperative pain management following lumbar fusion surgery. Interdiscipl Neurosurg 2023;33:101767.

[25] Aezi G, Shafizad M, Firouzian A, *et al*. Effects of tizanidine and clonidine on postoperative pain after lumbar fusion surgery. Interdiscipl Neurosurg 2023;31:101680.

[26] Emadi SA, Baradari AG, Charati JY, *et al*. SOFA and modified SOFA score for accessing outcomes among trauma patients in intensive care unit. Int J Surg Open 2022;47:100559.

[27] Satvaldieva E, Kuralov ETU. Optimisation of acute pain treatment in children in abdominal surgery at the stages of the perioperative period. ScienceRise Med Sci 2022;5:8–15.

[28] Luo J, Min S. Postoperative pain management in the postanesthesia care unit: an update. J Pain Res 2017;10:2687–98.

[29] Fassoulaki A, Patris K, Sarantopoulos C, *et al*. The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesth Analg 2002;95:985–91.

[30] Niraj G, Rowbotham DJ. Persistent postoperative pain: where are we now? Br J Anaesth 2011;107:25–9.

[31] Arsalani-Zadeh R, ElFadl D, Yassin N, *et al*. Evidence-based review of enhancing postoperative recovery after breast surgery. Br J Surg 2011;98: 181–96.

[32] Ning J, Luo J, Meng Z, *et al*. The efficacy and safety of first-line therapies for preventing chronic post-surgical pain: a network meta-analysis. Oncotarget 2018;9:32081–95.

[33] Naidu D, Geiger-Hayes J, Saphire ML, *et al*. A multi-centered case series highlighting the clinical use and dosing of lidocaine and mexiletine for refractory cancer pain (Sci202). J Pain Symptom Manage 2023;65: e640–1.

[34] Kiabi FH, Emadi SA, Shafizad M, *et al*. The effect of preoperative sublingual buprenorphine on postoperative pain after lumbar discectomy: a randomized controlled trial. Ann Med Surg 2021;65:102347.

[35] Hasanzadeh-Kiabi F, Negahdari B. Applications of drug anesthesia in control chronic pain. J Invest Surg 2019;32:232–7.