Randomised Controlled Trial

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Comparing postoperative pain relief: ketorolac and Nasocalcin spray versus lidocaine and Nasocalcin spray in abdominal surgery patients

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Objectives: Postoperative pain management is critical for patient recovery after abdominal surgery. This study compared intravenous lidocaine and ketorolac for reducing postoperative pain and opioid use, along with Nasocalcin nasal spray.
Methods: In this randomized controlled trial, 58 abdominal surgery patients were allocated to receive either intravenous lidocaine plus Nasocalcin spray ($n = 29$) or intravenous ketorolac plus Nasocalcin spray ($n = 29$) before surgery. Pain intensity (visual analog scale) and postoperative opioid consumption were assessed at 1, 6, 12, and 24 h after surgery.
Results: Patients receiving ketorolac plus Nasocalcin spray reported significantly lower pain scores at all time points compared to lidocaine plus Nasocalcin ($P < 0.001$). Average 24-h pain scores were 4.5 with ketorolac versus 5.1 with lidocaine. Mean opioid consumption was also lower in the ketorolac group (31.9 mg) versus the lidocaine group (43.9 mg, $P < 0.001$).
Conclusion: Preoperative ketorolac plus Nasocalcin nasal spray resulted in superior pain relief and less opioid use compared to lidocaine plus Nasocalcin after abdominal surgery. Ketorolac may be a more effective analgesic option, while Nasocalcin spray is a safe adjunct. These findings can inform clinical practice for optimizing postoperative analgesia.

Keywords: abdominal surgery, ketorolac, lidocaine, Nasocalcin spray, pain management

Introduction

Postoperative pain management is a critical aspect of comprehensive patient care following abdominal surgery, considering the significant pain challenges that patients commonly experience in the aftermath of such procedures[1,2]. The failure to address postoperative pain adequately can lead to disturbances in sleep, physical functioning, and emotional state, underscoring the need for effective pain relief strategies[3]. Timely and effective pain management contributes to favorable outcomes such as accelerated mobilization, reduced hospital stays, diminished costs, and higher patient satisfaction rates[4]. Pre-emptive analgesia is a pharmacological technique of administering analgesics before the onset of noxious stimuli caused by tissue damage during surgery[5]. It is a preventive approach to postoperative pain management that aims to block the transmission of pain signals to the brain and prevent central sensitization. Narcotics are commonly used to manage moderate to severe postoperative pain, but their side effects, such as nausea, vomiting, and constipation, have decreased their acceptability[6]. The main goal of perioperative pain control is to ensure patient comfort while minimizing the potential for adverse effects[6]. Effective management of postoperative pain has been shown to facilitate early ambulation, reduce side effects, and even curtail the risk of persistent postoperative pain[7,8]. Lidocaine offers promising potential for mitigating postoperative pain and reducing opioid requirements[9]. Its mechanism of action centers on the blockade of nerve signals and local pain relief[10]. Recent studies emphasize lidocaine's role in inhibiting neural conduction and inflammation during the perioperative period[11]. Lidocaine's significance in acute pain control is further underscored by its applications in managing spinal pain, disc herniation, and other post-surgery pain scenarios[12]. Lidocaine infusions have produced pain relief in patients[13] found that significant pain relief was produced by

HIGHLIGHTS

- Postoperative pain management is critical for patient recovery after abdominal surgery.
- Preoperative ketorolac plus Nasocalcine nasal spray resulted in superior pain relief and less opioid.
- Ketorolac may be a more effective analgesic option, while Nasocalcine spray is a safe adjunct.
- These findings can inform clinical practice for optimizing postoperative analgesia.

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moderate lidocaine dosages of 5.5 mg/kg[14]. Additionally, unlike opioids, lidocaine does not demonstrate any significant risk for addiction and abuse[15,16]. Calcitonin is a polypeptide hormone regulating the metabolism of calcium in the body[17]. For many years calcitonin has been used to maintain and improve bone mineral density and to reduce the fracture rate[18]. Many studies showed that calcitonin had an analgesic role in several painful circumstances[19]. This pain-ameliorating effect is irrelevant to its osteoclastic inhibitory effect and mechanisms like altering Na + channel and serotonin receptor expression or hypothesis including the endorphin-mediated mechanism were used to explain this effect[20]. The pain-relieving properties of calcitonin have been documented in conditions such as vertebral fractures, diabetic neuropathy, migraines, and neuropathic pain[21]. The diverse applications of calcitonin highlight its potential as an analgesic agent in different pain scenarios[22].

Ketorolac, a non-steroidal anti-inflammatory drug (NSAID), has garnered attention as an effective adjuvant for postoperative pain management, often employed in combination with opioids. Studies have consistently demonstrated its comparability to opioids in terms of analgesia after various surgical procedures. Operating by inhibiting cyclooxygenase enzymes, ketorolac curtails prostaglandin synthesis, thereby reducing both acute inflammation and peripheral nociception[23]. Ketorolac, as a selective COX-1 inhibitor with minimal impact on COX-2, has been shown to provide effective pain relief and an opioid-sparing effect when used alongside patient-controlled opioid analgesia[24]. The effectiveness of ketorolac lies not only in its intrinsic analgesic and anti-inflammatory properties but also in its role in minimizing opioid-related adverse effects[25]. Existing pain management strategies after abdominal surgery encompass a range of options, including opioid-based medications and local anesthetics[26]. However, traditional approaches are not without limitations, often leading to side effects and suboptimal outcomes, this underscores the necessity for a comparative analysis to bridge the existing research gap and provide evidence-based recommendations for clinicians[27]. The comparison of lidocaine and Nasocalcin spray with ketorolac and Nasocalcin spray offers a unique opportunity to enhance our understanding of pain relief mechanisms and improve patient outcomes.

Patients and methods

This two-blind randomized controlled trial study was approved by the Ethics Committee of the Islamic Azad University, Tehran Medical Branch. The process of randomization was conducted by a research team member not involved in patient care. This study employed a two-blind design, ensuring that both patients and assessors were unaware of the treatment assignment.

The study includes patients who were candidates for abdominal surgery who were referred to hospitals affiliated with the Islamic Azad University, Tehran Medical Branch in 2022–2023. The sample size of 58 patients (29 in each group) was calculated using G-*Power software with an effect size of 0.3, a type I error of 0.05, and a power of 80%. The study included patients aged 15–75 years with an ASA physical status of 1 or 2 who had signed a consent form and had not consumed drugs or alcohol. Patients were excluded from the study if they had a reduced consciousness level, hemodynamic instability, unusual bleeding during surgery, or a surgery that lasted longer than 4 h.

Participants were randomly assigned to either the control group or the experimental group using a random number table. The drugs were categorized into Lido group and Keto group to ensure blinding. Lido group received Nasocalcin spray and 2% lidocaine injections, while Keto group received Nasolcalsin spray with intravenous ketorolac before surgery. The 200 mg nasal spray dose is weight-based: one puff for patients up to 60 kg, and two puffs for patients greater than 60 kg. Intravenous ketorolac was administered at 30 mg, and, 2% lidocaine was injected intravenously. Patients were induced to general anesthesia with propofol 2 mg/kg or midazolam 0.01 mg/kg, followed by fentanyl 2–3 g/kg and atracurium 0.5 mg/kg. Maintenance anesthesia was achieved with isoflurane 1–2% and N2O oxygen (50/50). Fentanyl was repeated hourly during surgery. Muscle relaxation was reversed with neostigmine-atropine at the end of surgery. Pain was assessed using the visual analog scale (VAS) at 1, 6, 12, and 24 h postoperatively. Patients with a VAS score greater than 5 received 30–50 mg of IV pethidine. A trained nurse recorded narcotic usage in a questionnaire at the end of the first day. The data was analyzed using SPSS version 26. Descriptive statistics, such as mean and standard deviation, were calculated for quantitative variables. Qualitative results were presented as frequency and percentage, with graphs and tables. Data normality were assessed using the Shapiro–Wilk test. *t*-tests were used for normally distributed data, while Mann–Whitney *U* tests were used for non-normally distributed data. The χ^2 test was used for categorical and qualitative variables. A P value of less than 0.05 was considered statistically significant.

This two-blind randomized controlled trial study was approved by the Ethics Committee of the Islamic Azad University, Tehran Medical Branch (IR. IAU.TMU.REC.1401.169) and registered in the Iranian Registry of Clinical Trials (IRCT20230710058733N1).

Research Registry UIN: researchregistry9546

The work has been reported in line with the CONSORT flowchart (Fig. 1) and checklist criteria[28].

Result

Demographic characteristics

The demographic characteristics of 58 patients show that: the average age of all patients was 47.5 ± 13.1 years, so that the lowest age was 19 and the highest age was 75 years. Among the studied patients, 14 (24.2%) were male and 44 (75.8%) were female. The average duration of surgery in patients was 103.8 ± 36.5 min. The study recorded varying postoperative pain scores, with an average score of 7.5 ± 0.7 at 1 h after the operation, which progressively decreased to 6.4 ± 1.1 at 6 h, 6.1 ± 1.1 at 12 h, and 4.7 ± 0.8 at 24 h after the surgical procedure. The average amount of narcotics received after the operation in the patients was 37.9 ± 12.6 mg (Table 1).

The results of the Shapiro–Wilk test in the table below show that the distribution of age-related data is not significant ($P > 0.05$). Also, the distribution of other quantitative data related to the amount of narcotics received after surgery, duration of surgery, pain 1 h after surgery, pain 6 h after surgery, pain 12 h after surgery, and pain 24 h after surgery is significant. ($P < 0.05$).

In the Keto group, 6 (20.7%) were male and 23 (79.3%) were female, and in the Lido group, 8 (27.6%) were male and 21 (72.4%) were female ($P = 0.53$).

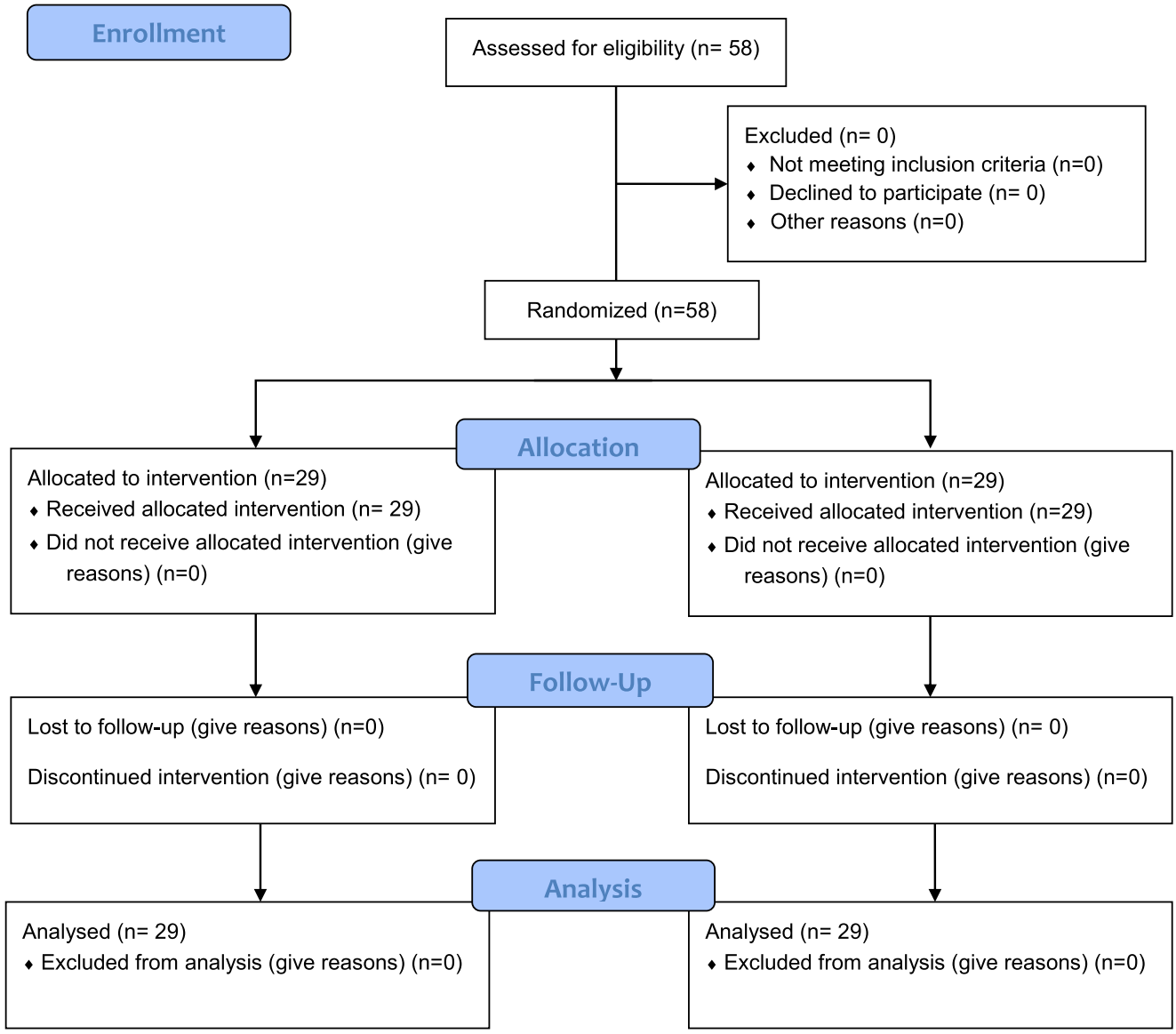

Figure 1. Consort flow diagram.

Using the independent *t*-test, it was determined that the average age of patients in Keto group was 46.8 ± 13.1 years, and in Lido group was 48.1 ± 13.4 years ($P = 0.70$).

Using the Mann–Whitney test, it was determined that the average duration of surgery in Keto and Lido groups was 109.6 ± 37.4 min, and 98.1 ± 35.2 min ($P = 0.19$), respectively (Table 2).

Postoperative pain scores

Utilizing the Mann–Whitney test, statistically significant differences in pain scores were observed at various time points following the operation; specifically, 1-h post-operation, patients in Lido group exhibited an average pain score of 6.5 ± 0.4, while the Keto group had an average score of 7.1 ± 0.2 ($P < 0.001$); at 6 h post-operation, the average pain score for the Keto group was 5.9 ± 0.6, and for the Lido group, it was 1.1 ± 7 ($P < 0.001$); at 12 h post-operation, patients Keto group had an average pain score

Table 1

Demographic characteristics and postoperative pain scores of 58 patients.

Characteristic	Value
No. patients	58
Average age	47.5 ± 13.1 years
Male, *n* (%)	14 (24.2)
Female, *n* (%)	44 (75.8)
Average duration of surgery	103.8 ± 36.5 min
Average postoperative pain score (1 h)	7.5 ± 0.7
Average postoperative pain score (6 h)	6.4 ± 1.1
Average postoperative pain score (12 h)	6.1 ± 1.1
Average postoperative pain score (24 h)	4.7 ± 0.8
Average amount of narcotic received	37.9 ± 12.6 mg

Table 2

Comparison of demographic characteristics between the two groups.

Characteristic	Ketorolac + Nasocalcin spray (Keto group)	Lidocaine + Nasocalcin spray (Lido group)	P*
No. patients, *N* (%)	23 (100)	21 (100)	0.53
Male, *N* (%)	6 (26.1)	8 (38.1)	0.70
Female, *N* (%)	17 (73.9)	13 (61.9)	0.53
Average age Mean ± SD	46.8 ± 13.1 years	48.1 ± 13.4 years	0.70
Average duration of surgery (min) Mean ± SD	109.6 ± 37.4 min	98.1 ± 35.2 min	0.19

*P value for Mann–Whitney test.

of 5.6 ± 0.8, while those Lido group had an average score of 6.5 ± 0.9 ($P < 0.001$); and finally, 24 h post-operation, the average pain score for patients in Keto group was 4.5 ± 0.7, whereas for those Lido group, it was 5.1 ± 0.8 ($P < 0.001$) (Table 3).

Amount of narcotics received after the operation

Using the Mann–Whitney test, it was determined that the average amount of narcotics received after the operation of patients in the Keto group was 31.9 ± 11.3 mg and the patients in the Lido group was 43.9 ± 10.8 mg ($P < 0.001$) (Table 4).

Repeated measures ANOVA

Repeated measures ANOVA, the pain intensity score has changed significantly in the four measured periods ($P < 0.001$). Also, the changes in the pain intensity score in the four measured intervals in the two compared groups had a significant difference ($P = 0.009$). The initial pain intensity at 1 h after surgery was significantly higher in the Lido group than in Keto group ($P < 0.001$). This trend persisted at subsequent assessment points (6-, 12-, and 24-h ×21post-surgery), with the Lido group consistently exhibiting higher pain intensity levels than the Keto group. However, the Keto group experienced a greater reduction in postoperative pain intensity after 24 h ($P < 0.001$).

Discussion

Adequate perioperative pain management is essential for ensuring the well-being of surgical patients[29]. Effective pain control before surgery is pivotal in preventing central sensitization and subsequent postoperative pain, which could otherwise lead to chronic pain syndromes and prolonged opioid use[30]. Preoperative analgesic strategies play a critical role in mitigating nociception, inflammation, and alterations in pain pathways resulting from surgical tissue injury[31].

This study's methodology involved a comparative investigation of the combination of ketorolac and Nasocalcin spray versus lidocaine and Nasocalcin spray. Key findings indicated that patients receiving ketorolac plus Nasocalcin spray experienced significantly lower pain scores and reduced narcotic requirements compared to those receiving lidocaine plus Nasocalcin spray at various postoperative time points. With the moderate dosage range described in this study, respiratory depression and sedation were not experienced, and most patients (95%) tolerated the infusions well. These findings highlight the potential benefits of ketorolac as a more effective analgesic option.

Recent studies have explored similar questions on optimizing postoperative analgesia. Zhang and colleagues in a 2020 retrospective study analyzed 2239 pancreatectomy patients from 2014 to 2017, dividing subjects into lidocaine infusion and non-lidocaine groups. They found the lidocaine group had less analgesic use and better 1- and 3-year survival compared to non-lidocaine controls, with lidocaine infusion associated with prolonged overall survival in the multivariate analysis[32].

In this study, Lidocaine pulse Nasocalcin spray provided moderate pain relief, with average pain scores of 7 at 6 h and 5.1 at 24 h postoperatively. No significant adverse events or complications were observed in both Lido and Keto groups. The lidocaine findings align with previous research by Yazici and colleagues on a randomized trial compared perioperative lidocaine infusion + PCA morphine, PCA morphine alone, and epidural bupivacaine for pain, recovery, and complications in 75 gynecologic surgery patients. They concluded that perioperative lidocaine infusion seems as effective as epidural and better than IV opioids alone for pain, nausea, and bowel function after gynecologic oncology surgery.

In a 2023 prospective cohort study, McNamara and colleagues gave 24 knee arthroplasty patients an intraosseous morphine-ketorolac infusion compared to historical morphine-alone controls. They found the infusion group had less pain and medication in the first four postoperative hours but no other differences, suggesting the infusion improves early but not later postoperative outcomes compared to morphine alone after knee arthroplasty[33].

In a 2023 study, Dabour and colleagues investigated orphenadrine/ketorolac (O/KT) combination infusion for 24 h as postoperative analgesia compared to orphenadrine/diclofenac (O/D) and placebo infusions after Modified Radical Mastectomy. O/KT infusion was superior to O/D infusion for opioid-sparing and pain scores. They concluded cocktails with ketorolac or diclofenac infusions for 24 h after mastectomy can improve pain sensation and reduce opioid consumption[34].

Table 3

Postoperative pain scores between the two groups.

Time	Ketorolac + Nasocalcin spray (Keto group)	Lidocaine + Nasocalcin spray (Lido group)	P*
1 h after surgery	6.5 ± 0.4	7.1 ± 0.2	($P < 0.001$)
6 h after surgery	5.9 ± 0.6	6.1 ± 0.7	($P < 0.001$)
12 h after surgery	5.6 ± 0.8	6.5 ± 0.9	($P < 0.001$)
24 h after surgery	4.5 ± 0.7	5.1 ± 0.8	($P < 0.001$)

*P value for Mann–Whitney test.

Table 4

Amount of narcotics received after the operation between the two groups.

Group	Average amount of narcotic received	P*
Ketorolac + Nasocalcin spray (Keto group)	31.9 ± 11.3 mg	0.001
Lidocaine + Nasocalcin spray (Lido group)	43.9 ± 10.8 mg	0.001

*P value for Mann–Whitney test.

Seyfi and colleagues in a 2018 RCT investigated adding ketorolac to lidocaine in intravenous regional anesthesia for upper extremity surgery. Forty patients were randomly divided into lidocaine only and lidocaine with ketorolac groups. Adding ketorolac significantly reduced postoperative pain for up to 24 h after opening the tourniquet[35].

Based on our result, Ketorolac provided statistically significantly greater pain reduction compared to lidocaine at all postoperative time points measured. At 6 h, ketorolac patients reported pain scores 7.1 on average versus 6.1 in lidocaine patients ($P < 0.001$). At 24 h, this difference in mean pain scores remained 5.1 in the ketorolac group versus 4.5 in the lidocaine group ($P < 0.001$). The magnitude of these differences appears clinically meaningful, with ketorolac providing superior analgesic effects.

Amin and colleagues in a 2022 double-blind clinical trial compared intravenous ketorolac plus lidocaine in Bier's block for surgery of traumatic upper limb injuries. Ketorolac reduced postoperative pain intensity and overall morphine was received without drug-related complications[36]. Ketorolac's greater efficacy could reflect its dual inhibition of COX-1 and COX-2 pathways involved in prostaglandin synthesis and inflammation, while lidocaine acts solely through sodium channel blockade[37,38].

In a 2023 retrospective study, Lyu and colleagues assessed salmon calcitonin nasal spray (SCNS) for patients with rotator cuff tears (RCTs) after arthroscopic repair. SCNS significantly reduced early postoperative pain level and improved shoulder function but did not decrease rotator cuff re-tear rate[39]. Roy and colleagues in a 2021 study evaluated calcitonin spray for bone healing after ORIF of mandibular fractures. Calcitonin spray reduces postoperative pain and improves fracture healing, and its economic efficiency still needs to be determined.

Nasocalcin spray could be considered an adjunctive therapy for abdominal surgery patients, but the addition of more potent analgesics like ketorolac may be warranted for adequate pain control[40].

Aghdam *et al.*[41] concluded that ketorolac should be included in pain management after laparoscopic surgery for patients without NSAID contraindications.

Zhang's prospective randomized controlled trial evaluated the effect of S-ketamine with sufentanil on gastrointestinal (GI) recovery and postoperative pain in gynecological patients undergoing open abdominal surgery. They concluded that S-ketamine accelerated GI recovery and reduced 24-h postoperative pain[42].

In Joshua's study, ketorolac showed an excellent safety profile both systemically and locally. Local application decreased postoperative pain, shortened hospital stays, and reduced opioid use. This study is the first to evaluate local ketorolac injections in musculoskeletal pathology, confirming its safety and effectiveness as an adjunct or alternative treatment for musculoskeletal ailments[43].

Wahyuningsih's study reported that lidocaine is an effective intravenous analgesic for acute pain after laparotomy surgery, providing effective postoperative analgesia at relatively low doses with minimal toxicity risk[44].

Singariya's study reported that intraoperative lignocaine and ketamine infusion reduced mean fentanyl consumption and pain intensity in the first 24 h postoperatively, leading to improved patient satisfaction for lower abdominal surgery under general anesthesia[45].

This study has some limitations that should be acknowledged. The sample size was relatively small, which limits the statistical power to detect smaller differences between groups. In addition, this was a single-center study with limited geographic diversity among participants. A multi-center study could improve the generalizability of the findings. Furthermore, the study only followed patients for a short time after surgery. Longer-term follow-up could provide more information on the duration of analgesic effects.

Finally, this study did not include a placebo control group due to ethical concerns about withholding pain treatment. Comparing it to a placebo would better isolate the effects of the analgesic regimens. Based on the limitations identified, future research could focus on larger multi-center trials with longer follow-up periods to better understand the long-term impacts of preoperative analgesia. Studies including placebo controls may be warranted if an appropriate ethical justification can be established.

Conclusion

Our study compared the effectiveness of lidocaine and ketorolac in reducing pain after abdominal surgery, along with the efficacy of Nasocalcin spray as a safe adjunct (add-on) in the context of postoperative pain management. The findings suggest that both lidocaine and ketorolac are effective in pain management, with ketorolac demonstrating superior pain reduction. Nasocalcin spray also proved effective. These results have significant implications for postoperative pain management practices, offering clinicians a choice between two effective analgesics and a safe alternative in Nasocalcin spray.

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.1401.169), 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., M.N.Z. and T.T.: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. M.Q., K.R. and R.S.H.: designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. Z.A., K.A. and M.Z.: 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.

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Guarantor

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Data availability statement

All relevant data and materials are provided with in manuscript.

Provenance and peer review

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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.1401.169), and with the Helsinki Declaration of 1975, as revised in 2013. This study was approved by the Research Ethics Board of Islamic Azad University.

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