



# Effectiveness of Topical Ketorolac in Post-hemorrhoidectomy Pain Management: A Clinical Trial

Negin Shahrokhzadeh <sup>1</sup>, Saeed Khorramnia <sup>2,\*</sup>, Amin Jafari <sup>3</sup> and Hassan Ahmadinia <sup>4</sup>

<sup>1</sup>Rafsanjan University of Medical Sciences, Rafsanjan, Iran

<sup>2</sup>Department of Anesthesiology, School of Medicine, Ali Ibn Abitaleb Educational and Treatment Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

<sup>3</sup>Department of Surgery, School of Medicine, Ali Ibn Abitaleb Educational and Treatment Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

<sup>4</sup>School of Health, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

\*Corresponding author: Department of Anesthesiology, School of Medicine, Ali Ibn Abitaleb Educational and Treatment Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran. Email: saeed.khorramnia@gmail.com

Received 2022 August 16; Revised 2023 January 23; Accepted 2023 January 27.

## Abstract

**Background:** Postoperative pain management is one of the major challenges of surgeons and anesthesiologists.

**Objectives:** This study aimed to determine the efficacy of topical ketorolac in post-hemorrhoidectomy pain management.

**Methods:** This clinical trial was conducted on 84 candidates for hemorrhoidectomy (grade-II hemorrhoids) who visited Ali Ibn Abitalib hospital of Rafsanjan, Kerman, Iran (2020 - 2021). The participants were selected through convenience sampling and randomly assigned to three groups of 28. The subjects were treated in topical (4 mL 0.5% Marcaine + 1 mL ketorolac at the surgical site), intramuscular (4 mL 0.5% Marcaine at the surgical site + 1 mL ketorolac intramuscularly), and control (4 mL 0.5% Marcaine at the surgical site) groups. Pain intensity was measured using the Numerical Pain Rating Scale 1, 6, 12, and 24 hours after surgery. The obtained data were analyzed using two-way repeated measures analysis of variance.

**Results:** Female and male patients constituted 46.4% and 53.6% of the participants, respectively. The mean pain intensity was significantly lower in the topical group than in intramuscular and control treatments in all four stages of pain assessment ( $P < 0.001$ ). Some participants were treated with pethidine due to high pain intensity. However, the mean pain intensity gradually reduced over time in all three groups.

**Conclusions:** Study findings suggested that the topical administration of ketorolac and Marcaine was more effective than Marcaine used alone for relieving pain in patients undergoing hemorrhoidectomy.

**Keywords:** Ketorolac, Hemorrhoidectomy, Pain

## 1. Background

Hemorrhoids, the most common disease in and around the anus, are swollen veins similar to varicose veins in the anus and lower rectum. The clinical symptoms of hemorrhoids include pain, bleeding, itching, and lumps near the anus. Hemorrhoids are classified under grades I-IV according to their size. Grade II or higher grades of hemorrhoids require surgery because they do not respond to pharmacotherapy. Hemorrhoidectomy is considered a very unpleasant treatment for patients because it is associated with apparent postoperative pain, as pain relief in 40% of patients undergoing a hemorrhoidectomy requires the administration of narcotics (1).

There are various methods for post-hemorrhoidectomy pain management, the most common of which is the administration of injectable narcotics,

usually combined with other drugs to increase their analgesic properties (2). Preemptive analgesia throughout the perioperative period with acetaminophen, gabapentin, ketamine, or dexamethasone is also recommended (3). Other methods, such as bilateral pudendal nerve block (4) and acupuncture (5), can also effectively relieve post-hemorrhoidectomy pain.

Ketorolac is an injectable non-steroidal anti-inflammatory drug (NSAID) that can be used alone or in combination with other drugs to control postoperative pain. Although there are reports concerning the topical administration of this drug to the surgical site for pain relief in minor to medium surgeries (6), few studies have addressed its topical administration in patients undergoing hemorrhoidectomy (7). However, this method has been employed in some cases of outpatient hemorrhoidectomies (8), and it is commonly used topically in clinical

cases for post-hemorrhoidectomy pain management.

Hashemi et al.'s study investigated the effect of the type of anesthesia on pain control after hemorrhoidectomy. The first, second, and third surgery groups underwent general anesthesia, spinal anesthesia, and local anesthesia. In the aforementioned study, the third group that received local anesthesia not only experienced less pain after surgery but also complications, such as headache, hypotension, urinary retention, and respiratory complications, were also less frequent in this group (9). Akhtar et al. investigated the use of topical ketorolac in the treatment of pain after minor to moderate surgical procedures. One infiltration group with Marcaine and one infiltration group with ketorolac were performed at the operation site. The results showed better pain control in the group receiving Marcaine (6). A study showed that ketorolac buccal infiltration could reduce the postoperative pain experienced by patients requiring endodontic treatment diagnosed with symptomatic irreversible pulpitis (10).

## 2. Objectives

Using analgesics with less risk in reducing pain after surgery has always been one of the challenges for experts. Finding useful solutions requires clinical research. Therefore, this study aimed to investigate the effects of topical ketorolac on post-hemorrhoidectomy pain management.

## 3. Methods

This study was approved by the Ethics in Research Committee of Rafsanjan University of Medical Sciences, Rafsanjan, Kerman, Iran (IR.RUMS.REC.1399.242) and registered on the Iranian Registry of Clinical Trials (IRCT20210922052556N1). The statistical population consisted of patients with grade-II hemorrhoids who were admitted to Ali ibn Abi-Talib hospital of Rafsanjan for hemorrhoidectomy within 2020 - 2021. The inclusion criteria were an age range of 15 - 55 years, the American Society of Anesthesiologists I or II, non-affliction with coagulopathy, no history of gastrointestinal bleeding or peptic ulcer, no drug dependence, and no history of diabetes and uncontrolled hypertension. The exclusion criteria were withdrawal from the study and complications during surgery. The sample size was calculated based on  $\alpha = 0.05$ ,  $\beta = 0.20$ ,  $\sigma_1 = 1.30$ ,  $\sigma_2 = 1.33$ ,  $K = 1$ , and  $\Delta = 1$ , at 28 subjects in each group.

After obtaining informed consent from the participants, they were randomly assigned to three groups of 28 by drawing lots. The first, second, and third participants were assigned to the control, topical, and intramuscular

groups, respectively. This process continued until the end of the study. An anesthesia resident taught the participants how to use the Numerical Pain Rating Scale (NPRS), one of the most reputable tools for measuring pain intensity, before the surgery. This tool measures pain intensity on an 11-point Likert scale from 0 (no pain) to 10 (the most severe pain). The participant chooses one of the numbers from 0 to 10 to describe pain intensity, and higher scores indicate greater pain severity (11).

All participants underwent surgery under general anesthesia. For this purpose, after administering 500 mL of normal saline, a mixture of 2 mg midazolam, 2 mL sufentanil, 2 mg/kg propofol, and 20 mg atracurium was injected. A laryngeal mask was also used for airway management in the patients. No medications were prescribed to control pain during the operation except in the subsequent cases. At the end of the surgery, the following interventions were performed for pain management:

Topical: 4 mL 0.5% Marcaine + 1 mL ketorolac at the surgical site

Intramuscular: 4 mL 0.5% Marcaine at the surgical site + 1 mL ketorolac intramuscularly

Control: 4 mL 0.5% Marcaine at the surgical site

It is noteworthy that the surgical procedure was performed by a single surgeon for all participants. Pain intensity was measured using the NPRS during the recovery (1 hour after surgery) and 6, 12, and 24 hours later. Pethidine was prescribed to the participants who reported a score of 7 or higher for pain intensity. The statistical analyst was blinded to group allocation.

The obtained data were statistically analyzed in SPSS software (version 21). The normal distribution of the data was evaluated using the Shapiro-Wilk test, and the results confirmed the normal distribution of the collected data ( $P = 0.07$ ). Box's M and Levene's tests were also employed to assess the equality of covariance matrices and the equality of variances of the studied groups, respectively. The studied groups were compared for the mean pain intensity at different times using two-way repeated measures analysis of variance (ANOVA). In addition, the main effects of treatment type, pain intensity measurement time, and interaction effects of treatment type and the times of pain measurement were also evaluated. The significance level for the tests was set to 0.05.

## 4. Results

In this study, 39 (46.4%) and 45 (53.6%) patients were female and male, respectively. There was no significant difference between the three groups regarding age ( $P = 0.866$ ). There was no significant difference between the

three groups in the mean age and body mass index ( $P = 0.0457$ ; [Table 1](#)).

The mean scores of pain severity decreased over time in all three groups. The mean scores of pain intensity in all four measurement times in the control were higher than those of the topical group, and the mean scores of pain intensity in all four measurement times in the topical group were higher than those of the intramuscular group ([Table 2](#)).

One hour after the surgery, eight, four, and three participants in control, intramuscular, and topical groups, respectively, were treated with pethidine due to high pain intensity. In addition, only those in the control group received pethidine 6 hours after the surgery for pain relief. None of the participants needed pethidine for pain management 12 and 24 hours after the surgery ([Table 3](#)).

Two-way repeated measures ANOVA was used to study the trends of changes in the scores for pain intensity in the three groups. Considering the significance of the effect of time, pain intensity in the participants showed a decreasing trend in general up to 24 hours after the surgery ( $P < 0.001$ ). The significance of the intervention effect also indicated significant differences between the three groups in pain intensity, as pain intensity in the topical group was lower than in the intramuscular group and lower in the intramuscular group than in the control group ( $P < 0.001$ ). The results demonstrated that the interactive effects of time and intervention were not statistically significant, indicating no significant differences between the three groups in terms of changes in pain intensity over time ( $P = 0.104$ ; [Table 4](#)).

Considering the significance of the intervention effect and the presence of three groups in the study, Tukey's test for post-hoc analysis was employed for pairwise comparisons between the groups. The results showed that the mean score of pain intensity in the intramuscular group was higher than in the topical group ( $P = 0.009$ ). The mean score of pain intensity in the control group was higher than in other groups ( $P < 0.001$ ; [Table 5](#)).

Among all measurement times, the highest and the lowest mean scores of pain intensity were those of the control and topical groups, respectively. The score of pain intensity decreased over time in all groups; however, the trends of changes in pain intensity were identical in all three groups (in the shape of three parallel lines) ([Figure 1](#)).

## 5. Discussion

This study addressed the effects of topical ketorolac on post-hemorrhoidectomy pain management. The three treatment methods investigated in this study were the

topical administration of Marcaine and ketorolac, intramuscular administration of Marcaine and ketorolac, and topical administration of Marcaine. The results showed the effectiveness of all these three interventions in relieving post-hemorrhoidectomy pain. However, pain intensity one hour after the surgery was significantly lower in the topical administration of the Marcaine and ketorolac group. In addition, the participants in this group needed lower doses of opioids than those in other groups within the first 24 hours after the surgery. This finding is consistent with the findings of Dehbozorgi, who studied the prophylactic effect of the intravenous administration of ketorolac on post-hemorrhoidectomy pain relief ([12](#)).

Vatankhah and Melekshoar reported that the intravenous injection of 30 mg ketorolac was more effective than the administration of 400 mg ibuprofen in pain relief among patients undergoing upper extremity orthopedic surgery, especially within the first 6 hours after surgery ([13](#)). The findings of Ebtehaj also indicated that the analgesic effect of the intramuscular administration of ketorolac was similar to that of the intramuscular injection of 75 mg pethidine in post-cesarean section pain management while causing fewer complications ([14](#)). Nevertheless, Zangoue et al. showed no significant difference between patients treated with ketorolac and pethidine in post-cesarean section pain intensity ([15](#)). Considering the fewer complications of ketorolac and the limitations of pethidine administration, ketorolac can be a suitable alternative to pethidine for post-cesarean section pain management. The results of two studies on patients undergoing inguinal hernia surgery ([16](#)) and lower limb orthopedic surgery ([17](#)) confirmed the effectiveness of ketorolac, compared to acetaminophen.

Abdoli et al. concluded that ketorolac could be a good alternative to morphine for pain control in patients with spinal traumas ([18](#)). In another study by McDonald et al., it was shown that the addition of ketorolac to the postoperative drug regimen reduced the need for opioids after open reduction and internal fixation of ankle fractures in the early postoperative period and showed mixed and minor effects on pain reduction ([19](#)). The findings of Ong and Tan indicated that the preoperative intravenous administration of 30 mg ketorolac was more effective than the injection of 50 mg tramadol in preventing postoperative dental pain ([20](#)). Another study compared the effectiveness of ibuprofen and ketorolac in reducing renal colic pain, and the results showed that ibuprofen caused analgesic effects faster than ketorolac. In addition, the complete pain relief rate was higher in patients treated with ibuprofen than in those who received ketorolac ([21](#)).

The results of another study demonstrated the better analgesic effects of intravenous ketorolac than nebulized

**Table 1.** Comparison of Quantitative and Qualitative Variables of Participants Undergoing Hemorrhoidectomy in Three Studied Groups<sup>a</sup>

Variables	Topical (n = 28)	Intramuscular (n = 28)	Control (n = 28)	P-Value <sup>b</sup>
Age, y	29.89 ± 8.80	39.32 ± 8.46	30.93 ± 8.33	0.548 *
Body mass index, kg/m <sup>2</sup>	26.9 ± 3.6	26.3 ± 2.4	25.9 ± 1.9	0.457
Gender				0.866 **
Female	14 (50.0)	13 (46.4)	12 (42.9)	
Male	14 (50.0)	15 (53.6)	16 (57.1)	

<sup>a</sup> Values are expressed as mean ± SD or No. (%).<sup>b</sup> One-way analysis of variance \*\*Chi-square test P < 0.05.**Table 2.** Mean Scores of Pain Intensity of Post-hemorrhoidectomy Pain at Different Measurement Times<sup>a</sup>

	Measurement Time	Topical (n = 28)	Intramuscular (n = 28)	Control (n = 28)
After surgery	Immediately	1.89 ± 1.73	2.57 ± 1.97	4.36 ± 2.23
	6 hours	1.75 ± 1.04	2.86 ± 1.24	4.43 ± 2.20
	12 hours	1.18 ± 0.82	1.75 ± 0.89	2.93 ± 1.02
	24 hours	0.50 ± 0.69	1.25 ± 0.59	2.43 ± 1.14

<sup>a</sup> Values are expressed as mean ± SD.**Table 3.** Frequency Distribution of Pethidine Administration to Participants Undergoing Hemorrhoidectomy<sup>a</sup>

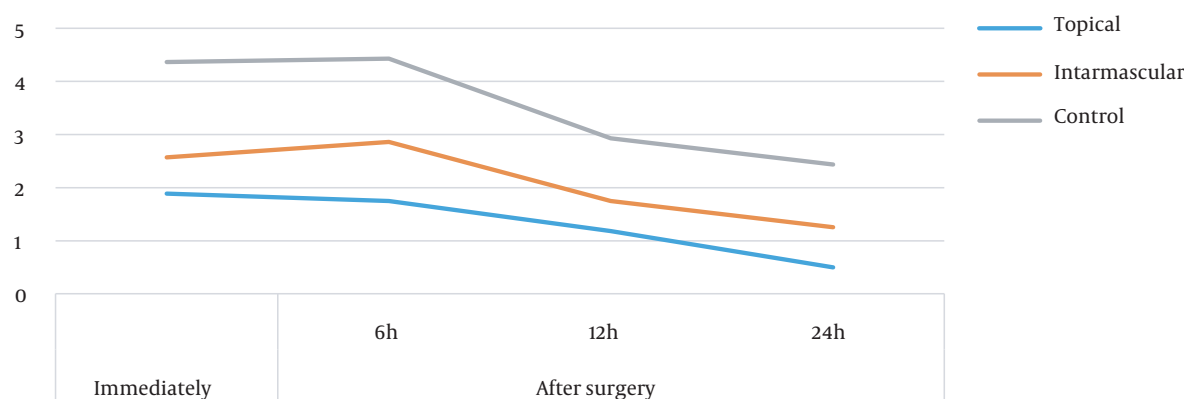
Time of Pethidine Administration	Group			Total	P-Value
	Topical	Intramuscular	Control		
<b>Immediately after surgery</b>					0.18
Yes	3 (10.7)	4 (14.3)	8 (28.5)	15 (17.8)	
No	25 (89.3)	24 (85.7)	20 (71.5)	69 (82.2)	
Total	28 (100)	28 (100)	28 (100)	84 (100)	
<b>6 hours after surgery</b>					-
Yes	0	0	3 (10.7)	3 (3.6)	
No	28 (100)	28 (100)	25 (89.3)	81 (96.4)	
Total	28 (100)	28 (100)	28 (100)	84 (100)	

<sup>a</sup> Values are expressed as No. (%).**Table 4.** Summary of Repeated Measures to Investigate Trends of Changes in Pain Intensity in Three Groups of Participants Undergoing Hemorrhoidectomy

Source of Variation	Sum of Squares	df	Mean Squares	F	P-Value
Time	136.272	1	136.572	119.282	< 0.001
Intervention + Time	5.337	2	2.668	2.331	0.104
Intervention	280.292	2	140.146	24.122	< 0.001
Error	470.598	81	5.810		

**Table 5.** Results of Tukey's Test for Post-hoc Analysis

I	J	Mean Difference (I-J)	SE	P-Value
Topical	Intramuscular	-0.773*	0.288	0.009
	Control	-1.978*	0.261	< 0.0001
Intramuscular	Control	-1.205*	0.241	< 0.0001



**Figure 1.** Changes in average pain score in three studied groups

fentanyl in patients with renal colic pain (22). The evidence indicated that injectable ketorolac and morphine produced almost the same analgesic effects in patients with sickle cell disease; nevertheless, ketorolac caused fewer complications (23). However, Tirupathi et al. conducted a review study and concluded that further clinical trials were needed to prove the effectiveness of ketorolac in pain control (24). By contrast, Isiordia et al. showed that the administration of 30 mg ketorolac, compared to 1-10 mg parecoxib, after the surgical removal of third molars resulted in better analgesic effects and higher patient satisfaction (25).

Numerous studies have also investigated the effectiveness of ketorolac in children and adolescents. Lynn et al. studied the efficacy of postoperative administration of ketorolac in infants aged 6-18 months and reported no adverse effects on surgical site drainage, oxygen saturation, and renal or liver functions (26). Due to the lack of reliable information and evidence about primary consequences, the efficacy and safety of ketorolac in reducing postoperative pain in children are still unknown (27). In addition, there are no randomized and controlled clinical trials with a placebo addressing the effects of ketorolac on infants. However, most published reports have demonstrated the efficacy and safety of ketorolac in appropriately selected infants (28). Although the intravenous administration of ketorolac to children for postoperative pain relief is not approved in many countries, it is commonly employed in clinical cases (28).

The analgesic effects of ketorolac have also been studied in animal models. In a study, ketorolac not only decreased pain but also significantly reduced the tolerance of the analgesic effects of morphine and the symptoms of withdrawal syndrome caused by the ad-

ministration of naloxone in rats (29). Guidelines for postoperative pain management suggest a combination of multidimensional/multi-mechanism approaches to achieve better postoperative outcomes. A multimodal approach means the simultaneous use of two or more analgesics (usually a combination of opioid and non-opioid ones) with different mechanisms of action. A multimodal approach not only minimizes the need for the administration of opioids but also results in greater pain relief when compared to using a single treatment. As a result, it reduces the side effects associated with narcotic painkillers. However, not all methods might be effective for all patients, and not all analgesics might be appropriate for outpatient surgeries or urgent surgical procedures (30).

The NSAIDs play a major role in pain management in various clinical conditions, such as headache, menstrual disorders, postoperative pain, spinal and soft tissue pain, rheumatoid arthritis, and osteoarthritis, with cyclooxygenase enzyme blockade (31). There is very low to moderate certainty evidence to prove the efficacy and safety of ketorolac as a treatment for postoperative pain relief. Although available evidence suggests that the intravenous administration of ketorolac might provide remarkable postoperative pain relief for most patients, future studies might affect this estimation. The side effects of ketorolac occur at a slightly higher rate than placebo and other NSAIDs. There is insufficient information available to assess whether the intravenous administration of ketorolac results in a different rate of gastrointestinal or surgical site bleeding, renal dysfunction, or cardiovascular events compared to other NSAIDs. Insufficient research has been conducted on old patients undergoing cardiovascular surgery who might be at risk of adverse events (32).

This study, similar to any other study, had some limitations. All three investigated groups (intervention cases) in the present study received topical analgesic drug treatment. It would have been better to have a group as a control in the study and compare the pain intensity to that group. However, this measure was abandoned due to the need to control the patients' pain after the operation and respect the patients' rights.

### 5.1. Conclusions

The topical administration of ketorolac and Marcaine was more effective than Marcaine used alone for relieving pain in patients undergoing hemorrhoidectomy. This study investigated the topical administration of ketorolac, which causes fewer complications than its intravenous administration.

### Acknowledgments

The authors would like to express gratitude to all the patients who cooperated with this study. The authors are grateful to the Vice-Chancellor for Research of Rafsanjan Medical School and the Vice-Chancellor for Research and Technology of Rafsanjan University of Medical Sciences.

### Footnotes

**Authors' Contribution:** Study concept and design: Saeed Khorramnia; Acquisition of the data: Negin Shahrokhzadeh; Analysis and interpretation of the data: Hasan Ahmadinia; Drafting of the manuscript: Negin Shahrokhzadeh; Critical revision of the manuscript for important intellectual content: Negin Shahrokhzadeh; Statistical analysis: Hasan Ahmadinia; Administrative, technical, and material support: Amin Jafari; Study supervision: Saeed Khorramnia.

**Clinical Trial Registration Code:** This study was registered on the Iranian Registry of Clinical Trials (Code: [IRCT20210922052556N1](https://www.irct.ir/record/IRCT20210922052556N1)).

**Conflict of Interests:** Funding or research support: Rafsanjan University of Medical Sciences; Employment: Saeed Khorramnia; Personal financial interests: none; Stocks or shares in companies: none; Consultation fees: paid; Patents: none; Personal or professional relations with organizations and individuals (e.g., parents and children, wife and husband, and family relationships): none; Unpaid membership in a governmental or non-governmental organization: none; Are you one of the editorial board members or a reviewer of this journal? no.

**Ethical Approval:** This study was approved by the Ethics in Research Committee of Rafsanjan University of Medical Sciences ([IR.RUMS.REC.1399.242](https://www.ir.rums.rec.ir/record/IR.RUMS.REC.1399.242)).

**Funding/Support:** This study was supported in part by grant number 980064 from Rafsanjan University of Medical Sciences.

**Informed Consent:** Informed consent was obtained from the participants.

### References

1. Popov V, Yonkov A, Arabadzhieva E, Zhivkov E, Bonev S, Bulanov D, et al. Doppler-guided transanal hemorrhoidal dearterialization versus conventional hemorrhoidectomy for treatment of hemorrhoids - early and long-term postoperative results. *BMC Surg.* 2019;**19**(1):4. [PubMed ID: [30630463](https://pubmed.ncbi.nlm.nih.gov/30630463/)]. [PubMed Central ID: [PMC6327383](https://pubmed.ncbi.nlm.nih.gov/PMC6327383/)]. <https://doi.org/10.1186/s12893-019-0469-9>.
2. Swarup A, Mathis KA, Hill MV, Ivatury SJ. Patterns of opioid use and prescribing for outpatient anorectal operations. *J Surg Res.* 2018;**229**:283-7. [PubMed ID: [29937003](https://pubmed.ncbi.nlm.nih.gov/29937003/)]. <https://doi.org/10.1016/j.jss.2018.04.005>.
3. Van Backer JT, Jordan MR, Leahy DT, Moore JS, Callas P, Dominick T, et al. Preemptive Analgesia Decreases Pain Following Anorectal Surgery: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial. *Dis Colon Rectum.* 2018;**61**(7):824-9. [PubMed ID: [29771804](https://pubmed.ncbi.nlm.nih.gov/29771804/)]. <https://doi.org/10.1097/DCR.0000000000001069>.
4. Imbelloni LE, Vieira EM, Carneiro AF. Postoperative analgesia for hemorrhoidectomy with bilateral pudendal blockade on an ambulatory patient: a controlled clinical study. *J Coloproctology.* 2012;**32**(3):291-6. <https://doi.org/10.1590/s2237-93632012000300012>.
5. Wu J, Chen B, Yin X, Yin P, Lao L, Xu S. Effect of acupuncture on post-hemorrhoidectomy pain: a randomized controlled trial. *J Pain Res.* 2018;**11**:1489-96. [PubMed ID: [30122979](https://pubmed.ncbi.nlm.nih.gov/30122979/)]. [PubMed Central ID: [PMC6084088](https://pubmed.ncbi.nlm.nih.gov/PMC6084088/)]. <https://doi.org/10.2147/JPR.S166953>.
6. Akhtar MI, Saleem M, Zaheer J. Wound infiltration with Bupivacaine versus Ketorolac for postoperative pain relief in minor to moderate surgeries. *J Pak Med Assoc.* 2009;**59**(6):385-8. [PubMed ID: [19534374](https://pubmed.ncbi.nlm.nih.gov/19534374/)].
7. Emile SH. Evidence-based review of methods used to reduce pain after excisional hemorrhoidectomy. *J Coloproctology.* 2021;**39**(1):81-9. <https://doi.org/10.1016/j.jcol.2018.10.007>.
8. O'Donovan S, Ferrara A, Larach S, Williamson P. Intraoperative use of Toradol facilitates outpatient hemorrhoidectomy. *Dis Colon Rectum.* 1994;**37**(8):793-9. [PubMed ID: [8055724](https://pubmed.ncbi.nlm.nih.gov/8055724/)]. <https://doi.org/10.1007/BF02050144>.
9. Hashemi MASI, Ghasemi Falavarjani K, Aliakbar Navahi R, Mirfallah K, Bakhtiari P. [Comparison of the Results of Intravitreal Injection of Triamcinolone Acetonide and Bevacizumab (Avastin) in Patients with Clinically Significant Macular Edema Unresponsive to Standard Treatment]. *Razi J Med Sci.* 2009;**16**:0. Persian.
10. Akhlaghi N, Azarshab M, Akhouni N, Meraji N. The effect of ketorolac buccal infiltration on postoperative endodontic pain: a prospective, double-blind, randomized, controlled clinical trial. *Quintessence Int.* 2019;**50**(7):540-6. [PubMed ID: [31187102](https://pubmed.ncbi.nlm.nih.gov/31187102/)]. <https://doi.org/10.3290/j.qi.a42654>.
11. Anannamcharoen S, Cheeranont P, Boonya-usadon C. Local perianal nerve block versus spinal block for closed hemorrhoidectomy: a randomized controlled trial. *J Med Assoc Thai.* 2008;**91**(12):1862-6. [PubMed ID: [19133521](https://pubmed.ncbi.nlm.nih.gov/19133521/)].
12. Dehbozorgi MH. [Role of preemptive intravenous ketorolac in prevention of post operative pain in patients undergoing hemorrhoidectomy operation] [thesis]. Fasa University of Medical Sciences; 2020. Persian.

13. Vatankhah M, Melekshoar M. [Comparison of the prophylactic effect of ibuprofen and intravenous ketorolac in pain control after upper extremity surgery: A Double-Blind Randomized Clinical Trial Study]. *Med J Mashhad Univ Med Sci*. 2021;**64**(2):2692-705. Persian.
14. Ebtehaj M. [Comparison of ketorolac and pethidine drugs in reducing pain after the second repeat cesarean section in patients referred to the delivery ward of Imam Hossein Hospital in 2015] [dissertation]. Tehran: Shahid Beheshti University of Medical Sciences; 2017. Persian.
15. Zangoue M, Bijari B, Abasspour Z, Tolyat M. Comparison of the Effect of Ketorolac and Pethidine on Pain Control after Cesarean Section Surgery. *J N Khorasan Univ Med Sci*. 2019;**11**(2):73-7. <https://doi.org/10.52547/nkums.11.2.73>.
16. Sadeghian M. [Comparison of the effect of ketorolac and venous apothelium on pain control after unilateral inguinal hernia repair surgery in patients referred to Imam Khomeini Hospital in 2014 - 2015] [dissertation]. Tehran, Iran: Tehran University of Medical Sciences; 2016. Persian.
17. Mirzaei M. [Comparative study of the infusion of ketorolac and acetaminophen in reducing postoperative pain and opioid consumption in patients undergoing orthopedic surgery of the lower limbs] [dissertation]. Ardabil, Iran: Ardabil University of Medical Sciences; 2018. Persian.
18. Abdoli A, Ghahramani S, Seif-Rabiei MA, Salimi R, Heshmati B. Comparison of the effect of ketorolac and morphine on pain management in patients with spinal trauma in emergency department: a randomized controlled clinical trial study. *J Isfahan Med Sch*. 2019;**37**(528):556-63. <https://doi.org/10.22122/jims.v37i528.10972>.
19. McDonald EL, Daniel JN, Rogero RG, Shakked RJ, Nicholson K, Pedowitz DI, et al. How Does Perioperative Ketorolac Affect Opioid Consumption and Pain Management After Ankle Fracture Surgery? *Clin Orthop Relat Res*. 2020;**478**(1):144-51. [PubMed ID: 31567579]. [PubMed Central ID: PMC7000065]. <https://doi.org/10.1097/CORR.0000000000000978>.
20. Ong KS, Tan JM. Preoperative intravenous tramadol versus ketorolac for preventing postoperative pain after third molar surgery. *Int J Oral Maxillofac Surg*. 2004;**33**(3):274-8. [PubMed ID: 15287311]. <https://doi.org/10.1006/ijom.2003.0515>.
21. Forouzanfar MM, Mohammadi K, Hashemi B, Safari S. Comparison of Intravenous Ibuprofen with Intravenous Ketorolac in Renal Colic Pain Management; A Clinical Trial. *Anesth Pain Med*. 2019;**9**(1):e86963. [PubMed ID: 30881914]. [PubMed Central ID: PMC6412918]. <https://doi.org/10.5812/aapm.86963>.
22. Rezaei B, Salimi R, Kalantari A, Astaraki P. Comparison of efficacy nebulized fentanyl with intravenous ketorolac for renal colic in patients over 12 years old. *Am J Emerg Med*. 2021;**44**:358-61. [PubMed ID: 32345561]. <https://doi.org/10.1016/j.ajem.2020.04.053>.
23. Talebi Doluee M, Rezvani Kakhki B, Heidarian Mir H, Fateminayyeri M, Madanitorbati F, Hosseini S. Pain Relief in the Sick Cell Crisis: Intravenous Morphine Versus Ketorolac; A Double-Blind, Randomized Clinical Trial. *Iran Red Crescent Med J*. 2019;**21**(4). <https://doi.org/10.5812/ircmj.83614>.
24. Tirupathi S, Rajasekhar S, Maloth SS, Arya A, Tummalakomma P, Lanke RB. Pre-emptive analgesic efficacy of injected ketorolac in comparison to other agents for third molar surgical removal: a systematic review. *J Dent Anesth Pain Med*. 2021;**21**(1):1-14. [PubMed ID: 33585680]. [PubMed Central ID: PMC7871182]. <https://doi.org/10.17245/jdapm.2021.21.1.1>.
25. Isirdia-Espinoza MA, Alonso-Castro AJ, Serafin-Higuera N, Castaneda-Santana DI, de la Rosa Coronado M, Bologna-Molina RE. Postoperative administration of ketorolac compared to other drugs for pain control after third molar surgery: A meta-analysis of double-blind, randomized, clinical trials. *Br J Clin Pharmacol*. 2022;**88**(6):2591-604. [PubMed ID: 35083768]. <https://doi.org/10.1111/bcp.15241>.
26. Lynn AM, Bradford H, Kantor ED, Seng KY, Salinger DH, Chen J, et al. Postoperative ketorolac tromethamine use in infants aged 6-18 months: the effect on morphine usage, safety assessment, and stereo-specific pharmacokinetics. *Anesth Analg*. 2007;**104**(5):1040-51. [PubMed ID: 17456651]. <https://doi.org/10.1213/01.ane.0000260320.60867.6c>.
27. Stone SB. Ketorolac in Postoperative Neonates and Infants: A Systematic Review. *J Pediatr Pharmacol Ther*. 2021;**26**(3):240-7. [PubMed ID: 33833624]. [PubMed Central ID: PMC8021237]. <https://doi.org/10.5863/j551-6776-26.3.240>.
28. McNicol ED, Rowe E, Cooper TE. Ketorolac for postoperative pain in children. *Cochrane Database Syst Rev*. 2018;**7**(7). CD012294. [PubMed ID: 29981164]. [PubMed Central ID: PMC6513208]. <https://doi.org/10.1002/14651858.CD012294.pub2>.
29. Anoush M, Afroogh M. Evaluation of the Effects of Ketorolac on Tolerance and Dependence to Morphine in Male Mice. *J Ilam Univ Med Sci*. 2019;**26**(6):183-93. <https://doi.org/10.29252/sjimu.26.6.183>.
30. Pergolizzi JJ, Taylor RJ, Raffa RB. Intranasal ketorolac as part of a multimodal approach to postoperative pain. *Pain Pract*. 2015;**15**(4):378-88. [PubMed ID: 25169467]. <https://doi.org/10.1111/papr.12239>.
31. Canadian Agency for Drugs and Technologies in Health. *Ketorolac for Pain Management: A Review of the Clinical Evidence*. Canadian Agency for Drugs and Technologies in Health; 2014.
32. McNicol ED, Ferguson MC, Schumann R. Single-dose intravenous ketorolac for acute postoperative pain in adults. *Cochrane Database Syst Rev*. 2021;**5**(5). CD013263. [PubMed ID: 33998669]. [PubMed Central ID: PMC8127532]. <https://doi.org/10.1002/14651858.CD013263.pub2>.