# Original Article: Evaluation of the Effectiveness of Metronidazole Ointment on Pain in Patients after Hemorrhoidectomy

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**Citation** F. Mahdavi, R. Azhough, **Evaluation of the Effectiveness of Metronidazole Ointment on Pain in Patients after Hemorrhoidectomy.** *GMJ Med.* **2021**, 5(1):323-328.

https://doi.org/10.22034/GMJM.2021.1.11

**Article info:**
**Received:** 15 Jun 2021
**Accepted:** 05 December 2021
**Available Online:** 05 December 2021
**Checked for Plagiarism:** Yes,
**Language Editor:** Ermia Aghaie
**Editor who Approved Publication:** Professor Dr. Ali Nokhodchi

**Keywords**:
Metronidazole, Pain, Defecation, Hemorrhoidectomy

## ABSTRACT

***Introduction:*** Recently, the use of metronidazole in reducing pain after hemorrhoids has been considered and it has been shown that the oral form of this drug can significantly reduce pain after hemorrhoidectomy; However, other studies have not confirmed the effect of oral metronidazole in reducing pain. The use of oral form has limitations compared to the local form due to its general effects. Therefore, in this study, the benefits of using metronidazole topical form in pain control after hemorrhoidectomy were evaluated.

***Material and Methods:*** This descriptive cross-sectional study was performed in 2019 with the participation of 94 hemorrhoidectomy patients in Imam Reza Hospital (Tabriz Medical Sciences); For half of the participants, metronidazole topical ointment was administered three times daily and for the other group, placebo ointment was administered. Patients' pain intensity was measured using a VAS questionnaire and compared between the two groups.

***Results:*** Intensity in the first hours after surgery as well as the first two weeks after surgery (measured daily) in the group receiving topical metronidazole was significantly lower than in the placebo group; The dose of acetaminophen codeine in the placebo group up to day 14 was significantly higher than the group receiving metronidazole.

***Conclusion:*** Topical metronidazole can reduce postoperative pain. In addition, the pain after defecation and the need for analgesia are significantly reduced. However, further studies are needed for the widespread use of this form of medicine in the clinic.

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## Introduction

Hemorrhoid is one of the most common diseases of the gastrointestinal tract, which causes pain and bleeding due to local damage to the black veins in the anal area during defecation [1].

If this disorder is not controlled and treated on an outpatient basis, surgery is one of the good methods in treating hemorrhoids. But hemorrhoidectomy can also cause complications such as pain, bleeding, urinary retention, infection, compression and thickening of the stool, and damage to the internal sphincter [2]. In the meantime, it seems that several factors are involved in the occurrence of pain after hemorrhoidectomy, such as patient tolerance, type B anesthesia, postoperative analgesia, as well as surgical techniques [3,4].

Therefore, in order for the patient to be able to tolerate this type of treatment, reducing the pain after hemorrhoids has always been an important goal [5]. Numerous studies have been performed to reduce pain after hemorrhoid surgery, including the use of 0.2% nitroglycerin ointment, which is helpful in relaxing the anal sphincter in the initial pain after hemorrhoidectomy, but the complication of headache following the use of This product appears sometimes unbearable for the patient and limits the use of this product [6].

Inhibition of the posterior areas around the anus by rupivacaine 0.75% to control pain, although it leads to an immediate analgesic effect, pain relief after surgery does not last long and is sometimes associated with serious problems [7,8].

The use of fentanyl percutaneously and a subcutaneous morphine injection pump, despite effective pain control, can be costly and addictive. The use of botulinum toxin after hematoid hemorrhoids, although significantly reduces pain, due to the high cost of treatment and its injection by skilled professionals, it is not possible to use it for the general public [9,10].

Recently, the use of metronidazole in reducing pain after hemorrhoids has been considered and it has been shown that the oral form of this drug can significantly reduce pain after hemorrhoidectomy; However, other studies have not confirmed the effect of oral metronidazole in reducing pain. The use of oral form has limitations compared to the local form due to its general effects. Therefore, in this study, the benefits of using metronidazole topical form in pain control after hemorrhoidectomy were evaluated.

## Material and Methods

***Study design:*** This is a cross-sectional descriptive study that was conducted in 2019 in patients undergoing hemorrhoidectomy at Imam Reza Hospital (Tabriz University of Medical Sciences) with the participation of 94 patients who were available by convenience sampling; It was done by observing the entry / exit criteria.

***Inclusion / Exclusion Criteria:*** Inclusion criteria included: age over 18 years, candidate for hemorrhoidectomy, grade 2, 3 and 4 hemorrhoids, clinically, having a fissure in the anal area. Exclusion criteria included: cardiovascular disease, surgical site infection, anal abscess, and drug addiction.

***Method of preparation of metronidazole ointment:*** First, metronidazole powder was prepared. Then, to prepare the ointment, several bases were used to knead the powder, including propylene glycol, liquid paraffin, glycerin and isopropyl alcohol, and among them, liquid paraffin was selected as the best material. Then metronidazole ointment was prepared with liquid paraffin based on Vaseline. In physico-chemical control experiments of the drug, to measure the amount of drug in the ointment, the spectroscopic method was performed at 319 nm and the chemical stability of the ointment prepared by the accelerated method at four degrees (40, 50, 60 and 70) degrees. Celsius was performed and the half-life of the ointment at 25 ° C was determined to be 467 days. The microbial control of the product was performed according to the USP standard method and the microorganism did not grow in the culture medium. The prepared ointment was used by the surgeon after the surgery and before the dressing pack, then it was attached to the patient's file or cape and entered the ward with

the patient and was given to the patient for later use. The patient was advised to rub 2 times a day for 2 weeks, each time the size of a fingertip equivalent to 2 cm around the anus (not inside it). All patients within 24 hours after surgery with a prescription, including: laxative (MOM), the topical form of metronidazole or placebo were discharged. Most patients were advised to take acetaminophen codeine or a nonsteroidal anti-inflammatory drug if additional analgesia was needed. Patients' condition was assessed at intervals of 6 and 12 hours, as well as the first, second, seventh and fourteenth days after surgery. In this way, in the first hours after surgery (12, 6 and 24 hours) by evaluating the hospital and for later periods by visiting the office or by phone, the evaluation was done. VAS criterion was used to communicate with the patient and understand the severity and extent of pain according to the patient's ability to cooperate. Analgesic consumption was recorded in the first, second, seventh and fourth days after surgery. In this section, the patient was asked whether he uses oral painkillers or not, and if so, whether it has decreased or not?

***Data analysis:*** The data were recorded in one form for each person and finally entered into SPSS Ver 20 software; Frequency and percentage, mean and standard deviation were used to display the data. T-test was used to compare the severity of pain between the two groups at different times. P value was considered significant for values less than 0.05.

***Ethical considerations:*** This study was approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1398.1061). Conscious consent was obtained from all patients. No cost was incurred from patients to participate in this study and to prepare metronidazole ointment. Patient information remained strictly confidential.

## Results

A total of 94 patients were included in the study, of which 70 were female and 24 were male. The female to male ratio was 20 to 5 in the metronidazole group and 30 to 14 in the placebo group. Fifty people in the metronidazel group with a mean age of 37 years (18 to 65 years) and 22 people in the placebo group with a mean age of 36 years (19 to 61 years) were evaluated. There was no significant difference between the two groups in terms of mean age (P=0.554).

Topical form of metronidazole significantly reduced pain after hemorrhoidectomy compared with the placebo group in the sixth and twelfth hours (P=0.031 and P=0.001) and the first to fourteenth days after surgery, respectively (Table 1).

**Table 1.** Comparison of postoperative pain in the two groups participating in the study

| Time | Metronidazole | Placebo | P Value |
|---|---|---|---|
| **1 Day** | 4.22±0.42 | 6.32±1.75 | 0.041 |
| **2 Day** | 4.03±0.19 | 6.14±1.95 | 0.036 |
| **3 Day** | 3.98±0.47 | 5.85±1.25 | 0.033 |
| **4 Day** | 3.82±0.42 | 5.72±1.31 | 0.035 |
| **5 Day** | 3.75±0.29 | 5.69±1.42 | 0.030 |
| **6 Day** | 3.51±0.39 | 5.55±1.19 | 0.029 |
| **7 Day** | 3.39±0.38 | 5.19±1.95 | 0.025 |
| **8 Day** | 3.28±0.39 | 5.03±1.32 | 0.014 |
| **9 Day** | 3.10±0.29 | 4.83±1.65 | 0.037 |
| **10 Day** | 2.89±0.59 | 4.73±1.98 | 0.041 |
| **11 Day** | 2.50±0.51 | 4.55±0.78 | 0.046 |
| **12 Day** | 2.12±0.37 | 4.27±0.45 | 0.041 |
| **13 Day** | 1.95±0.48 | 3.49±0.45 | 0.049 |
| **14 Day** | 1.59±0.59 | 3.14±0.15 | 0.049 |
| **T Test** | | | |

The dose of acetaminophen codeine for pain control in the first days to 14 days after surgery also indicated that the dose of this drug in the placebo group was much higher than the metronidazole group. A comparison of the amount of pain control drug between the two groups of patients is presented in Table 2.

**Table 2:** Comparison of the amount of pain relieving drug between the two groups participating in the study

| Time | Metronidazole | Placebo | P Value |
|---|---|---|---|
| **1 Day** | 1.95±0.99 | 3.75±1.85 | 0.009 |
| **2 Day** | 1.88±0.91 | 3.63±1.65 | 0.014 |
| **3 Day** | 1.70±0.85 | 3.59±1.59 | 0.041 |
| **4 Day** | 1.55±0.82 | 3.42±1.41 | 0.035 |
| **5 Day** | 1.39±0.71 | 2.34±1.32 | 0.025 |
| **6 Day** | 1.25±0.61 | 2.25±1.36 | 0.024 |
| **7 Day** | 1.14±0.55 | 2.15±1.95 | 0.036 |
| **8 Day** | 1.01±0.49 | 2.02±1.14 | 0.041 |
| **9 Day** | 0.94±0.49 | 2.00±1.99 | 0.042 |
| **10 Day** | 0.80±0.47 | 2.00±1.36 | 0.044 |
| **11 Day** | 0.75±0.74 | 1.85±0.85 | 0.049 |
| **12 Day** | 0.66±0.71 | 1.63±0.65 | 0.048 |
| **13 Day** | 0.50±0.66 | 1.42±0.95 | 0.041 |
| **14 Day** | 0.45±0.32 | 1.35±0.24 | 0.044 |
| **T Test** | | | |

## Discussion

With home remedies and behavioral changes failing and correcting bad lifestyle habits, it is necessary to adopt medical methods to treat hemorrhoids. Of course, the choice of treatment also depends on the type and rate of disease progression, in the early stages of the disease, step-by-step treatment is usually chosen [11].

The main purpose of hemorrhoid medication is to control the acute symptoms of hemorrhoids instead of treating the disease itself [12]. In fact, hemorrhoids can only control the symptoms of the disease. Medications recommended for hemorrhoids are usually in the form of topical tablets, suppositories, and ointments [13].

Hemorrhoids occur as varicose veins in and around the anal vein, and a drug called Phlebotonics, which is made from plant extracts (containing flavonoids) and synthetic compounds, can help improve venous contractility, increase vasodilation, and increase permeability through an unspecified mechanism. Slowly It is also very effective in treating chronic venous insufficiency [14]. Statistics obtained in 2012 have proven the significant beneficial effects of this drug in controlling bleeding, itching and viscous discharge of this disease. It is also useful in reducing the symptoms after hemorrhoid surgery. Hydrocortisone and lidocaine are also temporary anti-inflammatory drugs that are effective in controlling pain and itching, but should not be taken permanently [15]. In this study, the topical form of metronidazole was able to significantly reduce postoperative pain in the metronidazole group compared with the placebo group. One of the possible reasons for the effect of metronidazole on the control of pain after hemorrhoidectomy is the direct anti-inflammatory effects of this drug, which can significantly reduce postoperative pain by reducing edema and premature inflammation of the surgical site [16]. Metronidazole reduces inflammation and postoperative pain by reducing the migration of neutrophils to the inflammatory site, inhibiting the production of hydrogen peroxide, hydroxyl radicals, and other oxidants that cause tissue damage in the area. These effects of the drug may justify pain control in the early hours of patients. Another reason for this finding may be related to the effects of this drug on anaerobic infections secondary to bacterial colonization in that area. The dimension also justifies the action [17]. A similar

finding has been confirmed in another study [18]. Another important factor in the study of the effects of the drug is the effect on postoperative pain, which is one of the major problems of patients after hemorrhoidectomy [19]. The results of this study indicate a significant difference between the two groups at 48 hours after surgery, a finding that was not mentioned in other studies. The cause of this effect of the drug can also be attributed to the anti-inflammatory effects of the drug and the reduction of edema in the area of the antibiotic effect and the specific type of drug formulation.

### *Limitations*

The small sample size of the participants in the study, as well as the failure to record the amount of activity after surgery, as well as the failure to record the duration of anesthesia and surgery were the limitations of this study; Due to the effectiveness of metronidazole ointment in reducing pain after hemorrhoidectomy, it is recommended to use this ointment to manage pain after surgery in these patients.

## Conclusion

Overall, the results of this study reinforce the view that topical metronidazole can reduce postoperative pain. In addition, the pain after defecation and the need for analgesia are significantly reduced. However, further studies are needed for the widespread use of this form of medicine in the clinic.

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