

The Efficacy of Oral Metronidazole in Reducing Pain Post-Hemorrhoidectomy: A Randomized Controlled Trial

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ABSTRACT

Objective: The study aims to compare the effect of oral metronidazole and placebo on the mean pain score of patients post-hemorrhoidectomy.

Study Design: A randomized controlled trial study.

Place and Duration of Study: This study was conducted at the POF Hospital, Wah Cantt, between 21st March and 21st September, 2019.

Materials and Methods: Patients with grade III and IV hemorrhoids on whom hemorrhoidectomy was performed were included in the study. Patients in the experimental group were given oral metronidazole 500 mg every eight hours for seven days, while the control group received a placebo. Patients' pain was assessed through visual analogue scores (VAS) on the seventh post-operative day. Data was recorded in a predesigned proforma.

Results: The VAS score post hemorrhoidectomy was significantly less in the experimental group (3.59 ± 0.55) compared to the control (6.13 ± 1.04).

Conclusion: Since bacterial colonization is inevitable after hemorrhoidectomy, metronidazole can help reduce post-operative pain by reducing bacterial proliferation and inflammation of the surgical site.

Key Words: Hemorrhoids, hemorrhoidectomy, metronidazole, pain score, Flagyl.

Citation of article: Munawar S, Zafar M, Azhar M, Ali M, Sadia G, Ali H. The Efficacy of Oral Metronidazole in Reducing Pain Post-Hemorrhoidectomy: A Randomized Controlled Trial. Med Forum 2023;34(6):94-97.

INTRODUCTION

Hemorrhoids are cushions of submucosal tissue containing venules, arterioles and smooth muscle fiber that play a critical role in the continence mechanism. Sometimes, physiological changes in the body can cause excessive straining and increased abdominal pressure on hemorrhoidal tissue, leading to congestion and prolapse¹.

In the population older than 40 years old, 58% experience some degree of hemorrhoidal disease. Based on their location and the degree of prolapse, hemorrhoids are categorized into four grades, a system known as Golighor's classification. Conservation treatment is often sufficient for the early stages (Grade I and Grade II hemorrhoids), while late-stage disease (Grade III and Grade IV hemorrhoids) usually requires surgical treatment.²

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Received: January, 2023

Accepted: April, 2023

Printed: June, 2023

The most effective hemorrhoidectomy methods are the Milligan-Morgan open hemorrhoidectomy and the Ferguson closed hemorrhoidectomy.³ With medical advancements in recent years, several pieces of surgical equipment have been developed and employed in performing hemorrhoidectomies, including bipolar electro thermal devices, ultrasonic scalpels, and circular staplers⁴.

This surgical procedure can be conducted by means of local infiltration, in association with general anesthesia or spinal block. The most serious subsequent complications are anal stenosis and incontinence, and the most common postoperative complications are pain, bleeding, and wound infection which ultimately cause prolonged stay in the hospital.⁵ Although hemorrhoids are a very common condition, hemorrhoidectomy is often not favored by patients for the fear of post-operative pain.⁶

Non-steroidal anti-inflammatory drugs (NSAIDs) are usually administered orally post operation to manage pain; however these can have lots of side effects, the risk of which is higher in older people.⁷ Metronidazole is a nitroimidazole, an antibiotic and antiprotozoal medication widely used against anaerobic bacterial infections in the field of proctology because of its efficacy, safety, low cost, and low rate of adverse events.⁸ It is the drug of choice for the treatment of amebic infections, pseudomembranous colitis, and in the treatment of brain abscesses. The nitro group of metronidazole is able to serve as an electron acceptor,

forming reduced cytotoxic compounds that bind to proteins and DNA, resulting in cell death.⁹ Since bacterial colonization is inevitable after hemorrhoidectomy, metronidazole helps reduce bacterial proliferation, inflammation, and thus post-operative pain.¹⁰ Angelina et al. conducted a systematic review of four randomized controlled trials (RCTs) of oral metronidazole in managing post-hemorrhoidectomy pain. They concluded that although metronidazole may be associated with reduced pain, further RCTs are needed to confirm this association.¹¹ Our study aims to determine the efficacy of oral metronidazole without the influence of oral NSAIDs in improving pain post-hemorrhoidectomy to recommend its use in Pakistan where there is insufficient literature on the subject. High efficacy of metronidazole in reducing post-operative pain can, in turn, reduce the need for oral NSAIDs after surgery and improve patient compliance to the procedure.

MATERIALS AND METHODS

Study design and sample selection: Patients with grade III or grade IV hemorrhoids who underwent hemorrhoidectomy at the POF Hospital, Wah Cantt, between 21st March and 21st September 2019 were enrolled in the study. The sample included both genders, and patients between 20 and 60 years old. Only patients characterized using the American Society of Anesthesiologists (ASA) physical status classification system as either ASA I or ASA II were included. A total of 140 patients were included in the study and were randomly assigned to a study group (n = 70) and control group (n = 70). Patients with a history of chronic liver disease or colonic, rectal, anal canal carcinoma were excluded.

Ethical Approval: Ethical approval was obtained from the College of Physicians and Surgeons of Pakistan and the hospital ethics committee. All patients provided written, informed consent for participation in the study. The study was conducted in accordance with the Declaration of Helsinki.

Procedure: The complete history of the patient was collected, and an examination was performed. Proctoscopy was performed by senior registrar in left lateral position with the local application of lignocaine anesthesia gel and the grade of the hemorrhoids was recorded. Patients provided informed consent for the hemorrhoidectomy. Open hemorrhoidectomy was performed under spinal anesthesia.

Patients in the study group were given oral 500 mg of metronidazole eight hourly for seven days, while the control group received a placebo with the same dosage and therapeutic scheme. All patients were given 30 ml of a lactulose syrup (Lilac) 12 hourly and an intramuscular injection of diclofenac sodium twelve hourly for 24 hours. None of the patients received oral NSAIDs after being discharged from the hospital.

Patients' pain was assessed through visual analogue scores (VAS), with zero showing no pain and ten showing maximum pain, on the seventh post-operative day. The scale is given in Figure 1. Data was recorded in a predesigned proforma.

Data Analysis: We stratified and compared several effect modifiers, including age, gender, ASA grade, and hemorrhoids grade, to determine whether the mean pain scores of certain subgroups were uniquely affected by the metronidazole intervention.

RESULTS

The general characteristics of patients are described in Table 1. Between March and September 2019, 140 patients were enrolled in the study. Of these, 80 patients (57.1%) were male and 60 (42.9%) were female. The mean age of patients in years was 41.94 ± 12.71 . The majority of patients, 86 patients (61.4%), could be characterized as ASA grade I patients. According to the hemorrhoidal disease classification, 31 patients (44.3%) presented with grade III hemorrhoids and 39 (55.7%) with grade IV hemorrhoids. Conversely, in the control group, 42 patients (60%) presented with grade III hemorrhoids and 28 (40%) with grade IV hemorrhoids. The mean pain score obtained using a visual analogue scale (VAS) for the study group and control group was 3.59 ± 0.55 and 6.13 ± 1.04 , respectively. The VAS scores of patients categorized as mild, moderate, and severe are given in Table No. 2. We stratified the effect modifier, age, and compared the mean pain scores of both groups post hemorrhoidectomy. Among patients aged 51 – 60 years, the mean pain score for the study and control group was 3.59 ± 0.55 and 6.13 ± 1.04 respectively, as shown in Table No. 3.

When stratifying for gender, for male patients, the mean pain score was 3.68 ± 0.58 for the control group and 6.07 ± 1.04 for the study group, as shown in Table 3. Furthermore, stratifying for ASA grades, the mean pain score among the study and control groups was 3.51 ± 0.54 and 6.18 ± 1.07 , respectively, as shown in Table 3. Finally, stratifying for the effect modifier, hemorrhoids grade, among patients with grade III hemorrhoids, the mean pain score was 3.42 ± 0.5 in the study group and 6.24 ± 1.03 in the control group, as shown in Table No. 3.

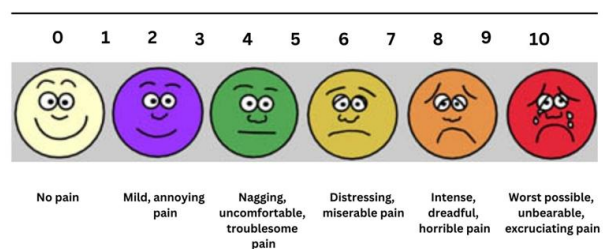


Figure No. 1: The VAS pain scale used to assess patients' subjective pain experience on the seventh post-operative day

Table No. 1: Baseline characteristics of patients

Characteristics	Study group (n = 70)	Control group (n = 70)	p value
Age (years)	40.99	42.89	
Gender			
Male	34	46	
Female	36	24	
ASA grade			
Grade I	37	49	
Grade II	33	21	
Classification			
Grade III	31	42	
Grade IV	39	28	

Table No. 2: VAS scores of patients on the 7th postoperative day

Characteristics	VAS score on 7 th day			
	Mild	Moderate	Severe	Total
Gender				
Male	14	65	1	80
Female	18	41	1	60
Age				
20–30 years	9	21	1	31
31–40 years	6	26	0	32
41–50 years	11	28	0	39
51–60 years	6	31	1	38

Table No. 3: Comparison of mean pain scores among the two groups stratified by effect modifiers

Effect Modifier	Study group	Control group	p value
Gender			
Male	3.68 ± 0.58	6.07 ± 1.04	0.012
Female	3.5 ± 0.5	6.25 ± 1.07	
ASA grade			
Grade I	3.51 ± 0.54	6.18 ± 1.07	
Grade II	3.67 ± 0.54	6 ± 1	
Classification			
Grade III	3.42 ± 0.5	6.24 ± 1.03	
Grade IV	3.72 ± 0.56	5.96 ± 1.07	

DISCUSSION

Hemorrhoids are vascular cushions, anatomical structures found in the anal canal which function as a comfortable barrier to ensure complete closure of the anus.⁹ The displacement of these anal cushions can result in hemorrhoids, a disease with high incidence (> 50%) and varying degrees of severity in the population older than 40 years.¹² The incidence of hemorrhoids does not seem to be linked to gender and has been associated instead with low fiber intake. Painless rectal bleeding during defecation is the most common clinical presentation of the disease. Grade I hemorrhoidal disease is the most common type. For severe forms of hemorrhoidal disease, usually grade III

and grade IV hemorrhoids, surgery is the most effective treatment.¹³

Bacterial colonization of the wound seems to happen immediately after hemorrhoidectomy, yet it does not appear to interfere with the natural healing process, provided the bacterial count remains at $<10^5$. Pain is a complex and subjective phenomenon that is difficult to appreciate and evaluate because patients differ in their individual pain sensitivity. Post-operative pain is frequently reported in patients who undergo surgery and is believed to be caused by the spasm of the anal internal sphincter and by secondary infection of the surgical site.¹⁴ NSAIDs are usually prescribed to patients after hemorrhoidectomy to help with pain relief. However, these are known to cause several side effects, particularly in older people.⁷

Balfour et al. studied the effects of oral metronidazole in 38 patients who had undergone closed hemorrhoidectomy.¹⁵ They found no significant difference in pain scores between patients who received metronidazole and those that did not. By contrast, Al-Mulhim et al. found a significant reduction in pain on post-operative day 7 with an eight hourly administration of 500 mg oral metronidazole.¹⁶ In one study conducted in Pakistan, Tatheer et al. found a significant reduction in post hemorrhoidectomy pain in patients who received topical vs. oral metronidazole.¹⁷

Certain patient characteristics which were most likely to impact pain scores were treated as effect modifiers. These included age, gender, ASA grades, and hemorrhoid grades. Upon stratifying for these factors, we found no statistically significant association between these patient characteristics and pain scores. This implied that age, gender, ASA grade, and hemorrhoid grades did not play an important role in determining the patients' mean pain score.

This study has certain limitations. Some studies have shown the increased efficacy and potential benefits of metronidazole administered via the topical route^{17,18} this study did not consider or compare the oral and topical routes of administration of metronidazole. Moreover, to ensure maximum patient compliance, we only conducted documented pain assessment on the seventh post-operative day and not on the first and third day, as in many other similar studies.

CONCLUSION

Since bacterial colonization is inevitable after hemorrhoidectomy, metronidazole can help reduce post-operative pain by reducing bacterial proliferation and inflammation of the surgical site.

Author's Contribution:

Concept & Design of Study: Sidra Munawar
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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