

Topical Metronidazole for Post-Anal Surgery Pain

Mais S. M. Shamssa*

*Lecturer at the Department of General Surgery/Kufa University and general surgeon at Al-Sadr Teaching Hospital/Najaf/Iraq

Abstract: *Objective:* metronidazole is a widely used antibiotic against anaerobic micro-organisms. Its efficacy in reducing post-anal surgery pain was evaluated in this study. *Design:* A randomized, single blind placebo-control study was conducted prospectively using 60 female patients with 4th grade hemorrhoids and low-lying anal fistulae, who were divided into two equal groups; both received topical three times a day applications of ointments (10% metronidazole versus placebo) for two weeks. Patients were provided with a chart to record their pain at 6hr, 12hr, 4d, 7d, 10d and 14d post-operatively (and the use of injectable non-narcotic analgesic, post-operative complications were also reported). All patients were reviewed 14 days after the surgery. *Results:* Twelve hours post-operatively, significant number of patients in both groups complained of severe pain. Twenty four hours postoperatively, a statistically significant reduction in post-operative pain among metronidazole group was noticed. This pain reduction became more from the 4th post-operative day and on. A statistically-significant reduction in on-defecation pain was noted from the 1st post-operative day among the metronidazole group while more than half of those treated with placebo remained symptomatic even after 2 weeks of surgery. A statistically significant difference in the need for non-narcotic parenteral analgesia was noted between the two studied groups whereby 80% of metronidazole-treated patients needed single daily injection while about 97% of the placebo group needed 2-3 injections per day. Foul smell discharge and pruritus were reported much less in the metronidazole-group than in placebo group ($P=0.0003$ and $P=0.0009$ respectively). Within the metronidazole-treated group, there was no difference in the reduction of post-operative pain, on-defecation pain and other post-operative complications between patients of hemorrhoidectomy and fistulectomy. *Conclusion:* Topical 10% metronidazole is effective in reducing post-operative pain in anal surgeries, reducing on-defecation pain, decreasing analgesic requirements, and minimizing foul smell discharge and pruritus.

Keywords: topical metronidazole, post-operative pain, hemorrhoidectomy, fistulectomy

1. Introduction

Anal surgeries are among the most commonly performed operations all over the world. The most common fear of patients undergoing such surgeries is the postoperative pain which can be quite annoying and may delay return to daily activities⁽¹⁾. Post-anal surgery pain is multifactorial; internal anal sphincter spasm, inflammation and superadded bacterial contamination of the operative site have a role^(2, 3, 4). Indeed the pain intensity has individual variation yet it's related to the extent of excision, defective wound healing and superadded infections^(5, 6). The use of new energy devices (Harmonic Scalpel and LigaSure) has been associated with less post-operative pain but they are expensive if compared with the conventional diathermy techniques^(7, 8). Many pharmacologic agents (with different mechanisms of action) have been tried to decrease the post-operative pain as anesthetics, internal sphincter relaxants, opioid and non-opioid analgesics, flavonoids, sucralfate & antibiotics⁽⁹⁾. Topical preparations are preferred over other dosage forms because of better bioavailability and fewer incidence of side effects⁽¹⁰⁾. Metronidazole is a nitroimidazole member that acts against anaerobic pathogens & protozoa and is used extensively because it is safe, cheap, efficacious, with relatively little side effects⁽¹¹⁾.

2. Patients and Methods

A randomized single-blind placebo-control study was conducted using 60 female patients who were diagnosed with hemorrhoids and anal fistulae at Al-Sadr Teaching Hospital /Najaf between 15th October 2016 and 15th April 2017 (40 patients with hemorrhoids, 20 patients with fistulae). Only patients with grade 4 hemorrhoids (with or without external component) and those with low lying anal fistulae were included in this study. Patients with

high type fistulae, anal fissures and lower grade hemorrhoids were excluded. All the patients were operated upon by the same surgeon under spinal anesthesia (using Marcaine[®] 0.5%) and were discharged home in the same operative day. Morgan-Milligan technique was used for hemorrhoidectomy. Fistulous tracts were completely excised (fistulectomy) and left to heal by secondary intention. The patients enrolled in the study were consented for participation in this trial, and each patient was provided with an ointment reservoir to apply at the wounds 3 times per day for two weeks. The patients were divided into two equal groups each comprises 20 with hemorrhoidectomy and 10 with fistulectomy. The first group was provided with metronidazole ointment while the second with a placebo ointment. The reservoirs were color-coded for purpose of differentiation by the caring doctor. Also they were given a chart (in Arabic) to record their post-operative pain (parenteral non-narcotic analgesic requirements, post-operative complications were also reported). All patients were reviewed two weeks after the surgery.

Preparation of the ointment:

Both the metronidazole and placebo ointment samples were prepared at the College of Pharmacy/Kufa University.

Placebo preparation: The conventional method of fusion was used for the preparation of Lidocaine 10% ointment. Mixture of lidocaine (10% w/w), PEG3350 (2% w/w) was melted on a hot plate by heating it to 75 °C. Then white petrolatum jelly (84% w/w) added to the mixture and melted. Then mixture was removed from the hot plate and was continuously stirred until it congealed

Preparation of metronidazole ointment: Formulation of metronidazole 10% ointment by simple ointment base. A weighed quantity white petrolatum (84% w/w) was taken and melted. To this melt, PEG 3350 (2% w/w), and PEG 400 (4% w/w) were added. The molten mass was removed from the heating source and the stirring was continued until the melt started congealing. When the temperature of the base reached room temperature, metronidazole (10% w/w) was incorporated by the levigation method.

Statistical analysis:

Data were analyzed using Chi-squared test with the help of a senior statistical colleague. P<0.05 was considered of statistical significance.

3. Results

The patients in both groups were comparable in their ages as shown in Table (1)

Age groups (years)	Used metronidazole (n=30)	Used placebo (n=30)
20-30	5	5
31-40	13	13
41-50	9	9
51-60	3	3
>60	0	0
Total	30	30

For about eight hours post-operatively, the patients of both groups did not complain of pain due to the use of long term spinal anesthetic during surgery. Twelve hours post-operatively, significant number of patients in both groups complained of severe pain (22 versus 23). Twenty four hours postoperatively, the number of patients who reported severe pain among the metronidazole group decreased, but the severe pain was still there in the placebo group (15 versus 23); such difference was statistically significant (P=0.04).

From the fourth post-operative day and on, an increasing number of patients in the metronidazole group became less symptomatic so that by two weeks only three patients were complaining of pain. This was different from patients on placebo treatment who remained symptomatic even after two weeks; such difference was statistically significant with P<0.05 as seen in Table (2). There was increase pain recorded at 7th post-operative day possibly due to increased effect of inflammatory edema and bacterial colonization.

Table 2: Post-operative pain among the studied patients as collected from their charts

Post-operative time	Used metronidazole (n=30)	Used placebo (n=30)	RR (95% CI)	P-value
12 hours	22	23	0.9 (0.7-1.3)	0.8
24 hours	15	23	0.7 (0.4-0.9)	0.04*
4 days	9	24	0.4 (0.2-0.7)	0.0008*
7 days	10	27	0.4 (0.2-0.6)	0.0002*
10 days	5	22	0.2 (0.1-0.5)	0.0005*
14 days	3	16	0.2 (0.1-0.6)	0.0035*

*significant

None of the patients passed motion till 10 hours post-surgery. Patients of both groups complained of severe pain on first defecation (25 versus 22). The on-defecation pain progressively decreased in the metronidazole group so that by 14th postoperative day only 5 patients (16.7%) complained of pain on defecation. In contrast, seventeen

(56.7%) of placebo-treated patients remained symptomatic on defecation even after two weeks from surgery. This difference in on-defecation pain improvement was statistically significant from the 1st post-operative day (P<0.05) as shown in table (3).

Table 3: Pain on defecation among the studied groups

Post-operative time	Used metronidazole (n=30)	Used placebo (n=30)	RR (95% CI)	P-value
12 hours	25	22	1.1 (0.8-1.4)	0.7
24 hours	17	30	0.6 (0.4-0.8)	0.0004*
4 days	12	30	0.4 (0.3-0.6)	0.0001*
7 days	12	30	0.4 (0.3-0.6)	0.0001*
10 days	10	28	0.4 (0.2-0.4)	0.0001*
14 days	5	17	0.3 (0.1-0.7)	0.005*

All patients required parenteral non-narcotic analgesic (s) in the post-operative period, but the frequency (and hence the amount) of administered analgesic varies between the two studied groups whereby 80% (24 patients) of metronidazole group needed the analgesic only once daily.

In comparison, about 97% (29 patient) of placebo-treated individuals required 2-3 shots of analgesics per day. Such difference was statistically significant as shown in Table (4).

Table 4: Non-narcotic parenteral analgesic requirements in the studied patients

Parenteral analgesic requirement	Used metronidazole (n=30)	Used placebo (n=30)	RR (95% CI)	P-value
none	0	0	0	1
Once daily	24	1	24 (3.5-166.2)	0.001*
Twice daily	5	17	0.3 (0.1-0.7)	0.005*
Thrice daily	1	12	0.08 (0.01-0.6)	0.01*

Apart from pain, patients reported other complications post-operatively. Three patients in the metronidazole group and five placebo-treated patients (P=0.5) developed urinary retention in the first 24 hours after surgery which responded to urinary catheterization for 6 hours.

One patient in each group developed bleeding between the 7th -10th post-operative days (secondary hemorrhage) and both responded to simple pressure and oral analgesic. There was statistically-significant difference in reporting pruritus and foul smell discharge between the two studied groups as shown in Table (5).

Table 5: Other reported complications in the studied patients

Complication	Used metronidazole (n=30)	Used placebo (n=30)	RR (95% CI)	P-value
Urinary retention	3	5	0.6 (0.2-0.3)	0.5
Bleeding	1	1	1 (0.1-15.3)	1
Foul smell discharge	5	23	0.2 (0.1-0.5)	0.0003*
Pruritus	4	20	0.2 (0.1-0.5)	0.0009*

The metronidazole group patients did complain of initial burning sensation upon applying the ointment but was transient and resolves spontaneously. No skin irritation was reported.

Within the metronidazole group, patients with hemorrhoidectomy did not have statistically-significant difference in post-operative pain, pain on defecation or other complications from those underwent fistulectomy. Tables (6), (7) and (8).

Table 6: post-operative pain among patients within metronidazole group

Post-operative time	Hemorrhoidectomy patients (n=20)	Fistulectomy patients (n=10)	RR (95% CI)	P-value
12 hours	16	6	1.3 (0.8-2.3)	0.3
24 hours	11	4	1.4 (0.6-3.2)	0.5
4 days	7	2	1.7 (0.4-6.9)	0.4
7 days	8	2	2 (0.5-7.7)	0.3
10 days	4	1	2 (0.3-15.6)	0.5
14 days	3	0	-----	0.4

Table 7: Pain on defecation among metronidazole group patients

Post-operative time	Hemorrhoidectomy patients (n=20)	Fistulectomy patients (n=10)	RR (95% CI)	P-value
12 hours	18	7	1.3 (0.8-1.9)	0.3
24 hours	11	6	0.9 (0.5-1.7)	0.8
4 days	7	5	0.7 (0.3-1.6)	0.4
7 days	7	5	0.7 (0.3-1.6)	0.4
10 days	7	3	1.2 (0.4-3.6)	0.8
14 days	4	1	2 (0.3-15.6)	0.5

Table 8: Other post-operative complications in metronidazole patients

Complication	Hemorrhoidectomy patients (n=20)	Fistulectomy patients (n=10)	RR (95% CI)	P-value
Urinary retention	3	0	-----	0.4
Bleeding	1	0	-----	0.8
Foul smell discharge	2	3	0.3 (0.1-1.7)	0.2
Pruritus	2	2	0.5 (0.1-3.04)	0.5

4. Discussion

The most common fear of patients undergoing anal surgeries is the postoperative pain which can be quite annoying and may delay return to daily activities⁽¹⁾; some patients may even refrain from having the surgery

⁽¹²⁾worsening their condition further over time. Post-anal surgery pain is multifactorial; internal anal sphincter spasm, inflammation and superadded bacterial contamination of the operative site have a role^(2, 3, 4). In an attempt to reduce post anal surgery pain, analgesics (both narcotic and narcotic) are prescribed⁽¹³⁾ but these medications are associated with many undesirable effects

and some patients are unable to take them because of their co-morbid conditions⁽¹⁴⁾. Adding lateral internal sphincterotomy to hemorrhoidectomy has reduced pain up to the 9th post-operative day⁽¹⁵⁾ but this intervention has its own complications⁽¹⁾. Post-operative oral flavonoids (Diosmin) and antibiotics has also been used with success to reduce post-hemorrhoidectomy pain^(15, 16). Topical preparations are preferred over other dosage forms because of better bioavailability and fewer incidence of side effects⁽¹⁰⁾. Local nitrates⁽¹⁷⁾, cholestyramine⁽¹⁸⁾, anesthetics⁽¹⁹⁾, sucralfate⁽²⁰⁾ and calcium channel blockers^(21, 22).

Metronidazole is a nitroimidazole member that acts against anaerobic pathogens & protozoa and is used extensively because it is safe, cheap, efficacious, with relatively little side effects⁽¹¹⁾. In proctology, metronidazole is used to treat anaerobic infections. Since bacterial contamination is common after anal surgery, so the use of metronidazole would be expected to help in decreasing bacterial proliferation, inflammation and post-operative pain^(23, 24, 25).

Solorio-Lopez et al (2015) found that use of oral metronidazole for 7 days after hemorrhoidectomy significantly reduced pain, analgesic requirement and time to resumption of daily activities⁽¹⁶⁾.

Compared with the systemic antibiotic therapy, topical delivery of an antibiotic has many advantages such as the high and sustained concentrations at the site of infection; reduced used volume; decreased risk of toxicity and possibly decreasing antibiotic resistance⁽²⁶⁾.

Nicholson and Armstrong (2004) demonstrated that topical application of 10% metronidazole has significantly decreased post-hemorrhoidectomy discomfort at days 7 and 14 post-operatively⁽⁴⁾. Also Ala S. et al (2008) showed that patients who applied topical metronidazole has significantly less post-operative pain than in those in the placebo group up to day 14⁽²⁷⁾. This is comparable to the results we reached in our study where pain reduction among the metronidazole-treated patients was significant from the 24th hour post-operatively and till the patients were reviewed at day 14 post-surgery.

Ala S. et al (2008) showed a significant reduction in analgesic requirements up to day 7 in their study of 47 patients⁽²⁷⁾. Similarly, in our study we found that 80% of metronidazole-treated patients were comfortable with single parenteral analgesic per day whereas about 97% of the placebo-treated patients needed 2-3 doses of parenteral analgesic on daily bases.

Ala S. et al (2008) reported lower on-defecation pain in metronidazole-treated patients (lowest in the 2nd post-operative day)⁽²⁷⁾. In our study, on-defecation pain progressively decreased in the metronidazole group so that by 14th post-operative day only 5 patients (16.7%) complained of pain on defecation. In contrast, seventeen (56.7%) of placebo-treated patients remained symptomatic on defecation even after two weeks from surgery.

We didn't find a study that discusses the effect of topical metronidazole in the reduction of foul smell discharge after anal surgery but low concentration of topical metronidazole (0.75%-1%) has been successfully used to decrease the odor in chronic wounds as pressure ulcers, fungating cancers⁽²⁸⁾. In our study, metronidazole-treated patients reported significantly less malodorous discharge than the placebo-treated patients ($P < 0.05$).

In this study, metronidazole-treated patients complained of significantly less pruritus than the placebo group ($P < 0.05$). However, no study was found for comparison.

We included 20 fistulectomy patients in this study who were divided equally between the two groups. No study was found dealing with the use of topical metronidazole after fistula surgery; but we found a study in which topical application of 7% sucralfate to fistulotomy wounds promoted wound healing and acted as analgesic⁽²⁹⁾.

References

- [1] Gordon's principles and practice of surgery for the colon, rectum and anus, 3rd edition, pages 157, 182-183
- [2] Habeeb F, Shakir E, Bradbury F, et al. Screening methods used to determine the antimicrobial properties of Aloe vera inner gel. *Methods* 2007;42:315-320.
- [3] Maenthaisong R, Chaiyakunapruk N, Niruntraporn S, Kongkaew C. The efficacy of Aloe vera used for burn wound healing: A systematic review. *Burns* 2007;33:713-718.
- [4] Nicholson T, Armstrong D. Topical metronidazole (10 percent) decreases posthemorrhoidectomy pain and improves healing. *Dis Colon Rectum* 2004;47:711-716.
- [5] Riss S, Weisser FA, Schwameis K, et al. The prevalence of hemorrhoids in adults. *Int J Colorectal Dis* 2012;27:215-20. DOI:10.1007/s00384-011-1316-3.
- [6] de Paula PR, Speranzini MB, Hamzagic HC, et al. Bacteriology of the anal wound after open hemorrhoidectomy. Qualitative and quantitative analysis. *Dis Colon Rectum* 1991;34:664-9. DOI:10.1007/BF02050347.
- [7] Chung CC, Ha JP, Tai YP, Tsang WW, Li MK. A double-blind, randomized trial comparing Harmonic Scalpel Hemorrhoidectomy, bipolar scissors hemorrhoidectomy and scissors excision: ligation technique. *Dis Colon Rectum* 2002;45:789-794.
- [8] Kwok SY, Chung CC, Tsui KK, Li MK. A double-blind, randomized trial comparing LigaSure and Harmonic Scalpel Hemorrhoidectomy. *Dis Colon Rectum* 2005;48:344-348.
- [9] Sammor T, Barazanchi AWH, Hill AG. Evidence-based management of pain after excisional hemorrhoidectomy surgery. A PROSPECT Review Update. *World J Surg*. DOI: 10.1007/s00268-016-3737-1.
- [10] Rahimi R, Abdollahi M. A systemic review of the topical drugs for post-hemorrhoidectomy pain.

- International Journal of pharmacology 2012;7:628-638. ISSN 1811-7775/DOI:10.3923/ijp.2012.628.637
- [11] Neshige S, Kanaya Y, Takeshima S, et al. Reversible changes on MRI in a patient with metronidazole-induced encephalopathy. *Rinsho Shinkeigaku* 2015;55:147-7. DOI:10.5692/clinicalneuro.55.174
- [12] Selvaggi F, Pellino G, Sciaudone G, et al. Development and validation of a practical score to predict pain after excisional hemorrhoidectomy. *Int J Colorectal Dis* 2014;29:1401-10. DOI: 10.1007/s00384-014-1999-3
- [13] Khubchandani I. Internal sphincterotomy with hemorrhoidectomy does not relieve pain. *Dis Colon Rectum* 2002;45:1452-1457.
- [14] Garimella V, Cellini C. *Clin Colon Rectal Surg.* 2013 Sep; 26 (3):191-6. DOI: 10.1055/s-0033-1351138
- [15] De Luca S, Tomasello G, Damiano G et al. The management of postoperative pain after hemorrhoidectomy: analysis of three methods. *Acta Med Mediterr* 2012; 28:301-304.
- [16] Solorio-Lopez S, Palomares-Chacon UR, Guerrero-Tarin JE et al. Efficacy of metronidazole versus placebo in pain control after hemorrhoidectomy. *Revista Espanola de enfermedades digestivas: organo oficial de la Sociedad Espanola de Patologia Digestiva* 2015;107:681-685.
- [17] Khan KI, Waqas A, Akmal M et al. Efficacy of combination of 0.2% GTN and lignocaine ointments in wound healing and pain relief after Milligan Morgan hemorrhoidectomy—a comparison with lignocaine and 0.2% GTN ointments separately. *Int J Surg* 2014;12:329-333.
- [18] Ala S, Eshghi F, Enayatifard R et al. Efficacy of cholestyramine ointment in reduction of post-operative pain and pain during defecation after open hemorrhoidectomy. *World J Surg* 2013;37:657-62. DOI:10.1007/s00268-012-1895-3.
- [19] Rahimi M, Kazemini AR, Pourtabatabaei N et al. Comparison of topical anesthetic cream (EMLA) and diclofenac suppository for pain relief after hemorrhoidectomy. *Surg Today* 2012;42:1201-5. DOI:10.1007/s00595-012-0222-9.
- [20] Ala S, Saeedi M, Eshghi F et al. Efficacy of 10% sucralfate ointment in the reduction of acute post-operative pain after open hemorrhoidectomy. *World J Surg* 2013;37:233-8. DOI:10.1007/s00268-012-1805-8.
- [21] Sugimoto T, Tsunoda A, Kano N et al. A randomized, prospective, double-blind, placebo-controlled trial of the effect of diltiazem gel on pain after hemorrhoidectomy. *World J Surg* 2013;37:2454-7. DOI: 10.1007/s00268-013-2124-4.
- [22] Perrotti P, Dominici P, Grossi E et al. Topical nifedipine with lidocaine ointment versus active control for pain after hemorrhoidectomy. *Can J Surg* 2010;53:17-24.
- [23] Silverman R, Benedick P, Wasvary HJ. A randomized, prospective, double-blind, placebo-controlled trial of the effect of a calcium channel blocker ointment on pain after hemorrhoidectomy. *Dis Colon Rectum* 2005;48:1913-6. DOI:10.1007/s10350-005-0135-4.
- [24] Huang H, Nord CE. Can metronidazole still be used for treatment of clostridium difficile infections? *Curr Infect Dis Rep* 2009;11:3-6. DOI:10.1007/s11908-009-0001-y.
- [25] Guy RJ, and Seow-Cohen F. Septic complications after treatment of hemorrhoids. *Br J Surg* 2003;90:147-156.
- [26] Lipsky BA, Hoey C. Topical antimicrobial therapy for treating chronic wounds. *Clin Infect Dis* 2009;49:1541-9.
- [27] Ala S, Saeedi M, Eshghi F, Mirzabeygi P. Topical metronidazole can reduce pain after surgery and pain on defecation in postoperative hemorrhoidectomy. *Dis Colon Rectum* 2008;51:235-238.
- [28] Paul JC, Pieper BA. Topical metronidazole for the treatment of wound odor: a review of the literature. *Ostomy Wound Manage.* 2008;54 (3):18-27
- [29] Gupta PJ, Heda PS, Shrirao SA, Kalaskar SS. Topical sucralfate treatment of anal fistulotomy wounds: a randomized placebo-controlled trial. *Dis Colon Rectum.* 2011;54 (6):699-704. doi: 10.1007/DCR.0b013e31820fcd89