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# Topical Metronidazole for Post-Anal Surgery Pain

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**Abstract:** ***Objective: metronidazole is a widely used antibiotic against anaerobic micro-organisms. It's 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 hemorroidectomy 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, hemorroidectomy, 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 15thApril 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 hemorroidectomy. 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 hemorroidectomy and 10 with fistulectomy. The first group was provided with metronidazole ointment while the second with a placeboointment. 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 7$^{th}$ 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 14$^{th}$ 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 1$^{st}$ 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 $7^{th}$ -$10^{th}$ 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 hemorroidectomy 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 | Hemorroidectomy 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 | Hemorroidectomy 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 | Hemorroidectomy 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 hemorroidectomy has reduced pain up to the 9th post-operative day [15] but this intervention has it's own complications [1].Post-operative oral flavonoids (Diosmin) and antibiotics has also been used with success to reduce post-hemorroidectomy 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 hemorroidectomy 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-hemorroidectomy 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].

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