Diseases of the Colon & Rectum

Topical Metronidazole (10 Percent) Decreases Posthemorrhoidectomy Pain and Improves Healing

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INTRODUCTION: Oral metronidazole has been previously demonstrated to decrease postoperative pain after open diathermy hemorrhoidectomy. The current study investigates the efficacy of topical metronidazole (10 percent) in reducing postoperative pain and promoting wound healing after Harmonic Scalpel® hemorrhoidectomy. METHODS: A prospective, randomized trial was conducted to compare posthemorrhoidectomy pain and wound healing with use of topical metronidazole (10 percent) *vs.* placebo carrier, applied to the surgical site. Surgical indications included grade 3 or 4 internal or external hemorrhoidal disease, with or without a fissure-in-ano. Pain was assessed using a visual analog score (VAS) preoperatively and on postoperative days 1, 2, 7, 14, and 28. Twenty-four-hour narcotic use (hydrocodone 10 mg) was recorded on postoperative days 1, 2, 7, 14, and 28. Digital photographs of the surgical site were taken at 14 days postoperatively. The photographs were independently ranked by three blinded observers according to a) postoperative edema, b) primary *vs.* secondary healing, and c) overall wound healing. RESULTS: Twenty patients were randomized in a prospective manner, ten to the topical 10 percent metronidazole group and ten to the placebo carrier group. Patients in the topical metronidazole group experienced significantly less postoperative pain at day 7 (VAS ± SEM, 3.4 ± 0.4 *vs.* 6.3 ± 0.5; $P = 0.002$) and day 14 (1.0 ± 0.4 *vs.* 3.2 ± 0.7, $P = 0.02$). There was no statistical difference in narcotic analgesic requirements between groups. In the metronidazole group, postoperative edema was ranked significantly lower (mean score, 3.0 *vs.* 7.0, $P < 0.01$) and overall wound healing ranked significantly better (4.0 *vs.* 7.0, $P = 0.03$) than in controls. CONCLUSION: Topical 10 percent metronidazole significantly reduces posthemorrhoidectomy discomfort at days 7 and 14 postoperatively. Postoperative edema is reduced and overall healing is improved, compared with that of carrier controls. [Key words: Hemorrhoidectomy; Metronidazole; Internal hemorrhoids; Postoperative pain]

The single most important challenge after surgical hemorrhoidectomy is the management of postoperative pain. Postoperative pain likely has two major components: first, discomfort from the surgical incision in the uniquely sensitive anoderm and perianal skin and second, discomfort from tissue inflammation resulting from bacterial infiltration of the wound. Decreasing pain from the surgical incision itself can be accomplished by minimizing surgical trauma, for example, by utilizing the Harmonic Scalpel® (Ethicon Endo-Surgery, Inc., Cincinnati, OH), which diminishes thermal injury to the subjacent tissue.[1,2] Decreased postoperative pain after Harmonic Scalpel® hemorrhoidectomy compared with that in electrocautery controls was reported by the senior author,[3] and has since been confirmed by other studies.[4,5]

Prevention of bacterial colonization of the hemorrhoidectomy site has received less attention. Performance of open *vs.* closed hemorrhoidectomy has been claimed to prevent secondary bacterial infection,[6] but has not been conclusively shown to decrease postoperative pain.[7,8] More recently, use of preoperative and postoperative antibiotics (metronidazole) has been studied to determine the effect of decreasing bacterial colonization of the surgical site.[9] In 1998, Carpenti *et al.*[9] demonstrated in a prospective, randomized trial that oral metronidazole significantly decreased postoperative pain after open diathermy hemorrhoidectomy. Results from a subse-

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quent trail by Balfour *et al.*,[10] who studied treatment with oral metronidazole after closed hemorrhoidectomy, showed no difference between groups. However, low pain scores and an insufficient number of patients in the series may have resulted in a Type II error. The current study examines the influence of topical metronidazole (10 percent) on postoperative pain and healing after closed Harmonic Scalpel® hemorrhoidectomy. The premise for topical application of metronidazole to the surgical site was to optimize local tissue concentrations, avoid systemic side effects, and improve bioavailability. An average application volume of 2.5 ml of 10 percent metronidazole cream contains 250 mg of metronidazole. This concentration was chosen to replicate the standard oral metronidazole dosage. Previous pharmacokinetic studies have demonstrated a very low degree of systemic absorption from topical metronidazole application: absorption of aqueous forms of topical metronidazole (MetroLotion® 0.75 percent) is approximately 100 times less than oral administration.[11]

PATIENTS AND METHODS

The study population included 20 patients with grade 3 or 4 hemorrhoidal disease, with significant external components, and with or without a fissure-in-ano. Patients with a neurologic deficit, chronic pain syndrome, or currently taking narcotic analgesics were excluded. All patients gave informed consent before involvement in the study. All patients underwent a closed three-quadrant Harmonic Scalpel® hemorrhoidectomy under general anesthesia, with the patient in prone jackknife position. All procedures were performed by the same surgeon (D.N.A.). The technique of Harmonic Scalpel® hemorrhoidectomy has been described elsewhere.[1,3] In patients requiring fissurectomy and sphincterotomy, the flat blade of the Harmonic Scalpel® was used to cauterize the fissure, and a left lateral internal sphincterotomy was performed, extending to the proximal extent of the fissure.

Before surgery was performed, patients were prospectively randomized into one of two groups. Randomization was performed in a single-blind manner and determined by witnessed coin toss. Identical tubes of metronidazole 10 percent in an inert carrier (petrolatum cream) and tubes containing the inert carrier (petrolatum cream) alone were obtained from a compounding pharmacy (Monfort's Compounding Center, Lawrenceville GA). Study patients applied approximately 2.5 cc of 10 percent metronidazole cream to the surgical site three times daily after a sitz bath or warm soak. Control patients applied the same quantity of the inert carrier three times a day after a sitz bath or warm soak. All patients were supplied with a standard narcotic analgesic (hydrocodone, 10 mg by mouth every 4–6 hours as needed; 25 tablets dispensed), instructed to take a fiber supplement (Konsyl, Konsyl Pharmaceuticals, Edison, NJ) twice daily and 30 cc mineral oil once daily, and maintain a high fluid intake.

Postoperative pain was evaluated using a visual analog score (VAS), which was recorded by the patient on days 1, 2, 7, 14, and 28. Patients in both groups ranked the level of pain from 0 (no pain) to 10 (very severe pain). Twenty-four-hour narcotic analgesic requirement (number of hydrocodone pills) was also recorded by the patient on days 1, 2, 7, 14, and 28. Patients were evaluated at two and four weeks postoperatively, and the completed data sheets were collected at the four-week visit. Pain scores at each time interval were compared between groups with Wilcoxon's rank-sum test (nonparametric analysis of ranked data). Twenty-four-hour analgesic requirements on each study day were compared between groups with a two-sample *t*-test (parametric analysis of quantitative data).

Wound healing was evaluated at two weeks by taking a high-quality color digital photograph of the surgical site. At the end of the study, three surgeons independently ranked the surgical incisions in a double-blinded manner. Each photograph was graded on a scale of 1 to 10, in three different categories: A, postoperative incisional edema (score: 1, absence of edema, to 10, extensive edema); B, primary *vs.* secondary wound healing (score: 1, well-healed incision, primary intention healing, to 10, wide open incision, secondary intention healing); and C, overall wound healing (1, overall well-healed incision, to 10, overall poor healing). For each category (A, B, and C), each of the three surgeons ranked all photographs and a mean rank for each photograph was calculated. Thus, all photographs had three mean ranks (one from each observer) for categories A, B, and C. Ranking in categories A, B, and C were then compared between metronidazole and control groups with the Mann-Whitney *U* test (nonparametric analysis of unpaired ranked data).

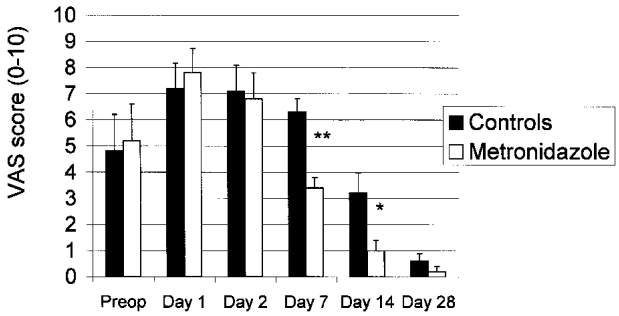

Figure 1. Pain scores (visual analog scores (VAS)) before and after hemorrhoidectomy in topical metronidazole group and controls. Metronidazole patients reported significantly less pain at days 7 and 14, compared with controls (mean ± SEM; $^{**}P = 0.002$, $^{*}P = 0.02$, respectively, Wilcoxon's rank-sum test).

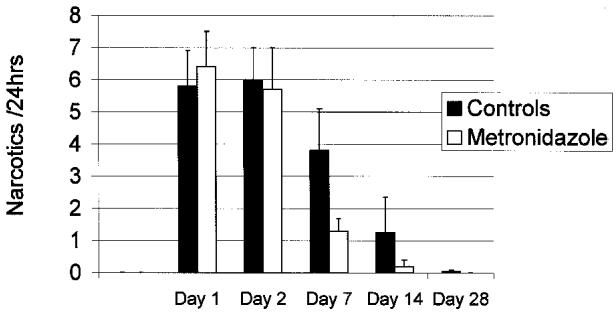

Figure 2. Posthemorrhoidectomy narcotic analgesic requirements. There was no statistical difference in narcotic requirements between the metronidazole patients and controls (mean ± SEM).

RESULTS

Twenty patients were prospectively enrolled in the study during the six-month study period. Ten patients received 10 percent metronidazole cream and ten patients received the inert carrier. None of the patients were lost to follow-up, and data collection was complete. The metronidazole and control groups were comparable in terms of age (mean ± standard error of the mean (SEM), 47.7 ± 3.2 years *vs.* 48.5 ± 3.1 years) and gender (males/females, 6:4 *vs.* 7:3). Three patients in the metronidazole group and four patients in the control group had an associated fissure-in-ano and underwent fissurectomy and sphincterotomy in addition to hemorrhoidectomy.

There was no significant difference between groups in preoperative pain scores or pain scores on days 1 and 2. Patients in the topical metronidazole group experienced significantly less postoperative pain at day 7 (VAS ± SEM, 3.4 ± 0.4 *vs.* 6.3 ± 0.5; $P = 0.002$) and day 14 (1.0 ± 0.4 *vs.* 3.2 ± 0.7; $P = 0.02$). There was no significant difference between groups on day 28 (Fig. 1).

There was no significant difference in narcotic requirements between metronidazole and control groups ($P = 0.32$; Fig. 2). To demonstrate significantly lower narcotic analgesic requirements in the metronidazole group at day 7 (and reach a power factor of 0.8), a total of 19 patients would have been required in each group.

Wound healing in the metronidazole group was significantly better than in controls when ranked according to category A, postoperative edema (mean score, 3.0 *vs.* 7.0; $P < 0.01$). In addition, category C, overall wound healing, ranked significantly better in the metronidazole group (mean score, 4.0 *vs.* 7.0; $P = 0.03$) than in controls. There was no difference between groups when incisions were ranked according to category B, primary *vs.* secondary healing ($P > 0.05$). Interobserver variation for all categories was 88.5 percent. Consistency was highest in category B (primary *vs.* secondary healing, 93 percent consistency), even though no difference was identified between groups. Interobserver consistency was 88 percent in category A (wound edema) and 83.5 percent in category C (overall healing).

DISCUSSION

The role of bacterial colonization in posthemorrhoidectomy pain is unknown.[12] Leaving the surgical site open to facilitate drainage and prevent bacterial infection has been proposed to decrease postoperative pain. In one prospective study of open *vs.* closed hemorrhoidectomy, Ho *et al.*[6] reported faster healing times (4.9 weeks) after open procedures, compared with 6.9 weeks after closed hemorrhoidectomy. By contrast, proponents of the closed technique[7,8] claim less postoperative pain, fewer complications, and shorter hospital stays, compared with open hemorrhoidectomy. With many additional variables at work,[7,8] the role of bacterial colonization in posthemorrhoidectomy pain is difficult to determine. Practically every posthemorrhoidectomy incision appears edematous during the first few days and weeks after surgery, and much of this tissue edema is almost certainly the result of factors other than bacterial infiltration.

Bacteriological studies of posthemorrhoidectomy incisions provide no clarification of the role of bacteria in postoperative pain, edema, or healing. Perianal abscess, cellulitis, and gangrene are remarkably rare after hemorrhoidectomy: Retrospective studies report

abscess or fistula in only 0 to 2 percent of otherwise healthy patients.[1,6–8,13–16] Even with this low incidence, most of these cases probably result from technical failures, rather than exclusively from bacterial invasion of the surgical site. De Paula *et al.*[17] examined the bacterial flora of posthemorrhoidectomy incisions for up to four weeks after surgery: all hemorrhoidectomy incisions were colonized by aerobic bacteria by day 20, yet all healed without obvious signs of sepsis. Surprisingly, no anaerobic organisms were isolated from any incision at any time in the study. Conversely, Brook and Frazier[18] cultured needle aspirates of "infected" hemorrhoids in 19 patients and isolated anaerobes alone in 6 patients (32 percent), mixed anaerobes and aerobes in 12 patients (63 percent), and aerobes alone in only 1 patient (5 percent). In both these studies, the predominant aerobe isolated was *E. coli*, and the most common anaerobes were *B. fragilis* and *Peptostreptococcus.*

Metronidazole, the most common antibiotic used against anaerobic bacteria, has a long-recognized and very useful role in treating a wide variety of anorectal conditions.[19–21] Its efficacy may be in part bactericidal, in addition to its lesser-understood anti-inflammatory actions.[22] This latter property is used in treatment of other inflammatory skin conditions, such as rosacea.[23,24] Metronidazole is frequently the first-line medication used in treating anorectal Crohn's disease,[19,21] a difficult and intractable anorectal condition that frequently results in proctocolectomy and a permanent ileostomy.

In 1998, Carapeti *et al.*[9] reported a potential role for oral metronidazole in diminishing postoperative pain after open diathermy hemorrhoidectomy. This prospective, double-blind study demonstrated a significant decrease in postoperative pain on days 5 to 7 in metronidazole patients, greater patient satisfaction, and earlier return to work, compared with placebo controls.

The rationale for using topical metronidazole in posthemorrhoidectomy pain relief was to increase drug bioavailability. The greater tissue concentrations would, in theory, potentiate the anti-inflammatory and antimicrobial actions, compared with an equivalent oral dose. The final 10 percent topical metronidazole concentration was chosen to reproduce the standard 250-mg oral dosage (since an average 2.5 cc application contains 250 mg metronidazole). Repeating the topical application three times a day again reproduces the standard oral regimen. The conversion of an equivalent oral to topical dose not only increases bioavailability but also avoids systemic side effects. Petrolatum was chosen as the carrier medium, because this is the most common carrier vehicle used for topical anorectal preparations, the medium is retained at the site of application for substantial period of time, and it has no adverse pharmacological interaction with metronidazole.

In the current study, no difference in postoperative pain was found on days 1 or 2, but the metronidazole group experienced significantly less pain by days 7 and 14. These findings are consistent with Carapeti's study, in which a similar visual analog score was used, which reported no difference between groups on days 1 through 4, but significantly less pain on days 5, 6, and 7.[9] Visual analog scores were not continued beyond day 7 in the Carapeti study. These findings suggest that pain in the first few days after hemorrhoidectomy is purely surgical in nature and unrelated to bacterial infiltration or tissue edema. In the current study, there was no statistical difference in narcotic analgesic requirements between groups, although metronidazole patients tended to require fewer narcotics on days 7 and 14. After day 2, narcotic requirements were so low that any statistical difference between groups would have required a larger number of patients (specifically, 19 in each group to demonstrate a statistical difference at day 7). The failure to demonstrate a difference in narcotic requirements may therefore be a Type II error.

Evaluation of wound healing in the current series is a new and previously unreported modality of evaluating posthemorrhoidectomy healing. By taking standard digital photographs at a standard two-week postoperative interval and evaluating these by three blinded observers, an impartial and semiquantitative measure of healing was established. Of note is the finding that incisional edema was consistently ranked less in the metronidazole group, compared with carrier controls' rankings. Tissue edema may result from secondary bacterial infiltration or it may be an exaggerated manifestation of the normal healing process. The diminished edema in the metronidazole group may have been a result of the drug's bactericidal or anti-inflammatory actions. Posthemorrhoidectomy edema usually manifested as raised and even "rolled-over" incisional margins, often with "fleshy" skin tags and tissue induration (Fig. 3). In the metronidazole group, the tissue margins appeared consistently flat, well defined, and with an absence of tissue edema, and skin tags were less prominent (Fig. 4). The diminished postoperative pain in the metronidazole

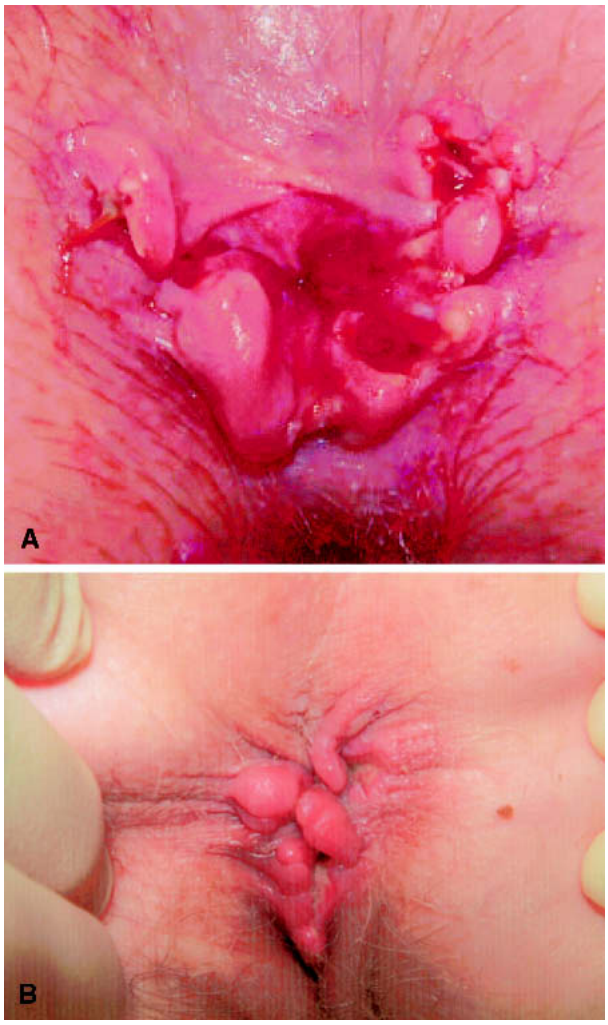

Figure 3. A, B. Control patients: posthemorrhoidectomy surgical incisions, two weeks after three-quadrant closed hemorrhoidectomy. Note extensive incisional edema, with "rolled-over" incision margins and "fleshy" skin tags. Both patients ranked consistently high for incision edema and ranked low for overall healing.

group may be directly or indirectly related to the diminished tissue edema, because both variables were recorded at the same two-week interval after surgery.

Overall wound healing in the metronidazole group was also ranked significantly better than by controls, again reflecting the relative absence of tissue edema, less prominent skin tags, and "cleaner" incisions. Primary *vs.* secondary healing was similar between groups. This factor is primarily caused by local disruption of the incisions, a frequent finding after closed hemorrhoidectomy, or to the large size or grade of the hemorrhoids. Since grade 4 hemorrhoids were equally distributed in both metronidazole and control groups, a similar rate of mechanical wound disruption may be expected in both groups.

Figure 4. A, B. Metronidazole patients: posthemorrhoidectomy incisions, two weeks after three-quadrant closed hemorrhoidectomy. Incisions appear healthy, even at two weeks after surgery (note persistent chromic catgut suture in a). The incision margins are flat, the suture line is intact, and no edematous skin tags are noted. Both patients ranked consistently low for incision edema and ranked high for overall healing.

The beneficial role of topical 10 percent metronidazole may be antibacterial or anti-inflammatory in nature. Topical application improves bioavailability and avoids side effects frequently seen with systemic use.

CONCLUSION

The current study demonstrates the efficacy of topical 10 percent metronidazole in diminishing postoperative pain and improving wound healing after Harmonic Scalpel® hemorrhoidectomy.

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