ORIGINAL PAPERS

Efficacy of metronidazole *versus* placebo in pain control after hemorrhoidectomy. Results of a controlled clinical trial

Sergio Solorio-López[1], Ulises Rodrigo Palomares-Chacón[1], Jesús Enrique Guerrero-Tarín[1], Alejandro González-Ojeda[2], José Antonio Cortés-Lares[2], Jorge Rendón-Félix[2], Jesús García-Rentería[2], Mariana Chávez-Tostado[2], Lizbeth Cuesta-Márquez[2], Marcela Salazar-Parra[2] and Clotilde Fuentes-Orozco[2]

[1]Department of Coloproctology. [2]Research Unit in Clinical Epidemiology. Specialties Hospital of the Western National Medical Center. Mexican Institute of Social Security. Guadalajara, Jalisco. México

ABSTRACT

Introduction: Hemorrhoidal disease occurs in 50% of people aged > 40 years and is the most common reason for anorectal surgery. Pain is the main complication. Multiple topical and systemic drugs have been investigated for pain control, but there is no ideal treatment. Metronidazole has been shown to decrease postoperative pain but is not used widely.

Objective: To evaluate the effect of oral metronidazole *versus* placebo and to assess postoperative pain following hemorrhoidectomy.

Material and methods: Controlled clinical trial in adult patients who underwent elective hemorrhoidectomy for grade III/IV hemorrhoids. Patients were assigned to receive metronidazole (500 mg q8 h orally; study group, SG) or placebo (control group, CG) for 7 days after surgery. Pain was assessed using a visual analog scale after surgery. Analgesic administration (time and use of analgesics) and resumption of daily life activities were also assessed.

Results: Forty-four patients were included, 22 in each group. Postoperative pain differed significantly between the SG and CG at 6 h (3.86 ± 0.56, 6.64 ± 1.49), 12 h (5.59 ± 1.33, 8.82 ± 0.79), 24 h (6.86 ± 1.49, 9.73 ± 0.45), day 4 (5.32 ± 2.10, 9.50 ± 0.59), day 7 (3.14 ± 1.03, 7.36 ± 1.39), and day 14 (2.14 ± 0.46, 5.45 ± 1.29). The first analgesia dose was required at 21.27 ± 5.47 h in the CG and 7.09 ± 2.36 h in the SG (p < 0.05), the time of analgesic use was 6.86 ± 1.61 days in the CG and 13.09 ± 2.48 days in the SG (p < 0.05), and resumption of daily activities occurred at 7.59 ± 1.56 days in the CG and 14.73 ± 3.76 days in the SG (p < 0.05).

Conclusion: Oral administration of metronidazole is effective in pain management after hemorrhoidectomy.

Key words: Hemorrhoidectomy. Metronidazole. Postoperative pain.

INTRODUCTION

Hemorrhoids are anatomical structures known as vascular cushions and are found in the anal canal, where they function as a comfortable barrier to ensure complete closure of the anus (1). Hemorrhoidal disease is defined as the symptomatic displacement of the anal cushions (2). Fifty percent of the population aged > 40 years has some degree of hemorrhoidal disease (prevalence: 4.4%), with grade I being the most common type. The incidence is similar in both men and women, and hemorrhoidal disease is associated with a low fiber intake. Painless rectal bleeding during defecation is the most common form of clinical presentation (3) and surgery is the most effective treatment for grade III and IV hemorrhoidal disease (1,2,4-6). Although surgery is an elective treatment for prolapsed or thrombosed hemorrhoids, pain remains the most common symptom found in postoperative patients (1,7) and is believed to be caused by spasm of the anal internal sphincter and secondary infection of the surgical site (8). Pain is a complex and subjective phenomenon that is difficult to appreciate and evaluate because patients differ in their individual pain sensitivity.

MATERIAL AND METHODS

Controlled clinical trial

The controlled clinical trial involved patients of either gender with diagnosed grade III or IV hemorrhoidal disease of class I or II in the American Society of Anesthesiologists classification. All patients received peripheral intravenous fluids and underwent surgery if they were hemodynamically stable. Spinal anesthesia was performed using a needle at the L3-L4 level. The subarachnoid space was accessed and bupivacaine 0.5% (10 mg) was injected within < 1 min. The Ferguson technique was used: The patient was placed in the jackknife position, aseptic and antiseptic techniques were used,

anal dilatation was performed through the rectal tract, and a Pratt scope was positioned to assess the extent of the disease. The hemorrhoidal plexus was removed with a scalpel incision, cauterization was used to ensure hemostasis, and chromic catgut 00 continuous sutures were used in all patients. All procedures were performed by the same surgeons (GLL, PCUR, GTJ). During the postoperative period, diclofenac was administered (100 mg orally, every 12 h), and paracetamol (1 g orally, every 8 h). Rescue analgesia was used if required when a patient reported pain > 5 on a visual analog scale (range, 0-10); analgesia was given as 150 μg of subcutaneous buprenorphine.

The patients were assigned to two groups: A study group (SG), which was treated with 500 mg of metronidazole given orally every 8 h for 7 days, and a control group (CG), which was treated with a homologated placebo using the same dosage and therapeutic scheme. The drug or placebo was administered to both groups 2 h after surgery. Homologated placebo was made from calcinated magnesia.

Randomization was performed using a closed-envelope system. The variables included in the analysis were: Age; gender; body mass index; postoperative pain measured on the visual analog scale at 6 h and 12 h, and days 1, 4, 7, and 14 after surgery (the last three via telephone); need for rescue analgesia during the hospital stay; first analgesia dose and its duration; complications during and after the surgical procedure; and the number of days required before resumption of daily life activities.

Patients were questioned specifically about the intensity of pain during defecation at home, and the highest value was used in the analysis. All patients were discharged from the hospital 24 h after the surgical intervention and were told to use a stool softener (psyllium from *Plantago*, 10 g daily) and to drink plenty of fluids to avoid constipation.

Sample size

The sample size was calculated by estimating that there would be a 45% reduction in the intensity of pain during the first 24 h and on days 4, 7, and 14 after surgery. Using this value and a 95% confidence interval and 80% power yielded a sample size of 22 patients per group. The envelopes were prepared by personnel unrelated to the study. In the operation room, each patient took an envelope randomly and delivered it to the responsible nursing staff in the postoperative care room, who gave the patients 21 tablets of either the antimicrobial prophylaxis or the placebo in a sealed blister pack.

Statistical analysis

Descriptive analysis included the mean and standard deviation for quantitative variables and raw numbers and percentages for qualitative variables. Inferential statistical analyses included parametric Student's t test for independent samples and the χ^2 test and/or Fisher's exact test. A p value of < 0.05 was considered significant. Office Excel 2007 (Microsoft Corp., Redmond, WA, USA) and SPSS version 20 for Windows (IBM Corp., Armonk, NY, USA) were used for data processing and statistical analysis, respectively.

Ethical considerations

The study was conducted according to the principles of the Declaration of Helsinki of 1989 and the Mexican Health Guidelines. The study protocol was approved by the Local Committee for Ethics and Health Research (2013-1301-71) and is registered at www.clinicaltrials.gov with the identifier number NCT02328144. All patients included gave their signed informed consent to participate in this study.

RESULTS

The general characteristics of the patients are described in table I. From July 2013 to October 2014, 44 patients were included (22 in each group). The SG comprised 17 male and five female patients, with a 3.4:1 ratio; the CG included 11 male and 11 female patients, with a 1:1 ratio (p = 0.58). The average age was 50.1 ± 16 and 42.4 ± 18.5 years in the SG and CG, respectively (p = 0.147). Body mass index was 33.2 ± 2.1 kg/m^2 in the SG and 32.2 ± 3 in the CG (p = 0.21). According to the hemorrhoidal disease classification, in the SG, 16 patients were classified as having grade III disease, and six patients had grade IV disease. In the CG, 21 patients had grade III disease, and one patient had grade IV disease (p = 0.47).

All procedures were completed without any adverse events. As shown in figure 1, the respective scores for pain on the visual analog scale for the SG and CG were 3.86 ± 0.56 and 6.64 ± 1.49 (p = 0.03) at 6 h; 5.59 ± 1.33 and 8.82 ± 0.79 (p = 0.02) at 12 h; 6.86 ± 1.49 and 9.73 ± 0.45 (p = 0.03) at 24 h; 5.32 ± 2.10 and 9.50 ± 0.59 (p = 0.001) on day 4; 3.14 ± 1.03 and 7.36 ± 1.39 (p = 0.002) on day 7; and 2.14 ± 0.46 and 5.45 ± 1.29 on day 14 (p = 0.001).

None of the patients in the study required rescue analgesia. All patients in the CG and six patients in the SG required the first analgesic dose after 6 h. Analgesic consumption was needed for 6.86 ± 1.61 and 13.09 ± 2.48 days for the SG and CG, respectively (p < 0.05). One

Table I. Baseline characteristics of patients

Characteristics	Study group (n = 22)	Control group (n = 22)	p value
Age (years)	50.1 ± 16.0	42.4 ± 18.5	0.147
Gender:			
Male	17	11	0.58
Female	5	11	
BMI (kg/m^2)	33.2 ± 2.1	32.2 ± 3.0	0.21
ASA I/II	22	22	NC
Classification:			
Grade III	16	21	0.47
Grade IV	6	1	

BMI: Body mass index; ASA: American Society of Anesthesiologists; NC: Not calculable.

patient in each group developed urinary retention (p = 0.75). The time until resumption of daily life activities was 7.59 ± 1.56 and 14.73 ± 3.76 days for the SG and CG, respectively (Fig. 2).

DISCUSSION

The exact pathophysiology of hemorrhoidal disease remains poorly studied and understood. The theory that hemorrhoids develop because of varicose veins in the anal canal is obsolete (1) and has been replaced by the theory that decay or deterioration of the cushions is responsible for hemorrhoid formation (9). Using the pectinate line as the reference, hemorrhoids are classified as external, internal, or mixed. The most common symptoms after hemorrhoidectomy include bleeding, edema, foul-smelling discharge, anal itching, and pain, the latter of which is the first to appear and the most feared by patients. Pain intensity can be influenced by excessive resection, defective wound healing, and concomitant and aggravated infections caused by constipation, diarrhea or fecal impact (4,11). In addition, pain is the main reason why patients avoid or delay surgery (12), which can worsen the prognosis over the medium and long term. Urinary retention and constipation are other surgery- and pain-related complications (13). Postoperative pain management is crucial in patients whose etiology is related to surgical trauma and bacterial colonization of the surgical wound (11).

There are many approaches and treatments for postoperative pain management after hemorrhoidectomy, including local treatments such as the use of nitrates, anion exchange resins (cholestyramine), complex aluminum sucrose sulfates (sucralfate), topical anesthetics, analgesics, and calcium channel blockers (such as nifedipine and diltiazem) (8,14-20). Metronidazole was discovered in 1950 and synthesized in 1957. It is an antimicrobial drug from the nitroimidazole family that acts primarily as a broad-spectrum antibiotic against anaerobic pathogens and protozoans (21,22). Metronidazole is used in clinical practice and surgery, and is also used with good results to treat Crohn's disease (23) and for *Helicobacter pylori* infection eradication (24) and colonic preparation before colorectal surgery (25). Metronidazole is used widely because of its efficacy, safety, low cost, and low rate of adverse events (21,26). In the proctology field, it is used in combination with other antibiotics against infections by anaerobic bacteria, according to the extent and severity of the injury. Considering that bacterial colonization is inevitable after hemorrhoidectomy, it is not surprising that antibiotics such as metronidazole help reduce bacterial proliferation, inflammation, and postoperative pain (18,22).

In 1998, Carapeti et al. (27) conducted a study with 40 patients who ingested 400 mg of prophylactic metronidazole for 7 days after surgery. They used a visual analog scale to assess postoperative pain daily for the first 7 postoperative days and on day 14. The patients' satisfaction improved and daily life activities resumed more quickly in these patients compared with controls, and the authors postulated that postoperative pain might be caused by secondary infection, which can be treated with antimicrobial prophylaxis. Balfour et al. (28) conducted a study involving the delivery of 400 mg of metronidazole every 8 h in 38 patients undergoing a closed hemorrhoidectomy. However, they found no significant difference between groups to support the use of metronidazole. By contrast, Al-Mulhim et al. (29) studied 84 patients who received the antibiotic and 82 patients who did not. The patients in the antibiotic group were treated with 500 mg of intravenous metronidazole combined with anesthesia, two additional doses of metronidazole at 2 and 10 h after surgery, and continued to receive 500 mg of oral metronidazole every 8 h for 3 days. They found a significant reduction in the intensity of pain on postoperative day 7 and faster resumption of daily life activities in the group that received metronidazole. In 2004, a study of 20 patients using 10% topical metronidazole cream showed a sustained increase in bioavailability of the drug, with a secondary benefit of reduced systemic effects.
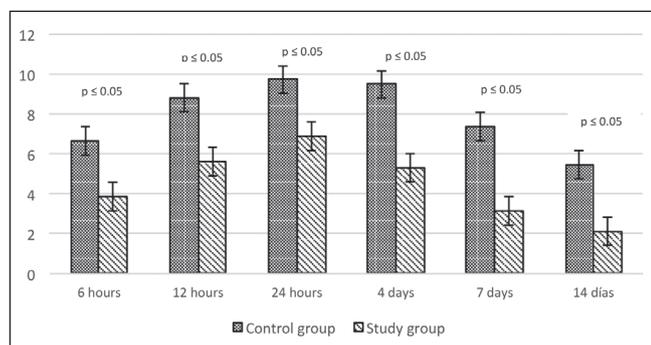

Fig. 1. Pain evolution in the postoperative period. Comparison of postoperative pain between the control group and study group. The groups differed significantly at all times.
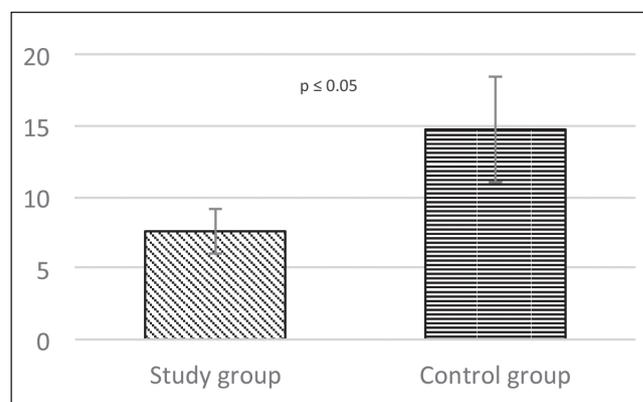

Fig. 2. Daily routine reincorporation. Comparison of days required until resumption of daily life activities during the postoperative period.

In our study, there was less postoperative pain 7 and 14 days after surgery in the SD compared with the CG. This suggests that postoperative pain in the first hours and days might be related to the surgical manipulation of tissues and subsequent edema and bacterial colonization (30). Ala et al. (31) confirmed that pain during the first hours and days following hemorrhoidectomy is caused mainly by local inflammation, whereas bacterial colonization is the main cause of pain several days after surgery. One important aspect to consider is that even though bacterial colonization of the wound occurs after hemorrhoidectomy, it does not appear to interfere with healing. In a clinical trial reported in 2014, Khan et al. (32) gave preoperative intravenous antibiotics (ceftriaxone or metronidazole at 1 g and 500 mg, respectively, n = 50 per group) to patients who underwent open hemorrhoidectomy. They found no significant differences between groups for pain intensity, healing time, and resumption of daily life activities, infectious events, or transient bacteremia.

Regardless of the technique used to perform a hemorrhoidectomy, bacterial colonization seems to occur immediately after surgery but does not affect the healing mechanism provided the bacterial count remains at $< 10^5$ bacteria per gram of tissue (11). When given as a topical or systemic drug, metronidazole may limit the inflammatory phase of scarring and may reduce the bacterial count sufficiently to allow the transition to the fibroblastic phase and rapid granulation of scarring, which thereby decreases postoperative pain. One-dose antimicrobial prophylaxis appears to have no effect on pain control (32) because the effect is limited as the antibiotic disappears from circulation; during this time, bacterial colonization occurs at various levels according to the extent of tissue injury, virulence of germs, and host conditions. Except for one study (28), other studies that have used topical antibiotic or oral treatment for at least 4 days after surgery have shown significant reduction in postoperative pain intensity (27,29-31). No major procedure-related complications or adverse events have been reported in relation to antimicrobial use.

Currently, there is not enough information about the local and systematic inflammatory responses to hemorrhoidectomy. Only local pain and inflammation have been reported, and the pathophysiological and immunological processes involved have not been studied. Similarly, there is no gold standard treatment or method for pain management in hemorrhoidal disease, which leaves this subject open for further discussion and research.

In conclusion, oral administration of metronidazole was an effective therapeutic intervention for pain control after closed hemorrhoidectomy. This finding suggests that the use of an initial analgesic treatment reduces postoperative pain during defecation. Daily life activities were also resumed earlier in the group that received metronidazole. The aim of the study was to confirm the previous literature regarding the use of metronidazole as an analgesic agent and to recommend the standardization of its use. Our findings suggest that future research should focus on the systemic inflammatory response underlying postoperative pain in patients after hemorrhoidectomy.

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