

Micronized Flavonoids in Pain Control After Hemorrhoidectomy: A Prospective Randomized Controlled Study

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Abstract

Purpose. We conducted a prospective randomized controlled study to evaluate the effect of micronized flavonoid fractions (MFF) on pain after hemorrhoidectomy.

Methods. The subjects were 112 consecutive patients randomly assigned either to receive MFF (group 1) for 1 week or not to receive MFF, as a control (group 2), after hemorrhoidectomy. The severity of pain and the number of intramuscular analgesic injections required were recorded for the first 3 days, then 1 week after hemorrhoidectomy. The number of days that intramuscular analgesic injections were required, hospital stay, and patient satisfaction were also assessed.

Results. On postoperative day (POD) 1, there were no significant differences between the parameters of the two groups, but on PODs 2 and 3, both the pain score ($P = 0.033$ and $P = 0.011$, respectively) and the number of patients who required intramuscular analgesic injections were significantly less in group 1 ($P = 0.022$ and $P = 0.007$, respectively). Moreover, the hospital stay was shorter and patient satisfaction was superior in group 1 ($P = 0.001$ and $P = 0.001$, respectively). After 1 week, the pain score and number of intramuscular analgesic injections given were significantly less in group 1 ($P = 0.001$ and $P = 0.021$).

Conclusion. Using MFF after hemorrhoidectomy reduced the severity of pain and intramuscular analgesic requirement.

Key words Daflon · Hemorrhoids · Micronized flavonoid · Pain control

Introduction

Hemorrhoidectomy is the most effective treatment for third- or fourth-degree symptomatic hemorrhoids,¹ but the associated postoperative pain is still a major concern,^{2,3} and the main reason patients refuse to undergo this procedure. The pathogenesis of hemorrhoids includes degeneration of connective tissue, stagnation and stasis of blood in the vascular plexus of the anal cushions,⁴ marginalization of white cells⁵ and their activation, and the release of inflammatory substances such as prostaglandins and free radicals⁶ resulting in sterile inflammation.⁷ This inflammation can cause pain after hemorrhoidectomy. Daflon 500 mg (Les Laboratoires Servier, Gidy, France) is a flavonoid fraction, purified and micronized to particles of less than 2 μm , containing 90% diosmin and 10% hesperidin,⁸ which inhibits certain pathways of inflammatory response.^{9–12} Micronized flavonoid fractions (MFF) have been shown to effectively resolve the acute and chronic symptoms of hemorrhoids, and significantly reduce the severity of pain caused by first- and second-degree hemorrhoids.^{13,14} Although they have become widely used, to our knowledge, only one other study by Ho et al.¹⁵ has described their use after hemorrhoidectomy.

This prospective randomized controlled study was conducted to investigate the efficacy of MFF on pain after hemorrhoidectomy.

Patients and Methods

A total of 112 consecutive patients with symptomatic third- or fourth-degree hemorrhoids who underwent hemorrhoidectomy between August 2001 and May 2002 were enrolled in this study, which was approved by the local ethics committee of the University Hospital, Mersin. Informed consent was obtained from all patients. Preoperative assessment included documenta-

tion of symptoms, routine clinical examination, and sigmoidoscopy to exclude other pathologies in the anus and rectum. Patients with concomitant anal disease such as fissure, abscess, fistula, Crohn's or ulcerative colitis, or rectal cancer, and those taking oral anticoagulants were excluded. Surgical hemorrhoidectomy was indicated to treat symptomatic hemorrhoidal prolapse in all 112 patients. First, we gave 133 ml sodium phosphate (Fleet enema, C.B. Fleet, Lynchburg, VA, USA) 6 h before surgery for bowel preparation. Postoperatively, the patients were randomly assigned either to receive MFF (group 1, $n = 56$) or not to receive MFF, as a control (group 2, $n = 56$) according to a computer-generated list. Assessment was done by an independent blinded observer. Hemorrhoidal prolapse was associated with anal pain in 26 and 24 patients from groups 1 and 2, respectively, with bleeding in 22 and 28 patients from groups 1 and 2, respectively, and with anal itching in 10 and 8 patients from groups 1 and 2, respectively.

All patients underwent standard three-column hemorrhoid excision under general anesthesia. The hemorrhoids were prolapsed and retracted from the anal canal and a V-shaped anal incision was made at the base of the hemorrhoids, which were dissected from the anal sphincter up to the level of the vascular pedicle. The pedicle was transfixed. We did not perform anal dilatation or lateral internal sphincterotomy in any patient.

The patients in group 1 were given MFF according to the standard regimen offered for the treatment of acute hemorrhoid disease, as 1500 mg orally twice a day for 3 days followed by 1000 mg orally twice a day for the next 4 days. A linear analogue pain scale from 0 to 10 was used to evaluate pain, where 0 corresponded to no pain and 10 to the most severe pain imaginable.^{3,16} The pain scores were recorded daily for the first 3 postoperative days (PODs) at about the same time each morning, then after 1 week in the control examination. Analgesics were given according to the following protocol: diclofenac sodium (Volteren, Novartis, Istanbul, Turkey) was given intramuscularly when the pain score was 5 or more and dipyrone (Novalgine, Hoechst Marion Roussel, Istanbul, Turkey) was given orally when the pain score was 4 or less. A surgeon from another team, who was blinded to MFF administration, assessed the pain score and decided the most appropriate analgesic to give. The quantity of analgesics was regulated according to each patient's requirement. Postoperative hemorrhage was recorded if the hemoglobin level dropped significantly, and the patient required resuscitation, blood transfusion, or any form of homeostasis. Patients were discharged from hospital when they no longer required intramuscular analgesics regardless of whether they had had a bowel movement. The patients were also asked to measure their overall level of satis-

faction, from 1 = poor to 4 = excellent, 1 week after their hemorrhoidectomy.

Statistical Analysis

Statistical analysis was done using the χ^2 and Mann-Whitney U -tests where appropriate, and the Wilcoxon signed-ranks test for satisfaction. Results are expressed as medians with ranges in parentheses or as a number with percentages in parentheses. According to Pocock's formula,¹⁷ about 50 patients in each arm should be evaluated to calculate an expected reduction in postoperative pain of 40% with an α error of 5% and a β error of 20%. The sample size was determined before the study and 56 patients were established in each arm to provide meaningful statistical power analyses.

Results

Group 1 consisted of 24 women and 32 men with a median age of 41 (22–86) years. Group 2 consisted of 22 women and 34 men with a median age of 45 (32–63) years. There was no significant difference in the gender or age distribution of patients between the two groups ($P = 0.065$ and $P = 0.424$, respectively). There were also no significant differences in the degree of hemorrhoids between the groups ($P = 0.399$). Postoperative local complications were not recorded; however, one patient in group 1 and two patients in group 2 required transfusion of one unit of packed cells after their hemorrhoidectomy. No patient required further surgical intervention due to bleeding.

All patients received postoperative analgesics according to the study analgesic protocol, which consisted of sufficient intramuscular injections of diclofenac sodium while in hospital or oral dipyrone tablets after discharge. The median pain scores (25%–75% range) and the number of patients who required intramuscular analgesic injections are presented in Tables 1 and 2, respectively. The differences in the median pain score and the number of patients who required intramuscular analgesic injections were not statistically significant between the two groups on POD 1 ($P = 0.450$ and $P =$

Table 1. Pain scores after hemorrhoidectomy

	POD 1	POD 2	POD 3	POD 7
Group 1	7 (3–8)	5 (2–7)	3.5 (0–5.5)	2 (0–3)
Group 2	6 (5–8)	6 (5–7)	5 (3.5–7)	3.5 (2–4)
P values ^a	0.450	0.033	0.011	0.001

Pain scores are expressed as medians with 25%–75% ranges in parentheses

POD, postoperative day

^a Mann-Whitney U -test

Table 2. Number of patients who required intramuscular analgesic injections

	POD 1	POD 2	POD 3	Total	DAR
Group 1	38 (67.9)	32 (57.1)	18 (32.1)	38 (67.9)	2 (0–3)
Group 2	46 (82.1)	43 (76.8)	32 (57.1)	48 (85.7)	3 (1.5–3)
<i>P</i> values ^a	0.063	0.022	0.007	0.021	0.046

Data are expressed as the number of patients (%) and days, with 25%–75% ranges in parentheses for duration of analgesic requirement (DAR)

^a χ^2 tests

Table 3. Comparison of urinary retention, hospital stay, and patient satisfaction levels

	Urinary retention	Hospital stay	Patient satisfaction			
			Poor	Moderate	Good	Excellent
Group 1	6 (10.7)	2 (1–3)	3 (10.7)		21 (75)	4 (14.3)
Group 2	8 (14.3)	2.5 (2–3)	7 (25)	3 (10.7)	18 (64.3)	
<i>P</i> values	0.388 [†]	0.001*			0.001 [‡]	

Data are expressed as the number of patients (%) with urinary retention, as the number of patients with each degree of satisfaction, and as days with 25%–75% ranges in parentheses for the hospital stay

[†] Mann-Whitney *U*-test; * χ^2 tests; [‡] Wilcoxon signed-ranks test

0.063, respectively). However, on PODs 2 and 3, both variables were significantly less in group 1 than in group 2 ($P = 0.033$ and $P = 0.022$ for POD 2; $P = 0.011$ and $P = 0.007$ for POD 3, respectively). The median pain score was also significantly less 1 week after hemorrhoidectomy in group 1 than in group 2 ($P = 0.001$).

The median time that intramuscular analgesic injections were required and the total intramuscular analgesics used were also significant less in group 1 than in group 2 ($P = 0.046$ and $P = 0.021$, respectively). Furthermore, the group 1 patients were discharged earlier than the group 2 patients due to less intramuscular analgesic requirements. These results were significant ($P = 0.001$). Six patients in group 1 and eight patients in group 2 complained of acute urine retention, which resolved either spontaneously or after warm compression. There were no significant differences between the two groups ($P = 0.388$). These results are summarized in Table 3. The patient satisfaction was superior in group 1 ($P = 0.001$, Table 3). There were no discernible side effects of MFF treatment in this series.

Discussion

Although hemorrhoidectomy is often performed for third- and fourth-degree symptomatic hemorrhoids,¹ the management of postoperative pain remains a major concern. Different surgical approaches, including diathermy,¹⁸ open, closed,¹⁹ semi-closed,²⁰ or harmonic scalpel²¹ hemorrhoidectomy have been performed in an effort to diminish postoperative pain; however, none of

these techniques has proven superior to any other in this respect. The importance of anal sphincter spasm in inducing pain after hemorrhoidectomy is controversial. Lateral internal sphincterotomy has been considered as an adjunct to hemorrhoidectomy in the treatment of hemorrhoids because of the raised anal pressure in this condition.²² However, a randomized controlled study by Mathai et al. showed that performing this procedure in addition to routine hemorrhoidectomy did not reduce the analgesic requirement or pain score.²³ Similar results were reported for anal sphincter relaxants such as trimebutine.²⁴ In contrast, the topical application of nitroglycerine after hemorrhoidectomy to reduce postoperative sphincter spasm resulted in significantly improved pain control.²⁵ The use of antibiotics such as metronidazole did not reduce postoperative pain after hemorrhoidectomy.²⁶

It was suggested that the main cause of pain is the very sensitive anal mucosa that is severely traumatized during hemorrhoidectomy.³ The inflammatory response of the anal mucosa may be a key factor in exacerbating the pain after hemorrhoidectomy.⁸ Thus, treatment modalities aimed at reducing the inflammatory response or injury have yielded satisfactory results in terms of postoperative pain. Recent studies have reported that stapled hemorrhoidectomy resulted in less postoperative pain, quicker recovery, and superior patient satisfaction than conventional hemorrhoidectomy.^{3,16} This is because stapled hemorrhoidectomy involves simultaneous excision of hemorrhoids and wound closure up to the sensitive anal mucosa, without dissection, thereby eliminating potential trauma to the anal wound

and reducing the inflammatory response of tissue.³ However, this procedure is still expensive (which could be compensated by the shorter hospital stay and earlier return to work), it requires a learning curve, and there is a potential for internal sphincter injury, if the anal sphincter is stretched by the bivalve retractor or the stapler head.²⁷

Many clinical studies have examined the efficacy of local anesthetic infiltration in the perianal region, in addition to general or spinal anesthesia, on pain after hemorrhoidectomy.^{28,29} These studies suggest that local anesthetic agents act primarily as a neural blockade, but they may also possess an anti-inflammatory action. Wound infiltration with a local anesthetic agent reduced both postoperative pain and requirements for supplemental analgesics following hemorrhoidectomy. A similarly positive effect was demonstrated with the infiltration of non-steroidal anti-inflammatory drugs (NSAIDs) to the surgical area.^{30,31} This effect has been explained by the cyclooxygenase enzyme inhibition of NSAIDs which may depress inflammatory responses by modifying the prostaglandin cascade in the surgical wound.

Flavonoids reduce the activity of key inflammatory enzymes, including phospholipase A₂, which releases arachidonic acid from the membrane phospholipids,³² cyclooxygenase, which is responsible for the production of prostaglandins and is the target of NSAIDs,^{11,12,33} and lipoxygenase, which catalyzes the formation of leukotrienes.^{34,35} Daflon has also been reported to inhibit free radicals, which may cause tissue damage,³⁶ reduce microvascular permeability, and enhance circulation. These effects play an important role in tissue protection. Randomized clinical studies have been done to study the effect of MFF in comparison with a placebo on patients with hemorrhoidal disease who were suffering from an acute hemorrhoidal attack. Cospite reported that the clinical severity of proctorrhagia, pain, inflammation, congestion, and edema were significantly reduced and the need for analgesics, as well as the duration and severity of current hemorrhoidal episodes, were also diminished when MFF were given.³⁷ According to one report, MFF provided significant benefits in stopping acute bleeding and preventing relapse in patients with acute bleeding hemorrhoids.¹⁴ To our knowledge, only one other study has investigated the effect of MFF after hemorrhoidectomy.¹⁵ This study reported a significant reduction in secondary hemorrhagia 7–14 days postoperatively, but it did not report earlier data.

The pain in the control group of this study was comparable to previous control results reported by Tan and Seow-Choen²¹ and Wasvary et al.²⁵ However, giving MFF after hemorrhoidectomy resulted in significantly less postoperative pain. The management of pain with MFF resulted in a shorter hospital stay, whereas the

median hospital stay of the control group (2.5 days) was comparable to that reported by Bleday et al.³⁸ and Carapetti et al.³⁹ The decrease in the number of patients who required intramuscular analgesic injections resulted in increased patient satisfaction. Moreover, using an MFF such as Daflon is not expensive, at about US \$10 per patient. On the other hand, the results of the MFF arm in this study are comparable to the results of stapled hemorrhoidectomy reported by Ganio et al.³ and Khalil et al.¹⁶ as a recently favored approach.

In conclusion, the severity of pain and the number of intramuscular analgesic injections needed after hemorrhoidectomy were significantly less with the use of MFF. Thus, the postoperative administration of MFF after hemorrhoidectomy appears to improve the quality of the recovery period.

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