

Use of Flavonoids for the treatment of symptoms after hemorrhoidectomy with radiofrequency scalpel

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Abstract. – **OBJECTIVES:** Control of postoperative symptoms is of paramount importance in proctologic surgery. Phlebotropic activity, protective effect on the capillaries and anti-inflammatory properties of the flavonoids have been reported in several studies. They have been used to treat a variety of conditions including chronic venous insufficiency, lymphedema and hemorrhoids. Numerous trials, assessing the effect of phlebotonics in treating the symptoms and signs of haemorrhoidal disease, suggest that there is a potential benefit. Our trial was conducted to evaluate whether the flavonoids reduce postoperative bleeding, pain and other symptoms after hemorrhoidectomy.

PATIENTS AND METHODS: We compared the results obtained in 24 patients undergoing open hemorrhoidectomy with radiofrequency scalpel. Our study cohort was randomized in two groups: the Group A received flavonoids in the postoperative period, the Group B has constituted the control group, without administration of study drug. Follow-up outpatient visits were performed on 7, 15 and 30 postoperative day (POD). During the visits the patients expressed through a list of specific questions, based on a scoring system (1 to 10), their opinion about the extent of postoperative symptoms as pain, bleeding, tenesmus, pruritus and perianal weight.

RESULTS: We observed that the results obtained after 7 days of surgery are similar in both study groups. Even after 15 and 30 days no significant changes were observed between the two groups about pain and bleeding. Instead, we observed significant differences regarding tenesmus (group A: 8.0 ± 1.1 vs Group B: 5.4 ± 1.5 at 15 POD, $p < 0.05$; group A: 9.1 ± 0.8 vs Group B: 5.7 ± 0.9 at 30 POD, $p < 0.05$), pruritus (group A: 7.1 ± 1.4 vs Group B: 4.8 ± 1 at 15 POD, $p < 0.05$; group A: 9.5 ± 0.5 vs Group B: 6.6 ± 0.8 at 30 POD, $p < 0.05$) and perianal weight (group A: 7.2 ± 0.9 vs Group B: 6.2 ± 0.8 at 15 POD, $p < 0.05$; group A: 9.75 ± 0.4 vs Group B: 7.3 ± 0.9 at 30 POD, $p < 0.05$).

CONCLUSIONS: Our results confirm the usefulness of this drug to reduce the prevalence and the importance of post-hemorrhoidectomy

symptoms and make more comfortable the postoperative period.

Key Words:

Flavonoids, Hemorrhoids, Hemorrhoidectomy, Radiofrequency scalpel.

Introduction

All methods for the surgical treatment of hemorrhoids have advantages and disadvantages. In most of cases, the surgical school and the beliefs of surgeon govern the choice of technique.

Given the numerous techniques, proposed and used in the world, can say that maybe there isn't a surgery for you.

Pain, bleeding and other minor symptoms, such as itching, tenesmus, post-discharge burning and perianal weight, are common problems after postoperative period in all methods. The symptoms are usually treated with analgesics, anti-inflammatory drugs, metronidazole, laxatives, and, if necessary, benzodiazepines.

All the techniques are directed primarily to solve haemorrhoidal pathology, but also, no less importantly, to reduce the importance of the postoperative symptoms. In fact, the fear of experiencing significant suffering is the main deterrent that keeps patients from the surgeon.

The purpose of this study was to evaluate the effectiveness of the flavonoids in order to reduce the occurrence of the post-hemorrhoidectomy symptoms.

Patients and Methods

For the development and description of this randomized clinical trial, we followed CONSORT criteria¹. This was a 1-month, parallel-group study in which 26 patients with grade IV haemorrhoids

were randomized to receive (Group A) or not to receive flavonoids (Group B) as post operative therapy. The trial was undertaken in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice² and with the ethical principles laid down in the Declaration of Helsinki³. Written informed consent was obtained from all patients. Randomization was carried out using closed envelopes, after careful explanation of the advantages and risks of the study. A follow-up visit took place on 7, 15 and 30 postoperative day (POD). During the visit a list of specific questions based on a scoring system (1 to 10, with 10 being the maximal satisfaction of preoperative expectations) was submitted to evaluate the satisfaction rate.

Exclusion criteria were the presence of previous proctologic surgery or associated proctologic diseases. For this reason, patients underwent accurate preoperative outpatient proctologic physical examination and sigmoidoscopy. Moreover, we excluded pregnant women and those who scored III or IV on the ASA score of the American Society of Anaesthesiologists⁴. Oral anticoagulants and anti-inflammatory drugs were discontinued at least seven days before the surgery.

Preoperative preparation consisted of enemas applied 4-5 hours before the operation. Metronidazole (400 mg I.V.) and Ceftriaxone (2 g I.V.) were administered for infection prophylaxis. Patients were placed in the lithotomy position. After proper cleaning and disinfection of the operating area with Povidone/Iodine, a Parks divaricator was inserted for a better exposure of the anal canal. A "V" incision was performed by Radiofrequency (RF) scalpel from the anal margin up to the dentate line until the origin of the vascular pedicle. Dissection of the mucosal edges was performed up to the internal sphincter. The freed vascular pedicle was then tied at its base with a transfixed stitch of absorbable suture (Vicryl[®] 2/0). Haemostasis was achieved by RF coagulation. The most external portion of the wound, on the skin margin, was not closed in order to drain the eventual serosanguinous oozing. No patient underwent internal sphincterotomy. The postoperative treatment consisted of Metronidazole (400 mg I.V. three times daily) on the first postoperative day and oral analgesics on demand (Diclofenac 50 mg per os). All patients were discharged on the first postoperative day. After 24-36 hours a mild laxative (Lactulose 10 ml per os three times per day) was administered to stimulate evacuation in those patients who still

did not evacuate spontaneously. The diet was integrated with paraffin oil and slugs for stool softening. Accurate local hygiene was implemented using irrigations with chloride solutions and disinfecting soaps.

At discharge, the patients were randomized in two groups. Group A: we prescribed flavonoids (tablets containing Quercetin 200 mg and Hesperidin 50 mg in combination with Resveratrol, Bromelain, Folic Acid, vitamins C and E) (Deflanil Plus[®]) at a dose of two times a day for a week and then at a dose of once a day for three weeks. We preferred this product because compared to others is formulated for once daily dosing. Group B represented the control group, without flavonoids therapy.

The primary aim of this study was to verify the effectiveness of the flavonoids in the occurrence of the symptoms post-hemorrhoidectomy. For this purpose a follow-up was performed by outpatient visits on 7, 15 and 30 POD with an accurate inspection of the wound with anoscopy. The patients were asked to express, by a list of specific questions, an opinion on the extent of postoperative symptoms such as pain, bleeding, tenesmus, pruritus and perianal weight.

Statistical Analysis

Descriptive statistics for qualitative variables were performed with occurrences and described with relative frequencies. Comparison was performed with the Student's *t* test for parametric continuous variables, the Mann-Whitney test for non-parametric variables and the Fisher's exact test for categorical variables in which the occurrence of observations within cells was inferior to 5. All *p* values were considered significant if less than 0.05.

Results

Between January 2011 and May 2013, 26 patients were randomized in two equal groups. One patient for each group were not present for follow-up examinations at day 30 and, therefore, were excluded from the final evaluation of results. At the time of analysis, Group A consisted of seven males (58.3%) and five females (41.6%) and group B of six males (50%) and six females (50%). Median age was 36 ± 4 years for group A and 38 ± 4 years for group B. Preoperative symptoms are presented in Table I and were present for at least two years.

Table I. Preoperative symptoms

Preoperative symptom	n. (%)
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Prolapse	26 (100%)
Bleeding	20 (76.9)
Pain	19 (73%)
Anal Itching	8 (30.7%)
Perianal Irritation	5 (19.2%)
Secretions	4 (15.3%)

No complications were recorded during hospitalization. The postoperative outpatient visits, occurred at POD 7, 15 and 30 no showed other complications that could alter the results of this study.

We analyzed the data contained in the list of specific questions, compiled by patients, on 7, 15, and 30 POD in order to evaluate the postoperative symptoms (Figures 1, 2, 3). The results obtained after 7 days of surgery were similar in both study groups. Even after 15 and 30 days there were no significant changes observed between the two groups about pain and bleeding; instead, we observed significant differences as regards the tenesmus (group A: 8.0 ± 1.1 vs Group B: 5.4 ± 1.5 at 15 POD, $p < 0.05$; group A: 9.1 ± 0.8 vs Group B: 5.7 ± 0.9 at 30 POD, $p < 0.05$), pruritus (group A: 7.1 ± 1.4 vs Group B: 4.8 ± 1 at 15 POD, $p < 0.05$; group A: 9.5 ± 0.5 vs Group B: 6.6 ± 0.8 at 30 POD, $p < 0.05$) and the perianal weight (group A: 7.2 ± 0.9 vs Group B: 6.2 ± 0.8 at 15 POD, $p < 0.05$; group A: 9.75 ± 0.4 vs Group B: 7.3 ± 0.9 at 30 POD, $p < 0.05$). There were no reported intolerance or complications due to the administration of study drugs.

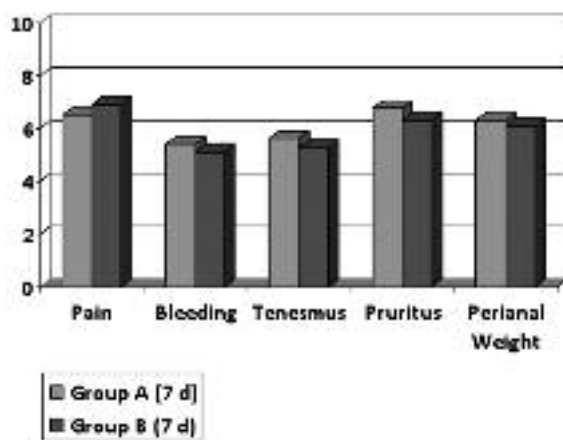


Figure 1. Comparison of symptoms scores (1-10) between group A (Flavonoids) and group B (Control) on 7 POD.

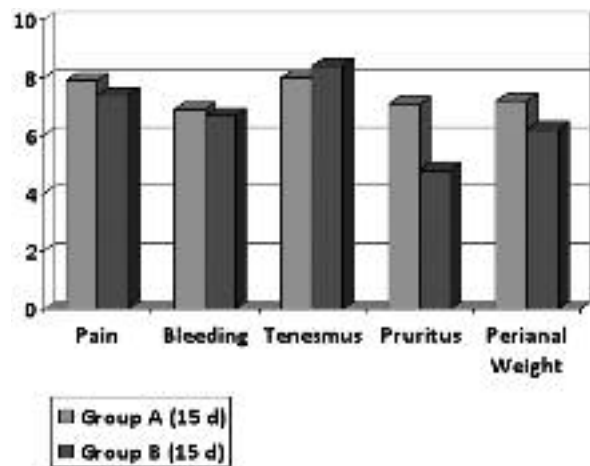


Figure 2. Comparison of symptoms scores (1-10) between group A (Flavonoids) and group B (Control) on 15 POD.

Discussion

The aim of this study was to demonstrate that the addition of flavonoids to routine postoperative treatment is better in order to reduce postoperative pain, bleeding, and other symptoms related to hemorrhoidectomy.

The study agents are polyphenolic compounds, secondary metabolites of higher plants, water-soluble and usually present as glycosides. Flavonoids are ubiquitous in nature and currently we know of more than 4.000 flavonoid glycosides. These compounds reduce the inflammation by inhibiting prostaglandin PGE2 e PGE2 α and thromboxane B2 release from macrofages and increasing endothelial nitric oxide synthase activi-

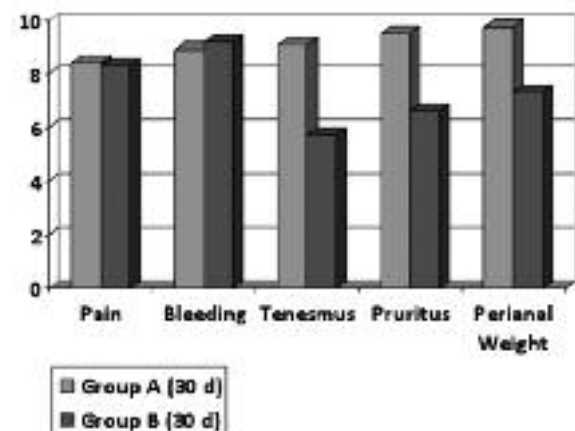


Figure 3. Comparison of symptoms scores (1-10) between group A (Flavonoids) and group B (Control) on 30 POD.

ty. Levels of oxygen-derived free radicals, generated during the inflammatory response, are also reduced. These proinflammatory mediators would otherwise excessively weaken the collagen in the vessels basement membrane and in the tunica media of venules. As a result, the inflammatory process is inhibited and edema subsequently reduced.

Flavonoids improve venous tone and reinforces capillary resistance. This protective effect on capillary fragility may prevent postoperative bleeding. In addition, they increase lymphatic drainage and protect the microcirculation from inflammatory mediators, resulting in reduced edema and pain⁵⁻⁸.

Postoperative pain and bleeding are important issues by patients who have undergone hemorrhoidectomy, regardless of the technique used. Other symptoms such as tenesmus, pruritus and perianal weight caused by local trauma are also reported and may appear later. Also, bloody mucosal soiling together is a consequence of excision. Pain and sometimes bleeding may recur at return of bowel movement. Other complications such as secondary hemorrhage, which usually occurs after 7 to 14 days, has a prevalence of less than 4% as reported in the literature⁶. In our study, no secondary hemorrhage occurred after the 7 POD.

All patients were subjected to open hemorrhoidectomy using RF scalpel, an innovative instrument that allows cutting and coagulating tissues in an atraumatic manner, contrarily to the electric bistoury⁹⁻¹⁰.

RF scalpel is a valuable new surgical tool that recently has been introduced even in Proctology¹¹⁻¹⁵. The most important different feature than the other devices is its cutting-coagulating ability deriving from radio-waves. The tissue temperature obtained does not exceed 70°C, so it is named as a “cold” scalpel. It is an important advantage when you operate in a delicate tissue such as anal canal mucosa, because atraumatic nature of the cut allows a dramatic reduction of tissue edema and postoperative pain. Moreover, healing processes are optimal and faster than normal with fewer long term complications.

The results that we obtain are optimal both about the problem of postoperative pain, both about the bleeding. Many authors associate the intervention of sphincterotomy to hemorrhoidectomy to reduce postoperative internal sphincter spasm which undoubtedly contributes to the genesis of pain^{16,17}. We never associated sphincterotomy to hemorrhoidectomy except in patients

with associated fissure or intense hypertonic sphincter, that from this study, however, were excluded. On the other hand just the advantages of RF scalpel make unnecessary the routine sphincterotomy.

In fact, the results that we have obtained in our previous studies are extremely advantageous compared to other traditional proctologic surgical techniques.

In this study the results regarding postoperative pain and the appearance of bleeding are similar in both groups of patients. The use of flavonoids has not, therefore, conditioned these complications. Instead, it is interesting to note that there is a statistical significance with regard to the tenesmus, the pruritus and the perianal weight at 15 POD, and even more markedly at 30 POD.

Many authors have studied the effects of Flavonoids in the treatment of medical proctologic disorders and after ambulatorial and surgical treatments^{18,19}. La Torre et al⁶ conducted a randomized trial of patients undergoing Milligan-Morgan hemorrhoidectomy. They observed an improvement in the postoperative comfort and a reduction of pain and bleeding. However the adopted method presents a percentage of complications higher than those detected with our RF technique. This explains the better results they have achieved in the group treated with flavonoids compared to the control group especially regarding pain and postoperative bleeding. In addition, our patients have not taken other drugs in the days after discharge, except for a mild laxative administered to stimulate evacuation in those patients who still did not spontaneously evacuated. Moreover we recommended a diet integrated with paraffin oil and slags and a hygiene using an accurate local irrigations with chloride solutions and disinfecting soaps.

According to other Authors^{5-8,18-21}, the efficacy of flavonoids in alleviating symptoms after hemorrhoidectomy may be attributable to their phlebotropic activity, protective effect against the capillary fragility and anti-inflammatory effect. These different actions imply that flavonoids are an “edema-protective” drug.

Conclusions

In this study Flavonoids (tablets containing Quercetin 200 mg and Hesperidin 50 mg in combination with Resveratrol, Bromelin, folic acid, vitamins C and E), at a dose of two times a day

for a week in single dose and then at a dose of once a day for three weeks, were administered in patients after hemorrhoidectomy with RF, in order to evaluate the their effectiveness.

Our results confirm the usefulness of this drug to reduce tenesmus, pruritus and perianal weight and thus make more comfortable the postoperative period.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

- 1) MOHER D, SCHULZ KF, ALTMAN DG. The CONSORT statement: revised commentations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001; 357: 1191-1194.
- 2) ICH harmonized tripartite guideline: Guideline for Good Clinical Practice. *J Postgrad Med* 2001; 47: 45-50.
- 3) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Int Bioethique* 2004; 15: 124-129.
- 4) ANON R. New classification of physical status. *Anesthesiology* 1963; 24: 111.
- 5) HO YH, FOO CL, SEOW-CHOEN F, GOH HS. Prospective randomized controlled trial of a micronized flavonoid fraction to reduce bleeding after hemorrhoidectomy. *Br J Surg* 1995; 83: 1034-1035.
- 6) LA TORRE F, NICOLAI AP. Clinical use of micronized purified flavonoid fraction for treatment of symptoms after hemorrhoidectomy: results of a randomized, controlled, clinical trial. *Dis Colon Rectum* 2004; 47: 704-710.
- 7) COLAK T, AKCA T, DIRLIK M, KANIK A, DAG A, AYDIN S. Mized flavonoids in pain control after hemorrhoidectomy: a prospective randomized controlled study. *Surg Today* 2003; 33: 828-832.
- 8) CONTI P, VARVARA G, MURMURA G, TETE S, SABATINO G, SAGGINI A, ROSATI M, TONIATO E, CARAFFA A, ANTINOLFI P, PANDOLFI F, POTALIVO G, GALZIO R, THEOHARIDES TC. Comparison of beneficial actions of non-steroidal anti-inflammatory drugs to flavonoids. *J Biol Regul Homeost Agents* 2013; 27: 1-7.
- 9) FILINGERI V, GRAVANTE G, CASSISA D. Physic of radiofrequency in proctology. *Eur Rev Med Pharmacol Sci* 2005; 9: 349-354.
- 10) FILINGERI V, GRAVANTE G, CASSISA D. Clinical applications of radiofrequency in proctology: a review. *Eur Rev Med Pharmacol Sci* 2006; 10: 79-85.
- 11) FILINGERI V, CASCIANI CU. Submucosal hemorrhoidectomy with a radiofrequency scalpel. *Minerva Chir* 1997; 52: 1255-1259.
- 12) GUPTA PJ. Radiofrequency coagulation: a treatment alternative in early hemorrhoids. *Indian J Gastroenterol* 2002; 21: 167.
- 13) GUPTA PJ. Radiofrequency coagulation: an alternative treatment in early grade bleeding hemorrhoids. *Tech Coloproctol* 2002; 6: 203-204.
- 14) FILINGERI V, ROSATI R, GRAVANTE G, PIETRASANTA D, FIORITO R, CASCIANI CU. Milligan-Morgan hemorrhoidectomy with a radiofrequency scalpel. *Minerva Chir* 2003; 58: 355-359.
- 15) FILINGERI V, GRAVANTE G, BALDESSARRI E, CRABOLEDDA P, BELLATI F, CASCIANI CU. A randomised trial comparing submucosal haemorrhoidectomy with radiofrequency bistoury vs. diathermic haemorrhoidectomy. *Eur Rev Med Pharmacol Sci* 2004; 8: 79-85.
- 16) MILITO G, ARULLANI A, BRANCALEONE C, CESCA D, FILINGERI V, CASCIANI CU. Subcutaneous lateral internal sphincterotomy in the treatment of chronic anal fissure. *Ital J Surg Sciences* 1983; 13: 275-279.
- 17) FILINGERI V, GRAVANTE G. A prospective randomized trial between subcutaneous lateral internal sphincterotomy with radiofrequency bistoury and conventional Parks' operation in the treatment of anal fissures. *Eur Rev Med Pharmacol Sci* 2005; 9: 175-178.
- 18) ALONSO-COELLO P, ZHOU Q, MARTINEZ-ZAPATA MJ, MILLIS E, HEELS-ANSELL D, JOHANSON JF. Meta-analysis of flavonoids for the treatment of haemorrhoids. *Br J Surg* 2006; 93: 909-920.
- 19) KHUBCHANDANI IT. Randomized clinical trial of micronized flavonoids in the early control of bleeding from acute. *Tech Coloproctol* 2001; 5: 57-58.
- 20) BASILE M, GIDARO S, PACELLA M, BIFFIGNANDI PM, GIDARO GS. Parenteral troxerutin and carbazochrome combination in the treatment of post-hemorrhoidectomy status: a randomized, double-blind, placebo-controlled, phase IV study. *Curr Med Res Opin* 2001; 17: 256-261.
- 21) HO YH, TAN M, SEOW-CHOEN F. Micronized purified flavonoid fraction compared favorably with rubber band ligation and fiber alone in the management of bleeding hemorrhoids: randomized controlled trial. *Dis Colon Rectum* 2000; 43: 66-69.