Prospective, Randomized, Controlled, Observer-Blinded Trial of Combined Infrared Photocoagulation and Micronized Purified Flavonoid Fraction Versus Each Alone for the Treatment of Hemorrhoidal Disease

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ABSTRACT

Background: Infrared photocoagulation (IRP) is commonly used in the treatment of hemorrhoids, but rectal bleeding can persist after this procedure. Adjuvant therapy may thus be considered for more definitive control of symptoms, particularly bleeding.

Objective: The goal of this study was to compare the efficacy of a treatment combining IRP and oral micronized purified flavonoid fraction (MPFF) versus each treatment used alone on bleeding cessation in patients with grades I, II, and III acute internal hemorrhoids.

Methods: This was a prospective, randomized, controlled, single-blind study. Consecutive outpatients were randomly assigned to a treatment combining MPFF and IRP or to each treatment separately. For each patient, bleeding status was reported at day 0 (day of inclusion) and compared with that at day 5 after treatment by observers blinded to treatment assignment. Follow-up visits were planned at days 7, 30, 60, and 90 of therapy, including monitoring of treatment-related side effects and self-reporting by patients of any problem related to hemorrhoidal disease.

Results: A total of 351 patients (180 women, 171 men) were enrolled in the study. Their mean age was 49.2 years (range, 29–71 years). Hemorrhoids were grade I in 33.6% (118 patients), grade II in 48.7% (171 patients), and grade III in 17.7% (62 patients) of the study population. Patients were randomly assigned to each of the 3 treatment groups (117 patients in each), with no significant difference between groups in the age, sex, or distribution of grade of hemorrhoids. The percentage of patients with no bleeding after 5 days of treatment was higher in the combined treatment group (74.8%) compared with MPFF alone (59.6%; $P = 0.023$) or with IRP alone (55.6%; $P = 0.004$). MPFF alone was as effective as IRP alone at stopping bleeding. Patients with grades I and II hemorrhoids responded significantly better (82.5% and 61.7%, respectively) to either treatment than those with grade III hemorrhoids (22.9%; $P < 0.001$). Of the 216 patients who were followed up for 90 days, 3 had a gastrointestinal adverse event, and 19 had a relapse of bleeding.

Conclusion: Five days of treatment combining MPFF with IRP significantly reduced bleeding status in these study patients with grades I and II acute internal hemorrhoids compared with each treatment used alone. (*Clin Ther.* 2005;27:746–754) Copyright © 2005 Excerpta Medica, Inc.

Key words: hemorrhoids, bleeding, micronized purified flavonoid fraction, infrared photocoagulation.

INTRODUCTION

Hemorrhoidal disease (HD), which results from the distal displacement of the anal cushions,[1] is a common and widespread condition.[2,3] The prevalence of HD is difficult to estimate. It varies between 4.4% and 86.0%, depending on the population studied, the definitions used, and the type of data collection methods employed.[1,2] There are more complaints of HD symp-

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toms among the higher socioeconomic classes; there is no ethnic predisposition.[3] The pathogenesis of HD remains incompletely understood but is multifactorial, involving vascular, inflammatory, and mechanical factors.[4] It has been suggested that this disease is one of the normal changes of aging rather than part of a disease process.[1] The current concept regarding the pathogenesis of HD is based on the deterioration with aging of the anchoring and supportive connective tissue system. In this process, the veins become distended as they lose their support, and the lining becomes more sensitive to pressure from straining. Stasis in the veins may occur with clot formations and swelling, as well as erosion of the lining with bleeding. HD then becomes symptomatic.[4] Other nonspecific symptoms include tenesmus, hemorrhoidal prolapse, soiling, burning, and pain.

Blood loss is the most frequent sign on patient presentation. Careful differential diagnosis is needed, using colonoscopy or barium enema, to exclude other possible causes of blood loss from the lower gastrointestinal tract.[5,6] Choice of treatment depends on the degree of hemorrhoidal prolapse, bleeding profusion, and the severity of the associated symptoms.[7,8] Although hemorrhoidectomy is still preferred for patients with large third- or fourth-degree hemorrhoids,[9] several nonsurgical and minimally invasive procedures—such as anal dilation, cryotherapy, sclerotherapy, bipolar diathermy, rubber band ligation, and infrared photocoagulation (IRP)—have been developed in the last 3 decades.[10-16]

IRP was introduced in 1977 by Neiger.[15] This sclerosing technique uses high-intensity light to burn grade I, II, or III internal hemorrhoids. First-degree (or grade I) hemorrhoids are merely visible vessels; second-degree (or grade II) lesions prolapse with defecation but return spontaneously; and third-degree (or grade III) lesions prolapse and require manual reduction. Despite no reports of serious complications or sequelae with IRP, mild discomfort, moderate pain, and serosanguineous discharge may occur.[17] In addition, numerous topical agents (eg, creams, lotions, suppositories, local anesthetics) and oral medications, such as the flavonoid compounds, are also used for the treatment of HD.

Micronized purified flavonoid fraction (MPFF),* an oral phlebotropic medication consisting of 90% diosmin and 10% flavonoids expressed as hesperidin, may suppress bleeding by a mechanism that limits endothelial activation and protects its integrity, thus inhibiting inflammatory mediators. This latter mechanism of action is specific to MPFF and has been extensively described in chronic venous insufficiency.[18,19] MPFF also increases venous tone, reduces stasis, and enhances lymphatic drainage.[19] In addition, a manufacturing process that allows the micronization of PFF into particles with a diameter <2 μm has been proven to enhance MPFF's bioavailability,[20] thus explaining its therapeutic efficacy on most symptoms of HD compared with other flavonoids.[21] Given these properties, it was hypothesized that MPFF could improve the efficacy of the IRP technique in suppressing rectal bleeding related to acute internal hemorrhoids. Moreover, the minor side effects of the IRP technique could be reduced by adding MPFF, thereby improving patient satisfaction.

The goal of the present study was to compare the efficacy of a treatment combining oral MPFF and local IRP with each treatment used alone on bleeding cessation in patients with grades I, II, and III acute internal hemorrhoids.

PATIENTS AND METHODS

This was a prospective, randomized, controlled, single-blind study. The study protocol was approved by the Hospital Ethics Committee. It was conducted in the Gastroenterology Unit of the "Saint Savvas" Hospital, Athens, Greece, according to a randomized design. In accordance with the Greek National Health System, the IRP interventions were free of charge. Twenty-five percent of the MPFF oral medication costs had to be met by patients.

Patients

After giving their written informed consent, ambulatory male and female patients, aged ≥18 years, presenting with rectal bleeding due to grades I, II, and III acute internal hemorrhoids, with no previous treatment for hemorrhoids within the 6 months preceding the study and without coexistent colon diseases, were eligible for inclusion. Exclusion criteria were pregnancy, a history of acute hemorrhoidal attacks occurring at least 6 months before enrollment, grade IV hemorrhoids, concomitant large-bowel and anal canal diseases, history of pelvic radiation, and use of anticoagulant and antiplatelet agents or nonsteroidal anti-inflammatory drugs.

*Trademark: Daflon® 500 mg (Les Laboratoires Servier, Neuilly-sur-Seine, France). Also registered as Alvenor®, Ardium®, Arvenum® 500, Capiven®, Detralex®, Elatec®, Flebotropin®, Variton®, and Venitol®.

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