MEDICAL TREATMENT OF HEMORRHOIDS USING FLAVONOIDs

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Hemorrhoids are one of the most common digestive diseases with a reported prevalence of 4.4%. The peak prevalence occurs between the ages of 45 and 65 years of age. An estimated third of patients affected by hemorrhoids seeks medical attention. The most common symptoms are bleeding, protrusion, and pain. Most clinicians advocate addition of adequate fluid and fiber intake to appropriately modulate the consistency of the bowel movements; however, this may prove inadequate with more severe hemorrhoidal disease. Micronized purified flavonoid fractions (MPFF) have been used extensively throughout Europe and Asia to treat hemorrhoidal disease for at least two decades.

The pathophysiology of hemorrhoidal disease in producing acute and chronic symptoms is likely multifactorial involving both anatomic and inflammatory components. The inflammatory component from venous stasis and resulting vascular fragility seems to represent a significant clinical component. The rationale for using MPFF is that it decreases venous stasis by improving venous tone and lymphatic outflow and suppressing the local inflammatory response. MPFF products are the most commonly composed of 90% micronized diosmin and 10% flavonoids expressed as hesperidin. The most common formulation used in Europe and Asia is Daflon®. A new form of this product known as Vasculera™, using a 95% micronized diosmin and 5% hesperidin formulation, is now available in the United States as a prescription medical food and can be found in the Analpram Advanced™ Kit.

There has been extensive research and long term clinical studies on MPFF products containing 90% micronized diosmin and 10% flavonoids expressed as hesperidin. The safety of these products has been confirmed through animal studies and corroborated with long-term human studies including pregnancy data. Data encompassing nearly 3000 patients over one year of use has failed to show any significant side-effects or contraindications to its use. Diosmin and related flavonoids are listed by the FDA in the Generally Regarded As Safe (GRAS) category and have been examined extensively for safety.

There has been a multiplicity of clinical studies involving MPFF in hemorrhoids using a variety of methodologies and parameters. The majority of the studies have been performed in Europe and Asia. These studies can be grouped into three major categories: MPFF as a single agent for control of hemor-
rhoidal symptoms, MPFF vs. office-based fixation procedures such as rubber band ligation and sclerotherapy, and MPFF as an adjunct to improve postoperative recovery from hemorrhoidectomy.

The medical management of hemorrhoidal disease is the ideal initial approach to the vast majority of hemorrhoidal complaints. The correction of dietary factors such as fiber and water intake and the teaching of correct defecation habits is safe, sound medical advice. The effectiveness of fiber supplementation for the treatment of nonprolapsing and minimally prolapsing hemorrhoids has been confirmed by recent meta-analysis. The use of topical agents with corticosteroids, anesthetics, astringents, antiseptics, or protectants can also provide short relief of symptoms but has little data to support long term use. The recommendation of dietary modification, short term topical agents and appropriate defecation hygiene is very appealing on a pragmatic view, as it allows the general clinician to address a significant percentage of hemorrhoidal complaints and minimize the use of expensive subspecialty care. The drawback of standard medical management is the lower efficacy rate for hemorrhoidal disease with greater degrees of prolapse and complexity. This lower efficacy for complex disease combined with an increasing nature of the patient populations, and randomization methodology weaken any inferences on the beneficial effect of flavonoids on hemorrhoids. A more detailed look at three double-blinded, placebo-controlled randomized studies provides more compelling view of the efficacy of MPFF in the treatment of hemorrhoidal disease. Cospite et al reported a significant decrease in both the clinical severity (anal discomfort, anal pain, and anal discharge) and anatomic features (inflammation, congestion, edema, and prolapse) after a 7 day course of diosmin (90% diosmin/10% hesperidin). The correlation of subjective and anatomic metrics is more compelling given the proposed mechanism of MPFF. The authors concluded that treatment with diosmin (90% diosmin/10% hesperidin) produced a quicker and more pronounced improvement of both signs and symptoms of acute hemorrhoids than placebo.

Godeberge’s study sought to validate the use of diosmin (90% diosmin/10% hesperidin) (see Figure 1) for chronic symptomology from hemorrhoidal disease utilizing a two month treatment period. Utilizing both an overall symptom score and an overall sign score, Godeberge was able to show a significant improvement over the two month period as compared to placebo. This improvement was also reflected in a pooling of sign and symptom scores to generate an overall assessment which was highly in favor of the diosmin (90% diosmin/10% hesperidin) cohort (see Figure 2).
Misra and Parshad's objective was to document whether hemorrhoidal bleeding could be stopped with sufficient speed by MPFF to defer surgery or office-based procedures. They reported a significant degree of cessation of bleeding in the 7 day treatment arm and a significant decreased risk of relapse in the 90 day treatment arm. The authors commented that the cessation of acute bleeding and decreased relapse with MPFF could aid in the reduction in scheduling office and outpatient subspecialty care thereby improving the overall delivery of patient care. In regard to perinatal care, Buckshee’s open study of diosmin (90% diosmin/10% hesperidin) in pregnant women for the treatment of internal hemorrhoids demonstrated significant efficacy on intention to treat analysis by day 4 of treatment. Despite poor methodology and size, there seems to be an appreciable benefit to this difficult to treat population of patients. In addition, there were no reports of adverse events to mother or fetus secondary to the use of MPFF.

The addition to MPFF to the standard medical approach of dietary modification, counseling of defecation hygiene, and topical care is compelling but the quality of evidence is at best moderate. Currently, the FDA has not formally recommended the use of flavonoids for the treatment of hemorrhoidal disease; however, the FDA has accepted the 95% diosmin/5% hesperidin flavonoids as a new dietary ingredient. Through a self-affirmation process, GRAS (Generally Recognized as Safe) status has been obtained, which allows clinicians to prescribe this agent as a medical food to be used under the supervision of a physician. The extensive use in Europe, especially France, is in direct contrast with the minimal use in the United States and begs the question if it is overutilized in France or underutilized in the United States. The most reasonable thought is that there is a place for the use of MPFF in well selected patients to augment medical and office-based procedures prior to the use of surgery.

Office-based procedural management of hemorrhoids continues to be a popular initial treatment for this common disease. The low morbidity and ease of modalities such as sclerotherapy and rubber band ligation are generally preferable to formal surgical management. Two studies have sought to do head to head comparison of MPFF vs. rubber band ligation and sclerotherapy, respectively. In 1999, Ho et al randomized 162 patients with bleeding non-prolapsing internal hemorrhoids to three arms of a study: fiber alone, rubber band ligation plus fiber, and MPFF (90% diosmin/10% hesperidin) for three weeks plus fiber. Rectal bleeding stopped more rapidly in the MPFF group (mean, 4 days) compared to the fiber alone group (mean, 11 days). There was no significant difference between the MPFF and rubber band ligation groups. They concluded that the addition of MPFF to fiber safely and rapidly relieved bleeding from non-prolapsed internal hemorrhoids. More recently, Yuke from Turkey randomized 126 patient with both first and second degree hemorrhoids to receive either three quadrant sclerotherapy with 3% polidocanol or MPFF (90% diosmin/10% hesperidin) 1000mg/day for 90 days. The patients were followed using three tools: Average Symptom Score, Average Anoscopy Score,
and subjective scale for 24 months. Both groups had improvements in all three parameters; however, the duration of beneficial effects were statistically more pronounced in the sclerotherapy arm. The authors concluded that sclerotherapy was a more effective modality than MPFF for long-term care of internal hemorrhoids.\textsuperscript{19}

These studies are quite provocative but they seem to leave more questions unanswered than solved. The inclusion of second degree hemorrhoids into the \textsuperscript{Yuksel}\textsuperscript{19} study make comparison to Ho’s study very difficult, as the severity of the hemorrhoidal anatomy and natural history are radically different in the two studies. Another weakness is the difference in duration of MPFF therapy between the two studies, as well as the variation in dosing regimens. The addition of MPFF to office-based fixation techniques such as rubber band ligation and sclerotherapy is theoretically compelling, but lacking the necessary studies to promote widespread use.

Hemorrhoidectomy continues to be an excellent and effective modality for the treatment of medically refractory hemorrhoidal disease; however, the morbidity of the surgery in terms of pain and bleeding is still a major consideration. Multiple studies have been performed utilizing variety of anti-inflammatory agents and antibiotics in an effort to decrease the attendant morbidity of an operative hemorrhoidectomy. There has been considerable interest in using MPFF compounds to alleviate the symptoms of pain and/or bleeding after operative hemorrhoidectomies.

To date, three studies have been performed evaluating the efficacy of MPFF in alleviating pain and/or bleeding from standard hemorrhoidectomies and one study evaluating its effectiveness in stapled hemorrhoidectomy. In 1995, Ho\textsuperscript{18} conducted a randomized prospective controlled trial evaluating the effectiveness of diosmin (90% diosmin/10% hesperidin) to decrease postoperative bleeding after standardized diathermy excision of hemorrhoids. In all, 228 consecutive patients had an elective diathermy hemorrhoidectomy and 114 were randomized to receive diosmin (90% diosmin/10% hesperidin) for seven days in addition to standard analgesia and non-steroidal anti-inflammatory drugs. There was no difference in length of hospital stay or post-operative analgesia; however, there was a significant decrease in bleeding between the diosmin (0.9%) group and control (6.1%) group (P = 0.03).\textsuperscript{20} In 2004, Colak\textsuperscript{21} reported the results of a prospective randomized controlled study exploring the ability of MPFF to decrease post hemorrhoidectomy pain. In all, 112 consecutive patients were randomized to receive either diosmin (90% diosmin/10% hesperidin) for 7 days or no MPFF. There was a statistically significant decrease in pain scores and the need for IM analgesia in the diosmin group on both the second and third post-operative days. In addition, the diosmin group had superior patient satisfaction scores (P = 0.001) and shorter hospital stays (P = 0.001). There was no difference in post-operative hemorrhage between the two arms of the study.\textsuperscript{21} In 2004, La Torre\textsuperscript{22} published his randomized control study comparing the addition of MPFF for 30 days to his standard post-operative protocol of ketorolac tromethamine (Toradol\textsuperscript{29}) and metronidazole. La Torre et al\textsuperscript{22} observed a statistically significant decrease in pain, tenesmus, pruritis, and bleeding starting from post-operative day 1 and continuing through the 60-day study period.\textsuperscript{22} Finally, Mlakar\textsuperscript{23} in 2005 studied whether the previous beneficial effects of MPFF for standard hemorrhoidectomies can be extended to the stapled hemorrhoidectomy model. Sixty-three patients were randomized so that 30 received a 7 day post-operative course of diosmin (90% diosmin/10% hesperidin). There was no demonstrable benefit in the diosmin group in regard to bleeding, pain, or analgesia requirements. The authors commented that the morbidity of a stapled hemorrhoidectomy is so minimal that MPFF would be unable to demonstrate any protective effects.\textsuperscript{23}

Although there seems to be clear efficacy of MPFF, in particular diosmin (90% diosmin/10% hesperidin), to provide significant benefits for the post-operative morbidity of a standard hemorrhoidectomy, a more rigorous study needs to be conducted in regard to the duration of MPFF within the setting of outpatient or short stay hemorrhoidectomy patients. Given the morbidity of a hemorrhoidectomy, any significant improvement in post-operative pain control and bleeding would be encouraged. The lack of benefit of MPFF for stapled hemorrhoidectomy is not surprising given the improved morbidity of the procedure compared to a standard hemorrhoidectomy.
In summary, MPFF have had significant popularity in Europe and Asia for hemorrhoidal disease and have been used across a heterogeneous population of patients. There seems to be a benefit for MPFF, such as diosmin, for selected hemorrhoid patients and there seems to be no significant side effects or contraindications. The widespread long term use of MPFF cannot be justified at this time without more comprehensive trials; however, it should be considered in several clinical situations:

- symptomatic hemorrhoid patients whom are failing standard interventions or have relative contraindications to office-based procedures (chronic anticoagulants)
- defer major hemorrhoid surgery if necessary
- an adjunct to decrease post-op hemorrhoidectomy morbidity

Further, clinical trials will hopefully provide the additional support needed to prescribe MPFF with confidence for the treatment of hemorrhoidal disease.

The Analpram Advanced™ Kit is currently the only hemorrhoid kit on the market to include a MPFF (Vasculera™).

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