

Article

Antioxidant and Cytotoxic Activities of *Centella asiatica* (L) Urb.

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Abstract: In the present study, the phenolic (Folin-Dennis) and flavonoid (colorimetric assay) constituents, antioxidant [2,2-diphenyl-2-picrylhydrazyl hydrate (DPPH) assay] and cytotoxic activities of an aqueous extract (AE) of *Centella asiatica* leaves were investigated. The aqueous extract (50 g/L) was obtained by infusion followed by cold maceration for 24 h. The levels of phenolic and flavonoid compounds were 2.86 g/100 g and 0.361 g/100 g, respectively. The AE showed elevated DPPH scavenging activity, with an IC₅₀ value of 31.25 µg/mL. The AE had a promising activity against mouse melanoma (B₁₆F₁), human breast cancer (MDA MB-231) and rat glioma (C₆) cell lines, with IC₅₀ values of 698.0, 648.0 and 1000.0 µg/mL, respectively. A positive correlation was established between the level of flavonoids, antioxidant and antitumor activities.

Keywords: *Centella asiatica*; Umbelliferae; phenolic constituents; DPPH; cytotoxic

1. Introduction

Aging is a natural process which is related to several morphological and biochemical changes that happens from maturity to senescence, making the organism vulnerable to diseases and toxicity, and eventually leading to cellular death. According to the hypothesis of oxidative stress on aging, the loss of functional capacity associated to senescence comes from accumulation of molecular oxidative damages [1] brought about by (toxic) free radicals produced during normal breathing. Free radicals were previously reported as being capable of damaging a lot of cellular components such as proteins, lipids and DNA [2].

To protect the cells from oxidative damages by oxidants, produced during oxygen metabolism, an antioxidant system is used by aerobic organisms. The main antioxidant agents such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GSH-Px), glutathione, ascorbic acid and tocopherol are important for cellular protection, due to their ability to eliminate free radicals, such as reactive oxygen species (ROS) [3]. Nowadays, there is an increasing interest in the biochemical functions of natural antioxidant extracts from vegetables, fruits, and medicinal plants, which can become candidates to prevent oxidative damage, promoting health. The phenolic constituents found in vegetables have received considerable attention for being the main components of antioxidant activity, in spite of not being the only ones. The antioxidant activity of phenolic constituents has been attributed to its oxide-reduction properties, which play an important role in the adsorption or neutralization of free radicals [4].

Medicinal plants have been a useful source for the research of new biologically active compounds. Different approaches are used to select a plant for research, specially the ethno-medical data approach. Unfortunately, the ethno-medical data is not always completely reliable, since it is difficult to diagnosed cancer well. Apart from the medicinal effects of traditional herbs, exploratory researches have been made and a wide variety of new biological activities from traditional medicinal plants have recently been reported, including anticancer activity [5].

Centella asiatica (L) Urb., popularly known in Brazil as cairuçu-asiático, centelha, codagem and pata-de-mula [6], is a cosmopolitan member of the Umbelliferae family that presents pantropical distribution. It is a perennial herb that has been used for centuries in Ayurvedic medicine to treat several disorders, such as insanity, asthma, leprosy, ulcers and eczema and for wound healing [7,8]. *Centella asiatica* contains triterpene glycosides such as centellasaponin, asiaticoside, madecassoside and sceffoleoside [9], and also asiatic acid and madecassic acid [10,11]. Asiaticoside is the most abundant triterpene glycoside in the water extract and it is transformed into asiatic acid *in vivo* by hydrolysis. Although the asiatic acid has shown cytotoxic activity on fibroblast cells [12] and induces apoptosis in different sorts of cancer [13-18], to date no scientific report related the presence of phenolic compounds of *Centella asiatica* to cytotoxic activity. Consequently, we have focused on establishing a relationship between the total phenolic content and antioxidant activity with cytotoxic activity, evaluating the activity against cancer cell lines using aqueous extract (AE) obtained from *Centella asiatica* leaves.

2. Results and Discussion

The AE showed a phenolic constituents level of 2.86 g/100 g. A recent report [19] showed that the method used quantifies mainly high-molecular weight tannins, such as hydrolysable tannin and other polyphenols that have a molecule of gallic acid in its structure, absorbing energy at the wavelength of 760 nm. In fact, values found in this study are in agreement with the results published recently which obtained values ranging from 3.23–11.7 g/100 g for different parts of *Centella asiatica* [20].

The flavonoids level in the AE was 0.361 g/100 g. Flavonoids are highly polar molecules of low molecular weight which absorb energy around 420 nm. Water is a polar extractant, so it will extract polar constituents, such as heterosides. In this work, water was used as liquid extractant and the level of flavonoids observed was high, suggesting that these flavonoid constituents might be in the heteroside form, since previous studies showed that flavonoids can be found in nature in the free state or in the form of glycosides [21,22].

The antioxidant activity of AE of *Centella asiatica* was evaluated by its ability to scavenge DPPH free radicals. The radical scavenging activity of the compounds can be measured by the decolorizing effect following the trapping of the unpaired electrons of DPPH. The AE showed a high antioxidant activity, with an IC₅₀ value of 31.25 µg/mL. Ascorbic acid and butylated hydroxytoluene (BHT) produced IC₅₀ values of 2.50 µg/mL and 7.58 µg/mL, respectively. Based on previous data, it is possible that the powerful antioxidant activity of polar extracts is due to the presence of substances with free hydroxyls [23]. In this context, flavonoids possess an ideal structure for the scavenging of free radicals, since they present a number of hydroxyls acting as hydrogen-donators which makes them important antioxidant agents [4,24].

The key role of phenolic compounds as free radical scavengers is emphasized in two important reports [25,26]. Antioxidative properties of essential oils and various extracts from many plants are of great interest in both academia and the food industry, since their possible use as natural additives has emerged from a growing trend to replace synthetic antioxidants by natural ones. Regarding this trend, the study of medicinal plant species has become of great importance, to find and test their bioactive compounds. The results indicate that AE obtained from *Centella asiatica* leaves showed the capacity to donate hydrogen; therefore they present DPPH scavenging activity. This activity might be due to the presence of phenolic and flavonic constituents detected in the samples. The results are in agreement with the recent study, which showed that *Centella asiatica* prevents the oxidative damage existing in several neuropathologies including stroke, Parkinson's disease and Alzheimer's disease, improving the antioxidant neurological state related to aging [27].

The cytotoxic activity (IC₅₀) of AE against four cancer cell lines and one normal cell line are shown in Table 1. The AE of *Centella asiatica* demonstrated a promising activity against human breast cancer (MDA-MB 231) and mouse melanoma (B₁₆F₁) (648.0 and 698.0 µg/mL, respectively), while that for rat glioma (C₆) the IC₅₀ was 1,000.0 µg/mL. On the other hand, the extract was not cytotoxic at the tested concentrations (up to 1,000.0 µg/mL) towards the human lung carcinoma (A₅₄₉) and normal hamster kidney (BHK-21) cell lines.

Table 1. Antitumor effects of AE of *Centella asiatica* against several cancer cell lines.

	Cell lines	IC ₅₀ (µg/mL)	Taxol® (µg/mL)
Tumoral	B ₁₆ F ₁	698.0	3.55 × 10 ⁻⁶
	MDA-MB 231	648.0	6.71 × 10 ⁻⁶
	C ₆	1000.0	3.43 × 10 ⁻⁶
	A ₅₄₉	> 1000.0	6.03 × 10 ⁻⁶
Normal	BHK-21	> 1000.0	1.06 × 10 ²

N=5; C₆ (rat glioma), MDA MB-231 (human breast cancer), A₅₄₉ (human lung carcinoma), B₁₆F₁ (mouse melanoma) and BHK-21 (normal hamster kidney fibroblast).

The cytotoxic activity of AE shown in this work presented in the same range of cytotoxicity (10–1,000 µg/mL) towards the B₁₆F₁, MDA-MB 231 and C₆ cell lines demonstrated in studies with extracts of other plants with cytotoxic potential in South Korea [5], Tanzania [28], Italy and Jordan [29]. Another report [17] shows that the purified asiatic acid, also present in the AE, decreased the viability of MDA-MB 231 cells in a dose-dependent manner.

Moreover, the extract was not cytotoxic against the A₅₄₉ (lung carcinoma) and BHK-21 (normal kidney cancer) cell lines. These results suggest a possible selectivity of the AE of *Centella asiatica* against some cancer cell lines, as observed for the cisplatin compounds, that are preferentially used for testicular [36] and ovarian cancer [37]. The selectivity of action could be related to the differences in morphology and physiology between tested cell lines, although this is not yet proven. These results are very encouraging, considering that most chemotherapeutic agents found on the market act both on tumor and normal cells [30] and cannot promote a specific treatment for the cancer without causing side effects as a result of damage to normal cells.

Although asiaticoside has not been reported in the scientific literature as a cytotoxic agent, the activity presented here may be related to its major presence in the extract, or even its performance in synergy with other constituents such as phenolic and flavonic constituents identified in this extract. Oxidative stress leads to the damage of membrane lipids, DNA, protein and cellular organelles, contributing to the development of cancer, early-aging, cardiovascular diseases, degenerative and neurological diseases and others. The phenolic constituents, especially the flavonoids, have high antioxidant capacity due to its properties of oxidation-reduction which plays an important role in the adsorption or neutralization of free radicals [4] showing raised biological protection. Since free radicals are involved in the establishment of cancer, the AE containing asiaticoside and other phenolic constituents can act reducing the number of free radicals (antioxidant activity), however at higher concentrations, promotes the cytotoxic effect, as observed in the results of cytotoxic assay.

3. Experimental

3.1. General

Leaves of *Centella asiatica* were collected in April 2006 from the campus of the Universidade Federal de Juiz de Fora (Minas Gerais, Brazil) and authenticated by Dr Fátima Regina Gonçalves Salimena from the Department de Botany, UFJF, Brazil. A voucher specimen (N° 24.610) is deposited

at the CESJ Herbarium of the Universidade Federal de Juiz de Fora (Minas Gerais, Brazil). Fresh plants were dried and used to prepare the aqueous extract (AE) as previously described [31]. Basically, the extract was prepared by infusion of *Centella asiatica* (200 g) in ultra pure water (4 L) followed by cold maceration for 24 h. The solution was filtered and then freeze-dried to yield a residue that was stored at -80 °C until use.

A spectrophotometric method explained AOAC [32] was adapted for the phenolic content assay. The AE, was dissolved in methanol to obtain a concentration of 0.5 mg/mL. Folin–Dennis reagent (100 µL) was added to a test tube containing the extracts or fractions (10 µL). Contents were mixed and a saturated sodium carbonate solution (200 µL) was added to the tube. Volume was adjusted to 2 mL by the addition of 1.69 mL of distilled water and the contents were mixed vigorously. Tubes were allowed to stand at room temperature for 25 min and then centrifuged for 5 min at 2,435× g. Absorbance of the supernatant was read at 760 nm. A blank sample of extract was used for background subtraction. Tannic acid was used as standard for the construction of the calibration curve (2–10 µg/mL). The assay was carried out in triplicate.

The procedure used for the quantification of flavonoids is based on the reaction between the flavonoids and aluminum chloride forming a yellow colored complex that can be measured in a spectrophotometer at a wavelength of 420 nm [33]. Rutin was used as standard for the construction of the calibration curve (2–30 µg/mL). For the quantification of the flavonoids content in the AE, an aliquot of 4 mL of chloroform and 6 mL of distilled water was added to 10 mL of the previously obtained sample. The resulting solution was mixed and centrifuged for 3 min at 2,435× g. Two milliliters of the aqueous phase was diluted to 25 mL with 10 mL of the reagent (pyridine, distilled water and aluminum chloride solution 17:80:3, v/v), 12.4 mL of a solution composed of water and dimethyl sulfoxide (1:2, v/v) and 0.6 mL of glacial acetic acid and, soon after vortexing the reaction mixture, the tube was placed in the dark for 15 min and the absorbance was measured at a wavelength 420 nm against the reagent blank. The construction of the calibration curve and the preparation of the sample solutions of the hydroalcoholic extracts for reading were done in triplicate.

The radical scavenging activity was determined by the 2,2-diphenyl-2-picrylhydrazyl hydrate (DPPH) method [34]. The DPPH molecule is a stable-free radical by virtue of the delocalization of the spare electron over the molecule; this delocalization produces a deep violet color, characterized by an absorption band in ethanol or methanol solution centered at about 517 nm. When a solution of DPPH is mixed with that of a substance, that can donate a hydrogen atom, this gives rise to the reduced form (diphenylpicrylhydrazine), with the loss of the violet color. An aliquot (0.5 mL) of ethanol solution containing of the AE obtained from leaves of *Centella asiatica* (0.97–250 µg/mL) was added to 1.5 mL of daily prepared ethanol DPPH solution (0.05 mM). The optical density change at 517 nm was measured 30 min later by a spectrophotometer. A blank was used to remove the influence of the color of the sample. An ethanolic solution of DPPH was used as negative control. Ascorbic acid and butylated hydroxytoluene (BHT) were used as reference drugs, at the same concentrations (0.97–250 µg/mL) as was used for the sample. Results were expressed as mean inhibiting concentration (IC₅₀). IC₅₀ parameter is defined as the concentration (µg/mL) of substrate that causes 50% loss of DPPH activity (color) and it was calculated by using the following equation: $IC_{50} (\%) = 100 \times (A_0 - A_s)/A_0$, where A_0 and A_s are the values for the absorbance of the negative control and the absorbance of the sample, respectively. Tests were carried out in triplicate.

The cytotoxicity assay was evaluated with several tumoral cell lines. To represent more than one embryonic origin cell line, the following cell lines were used in this study: mouse melanoma (B₁₆F₁), human breast cancer (MDA MB-231), rat glioma (C₆), human lung carcinoma (A₅₄₉) and normal hamster baby kidney line (BHK-21). The MDA-MB 231 and B₁₆F₁ were provided by Dr Ricardo Brentani (Instituto Ludwig de Pesquisa Contra o Câncer, São Paulo, Brazil). The BHK-21 (Baby Hamster Kidney), was provided by CPAFA (Centro Pan-americano de Febre Aftosa, Rio de Janeiro, Brazil). The A₅₄₉ and C₆ were provided by Dr. Hugo Armelin (Instituto de Química da Universidade de São Paulo, São Paulo, Brazil).

The cytotoxic potential was evaluated using the MTT assay [35]. Cells (10³ cells/well) were seeded in RPMI 1640 (Sigma Chemical Co.) medium supplemented with 10% fetal bovine serum (FBS) in 96-well culture plates (Falcon, NJ, USA) and were incubated in a humidified atmosphere with 5% CO₂, 37 °C, for 24 h until total adhesion to surface. The medium was replaced with fresh supplemented medium containing different concentrations of AE of *Centella asiatica* (0.1–1000 µg/mL). Cells were then incubated at 37°C for 48 h. After this time, the medium was newly refreshed with the same concentration of AE and the plate was incubated again for 72 h. After incubation time, 10 µL of a 5 mg/mL stock solution of MTT in PBS was added to each well containing the cells and incubated again for 4 h. Then, the supernatant without cells was aspirated from each well and 100 µL of DMSO was added to dissolve the dark blue formazan crystals resulting from MTT reduction by homogenization in plate shaker. The extent of MTT reduction to formazan within cells was measured by absorbance at 600 nm using a scanning microplate reader (Stat Fax–2100, Awareness Tecn.). Cultures used as controls did not receive extract.

The percentages of inhibition of cell viability were calculated with the values of viability of cell exposed to the AE and with non-exposed cells, using the *software* GraphPad Prisma 3.0 (GraphPad Software, Inc.). The 50% inhibitory concentrations for cellular population (IC₅₀) were calculated by linear regression (SigmaPlot 10.0, Systat Software, Inc.) in the interval of the corresponding concentrations to the curve of MTT metabolization vs. log of the used concentrations.

4. Conclusions

The results of this study demonstrate the antioxidant capacity of the AE of *Centella asiatica* related to its phenolic and flavonoid constituents and its antitumor potential against cancer cell lines. The results suggest that the potent antioxidant and antitumor activity are justified by the high concentration of phenolic constituents, mainly the flavonoids present in the extract. This study indicates that bioactive molecules present in *Centella asiatica* can be used as a prototype for development of new drugs and/or as a source of antioxidant and antitumor pharmaceutical raw material.

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Are venotonic drugs effective for decreasing acute posttraumatic oedema following ankle sprain? A prospective randomized clinical trial.

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Source

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Abstract

OBJECTIVE:

Lower leg oedema after trauma may cause various degrees of pain, disability and delay in patient recovery. In this prospective randomized study, we hypothesized that venotonic drugs had no effect in clinical outcome of patients with ankle sprain.

PATIENTS AND METHODS:

Eighty-one patients with type II and III ankle sprain were screened and randomly assigned for receiving standard conservative treatment alone (control group, 39 patients) or with oral intake of a venotonic drug (micronized purified flavonoid fraction, Daflon 1,000 mg \times 3) for 20 days (study group, 42 patients). Measurement of the circumference of ankle region in two different locations and assessment of pain intensity with the Visual Analogue Score were performed at the time of patients' admission and during the 7th and 20th posttraumatic day.

RESULTS:

Patients demographics were comparable in both groups. There were no significant differences between the two groups regarding the values of perimeter of ankle joint or pain intensity at all the examined time points.

CONCLUSIONS:

Venotonic drugs seem not to decrease the posttraumatic oedema or pain in patients who suffer from moderate or severe ankle sprain.

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Hemorrhoids and Varicose Veins: A Review of Treatment Options

Douglas MacKay, ND Candidate 2001

Abstract

Hemorrhoids and varicose veins are common conditions seen by general practitioners. Both conditions have several treatment modalities for the physician to choose from. Varicose veins are treated with mechanical compression stockings. There are several over-the-counter topical agents available for hemorrhoids. Conservative therapies for both conditions include diet, lifestyle changes, and hydrotherapy which require a high degree of patient compliance to be effective. When conservative hemorrhoid therapy is ineffective, many physicians may choose other non-surgical modalities: injection sclerotherapy, cryotherapy, manual dilation of the anus, infrared photocoagulation, bipolar diathermy, direct current electrocoagulation, or rubber band ligation. Injection sclerotherapy is the non-surgical treatment for primary varicose veins. Non-surgical modalities require physicians to be specially trained, own specialized equipment, and assume associated risks. If a non-surgical approach fails, the patient is often referred to a surgeon. The costly and uncomfortable nature of treatment options often leads a patient to postpone evaluation until aggressive intervention is necessary. Oral dietary supplementation is an attractive addition to the traditional treatment of hemorrhoids and varicose veins. The loss of vascular integrity is associated with the pathogenesis of both hemorrhoids and varicose veins. Several botanical extracts have been shown to improve microcirculation, capillary flow, and vascular tone, and to strengthen the connective tissue of the perivascular amorphous substrate. Oral supplementation with *Aesculus hippocastanum*, *Ruscus aculeatus*, *Centella asiatica*, *Hamamelis virginiana*, and bioflavonoids may prevent time-consuming, painful, and expensive complications of varicose veins and hemorrhoids.

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Introduction

Every general practitioner sees a large number of patients who suffer from problems associated with venous insufficiency. Two of the most common manifestations of venous insufficiency are varicose veins and hemorrhoids. The prevalence of these two conditions is astonishing. In population studies the prevalence of varicose veins has been reported to be 10-15 percent for men and 20-25 percent for women.¹ In a recent cross-sectional study, the age-adjusted prevalence of varicose veins was 58 percent for men and 48 percent for women.² Over three-quarters of individuals in the United States have hemorrhoids at some point in their lives, and about half of the population over age 50 requires treatment.³

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The Merck Manual defines hemorrhoids as “Varicosities of the veins of the hemorrhoidal plexus, often complicated by inflammation, thrombosis, and bleeding.”⁴ It has been suggested this is an oversimplification of the nature of hemorrhoids. A more recent definition is, “Vascular cushions, consisting of thick submucosa containing both venous and arterial blood vessels, smooth muscle, and elastic connective tissue.”⁵ While everyone has this tissue, it is the enlargement, bleeding and protrusion that create pathology. The crossroads to the development of varicose veins and hemorrhoids is the loss of vascular integrity. Considering the combined prevalence of varicose veins and hemorrhoids, venous insufficiency and its manifestations are an extremely common medical problem that every physician should be prepared to treat.

Hemorrhoids

Historical Perspective on Hemorrhoids

Hemorrhoids are mentioned in ancient medical writings of every culture, including Babylonian, Hindu, Greek, Egyptian, and Hebrew. The word “hemorrhoid” is derived from the Greek “haema” = blood, and “rhoos” = flowing, and was originally used by Hippocrates to describe the flow of blood from the veins of the anus.⁶ Prior to the 1800s hemorrhoids were treated simply by poultice, bed rest, or, in difficult cases, by the application of a red hot poker. A simpler method was prayer to the patron saint of hemorrhoid sufferers, St. Fiacre, an Irish priest who lived in the seventh century.⁷ Injection therapy was begun in 1869 by Morgan of Dublin using iron persulfate, and was a relief to many who had endured the medical treatment of the time.⁸ As late as 1888 the only other recommended treatment (apart from the above mentioned) was abstinence from alcohol, sitting in cane chairs, and half a pint of cold spring water injected into the rectum after a morning fast.⁹ The

founding of St. Mark’s Hospital in 1935 by Fredrick Salmon, who is given credit for the first ligation of hemorrhoids, marked a turning point in the treatment of hemorrhoids.¹⁰

Hemorrhoid Histology

As mentioned, there are variant definitions of the histology of the hemorrhoid tissue, but they are universally classified according to anatomical origin. Internal hemorrhoids consist of redundant mucus membrane of the anal canal with the origin above the dentate (ano-rectal) line. External hemorrhoids have an epithelial component and originate below the dentate line.⁷ Internal hemorrhoids are further graded based on the extent to which the tissue descends into the anal canal (Table 1).

Differential Diagnosis

When a patient presents with rectal discomfort, swelling, pain, discharge, and bleeding at the time of defecation, it is prudent not to assume it is a result of hemorrhoids; a full evaluation is indicated, including a rectal examination, a proctoscopic exam, and in some cases a sigmoidoscopy. There are several conditions producing symptoms similar to hemorrhoids that must be considered. To rule out grave causes of ano-rectal bleeding, such as anal or rectal carcinoma, one gastroenterologist suggests, “All patients over forty years old, even with typical hemorrhoidal bleeding, must undergo flexible sigmoidoscopy (or colonoscopy).”⁷

Other types of ano-rectal pathology that must be ruled out include anal fissures, which can cause pain with defecation and be associated with rectal bleeding. The pain will be described as burning or tearing, as opposed to the achiness or feeling of fullness after defecation described by patients with hemorrhoids. Perirectal abscesses are less common in the general population but should be considered in patients with diabetes or other immunocompromising conditions.¹¹ Anal

Table 1: Grading of Hemorrhoids

First degree

"The mucosa barely prolapses, but with severe straining may be trapped by the closing of the anal sphincter. Subsequently, venous congestion occurs occasionally, resulting in discomfort and/or bleeding. Clinically speaking there is no obvious external abnormality."

Second degree

"With further protrusion of the mucosa, the patient complains of an obvious lump, but this disappears spontaneously and rapidly after defecation unless thrombosis occurs."

Third degree

"In chronic hemorrhoidal disease, the persistent prolapsing produces dilatation of the anal sphincter, and the hemorrhoids protrude with minimal provocation and usually require manual replacement."

Fourth degree

"These are usually described as external hemorrhoids and are protruding all the time unless the patient replaces them, lies down, or elevates the foot of the bed. In these fourth degree hemorrhoids, the dentate line also distends, and there is a variable external component consisting of redundant, permanent perianal skin."

From Dennison AR, Whiston RJ, Rooney S, et al. The management of hemorrhoids. *Am J Gastroenterol* 1989;84:475-481.

fistulas can cause drainage, soiling of underwear, and discomfort. Mucosal diseases such as ulcerative proctitis, colitis, or Crohn's disease can present with rectal bleeding and should be ruled out. Perianal condylomas cause pruritis, local irritation, pain and bleeding. Skin tags can be remnants of past external hemorrhoids and commonly co-exist with fissures. A rectocele can cause fullness in the rectum, giving the patient a similar sensation to an internal hemorrhoid.

It is common for patients to associate pruritis ani with hemorrhoids. In some cases swelling of external hemorrhoids and skin tags can prevent proper anal hygiene, which can cause marked itching. Hemorrhoids themselves do not produce significant itching.³ When a patient presents with pruritis ani, many

assume it is the sequela of hemorrhoidal disease. However, a mindful physician will consider causes such as allergic reactions, perianal dermatitis, microorganisms, parasites, oral antibiotics, hygiene, systemic disease (e.g., diabetes mellitus, liver disease), heat, and hyperhidrosis.⁴

Etiological Factors

The exact cause of enlarged and symptomatic hemorrhoids is debated, and numerous etiologies have been suggested. Some of the earliest proposed etiologies included temperament, body habits, customs, passions, sedentary life, tight-laced clothes, climate, and seasons.¹² Recent studies implicate gravity, intrinsic weakness of the blood vessel wall, heredity, increased intra-abdominal pressure

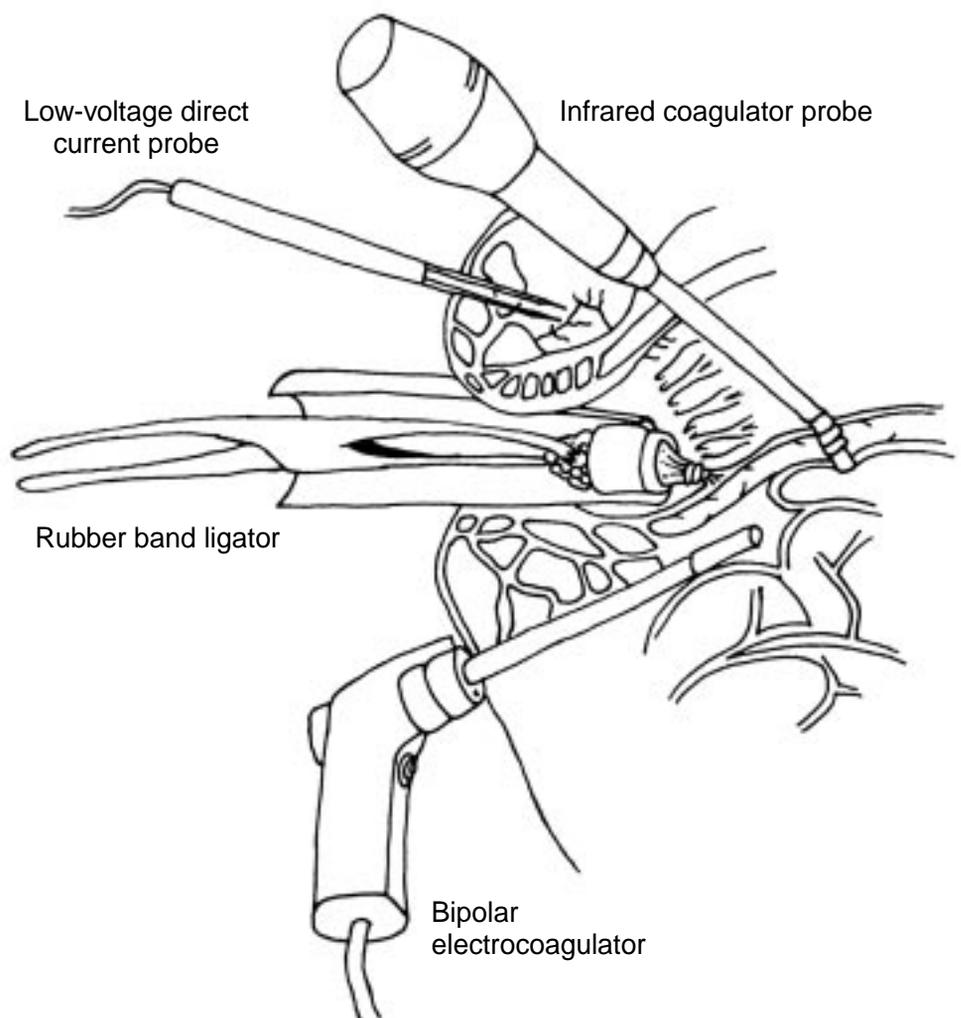
from many causes, including prolonged forceful valsalva during defecation or resistance training, obstruction of venous outflow secondary to pregnancy or pelvic masses, and constipated stool in the rectal ampulla.^{11,13} As a patient ages and has continual presence of one or more of the factors mentioned, the integrity of the hemorrhoid “cushions” deteriorates, and the hemorrhoids begin to bulge and descend into the anal canal. When the cushion bulges into the canal, it is exposed to potential trauma and irritation from the passage of stool.

Conventional Approaches

Despite thousands of years and millions of patients with pain, discomfort, and perceived embarrassment of hemorrhoids, the exact nature and cause of the condition is not clear, and the standard treatments are, at best, imperfect. Dietary manipulation, vascular tonifying agents, injection sclerotherapy, cryotherapy, manual dilation of the anus, infrared photocoagulation, bipolar diathermy, direct current electrocoagulation, rubber band ligation, and hemorrhoidectomy are all standard considerations for the treatment of hemorrhoids.

The treatments can be grouped into conservative (diet and vascular tonification); non-excisional (sclerotherapy, cryotherapy, manual dilation, photocoagulation, diathermy, and electrocoagulation); and surgical methods (ligation and hemorrhoidectomy). “Conservative methods with or without nonexcisional treatments are preferred to surgical methods.”¹²

Figure 1: Surgical and Non-surgical Approaches to Hemorrhoid Treatment



Key to Figure 1:

Rubber Band Ligation:

A device is used to place one or two small rubber bands securely around the base of the hemorrhoid. The rubber bands are left in place to close off the blood supply to the hemorrhoid. The hemorrhoid and the rubber bands fall off after seven to ten days, leaving a small sore that will heal over time.

Direct Current Electrocoagulation:

A small probe is inserted into the hemorrhoid, and very low levels of electrical current are applied for six to ten minutes. The electrical current closes off the blood supply to the hemorrhoid. One group of hemorrhoids is treated at a time, so patients must return for additional treatments.

Infrared Coagulation:

The device is used to deliver four to five 1.5-second applications of infrared light to close off the blood supply to the hemorrhoid. One area is treated per office visit. Additional visits may be necessary, usually one month apart. Patients may experience a little bleeding between the fourth and tenth days after the procedure.

Bipolar Electrocoagulation:

The probe is used to deliver electrical current for two seconds to the hemorrhoid. This will close off the blood supply to the hemorrhoid. This procedure is similar to infrared coagulation and direct current electrocoagulation.

Adapted from: Pfenninger JL, Surrell J. Nonsurgical treatment options for internal hemorrhoids. *Am Fam Physician* 1995;52:821-834.

Figure 1 illustrates surgical and non-surgical approaches to hemorrhoid treatment.

Some of the conventional approaches are not without potential complications. Injection sclerotherapy has resulted in cases of anaphylactic shock.¹⁴ Cryotherapy is cumbersome to perform and is associated with severe rectal pain and discharge.¹⁵ Manual dilation often requires general anesthetic and admission to the hospital. If dilation is not performed carefully the results may be disastrous.¹⁶ Septic complications, including death, have resulted from rubber band ligation.¹⁷ Hemorrhoidectomy, although indicated in extreme

cases unresponsive to conservative treatment, is extremely painful and requires a four to six week recovery.

Nonexcisional Techniques in Hemorrhoid Treatment

The potential disadvantages of sclerotherapy, banding, manual dilation, and surgery have led to the development of a new generation of nonexcisional techniques for the treatment of hemorrhoidal disease. Infrared photocoagulation, bipolar diathermy, and electrocoagulation are the most recent additions to

the plethora of modalities to consider. These modalities aim to affect sclerosis of the vascular root and to fix the mucosa to the underlying submucosa and muscle.¹⁸ There have been several studies showing the efficacy of these treatments as comparable to the semi-invasive therapeutic modalities. A study of 758 patients with symptomatic hemorrhoidal disease concluded that all three techniques, performed on an outpatient basis with little or no sedation, are effective modalities for first- and second-degree hemorrhoids. Moreover, direct current electrocoagulation was associated with less discomfort and fewer complications and can be effective in third- and fourth-degree hemorrhoids.¹⁹

Although direct current electrocoagulation was utilized in 1867, and explained by Wilbur E. Keesey, MD in 1934, doctors today oddly consider it one of the new generation of modalities.²⁰ A study of 120 patients using direct current electrocoagulation treating a total of 590 hemorrhoid segments reported all patients were successfully treated and remained symptom free at a mean duration of follow-up of 23 months. The researchers concluded that direct current electrotherapy is an effective, painless, and safe outpatient treatment approach to all grades of internal and mixed hemorrhoid disease.²¹ Direct current electrotherapy has also been shown to be effective, safe, and cost effective in the treatment of chronic anal fissures associated with internal hemorrhoids.²² One author suggests patients postpone evaluation of suspected hemorrhoids due to fear of the treatment modality, hospitalization, cost, and time of disability, leading to progression of the hemorrhoid or late diagnosis of serious gastrointestinal disease.²¹ Patients must be made aware of less invasive, relatively inexpensive, outpatient treatment options.

Varicose Veins

Epidemiological Factors in Varicose Veins

Chronic venous disease of the lower limbs is one of the most common medical conditions seen in clinical practice.²³ There is some disagreement over the actual prevalence of chronic venous insufficiency due to the lack of a standardized definition. There have been several large epidemiological studies with varied criteria for venous disease. Definitions range from “any prominent superficial vein in the lower extremity” to “a vein which has permanently lost its valvular efficiency and, as a result of continuous dilation under pressure, in the course of time becomes elongated, tortuous, pouched and thickened.” Callam, reviewing an analysis of published data on the epidemiology of varicose veins, assessed all of the studies with regard to age range and distribution of study population; criteria used to diagnose varicose veins; geographical site of the study population; and methods used to assess venous disease. He reported half of the adult population manifesting minor venous disease, and less than half (women 20-25%; men 10-15%) having visible varicose veins.²⁴

Diagnostic Factors

Patients will often self-diagnose varicose veins and present to the physician with elongated, dilated, tortuous superficial veins (usually in the legs) whose valves have become incompetent. Patients may experience aching, fatigue, or heat that is relieved by elevation or wearing compressive hosiery. Symptoms are not always related to the degree or size of the varicose veins.²⁵ Patients who present with asymptomatic varicosities often seek treatment for cosmetic reasons. Primary varicose veins are not associated with deep venous disease, and treatment is indicated to relieve symptoms and improve appearance. Treatment is rarely required to prevent further complications. Varicosities that occur

secondary to obstruction and valvular incompetence of the deep venous system are much more serious because of the associated risk of pulmonary thromboembolism.¹

Physicians evaluating a patient for presumed varicose veins must rule out other possible causes for the presenting symptoms: lumbar nerve root irritation can cause an aching sensation in the leg; peripheral neuritis causes a burning sensation in the leg; and arterial insufficiency may present with intermittent claudication. A deep vein thromboembolism can present with calf pain, and patients on estrogen have an increased risk. Osteoarthritis of the hip and knee are also considerations in the differential diagnosis of varicose veins. The pain associated with varicose veins is uniquely relieved with leg elevation.

Pathogenesis and Etiological Factors

The pathogenesis of varicose veins is thought to include increased venous and capillary pressures, increased capillary permeability, chronic edema, repeated inflammation, and stasis.¹ Some of the risk factors associated with developing varicose veins are obesity, high systolic blood pressure, cigarette smoking, low levels of physical activity, pregnancy, abdominal or pelvic masses, ascites, and occupations that require prolonged standing.^{1,25,26}

Conventional Treatment of Varicose Veins

Standard treatment for varicose veins is mechanical compression, sclerotherapy, or surgery. Compression therapy is achieved with lightweight hosiery for small, mildly symptomatic varicose veins. Advanced cases require a heavier elastic support stocking. Mechanical compression is inconvenient, uncomfortable, and subject to poor compliance.²⁷ Additionally patients can apply the elastic bandage too tightly, producing a tourniquet effect. Even when applied correctly, bandages can rapidly

loosen and become ineffective.²⁵ Injection sclerotherapy is used to treat all degrees of primary varicose veins. The aim of sclerotherapy is to destroy the vein by fibrosis. Sodium tetradecyl sulfate 1% solution is injected, while the vein is emptied of blood, causing damage to the intima of the vein and permanent fibrosis. Sclerotherapy does not require hospitalization, and the patient resumes normal activity after the procedure. Painful varicose veins with recurrent phlebitis or skin changes are considered indications for surgery.²⁵ General practitioners must refer to a vascular surgeon for surgery and should consider this only if indicated.

Dietary and Hydrotherapy Approaches to Hemorrhoids and Varicose Veins

Dietary Recommendations

Diet therapy is a widely accepted modality in the management of hemorrhoids and varicose veins. Many physicians consider the first line of therapy to be a high fiber diet with commercial fiber supplements and enough oral fluids to produce soft, but well formed and regular bowel movements.²⁸ A low fiber diet can result in small hard stools that can cause patients to strain during bowel movements. This strain increases intra-abdominal pressure, subsequently increasing pressure on the veins of the lower legs and the hemorrhoidal cushions. Over time this can deteriorate vascular integrity. A high fiber diet is an important component to the prevention and treatment of both hemorrhoids and varicose veins.²⁸ This in addition to hydrotherapy, proper anal hygiene, and avoiding activities that require the patient to strain are the foundation of the approach of many family practitioners to these conditions.

Hydrotherapy

The warm sitz bath is the hydrotherapy indicated for conditions associated with increased pelvic congestion.^{25,29,30} The warm sitz

bath is an effective non-invasive therapy for uncomplicated hemorrhoids and varicose veins, but requires a high degree of patient compliance.

Specific Nutrients and Botanicals for the Prevention and Treatment of Varicose Veins and Hemorrhoids

A major component of a safe and effective therapy for both varicose veins and hemorrhoids, that is often overlooked, is the use of botanical and nutritional therapies. Several botanical extracts have been shown to improve microcirculation, capillary flow, and vascular tone, and strengthen connective tissue of the perivascular amorphous substrate. The goals of botanical and nutritional support are consistent with the philosophy of treating the cause of a disease. Conversely, the bulk of standard treatments for varicose veins and hemorrhoids are geared toward removing the problem or palliating the disease. Additionally, the low compliance associated with treatments such as hydrotherapy, mechanical compression therapy, and diet and lifestyle changes renders oral dietary supplementation an attractive option. The use of nutritional and botanical agents for the treatment of hemorrhoids and varicose veins is possibly the missing link to an effective conservative approach to these diseases. Early intervention with conservative therapies may prevent time-consuming and expensive complications of varicose veins and hemorrhoids.

Centella Asiatica (Gotu Kola)

Centella asiatica is a tropical medicinal plant with a long history of therapeutic use. An important active constituent of *Centella asiatica*, asiaticoside, was isolated and purified in 1940 and the first systematic clinical studies were carried out in 1945.³¹ Pharmaceutical *Centella* preparations are titrated for the pentacyclic triterpene derivatives asiatic acid, madecassic acid, and

asiaticoside.³² Most clinical studies of *Centella asiatica* used either undefined alcohol or aqueous extracts or one of the following extracts: TECA, TTFCA, or TTF. The extracts TECA (titrated extract of *Centella asiatica*) and TTFCA (total triterpenoid fraction of *Centella asiatica*) are combinations comprised of asiatic acid (30%), madecassic acid (30%), and asiaticoside (40%). The *Centella* extract TTF (total triterpenic fraction) is comprised of asiatic acid and madecassic acid (60%) in a ratio not clearly defined, in combination with asiaticoside (40%).³²

Rigorous clinical investigation of *Centella asiatica* has been conducted on chronic venous insufficiency and varicose veins. *Centella* has the potential to enhance connective tissue integrity, elevate antioxidant levels in wound healing, and improve capillary permeability.³³⁻³⁵ A randomized, multicenter, placebo-controlled, double-blind study investigated *Centella* extract in the treatment of venous insufficiency. Ninety-four patients received either TECA in two different doses (120 mg/day; 60 mg/day) or placebo over a two-month period. Results were evaluated subjectively by the patients' symptoms and objectively by plethysmography. The TECA groups resulted in significant improvements ($p < 0.05$) in symptoms of heaviness in the lower limbs, edema, and overall evaluation by the patient. Venous distensibility, measured by a mercury strain gauge plethysmograph at three occlusion pressures, was improved for the TECA groups but aggravated for the placebo group.³⁶ The differences in the effect of the different TECA doses were not significant, but did reveal a dose-effect relationship.

Mucopolysaccharides are one of the main components of the amorphous cellular matrix (ground substance) that maintains vascular integrity. The biochemical action of *Centella* extract was shown to reduce serum levels of lysosomal enzymes involved in the degradation of mucopolysaccharides. The

TTFCA extract was administered (30 mg three times daily) to 20 patients with severe varicose veins in the leg over an observation period of three months. Prior to the treatment, elevated baseline serum lysosomal enzymes were established (beta-glucuronidase 1.8 +/- 0.4 microM/min/L, beta-N-acetylglucosaminidase 23.1 +/- 0.4 microM/min/L, and arylsulfatase 0.078 +/- 0.003 microM/min/L) indicating an increased mucopolysaccharide turnover in subjects with varicose veins. During the treatment period these levels fell progressively. At the end of the three-month trial there was a significant reduction in the serum levels of the lysosomal enzymes (beta-glucuronidase 1.2 +/- 0.05 microM/min/L, beta-N-acetylglucosaminidase 17.7 +/- 0.7 microM/min/L, arylsulfatase 0.042 +/- 0.003 microM/min/L). These reductions were interpreted as evidence of a positive effect of the TTFCA extract on the pathogenesis of varicose veins.³⁷

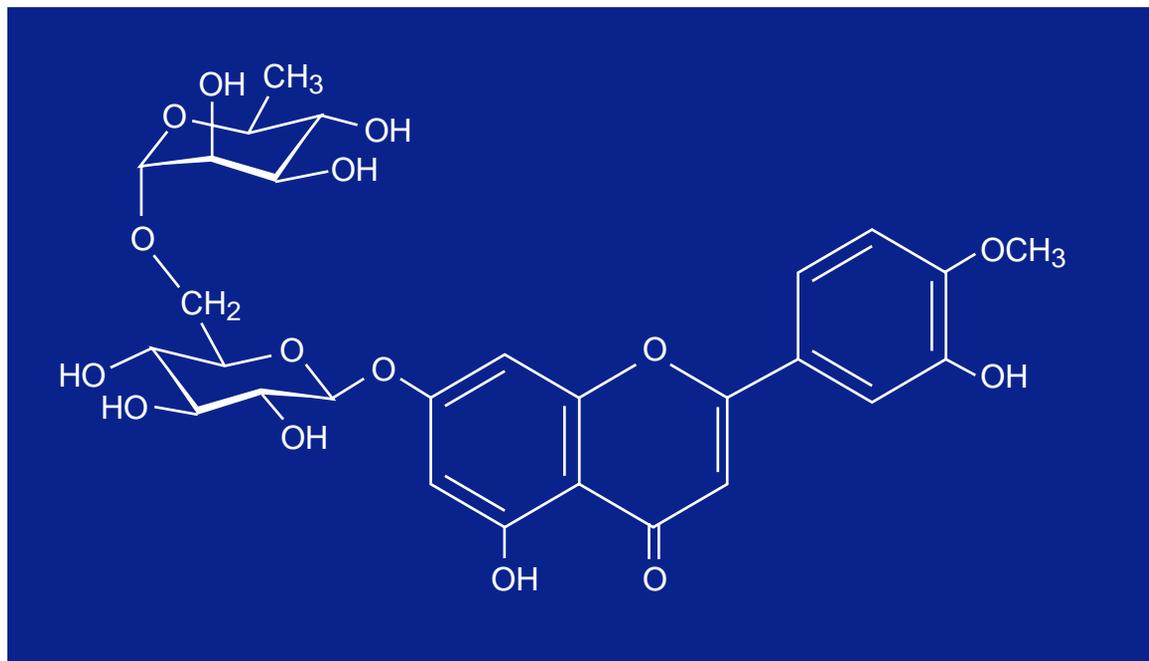
In a double-blind, placebo-controlled study the effects of Centella extract on capillary filtration rate was investigated. *Centella asiatica* (TTFCA) extract was administered to 62 patients at two different doses (90mg/day; 180mg/day). Capillary filtration rate was evaluated in comparison to placebo. At the end of the four-week treatment period there was a dose-dependent reduction in capillary filtration rate measured by plethysmography. In comparison with the placebo group, the dose-dependent improvements seen in the TTFCA group were significant. The reduced capillary filtration rate was associated with improvement in microcirculation and in clinical symptoms.^{35,38} In addition, local application of TTFCA extract has been shown to improve vascular tone. In a double-blind study involving 80 patients, Centella extract was applied locally three times daily to patients with various venous disorders (including hemorrhoids and varicose veins). Patients, physicians, and ultrasonic examination noted subjective and objective improvements in symptoms.³⁹

Bioflavonoids: Diosmin, OPCs, and Hesperidin

Bioflavonoids, particularly diosmin (Figure 2), oligomeric proanthocyanidin complexes (OPCs), and hesperidin, have demonstrated efficacy in the treatment of hemorrhoids and varicose veins. These bioflavonoids exhibit phlebotonic activity, vasculoprotective effects, and antagonism of the biochemical mediators of inflammation.⁴⁰ OPCs, diosmin, and hesperidin have been the subject of numerous clinical trials on efficacy and safety in the treatment of varicose veins and hemorrhoids.

There has been extensive research on the flavonoid mixture containing 90-percent diosmin and 10-percent hesperidin (Daflon 500, Les Laboratoires, Servier, France). Several randomized controlled studies have established its efficacy in the treatment of varicose veins and hemorrhoids. The safety of these flavonoids has been established through animal studies, and confirmed clinically in long-term trials. Data collected on more than 2,850 patients treated with 450 mg diosmin and 50 mg hesperidin twice daily for up to one year confirms it is well tolerated and has no contraindications to its use.^{41,42} Side effects are rare and mild with an incidence and nature similar to that found with placebo in double-blind, controlled trials.⁴¹

A double-blind, placebo-controlled trial of 120 patients reported the efficacy of Daflon in the treatment of acute and chronic symptoms of hemorrhoids.⁴³ The group was divided in half and matched at entry for general characteristics, clinical features, length of history, and acute episodes. Patients received the flavonoid mixture at a dose of two 500 mg tablets daily or placebo for two months. Subjects were evaluated on pain, pruritis, discharge, bleeding, edema, erythema, and bleeding on examination. Mean parameter scores and overall symptom scores fell significantly in the treated group. A similar

Figure 2: Diosmin

double-blind, placebo-controlled study examined 100 patients suffering an acute hemorrhoid attack. These patients received Daflon in a loading dose of three 500 mg tablets twice daily for the first four days and two tablets twice daily the following three days. The clinical severity of proctorrhagia, anal discomfort, pain, and anal discharge diminished to a greater extent in the treatment group.⁴⁰

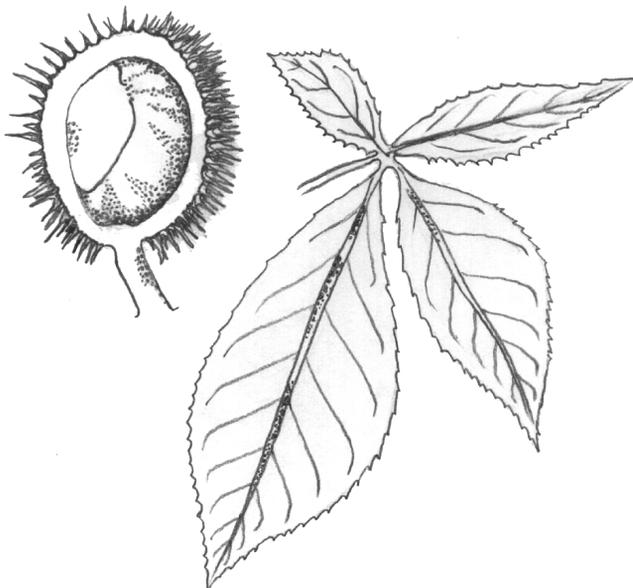
During pregnancy many of the treatment options for hemorrhoids, such as injection, rubber band ligation, and surgery are contraindicated.⁴⁴ A study of pregnant women suffering from acute hemorrhoids who were treated with Daflon showed remarkable results. Fifty women were treated for eight weeks before delivery and four weeks after delivery using a seven-day loading dose of six tablets for four days, and four tablets for three days, followed by a maintenance dose of two tablets per day. Over half of the women reported relief from symptoms by the fourth day of treatment and fewer relapses occurred during the antenatal period. Treatment did not affect

pregnancy, fetal development, birth weight, infant growth, or feeding.⁴²

Animal studies have shown flavonoids reduce neutrophil activation, mediate inflammation, and decrease soluble endothelial adhesion molecules.⁴⁵ Human trials have shown the ability of flavonoids to improve venous tone and vein elasticity assessed by plethysmography and to decrease plasma markers of endothelial activation.^{46,47} Additionally, clinical trials conducted in Germany using Daflon (two 500 mg tablets daily) showed highly statistically significant improvements in chronic venous insufficiency, venous leg ulcers, and hemorrhoids.⁴⁸

Professor Jacques Masquelier of the University of Bordeaux in France patented a method of extracting OPCs from pine bark in 1951 and from grape seeds in 1970.⁴⁹ Since that time OPCs have become known primarily for their antioxidant and free radical scavenging properties, but have also been shown to inhibit the enzymes hyaluronidase, elastase, and collagenase.^{50,51} These enzymes can degrade connective tissue structures, leading to

Figure 3: Aesculus Hippocastanum



Aesculus Hippocastanum
(Horse Chestnut)

Horse chestnut seed extracts (HCSE) (Figure 3) are used clinically to relieve the subjective symptoms and reduce the objective signs of chronic venous insufficiency.⁵⁶ The active component of the extract is thought to be the triterpenic saponin, aescin.⁵⁷ HCSE has been shown to exhibit venotonic, vascular protective, anti-inflammatory, and free-radical scavenging properties.⁵⁸ *In vitro* studies have shown HCSE inhibited the activity of the enzymes elastase and hyaluronidase. These enzymes are involved in enzymatic proteoglycan degradation, which compromises part of the capillary endothelium and the extravascular matrix.⁵⁷ These properties make HCSE ideal for the treatment of both varicose veins and hemorrhoids.

HCSE appears to reduce abnormally increased capillary permeability and associated edema.⁵⁹ A randomized, partially-blinded, placebo-controlled study of 240 patients showed a gradual decrease in edema, reaching a maximum at the end of the 12-week trial. This study used 50 mg aescin twice daily for 12 weeks, which resulted in a 25-percent reduction of mean edema volume.⁵⁹ The authors proposed that further edema reduction is possible because a steady state was not achieved in the 12-week trial period. An HCSE study using rats showed 200 mg/kg body weight of aescin effectively reduced increased vascular permeability, induced by both acetic acid and histamine, and inhibited hind paw edema induced by carrageenin.⁶⁰

A criteria-based, systematic review of double-blind, placebo-controlled trials of oral HCSE for patients with chronic venous insufficiency was published in the *Archives of Dermatology* in 1998. This review identified 13 studies with 1,083 total patients that met the strict inclusion criteria. The author concluded that HCSE is safe and effective in the symp-

increased vascular permeability. OPCs have demonstrated preferential binding to areas characterized by a high content of glycosaminoglycans such as the capillary walls.⁵² This feature makes them effective in decreasing vascular permeability and enhancing capillary strength, vascular function, and peripheral circulation.

In a double-blind study, 71 patients with peripheral venous insufficiency received 300 mg OPCs from grape seed per day. A significant reduction in functional symptomatology was observed in 75 percent of the treated patients compared to 41 percent of the patients given placebo.⁵³ In another study, measurements confirmed that a single administration of 150 mg OPCs increased venous tone in patients with widespread varicose veins.⁵⁴

In a double-blind clinical trial, a group of geriatric patients with low capillary resistance were treated with 100-150 mg OPCs or placebo. Over half of the patients in the treatment group demonstrated noticeable improvement in capillary resistance after approximately two weeks. All patients in this group reached the maximum attainable results after three weeks.⁵⁵

omatic short-term treatment of chronic venous insufficiency.⁶¹ Additional rigorous randomized, controlled trials are essential to verify HCSE's usefulness in chronic venous insufficiency and to explore the safety of long-term use.

Ruscus Aculeatus **(Butcher's Broom)**

Extract of *Ruscus aculeatus* is effective in increasing venous tone because of its anti-inflammatory and astringent properties.⁶² The active biochemical constituent is proposed to be the saponin glycoside ruscogenin.⁵⁷ Herbalists of various cultures have historically used *Ruscus aculeatus* for the treatment of varicose veins and hemorrhoids.⁶³ There is an increasing body of scientific literature to support these traditional folk medicine uses.

Increased macromolecule permeability through gaps between endothelial cells of post-capillary venules is associated with inflammatory reactions and edema. A group of French researchers used the hamster cheek pouch experimentally as an *in vivo* model of macromolecule permeability. Their early experiments showed intravenous Ruscus extract significantly inhibited the macromolecular permeability-increasing effect of bradykinin, leukotriene B₄, and histamine.⁶⁴ Later studies showed Ruscus extract applied topically dose-dependently inhibited the macromolecular permeability-increasing effect of histamine.⁶² The efficacy of topical Ruscus extract indicates the response is a result of the extract and not a product of its metabolism. Ruscus extract has also shown *in vivo* inhibition of elastase, part of the enzyme system involved in degrading perivascular structural components.⁵⁷

Human trials have shown patients with chronic venous insufficiency given oral Ruscus extract maintained venous tone and improved venous emptying in comparison to placebo-treated patients.⁶⁵ In another study patients with chronic venous insufficiency given oral Ruscus extract had a decrease in

capillary filtration rate, measured by plethysmography within two hours of administration.⁶⁶ Additionally, healthy volunteers exhibited a decrease of ten percent in venous capacity two hours after ingestion of oral Ruscus extract.⁶⁷

Hamamelis Virginiana **(Witch Hazel)**

Witch hazel extract, high in tannins and volatile oils, is a well-known medicinal tree from the deciduous forest of Atlantic North America. Witch hazel has a long therapeutic tradition and is used primarily for its astringent, anti-inflammatory, and local hemostatic effects.⁶⁸ In folk medicine it has been used for venous conditions, including hemorrhoids and varicose veins. Witch hazel decoctions are easily found on the shelf of most pharmacies, yet the literature available regarding its efficacy and mechanisms of action is limited. Witch hazel bark is used topically in minor injuries of the skin, local inflammation of the skin and mucous membranes, hemorrhoids, and varicose veins.⁶⁹

Studies have investigated the mechanism of action responsible for the astringent and antiphlogistic properties of Witch hazel. Witch hazel extract has been shown *in vivo* to inhibit alpha-glucosidase as well as human leukocyte elastase, enzymes which contribute to the degradation of connective tissue. Vascular integrity is compromised by the increase in activity of these enzymes. Witch hazel also exhibited a strong antiphlogistic effect in the croton oil ear edema test in the mouse.⁷⁰ The authors of these clinical trials proposed the antiphlogistic activity of Witch hazel extract is likely due to the presence of proanthocyanidins consisting of flavan units such as (+) – catechin, and (-) – epicatechin. Considering the widespread availability of Witch hazel extracts, it is essential for more scientific literature to be published regarding its efficacy in the treatment of hemorrhoids and varicose veins.

Conclusion

General practitioners encounter a large number of patients suffering from the manifestations of decreased vascular integrity, two of the most common being varicose veins and hemorrhoids. Conservative therapies such as diet, hydrotherapy, mechanical compression for varicose veins, topical agents for hemorrhoids, and lifestyle factors are the standard non-invasive approaches to these conditions. The next line of therapy involves the use of semi-invasive non-surgical modalities including electrocoagulation, sclerotherapy, cryotherapy, photocoagulation, and diathermy. These modalities require specific training, specialized equipment, and are associated with some risk.

As with all disease, the primary treatment for varicose veins and hemorrhoids is prevention. Patients with risk factors for developing these conditions should be identified through history and physical exam before aggressive intervention is necessary. The use of diet, lifestyle, and hydrotherapy in addition to botanical agents such as *Aesculus hippocastanum*, *Ruscus aculeatus*, *Centella asiatica*, *Hamamelis virginiana*, and bioflavonoids can intervene in the pathogenesis of decreased vascular integrity. Early intervention with these non-invasive therapies may prevent time-consuming and expensive complications of both varicose veins and hemorrhoids.

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How we can improve patients' comfort after Milligan-Morgan open haemorrhoidectomy

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Abstract

AIM: To demonstrate the value of Diosmin (flavonoidic fraction) in the management of post-haemorrhoidectomy symptoms.

METHODS: Eighty-six consecutive patients with grades III and IV acute mixed hemorrhoids admitted to the

Anorectal Surgical Department of First Affiliated Hospital, Xinjiang Medical University from April 2009 to April 2010, were enrolled in this study. An observer-blinded, randomized trial was conducted to compare post-haemorrhoidectomy symptoms with use of Diosmin flavonoidic fraction vs placebo. Eighty-six patients were randomly allocated to receive Diosmin flavonoidic fraction 500 mg for 1 wk ($n = 43$) or placebo ($n = 43$). The Milligan-Morgan open haemorrhoidectomy was performed by a standardized diathermy excision method. Pain, bleeding, heaviness, pruritus, wound edema and mucosal discharge were observed after surgery. The postoperative symptoms and hospitalization time were recorded.

RESULTS: The mean age of the Diosmin group and controls was 53.2 and 51.3 years, respectively. In Diosmin group, haemorrhoid piles were of the third degree in 33 patients and the fourth degree in 10; and in the control group, 29 were of the third degree and 14 were of the fourth degree. There was no statistically significance in age, gender distribution, degree and number of excised haemorrhoid piles, and the mean duration of haemorrhoidal disease between the two groups. There was a statistically significant improvement in pain, heaviness, bleeding, pruritus from baseline to the 8th week after operation ($P < 0.05$). Patients taking Diosmin had a shorter hospitalization stay after surgery ($P < 0.05$). There was also a significant improvement on the proctoscopic appearance ($P < 0.001$). However, there was no statistical difference between the two groups in terms of wound mucosal discharge. Two patients experienced minor bleeding at the 8th week in Diosmin group, and underwent surgery.

CONCLUSION: Diosmin is effective in alleviating post-operational symptoms of haemorrhoids. Therefore, it should be considered for the initial treatment after haemorrhoid surgery. However, further prospective randomized trials are needed to confirm the findings of this study.

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Key words: Flavonoidic fraction; Postoperative complication; Haemorrhoids**Peer reviewers:** Giuseppe Brisinda, MD, Catholic Medical School, University Hospital "Agostino Gemelli", Largo Agostino Gemelli 8, Rome 00168, Italy; Mariusz Madalinski, MD, Department of Gastroenterology, IpswichHospital, Heath Road, IpswichIP4 5DP, United KingdomA ba-bai-ke-re MMTJ, Huang HG, Re WN, Fan K, Chu H, Ai EHT, KE Li-Mu MMTTEX, Wang YR, Wen H. How we can improve patients' comfort after Milligan-Morgan open haemorrhoidectomy. *World J Gastroenterol* 2011; 17(11): 1448-1456 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v17/i11/1448.htm> DOI: <http://dx.doi.org/10.3748/wjg.v17.i11.1448>

INTRODUCTION

Hemorrhoid is one of the most common anorectal disorders. Although haemorrhoidectomy is considered as a minor inpatient procedure, it is usually associated with significant postoperative complications, including pain, bleeding, heaviness, pruritus, mucosal discharge and anal stenosis, resulting in a protracted period of recovery. The Milligan-Morgan open haemorrhoidectomy is the most widely practiced surgical approach for the management of hemorrhoids and is considered the "gold standard". Hemorrhoids are divided into 4 stages depending on symptoms and degree of prolapse. The 3rd and 4th stages are indicated for Milligan-Morgan open haemorrhoidectomy. Hemorrhoidectomy is usually associated with considerable pain, bleeding, and mucosal discharge after operation^[1], which seem to be multifactorial, such as individual tolerance, mode of anesthesia, postoperative analgesics, and surgical technique^[2].

Pain is a major postoperative complication after haemorrhoidectomy. Although Longo's procedure (the procedure for prolapse and hemorrhoids, PPH) has been widely used in recent years, it can also be confronted with the postoperative management dilemma after the procedure. A Meta-analysis comparing the PPH procedures and open haemorrhoidectomy did not show any significant differences in terms of post-operative pain. Although the post-operative bleeding and blood loss were significantly lower in the PPH group, there was no statistical difference in the aspect of other complications such as pain, pruritus, and mucosal discharge. In identifying approaches to reduce the symptoms after haemorrhoidectomy, published studies have mainly focused on the choice of surgical technique or the prevention of secondary infection in the wound^[3-8]. The superiority of stapled haemorrhoidectomy in terms of less post-operative pain and quicker recovery was confirmed by a more recent systematic review of 25 randomized trials that compared stapled haemorrhoidectomy and conventional haemorrhoidectomy^[9]. However, the control

of hemorrhoid symptoms is not striking. Both open and closed haemorrhoidectomy have been evaluated in terms of postoperative pain. Two predominant factors responsible for post-operative pain include discomfort from the surgical wound in the sensitive anoderm as well as perianal skin and edema from tissue inflammation around the wound^[10]. Alleviation of pain from the surgical incision should be achieved by minimizing tissue dissection and using different electrosurgical devices, such as diathermy, Harmonic scalpel[®], and ligature[™], which diminishes thermal injury to the subjacent tissues^[11]. For reduction of pain from the open wound of haemorrhoidectomy, various kinds of medication, including metronidazole, glyceryl trinitrate (0.2%), steroids, local anesthetics (bupivacaine), anti-inflammatory drugs, hemorrhoid creams, are being used with variable outcome^[11-13]. These studies indicated some limitations with these medications such as short duration of action and occurrence of serious side effects.

Postoperative bleeding is another important complication in hemorrhoids due to its frequency, which varies between 0.6% and 10%^[14,15]. Post-haemorrhoidectomy bleeding is commonly associated with the passage of a hard stool. Sometimes bleeding may be alarming, because it may cause anemia very rapidly in patients. The causes of post-operative bleeding are not easily explained: in some cases it should be attributed to falling off of a scar due to electrocoagulation, whereas in other cases it is due to the lack of a thrombus, its expulsion or its dissolution, concomitant with the falling or reabsorption of the transfixed stitch.

Diosmin, flavonoidic fraction, which is derived from some plants or the *flavonoid Hesperidin*, is promoted as a high-quality active ingredient in vein improvement supplements. Diosmin reduces inflammation and increases vein tonicity, two important factors that contribute to hemorrhoids. Researches indicate that Diosmin also appears to significantly shorten the duration of haemorrhoid bleeding as well as reduce the postoperative pain^[16]. A 2000 Italian study of 66 haemorrhoid patients reported that Diosmin decreased pain by 79% and bleeding by 67% during the first week of treatment, followed by an astonishing 98% and 86% reduction in these symptoms by the second week^[17]. After haemorrhoid surgery, flavonoids were found to relieve pain, bleeding and other symptoms more rapidly than standard antibiotic/anti-inflammatory treatment alone, with especially significant symptom relief during the first 3 d after surgery^[18].

This study was designed to evaluate the influence of Diosmin on reducing postoperative pain, bleeding, heaviness, pruritus, and mucosal discharge after the Milligan-Morgan open haemorrhoidectomy in a randomized, observer-blinded, placebo-controlled clinical trial.

MATERIALS AND METHODS

Study design

Protocol synopsis for this trial and supporting CONSORT checklist were used as supporting information

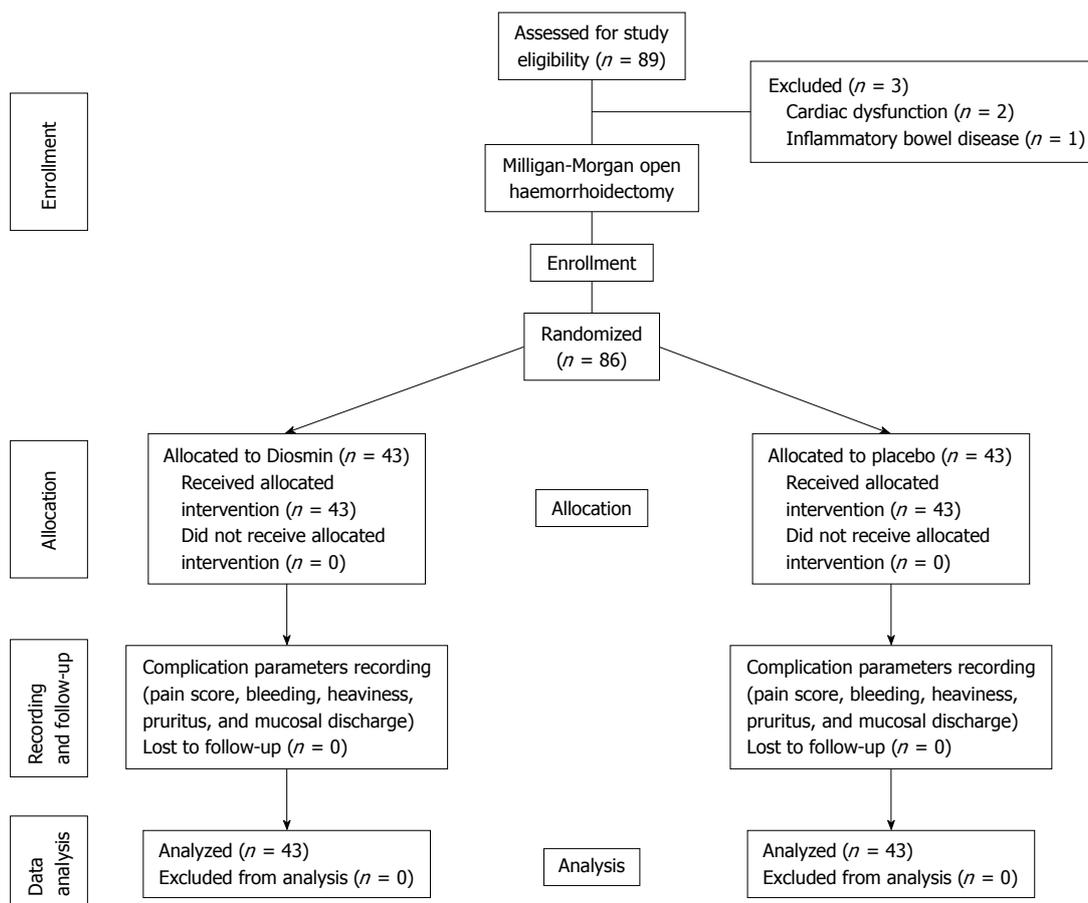


Table 1 Demographic data in Diosmin and control groups

	Diosmin group ¹ (n = 43)	Control group ² (n = 43)	P value
Mean age(yr)	53.2 (11.2)	51.3 (10.4)	0.6332
Male/female ratio	26/17	24/19	0.6620
No. of resected hemorrhoids	3.4 ± 0.4	3.8 ± 0.5	0.1522
Grades III/IV hemorrhoids	33/10	29/14	0.9247
Mean duration of hemorrhoidal disease (mo)	21.6 (12.6)	22.8 (14.5)	0.6821
Operating time (min)	15.8 (1.9)	16.9 (1.5)	0.1295
No. of constipation	28	26	0.8235

¹Patients treated with Diosmin; ²Patients treated with placebo drug.

(Figure 1). Diosmin clinical trial was a phase II randomized, prospective, observer-blinded, placebo-controlled clinical trial.

Inclusion/exclusion criteria

Patients aged 12-75 years with an indication for haemorrhoidectomy were eligible for the study, provided that they met the following inclusion criteria: symptomatic and prolapsing hemorrhoids Grade III or IV and informed consent. Patients complicated with fistula or anal fissure, inflammatory bowel disease, dermatitis, proctitis, pregnancy or severe cardiovascular state or pulmonary complication were excluded from the study.

Patients

The study was conducted using a computer-randomized design. A total of 86 consecutive patients with the grades III and IV acute mixed hemorrhoids admitted to Anorectal Surgical Department of First Affiliated Hospital, Xinjiang Medical University from April 2009 to April 2010, were enrolled in this study. Demographic data (age and gender), disease grades, preoperative constipation status, mean duration of disease, operating time and number of resected piles were recorded for each patient. There were no statistical differences between the two groups in these aspects (Table 1).

Medical and research ethics

The trial was conducted in accordance with the principles of the Declaration of Helsinki^[19], the Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products^[20]. The study protocol was approved by China governmental law and local regulations of Xinjiang Uygur Autonomous Region. This study was also conducted according to a protocol approved by the Medical Ethics Committee of First Affiliated Hospital of Xinjiang Medical University. Informed consent was obtained from all the patients or their relatives before the trial. The whole study consisted of two periods of observation (4 wk for each period). The last visit should be terminated in 90 d after operation.

Formal written informed consent was obtained from each patient after the preliminary assessment of patient's detailed history of the disease and general and systemic examination. The patients were subjected to a few baseline investigations (haemoglobin, bleeding time, clotting time, urine complete examination). They were randomly subjected to Diosmin or placebo depending on their choice, after discussing the advantages and disadvantages of both drugs with them. The study was "blind" and the observers evaluating the complication symptom parameters were unaware of the individual treatment schedules. Blinding and coding of the drugs were done by an independent monitor who was not an investigator after repacking the look-alike capsules by a pharmaceutical company in Xinjiang. The codes were broken only after completion of the study.

Surgery

Two fixed anorectal surgeons performed all the procedures with the patient in the supine lithotomy position or jackknife position. All patients underwent proctoscopy in order to exclude other diseases in the rectum before surgery. The operations were carried out under spinal anesthesia with 15 mL bupivacaine with 1:200 000 adrenalin. Further 5 mL of the same solution was used to dissect the haemorrhoidal nodules from the internal sphincter. Except 3 patients, who had a considerable rectal mucosal prolapse and were treated with stapled haemorrhoidopexy, all the patients underwent the standard Milligan-Morgan haemorrhoidectomy.

We removed the haemorrhoidal nodule using an upside-down V-shaped incision on the anal dermis, without widening the surgical wound while approaching the sphincters. This was done in order to maintain ample mucous membrane bridges. Possible secondary nodules were removed through submucosa. Ligature of the vascular pedicle was performed clear of the internal sphincter. The extent of surgical incision was tailored according to the number of haemorrhoidal complexes. Hemorrhoids were excised to the anorectal junction or dentate line. The intervening skin and anoderm bridges were preserved adequately. Coagulation with electrotome on the anal sphincters was avoided for all patients. The edges of the residual surgical wound have to be as sharp as possible. No packs were left in the anus postoperatively. After operation, patients in both groups were prescribed fiber supplements and naproxen sodium 550 mg tablets or intramuscular pethidine (1 mg/kg body weight) as required. All patients were also advised to gently shower their perianal wounds with lukewarm water twice daily, and after bowel movements. The data concerning the complications were compared between the two groups of patients. No antibiotic prophylaxis or any kind of analgesics has ever been administered.

Randomization

Computer-based sequential method was used for the randomization at the completion of surgery into one of the

two groups. This computer generated random codes used for envelopes containing the information "Diosmin" or "Placebo". These envelopes were prepared by a statistician who was not involved the patient's treatment or other work specific to the study. The computer randomization was completed in the Medical Statistical Center of Xinjiang Medical University.

Diosmin treatment

All patients were routinely discharged on the first postoperative day unless otherwise clinically indicated. Eighty-six patients each were either given Diosmin 500 mg or received placebo medication according to the computer-randomized result. Diosmin 500 mg was given at a dose of 3 tablets twice daily, after meals, for 3 d followed by 2 tablets twice daily from day 4 to day 7. Each complication symptom was recorded at hours 6 and 12 and on days 1, 2, 7 and 14 after operation. On the 7th day, the symptoms and any relief were recorded and the dose was further reduced to one tablet twice daily for the next 15 d. Consequent follow-ups were made on days 15, 30 and 90.

Assessment of postoperative symptoms

The Milligan-Morgan open haemorrhoidectomy was performed by a standardized diathermy excision method. Diosmin was started on the 6th day after surgery. A standardized questionnaire was completed which included postoperative information about pain, bleeding, heaviness, pruritus, wound edema and mucosal discharge. The evolution of these symptoms during the postoperative period was assessed by means of patient's self-questionnaires. Two predominant observatory parameters were postoperative pain and bleeding. Pain was assessed using verbal response and visual analog scale at hours 6 and 12 and on days 1, 2, 7 and 14, respectively after operation. The verbal response scales had four options: no pain, mild pain, moderate pain, and severe pain. The visual analogue scale consisted of a 10-cm line with the words "no pain" on the left hand side and "worst pain imaginable" on the right. Two types of pain were assessed, pain on defecation and pain during the preceding 24 h. The scales for pain on defecation were completed immediately after defecation and the scales for 24 h pain completed each evening. In order that pain could be assessed for seven postoperative days, patients were asked to complete the forms at hospital. Patients were discharged from hospital at the discretion of their consultants.

The use of narcotic drugs, antibiotics and laxatives, complication symptoms and hospital stay in all the patients were recorded after surgery. At the conclusion of the study, the codes were broken and the results were analyzed. The visual analogue scores were measured in cm, and the score for each 24 h was a single value. The score for pain on defecation was the mean value of scores during that day.

Statistical analysis

Before initiating the trial, sample size was calculated us-

Table 2 Postoperative course of Diosmin and control groups

	Diosmin group ¹ (n = 43)	Control group ² (n = 43)	P value
Median hospital stay (d)	6.1 (1.3)	7.3 (3.4)	0.0306
Median time to first bowel action (h)	48 (4.2)	56 (4.6)	0
Median No. of bowel actions in the first week	9 (2.3)	14 (3.1)	0

¹Patients treated with Diosmin; ²Patients treated with placebo drug. P value was the result of Mann-Whitney U test.

Table 3 Postoperative symptoms of Diosmin and control groups n (%)

	Diosmin group ¹ (n = 43)	Control group ² (n = 43)	P value
Minor bleeding			
At 2 wk	3 (6.97)	11 (25.58)	0.0409
At 8 wk	2 (4.65)	3 (4.64)	0.6449
Heaviness			
At 2 wk	4 (9.30)	14 (32.56)	0.0171
At 8 wk	2 (4.65)	8 (18.60)	0.0436
Pruritus			
At 2 wk	9 (20.93)	18 (41.86)	0.0365
At 8 wk	3 (6.97)	10 (23.25)	0.0351
Mucosal discharge			
At 2 wk	7 (16.28)	11 (25.58)	0.2890
At 8 wk	2 (4.64)	4 (9.30)	0.3972

¹Patients treated with Diosmin; ²Patients treated with placebo drug.

ing SPSS software 15.0 version. A power calculation estimated that 40 patients would be needed in each group to demonstrate a reduction of 20% pain with a power of 80% and at a 5% significance level. Discrete variables were analyzed using χ^2 test with Yates correction when appropriate. Continuous variables were analyzed by Wilcoxon signed tests for paired observations. Pain scores at each time interval were compared between groups with Wilcoxon's rank-sum test (nonparametric analysis of ranked data). A two-tailed Spearman's correlation coefficient was calculated where indicated. Statistical significance was assumed when $P < 0.05$. Statistical evaluation was done as intend-to-treat analysis. When not otherwise specified, data were presented as median and range.

RESULTS

After standard hemorrhoid surgery, 86 patients were allocated to receive Diosmin (experimental group, $n = 43$) and placebo capsules (control group, $n = 43$). None of the patients in either study group complained of any severe symptoms during the 90-d follow-up after treatment. The two groups were well matched for age, sex, disease grades, and number of piles. There were no statistical differences between the two groups in these aspects (Table 1).

The Diosmin group defecated earlier ($P = 0.00$), had more frequent bowel actions in the first postoperative week ($P = 0.00$), and had a shorter hospital stay ($P = 0.03$)

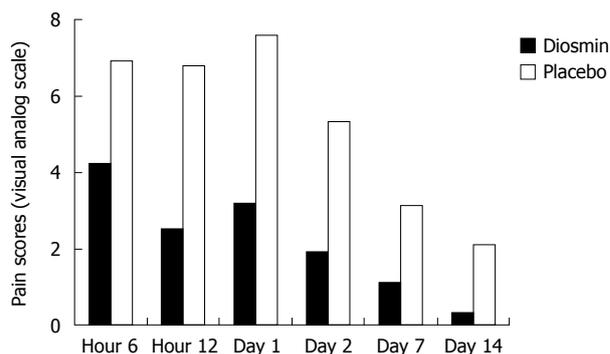


Figure 2 Postoperative pain scores in Diosmin and placebo groups. Pain scores ranged from 0 (no pain) to 10 (very severe pain).

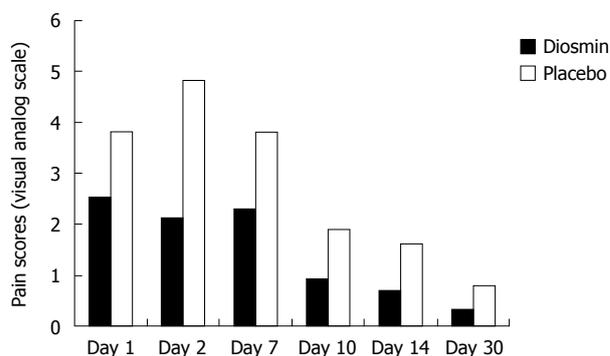


Figure 3 Pain on defecation in Diosmin and placebo groups. Pain scores ranged from 0 (no pain) to 10 (very severe pain).

compared with the placebo group (Table 2). No patient withdrew from the study because of any complaints. Significantly more placebo patients were troubled by minor rectal bleeding at 2 wk, although these rates were similar at 8 wk. The follow-up after 8 wk found that two patients experienced minor bleeding in Diosmin group, and therefore, underwent surgery. There was a statistically significant ($P < 0.05$) improvement in pruritus and heaviness at both 2 and 8 wk (Table 3). In addition, there was no statistical difference between the two groups in terms of wound mucosal discharge.

Patients in Diosmin group experienced significantly less pain at 6 and 12 h after surgery ($P = 0.03$, $P < 0.01$), and on days 1, 2, 7, 10, and 14 ($P = 0.02$, $P < 0.01$, $P = 0.02$, $P = 0.03$, $P < 0.01$) (Figure 2). There was also significant ($P < 0.001$) improvement on the proctoscopic appearance. Patients in the experimental group had significantly less defecation pain compared with the placebo group on days 1, 2, 7, 10, 14, and 30 ($P = 0.03$, $P < 0.01$, $P < 0.01$, $P = 0.02$, $P = 0.04$, $P = 0.04$) (Figure 3). No significant Diosmin-related complications or allergic reactions were reported by any patient. A similar number of patients reported burning with both treatments at the 2nd week after surgery (3 in Diosmin and 2 in placebo).

DISCUSSION

Haemorrhoid is a common disease affecting people of

all ages and both sexes. It is estimated that 50% of the people older than 50 years have hemorrhoid symptoms at least for a period of time. The causes of haemorrhoidal disease are multiple, but most are attributable to difficult passage of stool or constipation. Over the last few years, there has been increasing attention on surgical procedures to treat haemorrhoids. Several comparative studies have been performed to evaluate the available procedures to treat grades II, III, and IV hemorrhoids, and new surgical techniques, such as haemorrhoidectomy with Harmonic scalpel[®][21-23] and LigasureTM[24], Doppler-guided haemorrhoidal plexus ligation^[25,26] and the stapled haemorrhoidopexy^[27-31]. The most recent medium- and long-term studies on ample case series provide data on the efficacy, the results and complications of these techniques^[24-31]. None of them proved to reduce complications such as pain and bleeding^[21]. The ideal method should combine the high safety and efficacy of the treatment, yielding low postoperative pain and bringing comfort to the patients. Such considerations are related to the severity of the disease and can be addressed by evidence-based medicine by randomized, controlled trial. According to a recent meta-analysis of the Cochrane library^[32,33], conventional haemorrhoidectomy as first described by Milligan and Morgan, is still the most widely used, effective, and definite surgical treatment for patients with symptomatic grades III and IV haemorrhoids. However, it is associated with significant postoperative complications such as pain, bleeding and mucous discharge. Although there is a consensus on the treatment of grades III and IV haemorrhoids, there is still confusion regarding the ideal treatment for these complications after surgery.

In 1971, Daflon, consisting of 90% Diosmin and 10% Hesperidin (Daflon 500; Serdia Pharmaceuticals, India and Vinosmin; Elder Pharmaceuticals, India), was firstly introduced in France by Bensaude *et al*^[34] for the treatment of haemorrhoids and other capillovenous diseases. Diosmin mainly works on the inflammatory pathology of haemorrhoids by increasing the contraction of veins and local lymphatic drainage and decreasing the synthesis of prostaglandins such as PGE2 and thromboxane B2^[35-37]. The anti-inflammatory effects of Diosmin are reflected in the reduction of capillary hyperpermeability and fragility in controlled clinical studies. Damom *et al*^[38] found the same effects of Diosmin in increasing the duration of vascular contraction and prostaglandin components which are responsible for the inflammatory process. Diosmin also increases the local lymphatic drainage. Side-effects of the drugs are limited according to Meyer^[39] who was first used Diosmin to treat hemorrhoid symptoms. He reported mild gastrointestinal and autonomic disturbances in 10% cases. A fixed micronized combination of the citrus bioflavonoids Diosmin (90%) and hesperidin (10%) has been widely used in Europe to treat diseases of the blood vessels and lymphatic system since 2000. The combination also appears to be beneficial for chronic venous insufficiency and venous stasis ulcers. Extensive safety evaluations have found that Diosmin/hesperidin was free

from toxicological risk. From 2005, Diosmin was used to treat vascular diseases^[40-45]. The obtained evidence strongly supports its use in haemorrhoids in recent years although only several randomized controlled trials were available.

In this randomized trial, we concluded that Diosmin leads to the rapid cessation of haemorrhoidal bleeding, alleviation of the associated symptoms and gives objective relief from complications of post-haemorrhoidectomy. This result is similar to Mlakar's study^[46]. In their study, Flavonoids was found very effective in the first 30 d of treatment and led to the rapid relief of various associated symptoms of haemorrhoid surgery. Because, up to now, there have only a few randomized controlled studies to investigate the effectiveness and safety of Diosmin to treat symptoms after haemorrhoidectomy in the world, we could not perform meta-analysis for these studies. In our study, Diosmin was more effective to control postoperative pain than placebo capsules during the early phase of the surgery. This is a highlight in our study. The Diosmin group defecated earlier ($P < 0.05$), had more frequent bowel actions in the first postoperative week ($P < 0.05$), and had a shorter hospital stay ($P < 0.05$) compared with the placebo group. This is and a striking result compared with Mlakar's study^[46]. In spite of some minor bleeding, no patient withdrew from the study because of any kind of adverse events. This may be associated with proper drug usage after surgery, especially in the early phases. Significantly more placebo patients were troubled by minor rectal bleeding at 2 wk, although these rates were similar at 8 wk. However, during the follow-up after 8 wk, we found that two patients had minor bleeding in experimental group, therefore, they underwent surgery. Postoperative bleeding is a particularly important complication in hemorrhoids treatment due to its frequency varying between 0.6% and 10%^[15,47]. Sometimes bleeding may be alarming, because it may cause anemia very rapidly in the patients. Several randomized controlled studies evaluated the use of oral micronized, purified flavonoid fraction in the treatment of haemorrhoidal bleeding. In these studies, bleeding was relieved rapidly, and no complication was reported. This is somewhat conflict with our bleeding cases. However, we used 500 mg Diosmin capsules compared with 450 mg micronized purified flavonoid fraction in Yo YH's study^[16]. The most important reason of our poor result related with bleeding is that we included grades III and IV piles, but Yo YH's study included only grades I, II, and III piles. A similar study of 100 patients reported that acute bleeding had subsided by the third day of treatment in 80% of patients receiving micronized flavonoids, 2 d sooner than in patients receiving a placebo. But, the different points compared with our trial, which were also disadvantages of their studies, were associated with the difference of their study designs. They compared micronized flavonoids medication with hemorrhoid surgery itself. Although we think Milligan-Morgan open haemorrhoidectomy is the most widely practiced "gold standard" surgical approach and the stages III and IV are the clear indication for this procedure, it is not necessary to alter the

indication for hemorrhoid surgery to medication. Another point is the cost of medication. A limitation of the drug is the lack of patient compliance due to the long duration of treatment and the high cost of the drug. The safety of the drug has already been proved but more studies need to be done to see if the total dose of Diosmin can be increased so as to increase the response rate and decrease the duration of postoperative treatment. A decrease in the cost of the drug should also be considered.

Purified flavonoid fraction is a botanical extract from citrus. It exerts its effects on both diseased and intact vasculature, increasing vascular tone, lymphatic drainage, and capillary resistance; it is also assumed to have anti-inflammatory effects and promote wound healing. In another recent randomized controlled trial, postoperative use of micronized, purified flavonoid fraction, in combination with short-term routine antibiotic and anti-inflammatory therapy, reduced both the duration and extent of postoperative symptoms and wound bleeding after haemorrhoidectomy, compared with antibiotic and anti-inflammatory treatment alone^[18].

Postoperative pain is the most important unacceptability which was also our predominant observatory parameter. Post haemorrhoid pain is difficult to assess, though verbal response scales and visual analogue scales are recognized methods. Maxwell concluded that the *t* test is "very robust" when comparing differences between visual analogue scale scores^[48], and we therefore used this method of analysis. On two occasions, the verbal response scale in pain was a day less than the visual analogue scale. This may be because the discrete verbal response scale is less sensitive than the continuous visual analogue scale. Another highlight in our study was that patients in Diosmin group experienced significantly less pain at hours 6 and 12 ($P < 0.05$), and on days 1, 2, 7, 10, and 14 after surgery ($P < 0.05$). At the same time, patients in the experimental group had significantly less defecation pain compared with placebo groups on days 1, 2, 7, 10, 14 and 30 after surgery ($P < 0.05$). The exact cause of pain after haemorrhoidectomy has not yet to be defined. Various factors believed to be responsible for the pain including incarceration of smooth muscle fibers and mucosa in the transfixed vascular pedicle, epithelial denudation of the anal canal, and spasm of the internal sphincter^[3]. Another reason for pain could be the development of linear wounds extending up to the anorectal ring, which appear similar to those of a chronic anal fissure^[18]. Postoperative pain was also associated with bacterial fibrinolysis and defecation stress^[49]. In our study, postoperative pain in the placebo group can be explained by the traction of the nonsensitive sliding haemorrhoidal tissue at the highly sensitive anal skin. The diminished postoperative pain in the Diosmin group might be related to its capillary resistance and diminished tissue edema and anti-inflammatory process. There was significant difference in different postsurgical days and weeks. Based on these results, we suggested that Diosmin has a clear action against anorectal postoperative pain. Therefore, it should be considered

initially for patients presenting with haemorrhoidal symptoms after surgery. In addition, there was also a significant improvement on the proctoscopic appearance ($P < 0.001$).

Although there was a statistically significant improvement in heaviness and pruritus from baseline to the 8th week postoperatively, however, there were no statistical differences between the two groups in terms of wound mucosal discharge ($P < 0.05$). Our hypothesis was that our nonabsorbable suture used for internal mucosa ligation is responsible for this poor result.

In a 12-wk study of 50 pregnant women suffering from acute hemorrhoids, micronized Diosmin/hesperidin therapy was reported to be a "safe, acceptable and effective" treatment, and 66% obtained relief from symptoms within 4 d^[50]. However, we suggest not using Diosmin for pregnant women, considering Diosmin is a new alternative for hemorrhoids.

This study has shown that Diosmin can reduce the complications from haemorrhoidectomy, especially in the early phase. We therefore suggest that this regimen should be a part of the routine postoperative management of patients for haemorrhoidectomy.

In conclusion, Diosmin (flavonoid fraction) has shown to be effective in alleviating symptoms after haemorrhoidal surgery and improving the proctoscopic appearance. Therefore, it should be considered initially for patients presenting with haemorrhoidal symptoms after surgery. However, further prospective randomized trials and longer follow-up are needed to confirm the findings of this study and observe the side effects of this drug.

COMMENTS

Background

Over the past few years, there has been increasing attention on surgical procedures to treat haemorrhoids. The Milligan-Morgan haemorrhoidectomy is still a major surgical approach for haemorrhoids. This study was designed to evaluate the influence of Diosmin on reducing postoperative pain, bleeding, heaviness, pruritus, and mucosal discharge after the Milligan-Morgan open haemorrhoidectomy in a randomized, observer-blinded, placebo-controlled clinical trial.

Research frontiers

Phlebotropic activity, protective effect on the capillaries and the anti-inflammatory effect of Diosmin have been reported in several studies in recent years. More recent clinical studies showed that flavonoid fraction such as Dalfon (phlebotropic agent) can reduce postoperative pain, bleeding and heaviness after haemorrhoidectomy.

Innovations and breakthroughs

This clinical trial has confirmed that Diosmin (flavonoid fraction) can reduce postoperative pain, bleeding and heaviness after Milligan-Morgan open haemorrhoidectomy.

Applications

Diosmin (flavonoid fraction) has shown to be effective in alleviating symptoms after haemorrhoidal surgery and improving the proctoscopic appearance. Therefore, it should be considered initially for patients presenting with haemorrhoidal symptoms after surgery. However, further prospective randomized trials and longer follow-up are needed to confirm the findings of this study and observe the side effects of this drug.

Terminology

Diosmin is derived from some plants or used as a high-quality active ingredient in vein improvement supplements. Diosmin reduces inflammation and increases duration of vascular contraction that contributes to hemorrhoids.

Peer review

The authors engagingly described a pathomechanism of anal pain after haemorrhoidectomy and Diosmin's action. The article is worth publishing.

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Medicamentous treatment of chronic venous insufficiency using semisynthetic diosmin--a prospective study.

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Source

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Abstract

INTRODUCTION:

Chronic venous insufficiency (HVI) is manifested by the progressive signs of venous stasis. This disorder is treated by: compressive bandaging, medicaments, sclerotherapy, surgery, etc.

AIM:

Prospective study of the effects of semisynthetic diosmin (clinical signs, quality of life, local biochemical parameters) on patients with HVI to whom no other method of treatment has previously been administered. METHOD APPLIED: This prospective study analysed the presence of risk factors and personal history of 80 patients with HVI. Diagnosis of HVI was based on the clinical appearance and the color duplex scan. Each patient's clinical signs (pain, oedema, feeling of heaviness and tightness in the lower leg), quality of life (physical, social, and psychological), and CEAP stage were assessed prior to and 30 days after the treatment with Phlebodia 600. For 15 patients with unilateral varicose veins, local values of lactates and gass analysis were taken under the conditions before and following the static load, and venous control samples were taken from the healthy leg. The acquired data were processed by means of descriptive statistics, while the significance of nonparametric features was measured by Wilcoxon test.

RESULTS:

HVI is somewhat more frequent among females than among males, on the left than on the right leg, and at the average age of 52.3 +/- 10.5. The patients with HVI are basically engaged in professions with static load and have positive family history. The patients mainly started medical treatment 12.5 +/- 8.6 years after the first symptoms of the disease. Clinical improvement was recorded on the state of 65/80 patients. After the treatment numerical values of some of the clinical signs were statistically lower compared to the values before the administration of semisynthetic diosmin: oedema (0.94:1.50), pain (1.10:1.84), feeling of heaviness (1.20:1.96), and tightness

(1.14:1.78). After the administration of the tested medication, parameters of physical, social, and psychological quality-of life were significantly improved ($p < 0,0001$), accompanied with significantly improved ($p < 0,0001$) CEAP stage of HVI (3.00:3.40). Local biochemical parameters had not been significantly changed.

CONCLUSION:

Administration of semisynthetic diosmin during 30 days results in significant improvement of clinical signs, quality of life and CEAP stage of HVI.

Μια από τις παθήσεις που εμφανίζεται συχνότερα στις γυναίκες από ότι στους άνδρες και κατέχει σημαντική δυναμική τόσο στην αισθητική, όσο και στη λειτουργικότητα του οργανισμού, είναι σίγουρα οι κηροσίδες των φλεβών των κάτω άκρων. Για να είμαστε δε ακριβέστεροι, θα λέγαμε πως το πρόβλημα εντοπίζεται στους κηροσίδες των επιπολής φλεβών, που αποτελούν το ένα από τα τρία φλεβικά συστήματα των κάτω άκρων και έχουν ως βασικά χαρακτηριστικά, το παχύ τοίχωμα και το μεγάλο αριθμό μυϊκών ινών.

Κύριο χαρακτηριστικό των φλεβών είναι η ύπαρξη βαλβίδων, που κατευθύνουν το αίμα από την περιφέρεια προς το κέντρο, αλλά και από το ένα φλεβικό σύστημα στο άλλο. Κάθε λοιπόν ανεπάρκεια των εν λόγω βαλβίδων, θα μπορούσε να οδηγήσει αυτόματα σε ευρυαγγείες (που είναι οι μικροί κηροσίδες κάτω από το δέρμα με τοξοειδή εμφάνιση) και κηροσίδες. Άλλοι λόγοι εμφάνισης του προβλήματος είναι η κληρονομικότητα, η μείωση των μυϊκών ινών του τοιχώματος των φλεβών, η ορθοστασία, η καθιστική ζωή, η εγκυμοσύνη, το κάπνισμα, η υψηλή συστολική πίεση.

Στη φαρέτρα του θεραπευτή υπάρχουν σήμερα διάφορες θεραπευτικές προσεγγίσεις για τους κηροσίδες, ανάλογες με το στάδιο της κατάστασης, ξεκινώντας από τις απλές συστάσεις για αλλαγή του τρόπου ζωής (και άρα καταπολέμηση της παχυσαρκίας, της καθιστικής ζωής, του καπνίσματος), μέχρι τη σκληροθεραπεία (σκληρυντικές ενέσεις που εφαρμόζονται τοπικά στους κηροσίδες), τη χειρουργική θεραπεία, αλλά και τη χρήση βοτανικών εκχυλισμάτων και διατροφικών στοιχείων, που αξίζει να δούμε εκτενέστερα.

Ένα από τα βότανα που έχουν πρωταγωνιστήσει σε δεκάδες μελέτες για τους κηροσίδες είναι η Centella Asiatica. Η Centella φαίνεται πως έχει τη δυναμική να προάγει την ακεραιότητα του συνδετικού ιστού, να συμπεριφέρεται αντιοξειδωτικά και να βελτιώνει τη διαπερατότητα των τριχοειδών αγγείων. Τυχαίοποιημένη, πολυκεντρική μελέτη σε ασθενείς με φλεβική ανεπάρκεια, των Pointel et al που δημοσιεύτηκε στο έγκριτο Angiology, επιβεβαίωσε την αξία του θεραπευτικού αυτού φυτού.

Παράλληλα άλλη μελέτη των Agraia et al, έδειξε πως η Centella Asiatica μειώνει τα επίπεδα ενζύμων που διασπούν ένα από τα βασικά συστατικά που ενεπλέκονται στην υγεία των αγγειακών τοιχωμάτων, τους μουκοπολυσακχαρίτες.

Η Centella Asiatica έχει χορηγηθεί και τοπικά-επιδερμικά ως εκχύλισμα, σε ασθενείς με κηροσίδες, δίνοντας και πάλι θετικά αποτελέσματα.

Εξέχουσες θεραπευτικές επιδράσεις σε περιπτώσεις κηροσών και γενικότερα φλεβικής ανεπάρκειας φαίνεται να κατέχουν και τα βιοφλαβονοειδή ή αλλιώς βιταμίνη P. Τα βιοφλαβονοειδή είναι αντιοξειδωτικές ουσίες με ουσιαστική συμβολή στη διατήρηση της ακεραιότητας των αγγείων και ανευρίσκονται σε σημαντικά ποσά στο κίτρο, το πορτοκάλι, το λεμόνι, το κρεμμύδι, το κακάο, το τσάι, το κρασί κ.α. Από τα φλαβονοειδή των οποίων η δράση επικεντρώνεται περισσότερο στη θεραπεία των κηροσών είναι η διοσμίνη, η εσπεριδίνη και οι προανθοκυανιδίνες. Μάλιστα τα δυο πρώτα, αποτελούν τη βάση για

ιδιοσκεύασμα που χρησιμοποιείται εδώ και χρόνια για φλεβικές ανεπάρκειες!!

Οι προανθοκυανιδίνες προάγουν την ελαστικότητα των ιστών, την περιφερική κυκλοφορία, επιδιορθώνουν το κολλαγόνο ενώ παράλληλα εμφανίζουν και έντονη αντιφλεγμονώδη δράση. Τα τελευταία χρόνια έχουν λανσαριστεί στην αγορά σκευάσματα με υψηλή περιεκτικότητα προανθοκυανιδίνων, που προέρχονται είτε από το κουκούτσι του σταφυλιού, είτε από πευκοβελόνες