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Drug Treatment of Haemorrhoids

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Contents

Abstract 1481
1. Drug Treatment of Haemorrhoids 1482
  1.1 Flavonoids 1482
    1.1.1 Micronised Purified Flavonoid Fraction 1482
    1.1.2 Diosmin 1484
    1.1.3 Troxerutin 1484
    1.1.4 Hydroxyethylrutosides 1484
  1.2 Ginkgo 1485
  1.3 Heparan Sulfate 1485
  1.4 Calcium Dobesilate 1486
  1.5 Local Application to the Anal Canal 1486
    1.5.1 Nitrates 1486
    1.5.2 Local Anaesthetic Preparations 1488
  1.6 Herbal and Other Extracts 1488
2. Conclusion 1490

Abstract

Drug treatment for various anorectal conditions has been known since ancient times. Today, modern as well as traditional drugs are being increasingly used in all grades of symptomatic haemorrhoids. These drugs (oral and local) are used as a part of conservative management or as an adjuvant to invasive outpatient procedures. Flavonoids, in the new formulation of micronised purified flavonoid fraction (MPFF) or as part of the ancient traditional medicine derivative of the Ginkgo tree, are used for relief of acute symptoms (for control of bleeding and re-bleeding in all grades of haemorrhoids). MPFF has been recommended for control of acute bleeding in patients waiting for a definitive outpatient treatment. Similarly, better known drugs such as calcium dobisilate (used in diabetic retinopathy and chronic venous insufficiency), nitrates and nifedipine have also been effective and well tolerated in the medical treatment of haemorrhoids. However, drug treatment is not aimed at curing haemorrhoids. The prime objective of drug therapy is to control the acute phase (bleeding) so that definitive therapy (banding, injection sclerotherapy, infrared photocoagulation, cryotherapy or surgery) can be scheduled at a convenient time.

Haemorrhoids, or varicose dilatation of the haemarrhoid plexus, have plagued mankind since the dawn of history and it is estimated that about 50% of the population has haemorrhoids by the age of 50 years. Treatment of anorectal disorders with suppositories, cautery and by excision was described by Hippocrates. After thousands of years the fundamentals of treating haemorrhoids remain more or less the same. Modern therapies for haemorrhoids include various medical (nonsurgical) and surgical options, with a trend towards outpatient procedures and day case surgery. In a British survey of general and subspecialist colorectal surgeons,[1] the majority of the surgeons prescribed routine advice on fluid and diet. Among the patients seen by the general surgeons 75% were treated with banding, 56% with injection sclerotherapy, 47% with haemorrhoidectomy, 9% with submucosal diathermy and 2% with stapled anoplasty. Haemorrhoids can also be destroyed by freezing using cryotherapy with nitrous oxide or liquid nitrogen,[2] or by heat using infrared photocoagulation.[3,4] Recently, the development of certain drugs found to be effective in haemorrhoids has generated a lot of interest. This review describes the clinical trials published on the use of these drugs in patients with haemorrhoids.

Haemorrhoids are classified according to the location and degree of prolapse.[5] Internal haemorrhoids arise proximal to the dentate line and are covered by mucosa, while external haemorrhoids arise below the dentate line and have squamous epithelium. Mixed (interno-external) haemorrhoids arise both above and below the dentate line. Haemorrhoids are further graded according to the degree of prolapse, that is, protrusion below the pectinate line (table I).

Table I. Classification of haemorrhoids

Grade	Description
1	Bleed but do not prolapse
2	Prolapse during defecation but return spontaneously
3	Prolapse during defecation but require manual reduction
4	Permanently prolapsed

1. Drug Treatment of Haemorrhoids

1.1 Flavonoids

Tables II and III provide summaries of clinical trials published on the use of flavanoids in patients with haemorrhoids.

1.1.1 Micronised Purified Flavonoid Fraction

Micronised purified flavonoid fraction (MPFF)[26] is an oral phlebotropic drug made up of 90% micronised diosmin and 10% flavonoids expressed as hesperidin. It is believed to improve venous tone and lymphatic drainage, and reduce capillary hyperpermeability by protecting the microcirculation from inflammatory processes.

Three placebo-controlled trials have investigated the efficacy of MPFF in the management of acute internal haemorrhoids and/or, in the longer-term, reducing the risk of relapse of acute haemorrhoidal symptoms. Cospite[6] randomised 100 patients with acute haemorrhoidal attack to receive MPFF or placebo in parallel under double-blind conditions. Overall improvement of anal discomfort, pain and anal discharge was greater in the MPFF group than in the placebo group, from day 2 through to day 7. Inflammation, congestion, oedema and prolapse were also more markedly improved in the MPFF group, along with a major reduction in the duration and severity of the current haemorrhoidal episode, and in the use of analgesics and topical medications.

In a 90-day (7 days acute phase then 83 days maintenance phase) randomised, double-blind study by Misra and Parshad,[7] treatment with MPFF (six tablets for 4 days followed by four tablets daily for 3 days) was compared with placebo in 100 outpatients

who presented with acute internal haemorrhoids of <3 days duration. Fifty patients were randomised to each group. Acute bleeding ceased by the third day in 40 (80%) patients who received MPFF compared with 19 (38%) who received placebo. Mean duration of acute bleeding (from onset to cessation) was 4.9 (SD 1.6) days (2.1 days less than in patients receiving placebo). Continued treatment[26] with two tablets daily in patients with no bleeding prevented a relapse in 30 of 47 patients compared with 12 of 30 receiving placebo. The only adverse effects reported were mild gastrointestinal symptoms. The same dosage of MPFF reduced the frequency, duration and/or severity of acute haemorrhoidal symptoms and improved the overall signs and symptoms of chronic (recurrent) haemorrhoids compared with placebo in a 60-day double-blind study of 120 outpatients with chronic symptoms of haemorrhoids.[8]

Two studies have also examined the use of MPFF in conjunction with laxatives or bulking agents. In a double-blind, comparative controlled study[9] of 100 patients with grade 1 and 2 haemorrhoids, significant improvement was reported in swelling and congestion by day 4 after adding MPFF to bulk laxatives compared with placebo plus the laxatives. Ho et al.[10] compared MPFF combined with fibre in diet, rubber-band ligation with fibre, and fibre diet alone in the management of bleeding non-prolapsed haemorrhoids in 162 patients. They reported the earliest control of bleeding in the MPFF combined with fibre group, with no complications or adverse effects.

Earlier, Ho et al.[11] published a prospective, randomised controlled trial on the effects of MPFF on bleeding after haemorrhoidectomy in 228 patients with prolapsed irreducible haemorrhoids. MPFF 500mg, two tablets three times daily for 3 days followed by one tablet three times daily for 4 days decreased the incidence of secondary haemorrhage from 6.1% to 0.9%, compared with the control group on laxatives, without any adverse effects.

The safety of MPFF during pregnancy and in clinical trials has also been examined. Buckshee et al.[12] treated 50 consecutive outpatients with grade 1 and 2 haemorrhoids during the last trimester of pregnancy with MPFF. They reported significant reduction of acute symptoms (bleeding, pain, rectal discomfort, anal exudation) and rectal inflammation by the seventh day, and 66% had relief from the acute attack by day 4. With maintenance treatment, significantly fewer and shorter relapses were experienced. The treatment was well tolerated and did not

Table II. Clinical trials of oral micronised purified flavonoid fraction (MPFF [Daflon®]) trials for the treatment of haemorrhoids

Study (year)	No. of patients	Grade of haemorrhoid	Drug(s)	Endpoint/results
Cospite[6] (1994)	100	All	MPFF vs placebo	Significant relief of acute symptoms and signs ($p < 0.001$)
Misra and Parshad[7] (2000)	100	1, 2	MPFF vs placebo	Cessation of bleeding by day 3 = 80% MPFF vs 38% with placebo
Godeberge[8] (1994)	120	1, 2	MPFF vs placebo	Significant improvement in overall signs and symptoms ($p < 0.01$)
Thanapongsathorn and Vajrabukka[9] (1992)	100	1, 2	MPFF + bulk laxatives vs placebo + bulk laxatives	Improvement at day 4 = subjective difference of $p < 0.01$
Ho et al.[10] (2000)	162	1, 2	Ispaghula husk vs MPFF + ispaghula vs rubber band ligation + ispaghula	Control of bleeding in 3.9 days (mean) with MPFF
Ho et al.[11] (1995)	228	4	MPFF vs control	Postoperative bleeding = 0.9% (vs 6.1% in control group)
Buckshee et al.[12] (1997)	50	1, 2	MPFF (no control group)	Relief of acute symptoms = 66% by day 4 Prevention of relapse = 53.6% in 60 days Safely used in pregnancy
Meyer[13] (1994)	>2850	All	MPFF vs placebo	Adverse effects = 10% (vs 13.9% with placebo)

Table III. Clinical trials of nonmicronised oral flavonoids for the treatment of haemorrhoids

Study (year)	No. of patients	Grade of haemorrhoid	Drug(s)	Endpoint/results
Diana et al.[14] (2000)	66	All	Diosmin	Reduction of pain = 79%, bleeding = 67% in first week and in second week = 98% and 86%, respectively
Basile et al.[15] (2001)	30	Post-haemorrhoidectomy	Troxerutin + carbazochrome vs placebo	Visual analogue scale on days 3 and 4 = difference of $p = 0.007$ and $p = 0.001$
Annoni et al.[16] (1986)	40	2, 3, 4	O-(β-hydroxyethyl)-rutosides vs placebo	Significant reduction of pain and bleeding
Wijayanegara et al.[17] (1992)	97	1, 2, 3	O-(β-hydroxyethyl)-rutosides vs placebo	Significant improvement in signs and symptoms Safely used in pregnancy
Benzi et al.[18] (1992)	42	All	O-(β-hydroxyethyl)-rutosides	Clinical efficacy = positive in 95% Clinical improvements of $p < 0.01$
Titapant et al.[19] (2001)	53	1, 2	Trihydroxyethylrutosides vs placebo	Improvement in symptoms only at 2 weeks and also in signs at 4 weeks

affect pregnancy, fetal development, birth weight, infant growth and/or feeding. Meyer[13] reported the safety of MPFF clinical trials of >2850 patients treated with MPFF 500mg at the dosage of two tablets per day for 6 weeks to 1 year. Only 10% of those treated developed adverse effects, essentially of a gastrointestinal or autonomic nature (causing 1.1% trial withdrawals) compared with 13.9% of patients on placebo. MPFF was found to be equally acceptable in the short term as well as in long-term treatment. Haemodynamic and laboratory parameters (haematology, liver and renal function) were not affected even by prolonged treatment for 1 year at the dosage of two tablets per day. A review article by Lyseng-Williamson and Perry[26] evaluated placebo-controlled trials of MPFF in patients with both acute and chronic haemorrhoids, and found that overall MPFF had a tolerability profile similar to that of placebo; the most frequently reported adverse events were gastrointestinal and autonomic in nature.

1.1.2 Diosmin

Diana et al.[14] gave purified (nonmicronised) diosmin, at a dose of two 450mg tablets twice daily for the first 7 days then one tablet twice daily for up to 2 months, to a group of 66 patients with haemorrhoids of grade 1–4. Their results showed the efficacy of diosmin in decreasing both pain and bleeding in the first (79% and 67%, respectively) and second (98% and 86%, respectively) treatment week.

Topical diosmin ointment was used in 50 patients with grade 1, 2, 3 or 4 haemorrhoids with strangulation and thrombosis, and without any previous treatment. The drug was most effective on oedema and erythema, producing 75% and 73% improvements as assessed in three consecutive weekly visits.[27]

1.1.3 Troxerutin

In a double-blind, placebo-controlled study by Basile et al.,[15] 30 patients were randomised to receive one of two treatments: troxerutin (a flavonoid) 150mg plus carbazochrome 1.5mg, or intramuscular placebo (3mL twice daily for 5 days, starting from the day of surgery). Analysis of scores based on pain, discharge, bleeding, inflammation and pruritus, analgesic intake, time to restore a physiological defecation, oedema and blood coagulation tests between the treatment groups revealed a significant difference at day 3 and day 4 in favour of the active combination treatment. No adverse events were reported. Neither the active combination nor placebo affected blood coagulation tests.

1.1.4 Hydroxyethylrutosides

Hydroxyethylrutosides (rutosides) are a standardised mixture of semisynthetic flavonoids, mainly mono-, di-, tri- and tetrahydroxyethylrutosides, which act primarily on the microvascular en-

dothelium to reduce hyperpermeability and oedema. In patients with chronic venous insufficiency or diabetes mellitus, hydroxyethylrutosides improve microvascular perfusion and microcirculation, and reduce erythrocyte aggregation. This mixture also has a possible protective effect on the vascular endothelium.[28]

Forty patients were treated with either oral O-(β-hydroxyethyl)-rutosides (oxerutin) 4 g/day or placebo in a double-blind, randomised comparative trial. O-(β-hydroxyethyl)-rutosides induced a statistically significant reduction of pain and bleeding compared with placebo.[16] Tolerability was good and similar for both treatments.

Hydroxyethylrutosides have been studied by several investigators in pregnant women with haemorrhoids. Wijayanegara et al.[17] studied the safety and efficacy of O-(β-hydroxyethyl)-rutosides 500mg given orally twice daily in the treatment of 97 patients with grade 1, 2 or 3 haemorrhoids in a double-blind, placebo-controlled, randomised trial of pregnant women. The hydroxyethylrutosides produced a significant improvement in patient-assessed subjective symptoms (pain, bleeding, exudation and pruritus) compared with placebo. There was also a significant improvement in clinician-assessed subjective and objective signs (bleeding, inflammation and dilatation of the haemorrhoidal plexus) after 2 and 4 weeks of treatment. Only a few minor adverse effects and no drug-related problems in the pregnancy or delivery were observed. Forty-two women with haemorrhoids of varying severity that had appeared during the last trimester of pregnancy or immediately postpartum were treated by administering O-(β-hydroxyethyl)-rutosides 3 g/day for 14 consecutive days.[18] The preparation was found to be efficacious (95%), easily managed and provided statistically significant improvements in clinical parameters, especially pain. Titapant et al.[19] investigated the safety and efficacy of trihydroxyethylrutosides (300mg twice daily) in the treatment of 53 patients with grade 1 and 2 haemorrhoids during pregnancy (week 16–34) in a double-blind, placebo-controlled randomised trial. After 2 weeks of treatment there was significant improvement of symptoms (but not in clinical signs) in the study group, which was superior to the placebo group. After a further 2 weeks of treatment, the results showed improvement of both clinical signs and symptoms. Only one mild transient adverse effect was reported in the trihydroxyethylrutosides group and there were no drug-related problems in the pregnancies, deliveries or infants.

1.2 Ginkgo

Ginkor-fort® [1] (an extract of *Ginkgo biloba* in combination with troxerutin and heptaminol) acts by increasing venous tonicity and vessel wall resistance, and decreasing its permeability. It also encourages venous blood return and drainage of lymphatic oedema.[23] Soullard and Contou[22] reported satisfactory results with Ginkor-fort® as preparatory therapy in 37 patients, with complete or partial relief from symptoms of heaviness, tenesmus, pruritus or rectorrhagia in a majority of the patients. Hep et al.[23] reported documented benefit in the use of Ginkor-fort® at a dosage of two capsules twice daily in the first week and then two capsules once daily in the second week of the treatment in a group of 45 patients (table IV).

1.3 Heparan Sulfate

Heparan sulfate was compared with O-(β-hydroxyethyl)-rutosides (oxerutin) in 40 female patients in a study by De Cecco[21] for the treatment of grade 2 and 3 haemorrhoids. Better control of pain and normalisation of hyperaemia and mucoid secretions was reported with heparan sulfate compared with the hydroxyethylrutosides. Heparan sulfate al-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

so induced the remission of skin rash and itching (table IV).

1.4 Calcium Dobesilate

Calcium dobesilate is used in the treatment of diabetic retinopathy, chronic venous insufficiency, haemorrhoids and other ill-defined vascular conditions. Cases of agranulocytosis in patients on calcium dobesilate have been reported.[29] Marsicano et al.[30] compared calcium dobesilate, dexamethasone plus lidocaine with prednisolone plus dibucaine in the treatment of grade 1 and 2 haemorrhoids. They observed that both combinations were equally effective in relieving symptoms, though it was faster with the calcium dobesilate combination. In a randomised double-blind study by Mentes et al.,[20] 29 patients with grade 1 and 2 internal haemorrhoids were treated with calcium dobesilate and a high-fibre diet for 2 weeks, while 16 patients received only a high-fibre diet. A success rate of 86.2% with cessation of bleeding at 2 weeks was achieved with calcium dobesilate. Significantly better symptom and anoscopic inflammation scores were also observed with the calcium dobesilate treatment (table IV).

1.5 Local Application to the Anal Canal

Table V provides a summary of clinical trials of topical antihaemorrhoidal drugs.

1.5.1 Nitrates

Anal sphincter spasm is believed to play an important role in pain with thrombosed external haemorrhoids and in post-haemorrhoidectomy patients. Sphincterotomy and anal dilatation has been found to decrease pain after haemorrhoidectomy and in other painful anal conditions. Studies show that nitric oxide is one of the most important inhibitory neurotransmitter in the internal sphincter. Nitric oxide (like nitroglycerin [glyceryl trinitrate]) may cause 'chemical sphincterotomy' without the risk of permanent incontinence.[43] Cundall et al.[44] found that there was a progressive relaxation of anal tone with increasing doses of locally applied nitroglycerin ointment without any serious adverse effects. Loder et al.[43] reported that the internal anal pressure decreased by a mean of 27% after administration of the drug. However, nitrates, even when applied topically, do cause headaches and many patients find this intolerable.[43]

The most commonly studied nitrate in patients with haemorrhoids is nitroglycerin (glyceryl trinitrate). Five patients with thrombosed external

Table IV. Clinical trials primarily investigating nonflavanoid oral agents for the treatment of haemorrhoids

Study (year)	No. of patients	Grade of haemorrhoid	Drug(s)	Endpoint/results
Mentes et al.[20] (2001)	45	1, 2	Calcium dobesilate + high-fibre diet vs high-fibre diet only	Cessation of bleeding at 2 weeks = 86.2% (with better symptom and anoscopic score at 2 weeks)
De Cecco[21] (1992)	40	2, 3	Heparan sulfate vs O-(β-hydroxyethyl)-rutosides (oxerutin)	Persistent pain in 45% (vs 55%)
Soullard and Contou[22] (1978)	37	All	Ginkor-fort®	Satisfactory results in 12 patients (incomplete = 13, moderate = 3, no effect = 9)
Hep et al.[23] (2000)	45	NA	Ginkor-fort®	Benefit seen
Reddy et al.[24] (1984)	82 (+ 26 with fissure)	All	Pilex® tablets and ointment	Very good response in 15% of grade 1 and 7% of grade 2 haemorrhoids, good in 50% and 41%, respectively
Tripathy[25] (2000)	30	1, 2, 3	Pilex® tablets and ointment vs tablets MPFF	90% complete relief in grade 1 and 2 haemorrhoids with Pilex® Pilex® better in reducing pain, inflammation and size

MPFF = micronised purified flavanoid fraction; NA = not available.

Table V. Clinical trials of topical anti-haemorrhoidal drugs

Study (year)	No. of patients	Grade of haemorrhoid	Drug and formulation	Endpoint/results
Tajana et al.[27] (1988)	50	All	Diosmin ointment	Decrease in oedema = 75%, in erythema = 73%
Marsicano et al.[30] (1995)	40	1, 2	Calcium dobesilate (with dexamethasone + lidocaine) vs prednisolone + dibucaine	Improvement in signs and symptoms faster in calcium dobesilate group
Gorfine[31] (1995)	5 (+ 15 with fissure)	External	0.5% nitroglycerin (glyceryl trinitrate) ointment	Relief of pain in 100% Complete ulcer healing in 2 weeks = 10 of 15 patients
Hwang Do et al.[32] (2003)	110	3, 4	0.2% nitroglycerin ointment vs placebo	Significant reduction in pain with ointment Wound healing at 3 weeks = 74.5% (vs 42%)
Wasvary et al.[33] (2001)	39	Post-haemorrhoidectomy	0.2% nitroglycerin ointment vs placebo	Postoperative pain = lower with ointment Narcotic use = higher with placebo ($p < 0.05$) NSAID use = higher with ointment ($p < 0.0003$) Morbidity = higher with ointment ($p < 0.002$)
Cavcic et al.[34] (2001)	150	Thrombosed	0.2% nitroglycerin ointment vs excision and incision	Best results with excision
Coskun et al.[35] (2001)	38	3, 4	Nitroderm TTS® band (nitroglycerin)	Significant reduction in pain (in patients with high preoperative anal pressure)
Briel et al.[36] (2000)	4	4	1% isosorbide dinitrate ointment	Relief of pain = 100% within 1 day Reduction of prolapse = 100% within 1 week
Van den Berg et al.[37] (2003)	25	4	1% isosorbide dinitrate ointment	Relief of pain and reduction of pile = 96%
Perrotti et al.[38] (2001)	98	External	0.3% nifedipine + 1.5% lidocaine ointment vs 1.5% lidocaine ointment	Complete relief of pain in 7 days = 86% (vs 50%) Oral analgesic use in 7 days = 8% (vs 54.1%) Resolution of acute thromboses = 92% (vs 45.8%)
Smith and Moodie[39] (1988)	89	2	Proctosedyl®[a] ointment and suppository vs Uniroid®[b] ointment and suppository	All groups equally effective (relief of itching and pain better with suppository)
Damianov and Katsarova[40] (1993)	25	Pregnant	Proctosedyl®[a] ointment	Elimination of clinical symptoms = 100%
Espinosa[41] (2000)	2287	All	Policresulene + dibucaine ointment (± suppository)	Investigators' score = highly satisfactory in 83.2% Patients' score = highly satisfactory in 82.2%
Dressler and Ehmann[42] (1992)	80	1, 2	Standardised leech extract with polidocanol + allantoin	Improvement in signs and symptoms = faster in test group

a Proctosedyl® formulation used contains framycetin, hydrocortisone, dibucaine (cinchocaine) and esculoside (aesculin).

b Uniroid® formulation used contains dibucaine, hydrocortisone, neomycin and polymixin B.

haemorrhoids and 15 patients with anal fissure or ulcer were treated with a regimen that included nitroglycerin 0.5% ointment applied topically. All patients reported dramatic relief of anal pain following application of nitroglycerin lasting from 2 to 6 hours. Complete healing of fissures occurred within 2 weeks in ten patients and within 1 month in two further patients.[31] Hwang Do et al.[32] reported a randomised, prospective, double-blind, placebo-controlled study of 110 patients with grade 3 or 4 haemorrhoids and patients undergoing haemorrhoidectomies for three or more haemorrhoids. The pain score in the nitroglycerin group showed a significant difference. The wound healing rates at 3 weeks postoperatively were 74.5% in the nitroglycerin group and 42% in the placebo group, with no significant increase in complications in the nitroglycerin group. Wasvary et al.[33] observed that peri-

anal application of nitroglycerin 0.2% ointment after haemorrhoidectomy (39 patients) significantly reduced narcotic analgesia requirements on the second postoperative day. However, they also observed that headaches and a subsequent need for non-narcotic medications might limit benefits of nitroglycerin. Additionally, in a study involving 150 patients with thrombosed haemorrhoids, Cavcic et al.[34] found excision to be a significantly better method of treatment of perianal thrombosis than incision or topically applied nitroglycerin 0.2% ointment in terms of postoperative pain, recurrence and the appearance of anal skin tags.

In an interesting study involving 38 patients with haemorrhoids, Coskun et al.[35] found that nitroglycerin as Nitroderm TTS® bands placed in the anal canal after haemorrhoidectomy effectively reduced anal resting pressure and relieved pain in patients with high preoperative anal resting pressure.

Two studies have investigated isosorbide dinitrate as a 1% ointment. Briel et al.[36] treated four male patients with acute strangulated haemorrhoids with local applications of isosorbide dinitrate 1% ointment, repeated every 3 hours during daytime for 2 weeks. Significant pain relief was achieved within 1 day, and within 1 week the haemorrhoids became reducible and could be treated adequately by rubber band ligation. Only transient mild headaches were experienced during the first 2 days. Twenty-five consecutive patients with grade 4 haemorrhoids were treated with isosorbide dinitrate 1% ointment.[37] In 24 patients, reduction of the strangulated haemorrhoids and relief of pain was achieved. Two patients experienced severe headache causing a temporary suspension of the treatment.

1.5.2 Local Anaesthetic Preparations

Perrotti et al.[38] compared local application of nifedipine plus lidocaine ointment and lidocaine ointment alone in a prospective randomised study involving 98 patients. Complete relief of pain was seen and use of oral analgesics reduced in the nifedipine-treated group after 7 days of therapy. Resolution of acute thrombosed external haemorrhoids was achieved after 14 days of therapy in 46 patients (92%) of the nifedipine-treated group compared with 22 patients (45.8%) of the control group. No systemic adverse effects were observed.

Two local anaesthetic/corticosteroid/antibacterial combinations (Uniroid® [dibucaine/hydrocortisone/neomycin/polymyxin B] and Proctosedyl® [framycetin/hydrocortisone/dibucaine {cinchocaine}/esculoside {aesculin}]) in ointment and suppository formulations were compared in a multicentre open study involving 89 patients with grade 2 haemorrhoids.[39] Both suppository and ointment formulations were broadly comparable and control of symptoms was achieved from week 2 onwards. Suppositories gave marginally greater relief in the early stages of treatment, while both ointment and suppositories were associated with similar reduction in bleeding from haemorrhoids. Damianov and Katsarova[40] reported excellent results, including elimination of clinical symptoms and good tolerability, with locally applied Proctosedyl® in 100% of 25 pregnant women with chronic haemorrhoids.

Espinosa[41] investigated the therapeutic efficacy and tolerability of polycresulene plus dibucaine (cinchocaine) administered locally as ointment and/or suppositories in 2287 patients with haemorrhoids. Highly satisfactory results were reported in 1904 patients, without any serious adverse effects. Ten percent of the patients had local discomfort, pruritus, burning or irritation at the beginning of treatment.

1.6 Herbal and Other Extracts

Standardised blood leech extract in a topical combination preparation also containing polidocanol and allantoin was used by Dressler and Ehmann[42] in a placebo-controlled, double-blind study involving 80 patients with grade 1 and 2 haemorrhoids. Improvement in symptoms and signs

during the 1-week treatment was more rapid under the test preparation than placebo. Improvement in histologically demonstrable signs of inflammation was also better in the preparation group. No adverse effects were observed.

Horse chestnut seed extract (aescin) has been reported to reduce symptom of haemorrhoids in a controlled evaluation.[45] The seeds of the horse chestnut plant are the source of a saponin known as horse chestnut extract or aescin, which has been shown to promote circulation through the veins.[46] Horse chestnut extract fosters normal tone in the walls of the veins. It also possesses anti-inflammatory properties and has been shown to reduce oedema. Gels or creams containing 2% horse chestnut extract can be applied topically three or four times per day for haemorrhoids.

In a study by Reddy et al.[24] involving 82 patients with haemorrhoids of all grades and 26 with fissure-in-ano treated with Pilex® (an ayurvedic preparation) tablets and ointment, subjective improvement within a week of initiation of treatment along with objective improvement were found in all patients with fissures and in the majority of patients with haemorrhoids. Another study[25] found Pilex® tablets and ointment to be as effective as a MPFF in controlling bleeding, in all grades of haemorrhoids. Pilex® was more effective than the MPFF in reducing pain, inflammation and size of haemorrhoidal mass in grade 1 and 2 haemorrhoids.

Studies involving the use of medicinal yeast extracts[47] and multiherbal indigenous formulations[48] have also been reported. Fifty patients of either sex aged between 22 and 63 years entered in the study for the evaluation of safety and efficacy of PIL-28.[49] PIL-28 contains powders of *Balsamodendron mukul*, *Shilajeet* (purified), *Melia azadirachta* and extracts of *Berberis aristata*, *Emblica officinalis*, *Terminalia chebula*, *Terminalia belerica*, *Cassia fistula*, *Bauhinia variegata* and *Mesua ferrea*. It is processed in *Commelina salicifolia*, *Mimosa pudica*, *Acorus calamus*, *Blumea lacera*, *Caesalpinia bonducella* and *Amorphophallus campanulatus*. In the group that entered the study by Vastrad and Pakkanavar,[49] 31 patients had external haemorrhoids, 10 had internal haemorrhoids and 9 had both internal and external haemorrhoids. The patients were given PIL-28 at a dosage of one tablet twice daily for 6 weeks. At the end of the 6 weeks of treatment, the patients were evaluated for efficacy and tolerability of PIL-28 tablets. The results revealed that response to PIL-28 was very good in 56% and good in 38% of the patients (patient-assessed outcomes), showing a marked improvement in general health along with a gross reduction of associated symptoms. There were no adverse effects observed during the treatment and follow-up period.

There are also many traditional remedies that may help to alleviate the symptoms of haemorrhoids. *Commiphora wightii* (Guggulu) is an astringent antiseptic with anti-inflammatory and demulcent properties that help to reduce the pain and inflammation of haemorrhoids.[50] *Emblica officinalis* (Amalaki) has laxative action, which is important in relieving constipation associated with haemorrhoids.[51] The antibacterial and astringent properties of *Emblica officinalis* prevent infection and help in healing of ulcers.[52] *Mimosa pudica* (Lajjalu) has anti-inflammatory, antiseptic and healing properties. It helps in shrinking haemorrhoid mass and shrinking varicose veins.[53,54] *Shilajeet* (mineral pitch) has astringent and anti-inflammatory properties, and is used in the treatment of painful, bleeding haemorrhoids and varicose veins.[55] *Terminalia chebula* (Haritaki) acts as a gentle laxative and helps in aid evacuation.[56] *Berberis aristata* (Daruharidra) is a formulation of herbs and minerals designed for the management of haemorrhoids; its laxative properties are useful in haemorrhoids.

2. Conclusion

Drugs can reduce oedema, relieve pain and help in thrombosis, but cannot definitively cure haemorrhoids.

Grade 1 haemorrhoids can be treated with diet and drugs or with sclerotherapy, banding or infrared therapy. Grade 2 haemorrhoids can be treated with sclerotherapy, ligation or infrared photocoagulation. At grade 3 and 4 after the acute phase, it is possible to cure haemorrhoids only with surgery.

Drugs can be an effective, well tolerated and safely used option in the treatment of acute-phase haemorrhoids while waiting for definitive outpatient modalities at a convenient time. With the discovery of newer drugs and the 'rediscovery' of ancient and traditional medicines, we now have a wide range of agents that can be used through local or systemic routes. Judicial use of these drugs will go a long way in bringing relief from haemorrhoidal disease for patients awaiting definitive treatment by one of the outpatient modalities.

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References

1. Beattie GC, Wilson RG, Loudon MA. The contemporary management of haemorrhoids. Colorectal Dis 2002; 4 (6): 450-4
2. Nivatvongs S. Haemorrhoids. In: Gordon PH, Nivatvongs S, editors. Principles and practice of surgery for the colon, rectum, and anus. 2nd ed. St Louis (MO): Quality Medical Publishing Inc., 1999: 193-215
3. Neiger A. Haemorrhoids in everyday practice. Proctology 1979; 2: 22
4. Reis Neto JA, Quilici FA, Cordeiro F, et al. Ambulatory treatment of haemorrhoids: a prospective randomized trial. Coloproctology 1992; 6: 342-7
5. Sardinha TC, Corman ML. Haemorrhoids. Surg Clin North Am. 2002 Dec; 82 (6): 1153-67, vi
6. Cospite M. Double blind, placebo-controlled evaluation of clinical activity and safety of Daflon 500mg in the treatment of acute haemorrhoids. Angiology 1994; 45 (6 Pt 2): 566-73
7. Misra MC, Parshad R. Randomized clinical trial of micronized flavonoids in the early control of bleeding from acute internal haemorrhoids. Br J Surg 2000; 87 (7): 868-72
8. Godeberge P. Daflon 500 mg in the treatment of hemorrhoidal disease: a demonstrated efficacy in comparison with placebo. Angiology 1994; 45 (6 Suppl.): 574-8
9. Thanapongsathorn W, Vajrabukka T. Clinical trial of oral diosmin (Daflon) in the treatment of hemorrhoids. Dis Colon Rectum 1992; 35 (11): 1085-8
10. Ho YH, Tan M, Seow-Choen F. Micronized purified flavonidic fraction compared favorably with rubber band ligation and fiber alone in the management of bleeding hemorrhoids: randomized controlled trial. Dis Colon Rectum 2000; 43 (1): 66-9
11. Ho YH, Foo CL, Seow-Choen F, et al. Prospective randomized controlled trial of a micronized flavonidic fraction to reduce bleeding after haemorrhoidectomy. Br J Surg 1995; 82 (8): 1034-5
12. Buckshee K, Takkar D, Aggarwal N. Micronized flavonoid therapy in internal hemorrhoids of pregnancy. Int J Gynaecol Obstet 1997; 57 (2): 145-51
13. Meyer OC. Safety and security of Daflon 500mg in venous insufficiency and in hemorrhoidal disease. Angiology 1994; 45 (6 Pt 2): 579-84
14. Diana G, Catanzaro M, Ferrara A, et al. Activity of purified diosmin in the treatment of hemorrhoids [in Italian]. Clin Ter 2000; 151 (5): 341-4
15. Basile M, Gidaro S, Pacella M, et al. Parenteral troxerutin and carbazochrome combination in the treatment of post-hemorrhoidectomy status: a randomized, double blind, placebo-controlled, phase IV study. Curr Med Res Opin 2001; 17 (4): 256-61
16. Annoni F, Boccasanta P, Chiurazzi D, et al. Treatment of acute symptoms of hemorrhoid disease with high-dose oral O-(beta-hydroxyethyl)-rutosides. Minerva Med 1986; 29 (37): 1663-8
17. Wijayanegara H, Mose JC, Achmad L, et al. A clinical trial of hydroxyethylrutosides in the treatment of haemorrhoids of pregnancy. J Int Med Res 1992; 20 (1): 54-60
18. Benzi G, Vanzulli A, Pozzi E, et al. Clinical study for the evaluation of the tolerability of O-(beta-hydroxy-ethyl)-rutoside in the treatment of hemorrhoids during the 3rd trimester of pregnancy and in the postpartum period. Minerva Ginecol 1992; 44 (11): 591-7
19. Titapant V, Indrasukhsri B, Lekprasert V, et al. Trihydroxyethylrutosides in the treatment of hemorrhoids of pregnancy: a double-blind placebo-controlled trial. J Med Assoc Thai 2001; 84 (10): 1395-400
20. Mentes BB, Gorgul A, Tatlicioglu E, et al. Efficacy of calcium dobesilate in treating acute attacks of hemorrhoidal disease. Dis Colon Rectum 2001; 44 (10): 1489-95
21. De Cecco L. Effects of administration of 50mg heparan sulfate tablets to patients with varicose dilatation of the hemorrhoid plexus (hemorrhoids). Minerva Ginecol 1992; 44 (11): 599-604
22. Soullard J, Contou JF. A study on the use of ginkor in proctology (author's transl) [in French]. Sem Hop 1978; 54 (37-40): 1177-9

23. Hep A, Robek O, Skricka T. Treatment of hemorrhoids from the viewpoint of the gastroenterologist: personal experience with the Ginkor Fort preparation. Vnitr Lek 2000; 46 (5): 282-5
24. Reddy SS, Nagabushanam M, Ramanuja Rao M, et al. Role of Pilex tablets and ointment in the treatment of piles and fissures. Probe 1984; XXIII (4): 213
25. Tripathy A. Comparative evaluation of Pilex with Daflon in hemorrhoids. Antiseptic 2000; 97 (9): 317
26. Lyseng-Williamson KA, Perry CM. Micronised purified flavonoid fraction: a review of its use in chronic venous insufficiency, venous ulcers and haemorrhoids. Drugs 2003; 63 (1): 71-100
27. Tajana A, Boccasanta P, Micheletto G, et al. Results of the use of topical diosmin (venosmine) in the treatment of acute hemorrhoid pathology. Minerva Med 1988; 79 (5): 387-90
28. Wadworth AN, Faulds D. Hydroxyethylrutosides: a review of its pharmacology, and therapeutic efficacy in venous insufficiency and related disorders. Drugs 1992; 44 (6): 1013-32
29. Ibanez L, Ballarin E, Vidal X, et al. Agranulocytosis associated with calcium dobesilate clinical course and risk estimation with the case-control and the case-population approaches. Eur J Clin Pharmacol 2000; 56 (9-10): 763-7
30. Marsicano LJ, Perez M, Urquiola G. Effectiveness and innocuousness of the association of calcium dobesilate, dexamethasone acetate and lidocaine versus prednisolone capronate with dibucaine clorohydrate in the treatment of hemorrhoids [in Spanish]. G E N 1995; 49 (4): 296-302
31. Gorfine SR. Treatment of benign anal disease with topical nitroglycerin. Dis Colon Rectum 1995; 38 (5): 453-6
32. Hwang Do Y, Yoon SG, Kim HS, et al. Effect of 0.2 percent glyceryl trinitrate ointment on wound healing after a hemorrhoidectomy: results of a randomized, prospective, double blind, and placebo-controlled trial. Dis Colon Rectum 2003; 46 (7): 950-4
33. Wasvary HJ, Hain J, Mosed-Vogel M, et al. Randomized, prospective, double blind, placebo-controlled trial of effect of nitroglycerin ointment on pain after hemorrhoidectomy. Dis Colon Rectum 2001; 44 (8): 1069-73
34. Cavcic J, Turcic J, Martinac P, et al. Comparison of topically applied 0.2% glyceryl trinitrate ointment, incision and excision in the treatment of perianal thrombosis. Dig Liver Dis 2001; 33 (4): 335-40
35. Coskun A, Duzgun SA, Uzunkoy A, et al. Nitroderm TTS band application for pain after hemorrhoidectomy. Dis Colon Rectum 2001; 44 (5): 680-5
36. Briel JW, Zimmerman DD, Schouten WR. Treatment of acute strangulated internal hemorrhoids by topical application of isosorbide dinitrate ointment. Int J Colorectal Dis 2000; 15 (4): 253-4
37. Van den Berg M, Stroeken HJ, Hoofwijk AG. Favorable results of conservative treatment with isosorbide dinitrate in 25 patients with fourth-degree hemorrhoids: a pilot study. Ned Tijdschr Geneeskd 2003; 147 (20): 971-3
38. Perrotti P, Antropoli C, Molino D, et al. Conservative treatment of acute thrombosed external hemorrhoids with topical nifedipine. Dis Colon Rectum 2001; 44 (3): 405-9
39. Smith RB, Moodie J. Comparative efficacy and tolerability of two ointment and suppository preparations ('Uniroid' and 'Proctosedyl') in the treatment of second degree haemorrhoids in general practice. Curr Med Res Opin 1988; 11 (1): 34-40
40. Damianov L, Katsarova M. Our experience in using the preparation Proctosedyl from the Roussel firm in pregnant women with hemorrhoids [in Bulgarian]. Akush Ginekol (Sofiia) 1993; 32 (3): 71
41. Espinosa DJ. Analytical review of multicenter studies with polycresulene for hemorrhoidal pathologies. Acta Gastroenterol Latinoam 2000; 30 (3): 177-86
42. Dressler H, Ehmann G. Local therapy of grade 1 and 2 hemorrhoids: effectiveness of a combination preparation with standardized blood leech extract. Fortschr Med 1992; 110 (16): 307-10
43. Loder PB, Kamm MA, Nicholls RJ, et al. 'Reversible chemical sphincterotomy' by local application of glyceryl trinitrate. Br J Surg 1994; 81 (9): 1386-9
44. Cundall JD, Gunn J, Easterbrook JR, et al. The dose response of the internal anal sphincter to topical application of glyceryl trinitrate ointment. Colorectal Dis 2001; 3 (4): 259-62
45. Nini G, Di Cicco CO. Controlled clinical evaluation of a new anti-hemorrhoid drug, using a completely randomized experimental plan. Clin Ther 1978; 86: 545-59
46. Guillaume M, Padioleau F. Venotonic effect, vascular protection, anti-inflammatory and free radical scavenging properties of horse chestnut extract. Arzneimittelforschung 1994; 44: 25-35
47. Schlemm DJ, Crowe MJ, McNeill RB, et al. Medicinal yeast extracts. Cell Stress Chaperones 1999; 4 (3): 171-6
48. Paranjpe P, Patki P, Joshi N. Efficacy of an indigenous formulation in patients with bleeding piles: a preliminary clinical study. Fitoterapia 2000; 71 (1): 41-5
49. Vastrad CS, Pakkanavar RV. Clinical evaluation of PIL-28, an herbal formulation in the management of haemorrhoids. Antiseptic 2002; 99 (9): 343-4
50. Nadakarni KM. Indian materia medica. Vol. I. Mumbai: Popular Prakashan Private Ltd, 1996: 167
51. Kirtikar KR, Basu BD. Indian medicinal plants. Vol. III. Derhadun: International Book Distributors, 1981: 2220
52. Nadakarni KM. Indian materia medica. Vol. I. Mumbai: Popular Prakashan Private Ltd, 1996: 480
53. Kirtikar KR, Basu BD. Indian medicinal plants. Vol. II. Derhadun: International Book Distributors, 1987: 915
54. Nadakarni KM. Indian materia medica. Vol. I. Bombay: Popular Prakashan Private Ltd, 1976: 799
55. Nadakarni KM. Indian materia medica. Vol. II. Bombay: Popular Prakashan Private Ltd, 1996: 23
56. Warrier PK, Nambiar VPK, Ramankutty C. Indian medicinal plants. Vol. 5. Madras: Orient Longman Ltd, 1997: 263

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