# Supplementary material

## Table S1. List of studies included in the systematic review.

| **Study, year, country/ interventions** | **Study design/ No of participants** | **Inclusion and exclusion criteria** | **Outcomes analyzed (MPFF vs control)** | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Parameter | Day | MPFF | Control | Significant? |
| **Investigations of direct effects of MPFF on acute hemorrhoidal disease (HD)** | | | | | | | |
| Cospite  [6, [7](#_ENREF_23)]  Italy  MPFF 3000 mg/day for 3 days, 2000 mg/day for 4 days  vs placebo | Double-blind RCT  N = 100  MPFF: n = 50  Placebo: n = 50  Mean age:a 43-45y  53% women | Inclusion criteria: adult outpatients or inpatients of any sex, with known HD, diagnosed by proctoscopy, with an uncomplicated acute hemorrhoidal crisis (without any previous treatment) for a maximum of 3 days. The patients had to have symptoms such as bleeding, anal discomfort, pain and pruritus, and objective proctoscopic signs  Exclusion criteria: patients requiring a surgical procedure, or with anal fistula or rectal prolapse | Systemic analgesic consumption (doses/day), mean ± standard deviation | 7 | 0.2 ± 0.1 | 1.6 ± 0.2 | Y |
| Percentage of patients **without** **symptoms**:b | | | | |
| Pain | 7 | 42/50 (84%) | 8/50 (16%) | Y |
| Anal discomfort | 7 | 19/49 (39%) | 3/49 (6%) | Y |
| Bleeding | 7 | 19/20 (95%) | 9/18 (50%) | Y |
| Discharge/leakage | 7 | 21/26 (81%) | 7/23 (30%) | Y |
| Overall satisfaction (patient rating of "satisfied" or "very satisfied")c | 7 | 42/50 (84%) | 21/50 (42%) | Y |
| Overall improvement (investigator rating of "very good", "good" or "useful")d | 7 | 45/50 (90%) | 29/50 (58%) | Y |
| Godeberge [46,47]  France  MPFF 1000 mg/day for 60 days  vs placebo | Double-blind RCT  N = 120  MPFF: n = 60  Placebo: n = 60  Mean age:a 46–48y  80% women | Inclusion criteria: ambulatory patients, aged >18y, with symptomatic HD (1st to 3rd degree); with an acute episode in preceding 2 months.  Exclusion criteria: complicated HD as a result of previous surgery, associated anal fissure, or requiring immediate surgery; bleeding disorder; treatment with a venotropic agent in the previous 2 months; anocutaneous parasitic infestation; recto-sigmoidal disorder | Percentage of patients **with an improvement in score**:e | | | | |
| Pain | 60 | 98% | 47% | Y |
| Pruritus | 60 | 86% | 58% | Y |
| Tenesmus | 60 | 98% | 50% | Y |
| Bleeding | 60 | 91% | 59% | Y |
| Discharge/leakage | 60 | 97% | 54% | Y |
| Edema | 60 | 98% | 47% | Y |
| Erythema | 60 | 95% | 48% | Y |
| Recurrence of acute episode on treatment | 60 | 40% | 76% | Y |
| Patient satisfaction | 60 | 90% | 40% | Y |
| Jiang & Cao [50]  China  MPFF 3000 mg/day for 4 days, then 1500 mg/day for 3 days  vs placebo | Double-blind RCT  N = 90  MPFF: n = 49  Placebo: n = 41  Mean age: 43.2y  46% women | Inclusion criteria: male or female patients, aged >18y, followed up as out- or inpatients, presenting for the first time with an acute hemorrhoidal episode (diagnosis confirmed by clinical and endoscopic examination) of <48h duration, with symptoms such as pain, pruritus and edema, and/or signs (bleeding, mucus leakage and prolapse), having not received other prior therapies (any phlebotropic medication, anticoagulant and antiplatelet agents, analgesic or anti-inflammatory drugs)  Exclusion criteria: presence of severe hemorrhoidal manifestations requiring surgery; anal fissure; permanent prolapsed hemorrhoids; and parasitic infection | Bleedingf (% score 2 or 3)  [mean score] | 4 | 2/49 (4.1%)  [1.3] | 2/41 (4.9%)  [1.5] | Y |
| 7 | 1/49 (2.0%)  [1.2] | 3/41 (7.3%)  [1.4] | Y |
| Painf (% score 2 or 3)  [mean score] | 4 | 9/49 (18.3%)  [2.0] | 8/41 (19.5%)  [2.1] | N |
| 7 | 3/49 (6.1%)  [1.4] | 6/41 (14.6%)  [1.8] | Y |
| Pruritusf (% score 2 or 3)  [mean score] | 4 | 1/49 (2.0%)  [1.2] | 2/41 (4.9%)  [1.3] | N |
| 7 | 0/49 (0.0%)  [1.1] | 2/41 (4.9%)  [1.3] | Y |
| Leakagef (% score 2 or 3)  [mean score] | 4 | 1/49 (2.0%)  [1.2] | 1/41 (2.4%)  [1.2] | N |
| 7 | 0/49 (0.0%)  [1.1] | 1/41 (2.4%)  [1.2] | N |
| Edemaf (% score 2 or 3)  [mean score] | 4 | 12/49 (24.5%)  [2.1] | 10/41 (24.4%)  [2.0] | N |
| 7 | 4/49 (8.1%)  [1.6] | 8/41 (19.5%)  [1.7] | N |
| Prolapsef (% score 2 or 3)  [mean score] | 7 | 0/49 (0.0%)  [1.1] | 2/41 (4.9%)  [1.3] | Y |
| Overall evaluation (patient) (% reporting "good" or "excellent") | 7 | 75.5% | 39.0% | Y |
| Overall evaluation (investigator) (% reporting "good" or "excellent") | 7 | 75.6% | 39.0% | Y |
| Misra & Parshad [[52](#_ENREF_30)]  India  MPFF 3000 mg/day for 4 days, then 2000 mg/day for 3 days, then 1000 mg/day for 83 days  vs placebo | Double-blind RCT  N = 100  MPFF: n = 50  Placebo: n = 50  Mean age:a 33–35y  21% women | Inclusion criteria: Outpatients of either sex, age >18y, with past history of HD of <18 months’ duration and presenting with acute rectal bleeding of <3 days’ duration, in association with visibly distended or displaced anal cushions grade 1 or 2 internal hemorrhoids identified on proctoscopic examination  Exclusion criteria: patients with anal fissure, inflammatory bowel disease, colorectal cancer or pregnancy; previous laser treatment or use of a flavonoid drug 1 month before inclusion. Previous treatment with analgesics, topical antihemorrhoidal ointments, non-steroidal anti-inflammatory drugs, steroids, anticoagulants or antiplatelet agents | Bleeding cessation | 3 | 40/50 (80%) | 19/50 (38%) | Y |
| 4 | 46/50 (92%) | 20/50 (40%) | Y |
| 5 | 46/50 (92%) | 26/50 (52%) | Y |
| 6 | 47/50 (94%) | 29/50 (58%) | Y |
| 7 | 47/50 (94%) | 30/50 (60%) | Y |
| Bleeding cessation to recurrence (interval days), mean ± standard deviation |  | 53.1 ± 22.7 | 34.2 ± 22.6 | N |
| Panpimanmas *et al.* [49]  Thailand  CQ  vs MPFF 3000 mg/day for 4 days, then 2000 mg/day for 3 days,  vs placebo | Double-blind RCT  N = 570  CQ: n = 191  MPFF: n = 189  Placebo: n = 190  Mean age: not reported  49−55% women | Inclusion criteria: acute rectal bleeding within five days  Exclusion criteria: previous hemorrhoidectomy, treatment with anticoagulant or acetylsalicylic acid, treatment with other antihemorrhoid drugs at that time, permanent prolapsed internal hemorrhoid requiring surgery, moderate to severe hypertension; cardiovascular diseases; renal failure, cirrhosis, pregnancy and lactation | Percentage of patients **with an improvement in score**:g | | | | |
| Bleeding (patient) | 7 | 118/174 (67.8%) | 132/178 (74.2%) | N |
| Pain (patient) | 7 | 57/174 (32.8%) | 58/178 (32.6%) | N |
| Discharge (patient) | 7 | 9/174 (5.2%) | 11/178 (6.2%) | N |
| Pruritus (patient) | 7 | 12/174 (6.9%) | 17/178 (9.6%) | N |
| Prolapse (patient) | 7 | 6/174 (3.4%) | 11/178 (6.2%) | N |
| Bleeding (investigator) | 7 | 28/174 (16.1%) | 25/178 (14.0%) | N |
| Edema (investigator) | 7 | 54/174 (31.0%) | 68/178 (38.2%) | N |
| Vajrabukka *et al.* [48]  Thailand  MPFF 3000 mg/day for 4 days, then 2000 mg/day for 3 days  vs placebo | Double-blind RCT  N = 226  MPFF: n = 121  Placebo: n = 105  Mean age:a 35–37y  50% women | Inclusion criteria: non-pregnant outpatients >18y of age with acute symptoms of hemorrhoids for no longer than 3 days, with pain, discomfort, bleeding and discharge symptoms  Exclusion criteria: permanently prolapsed hemorrhoids (grade 4) or associated anorectal diseases such as anal fissure, fistula-in-ano and abscesses | Percentage of patients **with an improvement in score**:h | | | | |
| Pain | 7 | 69/88 (82.1%) | 66/78 (84.6%) | N |
| Anal discomfort | 7 | 57/85 (67.1%) | 39/69 (56.8%) | N |
| Bleeding | 7 | 79/92 (85.9%) | 73/90 (81.1%) | N |
| Discharge/leakage | 7 | 40/51 (78.9%) | 27/42 (64.7%) | N |
| Thanapongsathorn & Vajrabukka [54]  Thailand  MPFF 6000 mg/day for 4 days, 2000 mg/day for 10 days  vs placebo | Double-blind RCT  N = 100  MPFF: n = 50  Placebo: n = 50  Mean age: 32y  59% women | Inclusion criteria: new and consecutive patients with acute symptoms due to first and second degree internal hemorrhoids (Goligher classification) | Subjective improvement | 4 | 74% | 60% | N |
| Objective improvement | 4 | 52% | 22% | Y |
| Subjective improvement | 14 | 98% | 94% | N |
| Objective improvement | 14 | 72% | 62% | N |
| Mokhtare *et al.* [53]  France  MPFF 3000 mg/day for 4 days, 2000 mg/day for 3 days + topicals vs topicals only | RCT  N = 94  MPFF: n = 47  Placebo: n = 47  Mean age: 51y  61% women | Inclusion criteria: Age >18y and a diagnosis of acute hemorrhoids (acute anal pain or bleeding)  Exclusion criteria: patients with history of previous anorectal or hemorrhoid surgery, hemorrhoids grade I–IV, lactation, pregnancy, medications (antidepressants, flavonoids), severe systemic disease, hypertension, seizures, cancer, sleep disorders, allergy to MPFF, and who were non-cooperative | Mean score ± standard deviation: | | | | |
| Total SF-12 | 21 | 24.3 ± 2.8 | 19.5 ± 2.9 | Y |
| General health | 21 | 31.1 ± 1.8 | 24.7 ± 3.2 | Y |
| Pain (VAS 0–10) | 21 | 4.32 ± 2.4 | 4.23 ± 2.2 | N |
| Decreased bleeding | 21 | 60% | 44.8% | Y |
| **Investigations of effects of MPFF treatment following a medical/surgical procedure** | | | | | | | |
| Colak *et al.* [[57](#_ENREF_21)]  Turkey  MPFF (dose not reported) vs no treatment for 7 days after hemorrhoidectomy | Observer-blind RCT  N = 112  MPFF: n = 56  No treatment: n = 56  Median age:a 41−45y  40−43% women | Inclusion criteria: patients with symptomatic third- or fourth-degree hemorrhoids who underwent hemorrhoidectomy  Exclusion criteria: patients with concomitant anal disease, such as fissure, abscess, fistula, Crohn's disease, ulcerative colitis or rectal cancer; those taking oral anticoagulants | Pain score (0–10), median (interquartile range) | 2 | 5 (2–7) | 6 (5–7) | Y |
| 3 | 3.5 (0–5.5) | 5 (3.5–7) | Y |
| 7 | 2 (0–3) | 3.5 (2–4) | Y |
| Analgesic consumption | 7 | 38/56 (67.9%) | 48/56 (85.7%) | Y |
| Analgesic consumption duration (days), median (interquartile range) | – | 2 (0–3) | 3 (1.5–3) | Y |
| Overall satisfaction rating (patient) “good” and “excellent”i | 7 | 25/28 (89.3%) | 18/28 (64.3%) | Y |
| Dimitropoulos *et al.* [[62](file:///C:\Users\MSIN_CB\AppData\Local\Microsoft\Windows\INetCache\Content.Outlook\NHN8TR8X\Revised%20Table%202%20(002).docx#_ENREF_24)]  Greece  IRP + MPFF 3000 mg/day for 5 days after IRP vs IRP + no additional treatment | Observer-blind RCT  N = 234  MPFF + IRP: n = 117  IRP: n = 117  Mean age: 49.2y  51% women | Inclusion criteria: ambulatory male and female patients, aged >18y, with rectal bleeding due to acute internal hemorrhoids (grades I–III); no previous treatment for HD within the 6 months preceding the study; no coexistent colon diseases  Exclusion criteria: pregnancy; history of acute HD attacks; concomitant large-bowel and anal canal diseases; history of pelvic radiation; use of anticoagulant and antiplatelet agents or nonsteroidal anti-inflammatory drugs | Bleeding cessation | 5 | 83/111 (74.8%) | 65/117 (55.6%) | Y |
| Bleeding recurrence | 90 | 4/83 (4.8%) | 9/65 (13.8%) | N |
| Ho *et al.* [[55](#_ENREF_27)]  Singapore  Hemorrhoidectomy + MPFF 3000 mg/day for 3 days then 1500 mg/day for 4 days,  vs no additional treatment (NAT) | Observer-blind RCT  N = 228  MPFF: n = 114  NAT: n = 114  Mean age: 39.5y  46% women | Inclusion criteria: patients with three columns of symptomatic irreducible prolapsed hemorrhoids | Bleeding (secondary) | 6–15 | 1/114 (0.9%) | 7/114 (6.1%) | Y |
| La Torre & Nicolai [58]  Italy  Hemorrhoidectomy +  MPFF 2000 mg/day for 10 days and 1000 mg/day for 20 days, vs no additional treatment (NAT) | RCT  N = 50  MPFF: n = 25  NAT: n = 25  Mean age:a 56–57y  37% women | Inclusion criteria: patients aged >18y with an indication for hemorrhoidectomy, a past history of HD longer than 6 months, symptomatic irreducible prolapsed hemorrhoids  Exclusion criteria: fistula or chronic anal fissure; inflammatory bowel disease; diabetes or other metabolic or endocrine disorders; alcoholism; drug abuse; coagulation disorders; previous anorectal surgery | Mean score, or mean score ± standard deviation: | | | | |
| Pain (VAS 0–10) | 3 | 3.48 | 6.16 | Y |
| 60 | 3.88 ± 2.28 | 8.32 ± 2.88 | Y |
| Pruritus (VAS 0–10) | 3 | 1.84 | 4.04 | Y |
| 60 | 1.96 ± 1.54 | 5.04 ± 2.49 | Y |
| Tenesmus (VAS 0–10) | 3 | 1.48 | 5.36 | Y |
| 60 | 1.68 ± 1.82 | 7.21 ± 3.13 | Y |
| Bleeding (VAS 0–10) | 3 | 2.00 | 4.40 | Y |
| 60 | 2.00 ± 1.29 | 5.24 ± 2.80 | Y |
| Lee *et al.* [56]  Korea  Hemorrhoidectomy +  MPFF 3000 mg/day for 4 days, then 2000 mg/day for 3 days  vs hemorrhoidectomy +  placebo | RCT  N = 54  MPFF: n = 27  Placebo: n = 27  Mean age:a 41−43y  51–56% women | Inclusion criteria: male or female, aged >18y, had undergone surgery for hemorrhoids (at least grade 2)  Exclusion criteria: pregnancy; lactation; rectal or colon cancer; gastrointestinal inflammation or infection; anal diseases other than HD; treatment with any other vasoactive agent, anticoagulants, adrenocortical hormones, nonsteroidal anti-inflammatory drugs, antiplatelet agents or other pharmaceutical HD treatments; and compliance of <80% or >120% with the study drug. | Percentage of patients **without** **symptoms**:j | | | | |
| Pain | 18 | 18/27 (66.7%) | 7/27 (25.9%) | Y |
| Anal discomfort | 18 | 11/27 (40.7%) | 5/27 (18.5%) | N |
| Postoperative bleeding | 18 | 24/27 (88.9%) | 6/27 (22.2%) | Y |
| Postoperative pus discharge | 18 | 23/27 (85.2%) | 10/27 (37.0%) | Y |
| Ho *et al.* [63]  Singapore  MPFF 3000 mg/day for 5 days, then 2000 mg/day for 3 weeks + fiber (ispaghula 7 g/day) for 3 months, vs fiber alone (7 g/day ispaghula) for 3 months | RCT  N = 105  MPFF + fiber: n = 39  Fiber alone: n = 66  Median age:a 41y  29% women | Inclusion criteria: patients with bleeding, non-prolapsed hemorrhoids | Time needed for rectal bleeding to stop after intervention (days), mean | 90 | 1.2 | 10.6 | Y |
| Mlakar & Kosorok [60]  Slovenia  MPFF 3000 mg/day for 5 days vs placebo after stapled hemorrhoidopexy | Observer-blinded RCT  N = 63 MPFF: n = 30 Placebo: n = 33 | Inclusion criteria: patients with third-degree hemorrhoids who underwent stapled hemorrhoidopexy | Duration of bleeding (days), mean | 7 | 2.30 | 1.97 | N |
| Pain (VAS 0–10), mean | 7 | 3.48 | 3.40 | N |
| Mlakar [59]  Slovenia  MPFF 3000 mg/day for 5 days vs placebo after hemorrhoidectomy | Observer-blinded RCT  N = 60  MPFF: n = 30  Placebo: n = 30 | Inclusion criteria: patients with third and fourth-degree hemorrhoids who underwent hemorrhoidectomy | Duration of bleeding (days), mean | 7 | 3.53 | 4.74 | Y |
| Bleeding (%) | 5 | 19 | 28 | Y |
| Shelygin *et al.* [61]  Russia  MPFF 1000 mg/day starting 7 days before sclerotherapy, then 2000 mg/day for 3 days and 1000 mg/day for 4 days after sclerotherapy, vs sclerotherapy alone | RCT  N = 124  MPFF + sclerotherapy: n = 63  Sclerotherapy alone: n = 61 | Inclusion criteria: patients from one to third degree hemorrhoids and who require sclerotherapy | Pain sensations (patient %) | 3 | 3 | 21 | Y |
| Discomfort (patient %) | 3 | 61 | 73 | N |
| 7 | 7 | 37 | Y |

CQ, *Cissus quadrangularis L.*; IRP, infra-red photocoagulation; MPFF, micronized purified flavonoid fraction; RBL, rubber band ligation; RCT, randomized controlled trial; SF-12, Short-Form 12; VAS, visual analog scale; y, years.

aMean age was calculated by treatment group.

bAll signs and symptoms graded on a four-point scale: 0 = none; 1 = mild; 2 = significant; 3 = severe. Percentages are percentages of patients with no symptoms at Day 7.

cThree-item assessment: "very satisfied", "satisfied", "not satisfied"

dFour-item assessment: "very good", "good", "useful", "null"

eAll signs and symptoms graded on a four-point scale from 0 (nil) to 3 (severe). Percentages are percentages of patients with a decrease in score (improvement) after treatment.

fAll signs and symptoms graded on a four-point scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe.

gAll signs and symptoms graded on a four-point scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. Percentages are percentages of patients with a decrease in score (improvement) after treatment.

hAll signs and symptoms graded on a four-point scale: 0 = nil, 1 = notable improvement, 2 = significant improvement, 3 = disappearance or cure. Percentages are percentages of patients with improvement (scored 1, 2, or 3) after treatment.

iFour-item assessment: "excellent", "good", "moderate", "poor". Distributions were compared using Wilcoxon signed-rank test.

jAll signs and symptoms graded on a four-point scale: 0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe intensity. Percentages are percentages of patients with no symptoms at Day 18.