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Efficacy and tolerability of micronized purified flavonoid fractions (MPFF) for haemorrhoids: A systematic review and meta-analysis

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ABSTRACT

Objective: To present a systematic review of randomised controlled trials (RCTs) examining the effects of MPFF in the management of haemorrhoid symptoms.
Methods: Electronic databases including CENTRAL, CINAHL, EMBASE, MEDLINE were searched up to April 2018 for relevant RCTs. Journal and conference proceedings were also searched. Two review authors independently selected trials, extracted data, assessed the risks of bias in included trials and graded the quality of evidence. Meta-analyses were conducted for studies presenting similar outcomes.
Results: Ten RCTs involving 1164 participants were included. These RCTs varied in terms of patients' grade of haemorrhoids, length of trials, and outcome assessed. Most of the studies did not describe adequately the process of randomisation and allocation concealment. The pooled analysis of data from three studies indicated that there was significant difference between groups for the bleeding outcome, favoring the MPFF group (RR 1.46; 95% CI 1.10–1.93; p = 0.008). Except for bleeding, the current evidence did not show MPFF has significant effects on all the other outcomes examined when compared with placebo. Even then, the quality of evidence for bleeding was judged as low due to the small number and inconsistent results among the included studies.
Conclusion: This review highlights the need for further rigorous research if MPFF was to be routinely used for the treatment of haemorrhoid symptoms.

1. Introduction

Haemorrhoids represent one of the most common conditions in man.[1] Haemorrhoids can be classified as internal or external based on their locations. Internal haemorrhoids are located inside the rectum while external haemorrhoids develop under the skin around the anus. Internal haemorrhoids are further categorized from Grade I to IV based on their severity with Grade IV being the most serious.[2] Available data[3] suggest the prevalence of haemorrhoids is highest for those aged 45–65 but their exact prevalence is difficult to estimate as many sufferers are reluctant to report their condition. Conventionally, dietary fibers have been the mainstay approach for patients with Grade I haemorrhoids whereas Grade II and some cases of Grade III haemorrhoids are corrected with non-operative outpatient therapies such as rubber band ligation. Surgical procedures are reserved for Grade III and IV or those with unsatisfactory results after management with medical treatment.[3] Despite the availability of various treatments for different grades of haemorrhoid symptoms, the treatments are still associated with risks of complications such as pain, bleeding, and recurrence.

Researchers have identified the significant effect plant derived polyphenols such as flavonoids, tannins, stilbenoids, catechins, lignans and phenolic acids which are beneficial for a vast array of inflammatory disorders. Examples include, allergy, asthma, autoimmune diseases, inflammatory bowel disease and haemorrhoids.[4] Recently, Micronized Purified Flavonoid Fractions (MPFF), marketed as Daflon® has been reported to be useful for the management of acute haemorrhoid symptoms.[5–7] Meanwhile, MPFF is an oral phlebotropic medication comprising a combination of micronised diosmin and hesperidin. Hesperidin is a flavanone glycoside extracted from citrus fruits[8] while diosmin is a flavone, which is biochemically, synthesised from hesperidin. The only difference in chemical structure between hesperidin and diosmin is that diosmin has an additional double bond between the two carbon atoms in its central carbon ring. The particle size of diosmin in MPFF is reduced to micron size (less than 2 μm) to increase its bioavailability and hence its efficacy.[9] The mode of action of MPFF is not completely understood, although it has been postulated that MPFF

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improves venous tonicity and lymphatic circulation in addition to reducing capillary permeability by protecting the microcirculations from inflammatory processes. These mechanisms are believed to contribute to the improvement of haemorrhoid symptoms such as pain, bleeding, and itching.[10]

Findings from published RCTs for the efficacy of MPFF on haemorrhoid symptoms are contradictory. Several studies[4,6,11] reported an improvement in bleeding while others[12,13] reported no significant improvement. Two earlier reviews, which did not specifically assess MPFF, included MPFF as one of the agents in a class of compounds classified as flavonoids[14] and phlebotonics.[15] As both published reviews were not focused on MPFF and undertaken some years ago, we aimed to review the evidence now available and form judgments about the quality of the evidence and strength of recommendations for the use of MPFF in the management of haemorrhoids.

2. Methods

2.1. Search strategy

A systematic search for appropriate studies involved multiple strategies. We used combinations of specific keywords such as 'micronised purified flavonoid fraction'; 'diosmin'; 'hesperidine'; 'Daflon' and 'haemorrhoid.' The following electronic databases were searched from their earliest record to April 2018: MEDLINE via Ovid Online; CINAHL via EBSCO host; Cochrane Databases and Cochrane Central Register of Controlled Trials. The searched for MEDLINE was limited to humans and a filter was applied to identify RCTs in all databases as described elsewhere.[16] We also hand searched haemorrhoid related topics in conferences and proceedings to identify posters and abstracts that were not identified with other searches.

2.2. Criteria for considering studies in this review

2.2.1. Selection process

All trials that compared the efficacy of MPFF alone with any control (placebo or other active control) for improving signs and symptoms of haemorrhoids were included. Trials that used MPFF as an intervention after surgery were excluded. There was no restriction on the basis of language, publication date or publication status. Two reviewers independently selected studies based on the predetermined eligibility criteria and disagreements between them were resolved by discussion with the third reviewer.

2.3. Data extraction and analysis

Data extracted for the primary and secondary outcomes were (a) number of patients with improvement in bleeding (b) number of patients with improvement in pain (c) number of patients with improvement in itching (d) adverse effects. Quantitative data were pooled using Revman 5.3. Relative risk (RR) was calculated for dichotomous data and the results were reported as RR with 95% confidence intervals (CI). Statistical significance was set at $p < 0.05$ for all outcomes. Studies that evaluated similar interventions in a similar population were pooled. If the I^2 statistic was deemed high (over 25%) the results from studies were pooled by the random-effect model.[17]

2.4. Assessment of risk of bias and quality of evidence

The risk of bias of the included studies was based on the Cochrane criteria.[18] Additionally, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of evidence of each outcome that could be quantitatively pooled.[19] The methodological criteria by which evidence was upgraded or downgraded were dependent on five primary domains (risk of bias, inconsistency, indirectness, precision and publication bias).

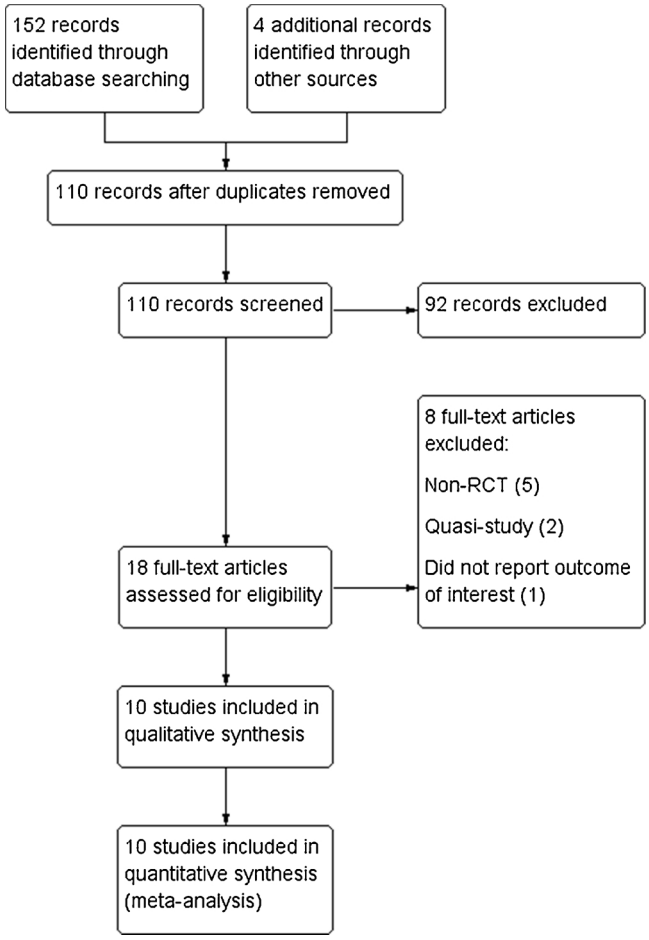

Fig. 1. Flow chart of studies selection.

3. Results

3.1. Description of included studies

Fig. 1 shows the flow of studies selection. Out of 156 records identified, full text was retrieved for 18 studies. Of these, 10 trials were included in this review and 8 were excluded for various reasons: five were non-RCT; two were quasi-study; one did not report on the outcome of interest.

Patients with haemorrhoids of all grades (I–IV) were involved in the included trials and the majority of the trials included participants with Grade I and II haemorrhoids (Table 1). The duration of follow-up varied widely from 7 days to 6 months while dosage of MPFF ranged from 1 g to 6 g daily.

3.2. Risk of bias in included studies

As shown in Fig. 2, most of the studies did not adequately describe the methods of sequence generation and allocation concealment and thus were judged to have an unclear risk of bias for these domains. All studies were judged to have low risk of attrition bias as both intervention and comparator groups for these studies had only reasonable number of outcome data missing or numbers of dropouts were balanced across groups. As for selective reporting bias, all studies were judged to have low risk because the authors reported all the pre-determined outcomes and also reported main outcomes reported by most other studies.

Other risks of bias considered were baseline comparability between the two groups of included studies and the reporting of financial