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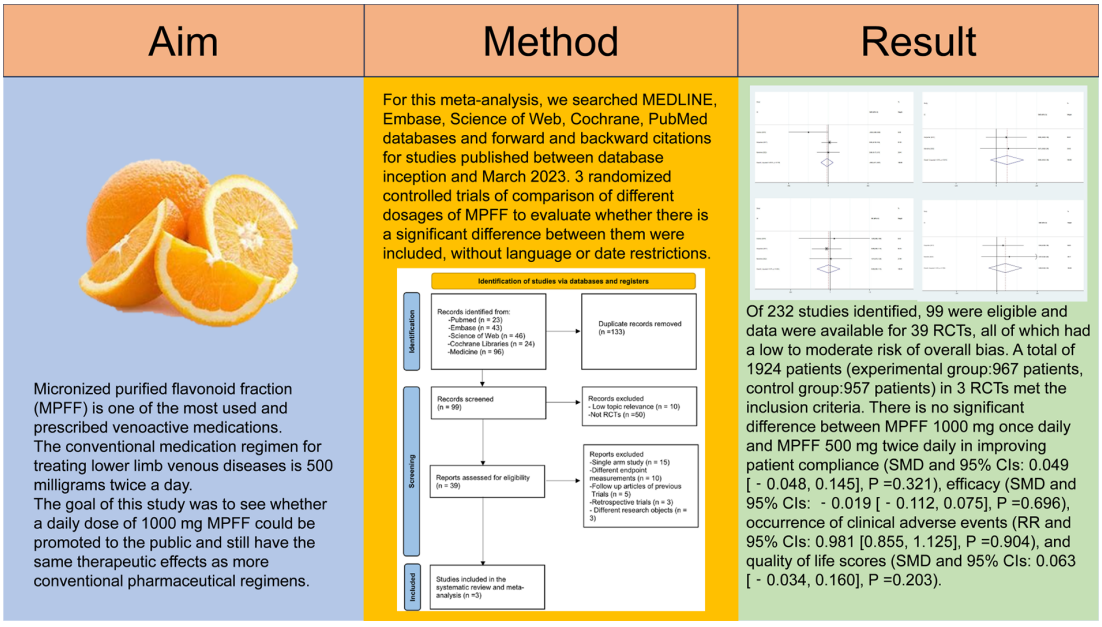
The Effects of Different Dosages on Micronized Purified Flavonoid Fraction's Treatment of Lower Limb Chronic Venous Disease: A Meta-Analysis

Hong-Jie Cui, MM[1] and Ying-Feng Wu, MD[2]

Abstract

Background: Micronized purified flavonoid fraction (MPFF) is a widely prescribed and extensively investigated venoactive drug (VAD). The standard dosage for MPFF is 500 mg administered twice daily. However, a new daily dose of 1000 mg has just been introduced. **Objective:** This study investigated whether a daily dose of 1000 mg MPFF could be implemented and embraced by the public and still has the same therapeutic effects as conventional pharmaceuticals. **Methods:** For this meta-analysis, we searched MEDLINE, Embase, Science of Web, Cochrane, and PubMed databases and forward and backward citations for studies published between database inception and March 2023. Three randomized controlled trials (RCTs) of comparison of different dosages of MPFF to evaluate whether there is a significant difference between them were included, without language or date restrictions. Due to the small sample size of the study included, we conducted a simple sensitivity test using a one-by-one exclusion method, and the results showed that the study did not affect the final consolidation conclusion. The quality of the evidence was assessed using the Cochrane risk-of-bias tool. **Results:** Out of 232 studies, 99 were eligible and 39 RCTs had data, all with low to moderate bias. Overall, 1924 patients (experimental group: 967, control group: 957) in 3 RCTs met the criteria. There is no significant difference in patient compliance, efficacy, clinical adverse events, and quality of life scores between MPFF 1000 mg once daily and MPFF 500 mg twice daily (standardized mean difference [SMD]: 0.049 [0.048, 0.145], p=0.321, risk ratio [RR]: 0.981 [0.855, 1.125], p=0.904, and SMD: 0.063 [0.034, 0.160], p=0.203). **Interpretation:** In symptomatic chronic venous disease patients, MPFF 1000 mg once daily and MPFF 500 mg twice daily improve patient compliance, lower limb discomfort, clinical adverse events, and quality of life scores similarly. Regular medical care should recommend MPFF 1000 mg daily more often.

Graphical abstract



Clinical Impact

Micronized purified flavonoid fraction (MPFF) is a popular venoactive medication (VAD) in modern medicine.

MPFF is effective in treating lower extremity venous problems.

Currently, besides conventional 500 mg tablets, there exist alternative dosage forms such as solutions, chewable tablets, and other novel formulations for MPFF.

The excessive frequency and amount of medication may have a negative impact on patient adherence.

Keywords

chronic venous disease, chronic venous insufficiency, micronized purified flavonoid fraction, dose regimen, meta-analysis

Introduction

Chronic venous disease (CVD) is very common globally, especially in European countries. The Gutenberg Health Study (GHS) of 10 664 middle-aged and elderly patients in west-central Germany found that the prevalence of CVD was as high as 85%[1]. Screening of 99 359 patients enrolled in Vein Consult Program (VCP) in multiple regions of the world suggests that the overall prevalence of CVD is around 65%[2]; Another large pooled analysis suggested a prevalence of 2% to 56% in men and 1% to 73% in women[3]. In mainland China, the prevalence of CVD is 8.9% to 10%.[4]

Micronized purified flavonoid fraction (MPFF), extracted from natural citrus, is a micronized mixture of diosmin (90%) and other active flavonoids (10%). Micronized purified flavonoid fraction, as one of the most representative venoactive drugs (VADs),[5,6] has been proven in numerous clinical studies to significantly improve the symptoms and signs of hemorrhoids.[7,8] Furthermore, venoactive therapy is a fundamental approach for CVD. It is appropriate to employ this treatment in individuals with symptomatic CVD, both prior to and following surgical or endovenous interventions for CVD. In individuals with early-stage CVD and lower Clinical-Etiological-Anatomical-Pathophysiological (CEAP) grades, MPFF has an advantage over placebo for symptom relief.[9] Micronized purified flavonoid fraction has been linked to improvements in leg symptoms, functional discomfort, patient quality of life, and ankle circumference, according to a systematic analysis of 7 double-blind, placebo-controlled randomized controlled trials (RCTs) involving 1692 patients.[10] The most recent European recommendations also say that people with symptomatic CVD who are awaiting surgical intervention or intervention, including MPFF, can benefit from VAD treatment.[11] Micronized purified flavonoid fraction also has been shown to have a considerable positive impact on patient symptoms in the non-surgical treatment of pelvic vein disorders (PeVDs), when compared with a placebo.[12–14]

Micronized purified flavonoid fraction is typically taken during lunch and supper, dividing the daily dose evenly into 2 doses (500 mg twice). There is substantial proof that increasing the number of daily doses can decrease patient compliance,[15–17] especially for chronic disease patients who require long-term and regular medication. Despite the fact that this conventional medication regimen has been demonstrated in clinical applications over the past few decades; Additionally, novel formulations of 1000 mg MPFF-containing chewable tablets and suspensions have been developed,[18] so it is important to know whether 2 distinct dosage regimens greatly affect treatment outcome of patients.

To figure out whether there is a difference in efficacy and compliance between 2 dosing regimens (500 mg twice vs. 1000 mg once) for patients with CVD of the lower limbs, we conducted a meta-analysis of RCTs.

Materials and Methods

Study Selection

The study protocol, including the formulation of the objectives of the analysis, inclusion/exclusion criteria, and assessments of quality, primary outcomes, and statistical methods, was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[19] We performed a comprehensive search for applicable studies indexed in Medicine, PubMed, Embase, Web of Science, and the Cochrane databases from inception to March 2023. A manual search was also performed for additional studies that met the inclusion criteria using the references of the included articles. The following search terms were used: "(MPFF 1000 mg OR MPFF 500 mg) AND (chronic venous disease or chronic venous insufficiency)."

[1]Department of Vascular Surgery, Xuanwu Hospital, Capital Medical University, Beijing, China
[2]Department of Vascular Surgery, Luhe Hospital, Capital Medical University, Beijing, China

Corresponding Author:
Ying-Feng Wu, Department of Vascular Surgery, Luhe Hospital, Capital Medical University, No. 82, Xinhua South Road, Tongzhou District, Beijing 101199, China.
Emails: wyfxgwk@163.com; xwhvs@163.com

Other search keywords include "Visual analog scale (VAS), Dose regimen, Tablets and suspension."

Inclusion and Exclusion Criteria

The inclusion criteria for this meta-analysis were as follows: (1) adult patients (≥18 years of age) and (2) any full texts of controlled trials that evaluated the outcomes of MPFF 1000-mg once daily versus MPFF 500-mg twice daily in adult patients with symptomatic CVD of lower limbs with (3) follow-up of at least 8 weeks. Exclusion criteria include (1) duplicate reports, (2) non-RCTs, (3) literature that does not contain at least 1 outcome indicator required for meta-analysis, (4) studies that did not report all study endpoints, and (5) in addition to the original research, any subsequent research and extended research on the same database.

Data Extraction and Literature Quality Assessment

Three researchers independently reviewed titles and abstracts of the first 232 records and discussed inconsistencies until consensus was obtained. Then, in pairs, the researchers independently screened titles and abstracts of all articles retrieved. In case of disagreement, consensus on which articles to screen full text was reached by discussion. If necessary, the third researcher was consulted to make the final decision. Next, 2 researchers independently screened full-text articles for inclusion. Again, in case of disagreement, consensus was reached on inclusion or exclusion by discussion, and if necessary, the third researcher was consulted. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines to select the final studies.[19] The primary clinical outcome of our meta-analysis was lower limb discomfort (LLD) and compliance. The secondary outcomes were quality of life (QoL) of patients and adverse events (AEs). We performed a meta-analysis of the included studies using the Review Manager (RevMan) version 5.4.1 (The Cochrane Collaboration, Copenhagen, Denmark) and STATA software (ver. 17.0MP; Stata Corp, College Station, Texas). The κ statistic was used to assess agreement between reviewers for study selection. Risk ratio (RR) and 95% confidence interval (CI) were used as summary statistics for AEs and were derived for comparison of MPFF 1000-mg once and MPFF 500-mg twice (the control therapy). In the evaluation of LLD, compliance and QoL of patients, we used SMD and 95% CI. Publication bias was evaluated by constructing a funnel plot using Egger's and Begg's tests. $p<0.05$ was considered to indicate a statistically significant publication bias. Heterogeneity was assessed using the Higgins I^2 index, where I^2 values $>50\%$ implied the presence of substantial heterogeneity. We assessed the quality of the included studies using the revised Cochrane risk-of-bias tool for RCTs.[20] This tool addresses 5 specific domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result. Two review authors independently applied the tool to each included study and recorded supporting information and justifications for judgments of risk of bias for each domain (low, high, and some concerns). Any discrepancies in judgments of risk of bias or justifications for judgments were resolved by discussion to reach a consensus between the 2 review authors, with a third review author acting as an arbiter if necessary.

Results

Included Studies

After reviewing the titles and abstracts, 3 RCTs[18,21,22] were included in the study. A flow diagram of the selection procedure is shown in Figure 1. The evaluation results of the Cochrane risk-of-bias tool are shown in Figures 2 and 3.

Outcome Measures and Data Analysis

A total of 1924 patients were included in the 3 studies (including 967 patients in MPFF 1000-mg once group and 957 patients in control group). Table 1 shows the baseline characteristics of the studies included in the meta-analysis; we collected data on (1) the report: author, year, and source of publication. (2) The study: sample characteristics, and definition and criteria of CEAP (Clinical-Etiology-Anatomy-Pathophysiology) used for CVD. (3) The participants: median age, proportion of males, body mass index, duration of CVD, median treatment time, proportion of patients who have received relevant treatment in the past and degree of relief of limb discomfort after MPFF treatment. Table 2 shows the primary endpoints and main characteristics of the studies.

We collected data on (1) the research design and features: primary endpoints, treatment assignment mechanism, adherence, and length of follow-up. (2) The intervention: type, duration, dose, timing, and mode of delivery. All the studies were carried out jointly by multiple centers across the whole world. All the included studies were evaluated by the Cochran Risk Scale without fatal bias. The disease severity of the patients included in the study is superior or equal to 4 cm on the VAS and with at least pain superior or equal to 3 cm on the VAS, corresponding to pain of at least moderate intensity. Patients were classified as clinical class C0s to C4s on the most affected leg, according to the CEAP classification. All indicators of our research have been investigated in almost all articles. Among them, the term "MPFF 1000-mg" was described as patients taking a drug at

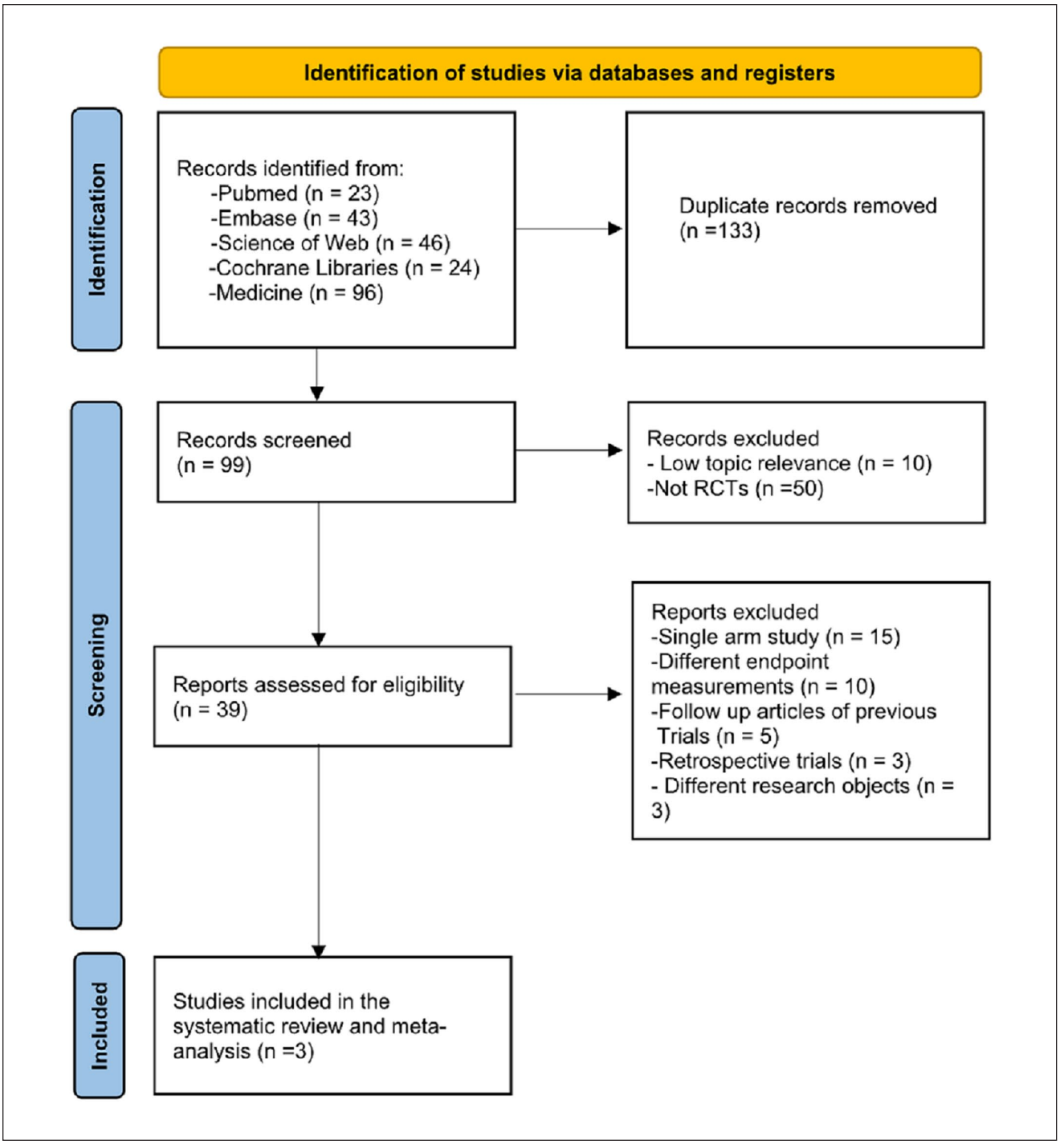


Figure 1. Flowchart of the meta-analysis.

breakfast that included 1000 mg of MPFF's active components while taking a placebo at lunch and supper. The term "MPFF 500-mg twice" was used to describe a drug that contains 500 mg of MPFF active components twice daily during 3 meals (breakfast and supper or lunch and evening), with a placebo administered during the third meal. Each patient group received the same dosage of the placebo as the patient group receiving MPFF. Lower limb discomfort is characterized by feelings of discomfort, restlessness, worry, anxiety, embarrassment, or inconvenience. The pain and heaviness of legs were also evaluated. While the definitions of these 3 parameters varied throughout the studies

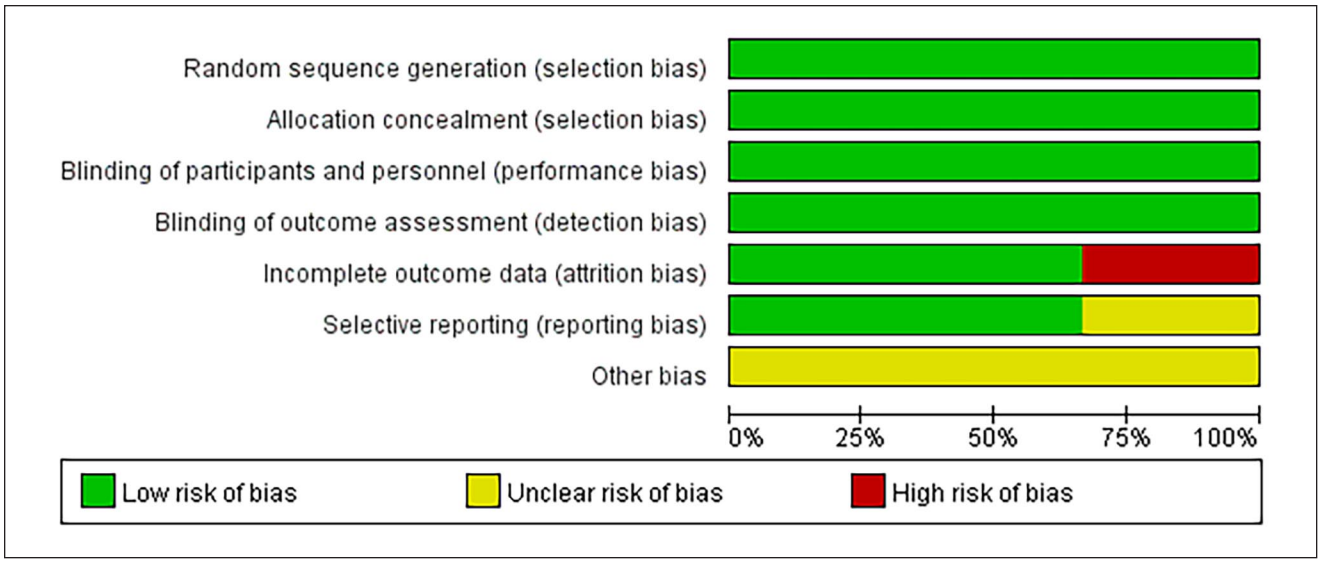


Figure 2. Result for risk of the meta-analysis bias graph.

and not all of them assessed all 3 indications, each study employed a standardized VAS scale to assess patients on the evening prior to their visit, so there is no significant difference between these 3 parameters. Compliance was described as the requirement that patients take their medications for the course of their treatment without skipping doses, refusing to take them, or underdosing. Emergent adverse events (EAEs) and treatment-related AEs, such as abdominal pain, diarrhea, nausea, headache, poisoning, and infection, were both considered AEs if they were reported by patients or noticed by researchers, AEs of Kirienko 2016 included reports of allergic dermatitis, although it was not explicitly specified if it was urticaria. VIQ-20 (Carpentier 2017) and its condensed variant CIVIQ-14 (Mansilha 2022) were used to assess the QoL of patients. Two extensively used scales, CIVIQ-20 and CIVIQ-14, are used to assess the precise effects of chronic venous insufficiency on the quality of life of patients with a CEAP score of C0-C4. Their dependability has been demonstrated, and they exhibit good consistency, responsiveness, and reproducibility.[23] We have implemented the Global Index Score standard universally due to the substantial number of scoring items. Varicose veins (CEAP) classification is divided into 6 levels: C0, no visible or palpable signs of venous disease; C1, telangiectasias or reticular veins; C2, varicose veins; C3, edema; C4, changes in skin and subcutaneous tissue secondary to CVD; C4a, pigmentation or eczema; C4b, lipodermatosclerosis or atrophie blanche; C4c, corona phlebectatica; C5, healed ulcer; C6, active venous ulcer.[24]

Outcomes

Meta-analysis outcomes in the entire study population are summarized in Table 3. When heterogeneity among studies was observed ($I^2>50\%$), a random-effects model was used. A fixed-effects model was used when no heterogeneity was demonstrated among studies.

Lower Limb Discomfort at 8 Weeks After Treatment

Three studies evaluated LLD at 8 weeks for MPFF 1000-mg versus MPFF 500-mg treatment. The results of meta-analysis in Figure 4 and Table 3 indicated that there was no significant difference in the improvement of LLD between the 2 treatment methods (SMD and 95% CIs: 0.019 [0.112, 0.075], p=0.696), and the fixed-effects model was used.

Quality of life of Patients After 8 Weeks After Treatment

Two studies evaluated QoL at 8 weeks for MPFF 1000-mg versus MPFF 500-mg treatment. The results of meta-analysis in Figure 5 and Table 3 indicated that there was no significant difference in the improvement of QoL between the 2 treatment methods (SMD and 95% CIs: 0.063 [0.034, 0.160], p=0.203), and the fixed-effects model was used.

Occurrence of Adverse Events After 8 Weeks After Treatment

Three studies evaluated the occurrence of AEs at 8 weeks for MPFF 1000-mg versus MPFF 500-mg treatment. The results of meta-analysis in Figure 6 and Table 3 indicated that there was no significant difference in the occurrence of AEs between the 2 treatment methods (RR and 95% CIs:

Table 1. Baseline Characteristics of the Patients Included in the Meta-Analysis.

Study	Study period	1000 mg MPFF once a day, n	500 mg MPFF twice a day, n	Mean age, years	Male, %	BMI (kg/m^2)	CVD duration, years	Mean duration of treatment, days	Previous treatments for CVD, %	CEAP class on the most affected leg, %									Alleviation of lower limb discomfort at the endpoint of the study, cm	
										C0	C1	C2	C3	C4a	C4b	C4c	C5	C6	1000 mg MPFF once	500 mg MPFF twice
Kirienko and Radak[22]	2013-2014	87	87	48.10 ± 12.40	16.70	25.20 ± 3.10	14.50 ± 11.10	56.30 ± 5.10	31.60	0.60	19.50	38.50	35.60	4.60	1.20	0	0	0	0-4.24 ± 0.72	0-4.00 ± 0.87
Carpentier 2017[21]	2013-2014	571	568	46.00 ± 12.00	14.20	25.00 ± 3.10	9.20 ± 10.80	54.90 ± 7.90	3.80	0.80	21.70	46.90	24.90	4.70	0.50	0	0	0	0-3.33 ± 2.40	0-3.37 ± 2.40
Mansilha[18]	2018-2019	309	302	47.70 ± 12.40	17.80	26.30 ± 4.00	8.00 ± 10.20	NA	22.30	0.30	17.80	44.80	33.20	3.30	0.50	0	0	0	0-3.57 ± 2.35	0-3.57 ± 2.50

Abbreviations: BMI, body mass index; CVD, chronic venous disease; CEAP, C0: no visible or palpable signs of venous disease; C1: telangiectasias or reticular veins; C2: varicose veins; C3: edema; C4a: skin changes ascribed to venous diseases such as pigmentation and venous eczema; C4b: skin changes ascribed to venous diseases such as lipodermatosclerosis and white atrophy; C4c: corona phlebectatica; C5: healed ulcers; C6: active venous ulcer; MPFF, micronized purified flavonoid fraction.

Table 2. Primary Endpoints and Main Characteristics of the Studies Included in the Meta-Analysis.

Study	Dosing scheme of experimental group	Dosing scheme of control group	Number of patients who did not withdraw at the endpoint of the experiment		Primary endpoints	Type of study	Acronyms of trial, registration
			1000-mg once	500-mg twice			
Kirienko and Radak[22]	1000 mg tablet MPFF morning + 500 mg tablet placebo midday + 500 mg tablet placebo evening	500 mg tablet MPFF morning+500 mg tablet placebo midday + 500 mg tablet MPFF evening	84	87	Leg pain and EAE	Multi-center RCT	NA
Carpentier 2017[21]	1000 mg sachet MPFF morning + 500 mg tablet placebo midday + 500 mg tablet placebo evening	1000 mg sachet placebo morning + 500 mg tablet MPFF midday + 500 mg tablet MPFF evening	540	536	LLD and QoL	Multi-center RCT	NA
Mansilha[18]	1000 mg chewable tablet MPFF morning + 500 mg film-coated tablet placebo midday and evening	1000 mg chewable tablet placebo morning+ 500 mg film-coated tablet MPFF midday and evening	291	293	LLD	Multi-center RCT	EUDRACT No. 2017-003633-28

EAE, emergent adverse event; LLD, lower limb discomfort, defined as symptoms of uneasiness, restlessness, distress, anxiety, embarrassment, or feeling of inconvenience; MPFF, micronized purified flavonoid fraction; NA, not available; QoL, quality of life.

Table 3. Main Results of Meta-Analysis.

Outcomes	Follow-up period	studies	RR and SMD (95% CI)	p	Meta-analysis model	H, I^2, p value
Mitigation of LLD	8 weeks	3	SMD −0.019 [−0.112, 0.075]	0.696	Fixed effects	3.73, 46.3%, 0.155
QoL	8 weeks	2	SMD 0.063 [−0.034, 0.160]	0.203	Fixed effects	0.01, 0%, 0.910
AE	8 weeks	3	RR 0.981 [0.855, 1.125]	0.904	Fixed effects	0.20, 0%, 0.781
Compliance	8 weeks	2	SMD 0.049 [−0.048, 0.145]	0.321	Fixed effects	0.12, 0%, 0.726

Abbreviations: AE, adverse event; LLD, lower limb discomfort; QoL, quality of life, evaluated by Global Index Score in the 14-item electronic chronic venous insufficiency quality of life Questionnaire (eCIVIQ-14); RR, risk ratio; SMD, standardized mean difference.

0.981 [0.855, 1.125], p=0.904), and the fixed-effects model was used.

Compliance After 8 Weeks After Treatment

Two studies evaluated compliance at 8 weeks for MPFF 1000-mg versus MPFF 500-mg treatment. The results of meta-analysis in Figure 7 and Table 3 indicated that there was no significant difference in the compliance of patients between the 2 treatment methods (SMD and 95% CIs: 0.049 [0.048, 0.145], p=0.321), and the fixed-effects model was used.

Sensitivity Analysis

Sensitivity analyses were performed to determine the influence of a single study on the overall effect estimate. Because 1 study (Kirienko 2016, a total of 174 patients) with a small number of patients was included, the pooled estimates for LLD (at 8 weeks) and AEs (at 8 weeks) were recalculated and omitted 1 study at a time. The results showed that there is no single study that has had an unstable impact on the overall results (Figures 8 and 9). However, we discovered that after removing Kirienko 2016, the overall significance in the sensitivity analysis of LLD moved from being skewed toward 1000 mg (experimental group) to being biased toward 500 mg (control group). Even though there was no statistically significant difference in the overall comparison, this shows that the result of a more significant improvement of LLD alleviation in the control group was transferred by it into what did in the experimental group. The explanation for this is that, in contrast to the close to 1600 patients in the other 2 tests, there were only 174 individuals in the sample of Kirienko 2016. The data in it may have been further skewed away from the median due to the large sample size differential (even though LLD remission levels were similar in the 2 groups).

Discussion

We undertook this updated meta-analysis to investigate the outcomes associated with different dosage regimens of

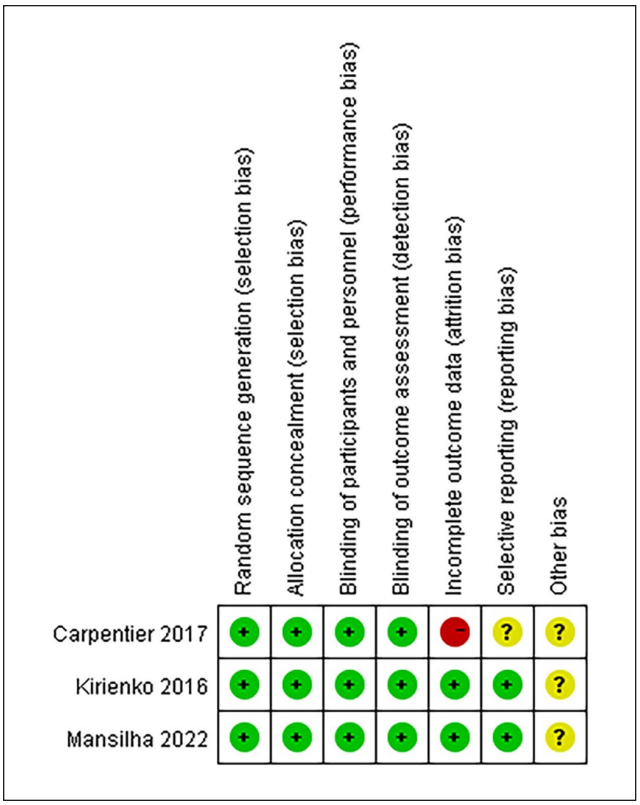


Figure 3. Result for risk of the meta-analysis bias summary.

MPFF for the treatment of patients with symptomatic CVD. The main findings are that during a follow-up of 8 weeks after starting medication, there were no statistically significant differences between the 2 different medication regimens (1000 mg once a day versus 500 mg twice a day) in terms of major outcomes such as relief of limb discomfort, improvement in QoL, adherence to medication, and incidence of AEs. It is worth noting that our work seems to be the first attempt to evaluate the effectiveness of different administration methods for MPFF.

Micronized purified flavonoid fraction (Name of product: Daflon 500 mg) is a well-known oral flavonoid that has vein-protecting and vein-promoting qualities. Historically, MPFF has been used to treat lower limb organic or idiopathic chronic venous insufficiency (CVI), which manifests as heaviness, discomfort, nocturnal spasms, acute hemorrhoids, or chronic hemorrhoids.[25] There have been reports of its use in PeVD or pelvic congestion syndrome (PCS). Various surgical, endovascular, and conservative techniques are available for treating PeVD, whereas transcatheter ovarian vein embolization is the recommended way for treating PeVD, VAD is a critical component of CVD treatment.[26,27] In a randomized investigation conducted by Simsek et al,[28] it was discovered that MPFF had a positive impact on venous tension, pelvic circulation, and pelvic symptoms in 20 young women with PCS. In a randomized placebo-controlled

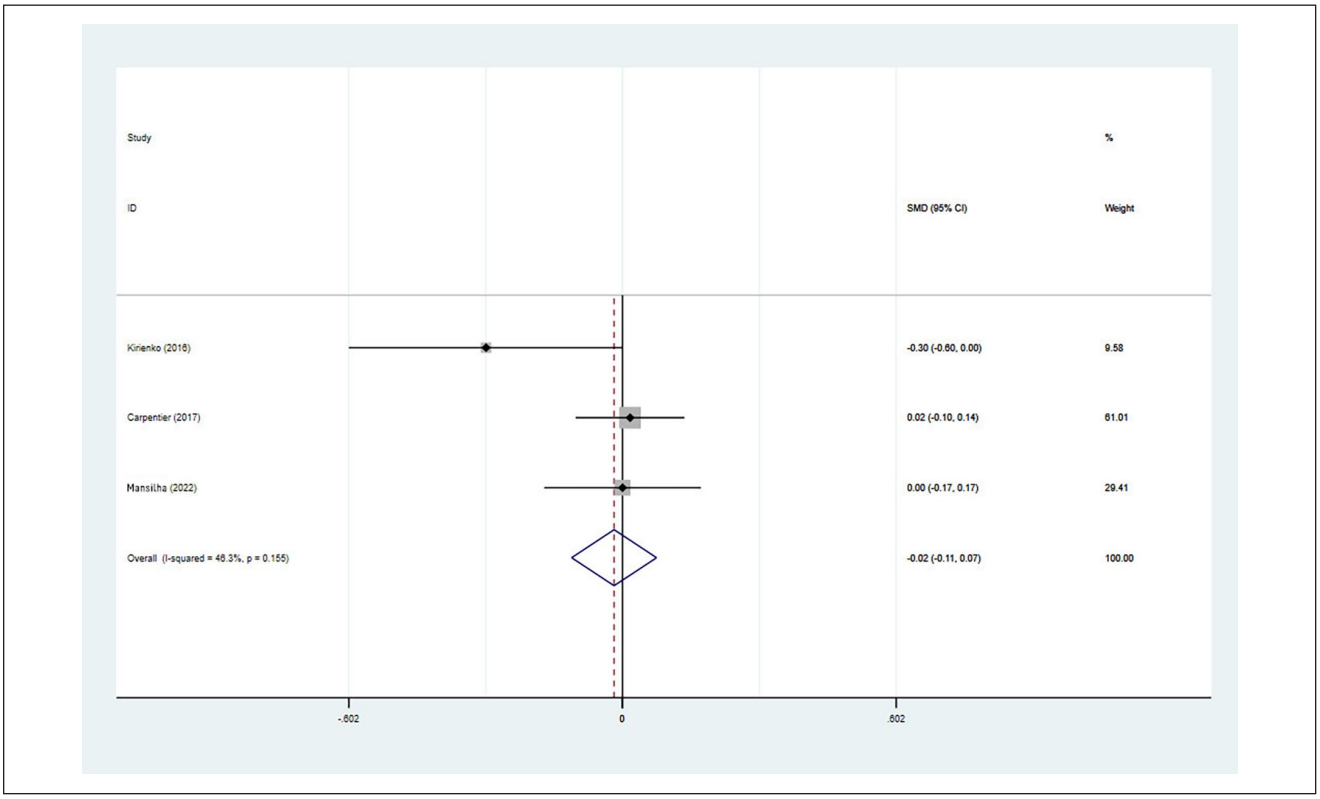


Figure 4. Eight weeks results in relief of lower limb discomfort in patients.

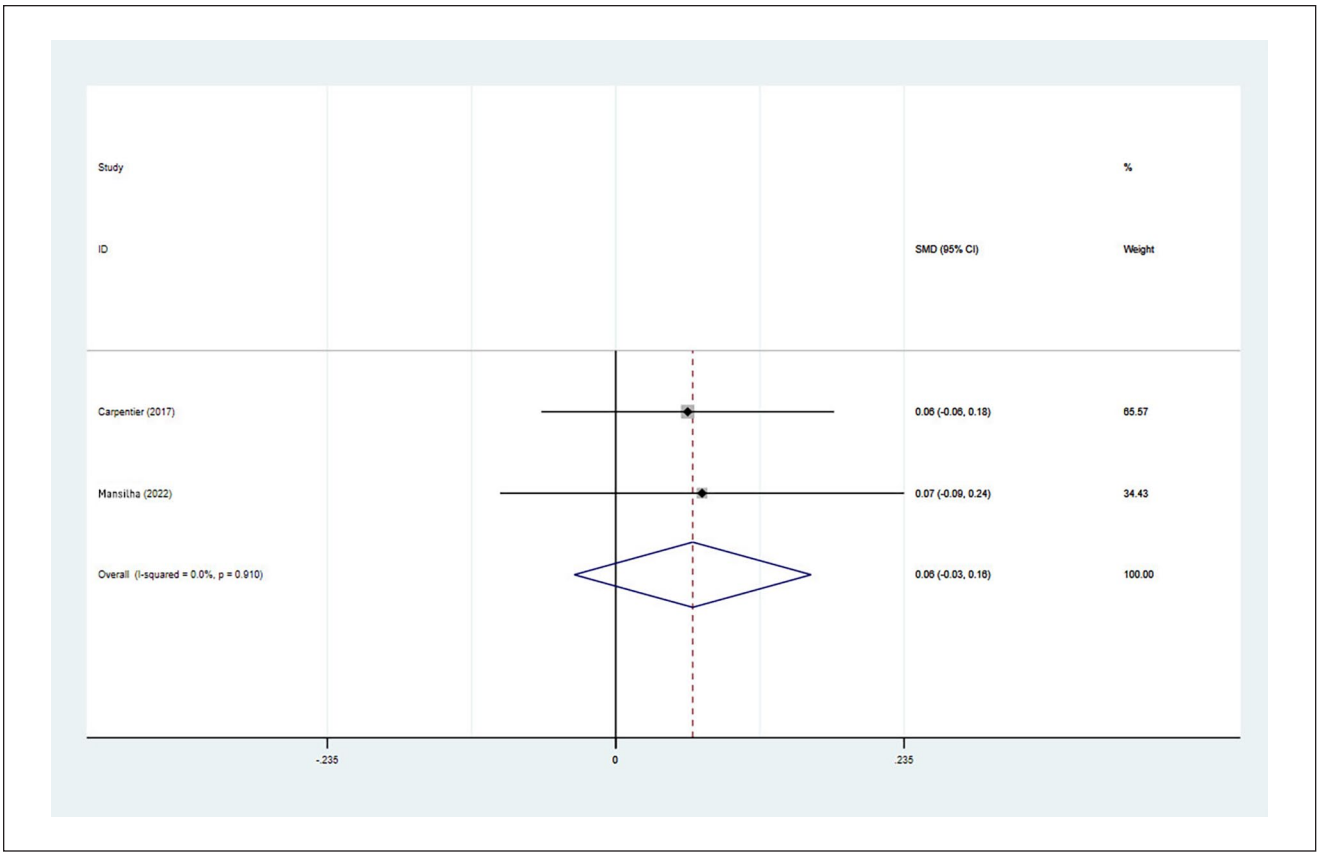


Figure 5. Eight weeks results in relief of quality of life (QoL) in patients.

trial conducted by Akhmetzianov et al,[29] it was observed that in the group receiving MPFF, the QoL index of 83 women with PCS decreased significantly from 45.1 ± 14.7 at the beginning of the treatment to 36.6 ± 10.6 at the end of the treatment. The mean change in this group was 8.2 ± 10.4. On the contrary, there was no significant change in the control group, with a mean change of −0.3 ± 4.0. The difference between the 2 groups was statistically significant ($p<0.001$). All 4 QoL parameters exhibited considerable improvement. The MPFF group exhibited a statistically significant drop in the average overall pelvic venous clinical severity score (PVCSS) score by 3.4±3.4 compared to the control group ($p<0.001$).

Furthermore, the primary constituent of MPFF, diosmin, possesses an array of biological properties such as anti-inflammatory, antioxidant, anti-diabetic, anti-hypertensive, and anti-osteoporosis actions.[30] Following oral treatment, the gut bacteria quickly change diosmin, absorbing it as its aglycone-diosmetin.[31,32] In individuals with a chronic venous illness caused by angiogenesis, MPFF can greatly inhibit inflammation by lowering the upregulation and expression of VEGF-C, VEGF-A, FGF2, and TNF-α.[33] It is well known that MPFF has very few adverse effects and a good tolerance. Furthermore, clinical investigations and animal trials have shown its safety.[34,35] The compliance of MPFF with various dosages and formulations, however, has not yet been thoroughly studied.

Prior to us, most researchers concentrated on the clinical effectiveness of MPFF and its horizontal comparison with other oral CVD medications. A randomized controlled trial's findings revealed that for the subgroup of people who developed symptoms and took MPFF (n=296), the improvement in VAS score (difference=0.5 cm) and QoL score (difference=3.1%) was significantly better than placebo after 4 months of treatment.[36] However, few studies have concentrated on the variations in the efficacy of MPFF due to certain objective factors like patient compliance and drug dosage forms. There were essentially solely post hoc and subgroup analyses of the same trial, apart from the few RCTs we included. Based on their own controlled studies, Maggioli and Carpentier performed subgroup analyses on mild patients with CEAP grade C0-C1. They discovered that the efficacy of 1000 mg MPFF once a day in mild patients was comparable to the original experiment and that it had extremely high safety. This further shows that mild patients should be encouraged to take 1000 mg MPFF.[37]

Using meta-analysis, we concentrate on synthesizing the viability and safety of these various pharmaceutical

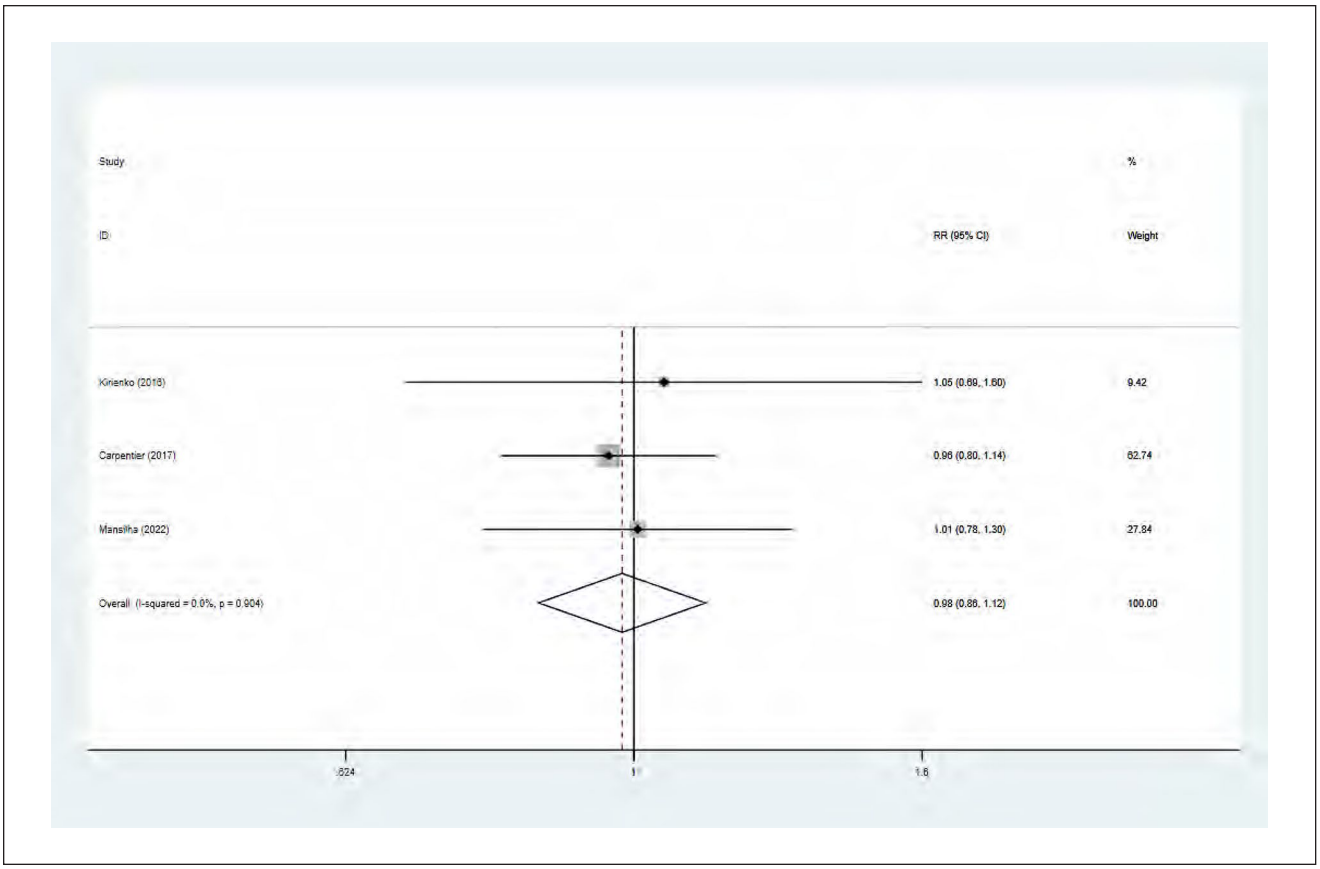


Figure 6. Eight weeks results in the occurrence of adverse events (AEs) in patients.

regimens. We think that more robust evidence will show up with additional experiments.

The clinical features of CVD change in accordance with the patient's CEAP classing. Patients with CVI (≥C4) may also experience edema, bleeding, phlebitis, and ulcers in addition to their usual symptoms of discomfort, pain, and itching in the affected limbs. Pharmacological therapy is a useful strategy for treating early patients with C1-C4 grades to reduce discomfort and edema.[38] Following MPFF treatment, Pittler and Ernst[39] found that patients' symptoms, CEAP grade, and QoL significantly improved. In their review of prior meta-analyses and experimental data, Ulloa[40] and Mansilha[41] expressed their conviction that MPFF can not only effectively relieve pain in patients with early-stage CVD but also lessen the severity of postoperative symptoms and indicators. However, there is no effective evidence to support whether MPFF is beneficial for the rehabilitation of surgical patients.

The effectiveness of MPFF in treating CVD is also promising in our analysis (whether it is 1000 mg once or 500 mg twice), which can significantly raise patients' VAS and QoL scores, in line with other authors' findings. Observations show that although MPFF is one of the most utilized VADs, Diosmin and Aescuven Forte are more commonly used in China.

The frequency of medications and patient compliance are frequently inversely proportional.[42] The duration of CVD as a chronic process makes it extremely difficult for individuals to follow their treatment regimens. Following a 1-year follow-up period, a retrospective investigation on the compliance of 6 oral drugs used to treat various chronic conditions revealed that patient medication compliance was less than ideal, with only two thirds of the medications having a median compliance of above 50%.[43] Patients with numerous chronic conditions that call for long-term care have extremely low drug adherence, according to the World Health Organization, particularly in underdeveloped and impoverished areas. Patients with venous thromboembolism who only took the drug once daily had 39–61% higher compliance than those who took the medication twice daily, according to Laliberté et al.[44] More than 20 patients who had been taking medication numerous times over a lengthy period were interviewed by Lauffenburger and colleagues, who discovered that personalization and simplification of regimens can help increase compliance.[45] The current goal of the new drug delivery systems is to further address

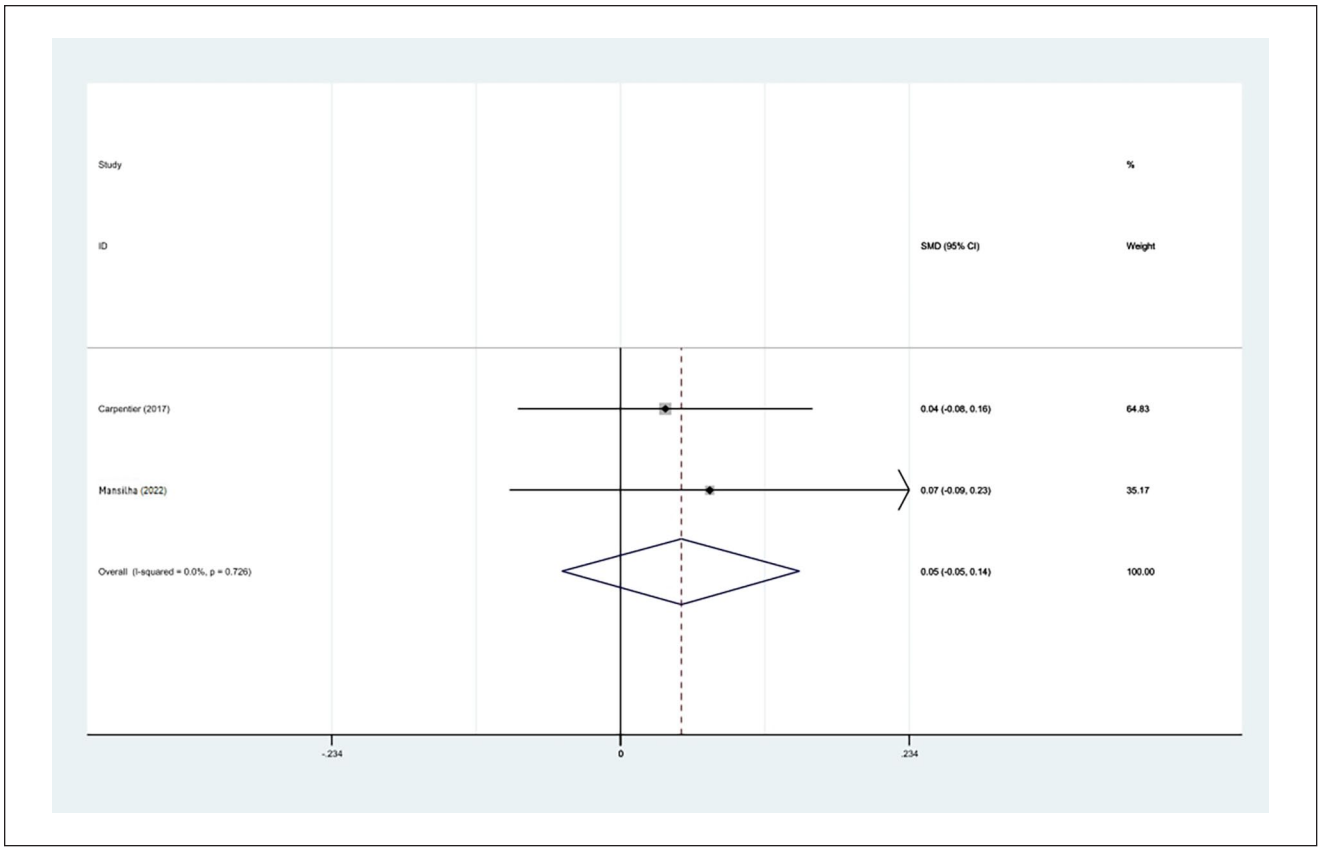


Figure 7. Eight weeks results in compliance in patients.

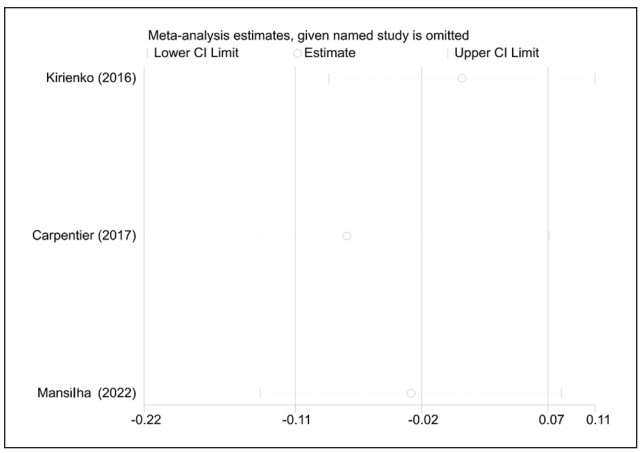


Figure 8. Sensitivity analysis of relief of lower limb discomfort in patients.

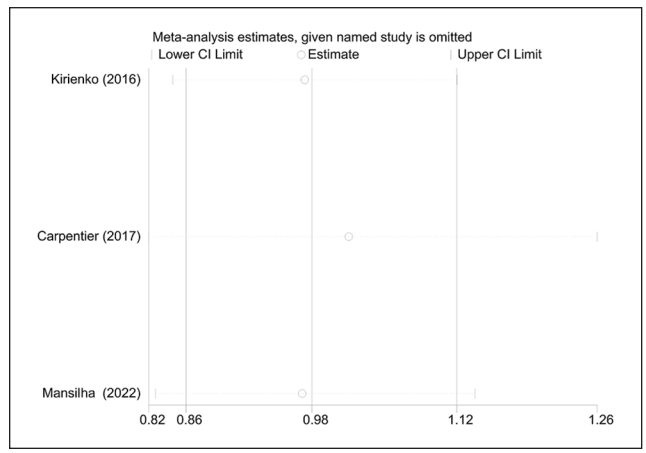


Figure 9. Sensitivity analysis of the occurrence of adverse events (AEs) in patients.

patient compliance difficulties regarding medication frequency, duration, and route of administration.[46]

According to our analysis, the patient's MPFF compliance was quite high (above 90%), which appears to go against the grain of the available research. In actuality, the study's administration duration was only 8 weeks long, significantly less than what is needed for long-term follow-up. This has several limits as well, and longer experimental cycles are required to close the evidence gap.

In this situation, it is necessary to investigate a novel approach that can improve patients' drug compliance while obtaining efficacy on par with conventional approaches.

The MPFF drug regimen (daily intake and multiple daily intake), which forms the foundation of our investigation, has attracted the attention of certain researchers. Long-term and repeated medicine is not an exception; indeed, factors including weight, smoking, and chronic conditions can all have a negative impact on a patient's adherence to treatment.[47] Therefore, to better promote this regimen among the community, we did this meta-analysis to show that once-daily dosing of 1000 mg MPFF is not inferior to or even superior to twice daily dosing of 500 mg MPFF in terms of efficacy, side effects, and compliance.

We should provide several justifications for the findings that are presented here. First, even though limited 3 RCTs were included, not all of them supplied the data we needed to analyze (e.g., only 2 studies measured QoL and compliance). Owing to the unavoidable systematic bias brought on by inadequate inclusion of studies, this further raises the risk of bias, which is something we are concerned about. In addition, all included studies only have a follow-up period of 8 weeks and do not provide findings for a longer time limit—6 months or 1 year—which could introduce bias.

Second, a 2-week run-in phase for patients following enrollment and prior to getting treatment was noted in all 3 studies. There may be a bias risk because only 1 trial (Carpentier 2017) explained that participants were given a placebo every day throughout this stage and the other 2 studies did not.

Thirdly, the administration procedures and medication dose forms used by the researchers could be biased. However, in the control group, Kirienko 2016 opted to receive 500 mg MPFF at breakfast and dinner, respectively, as a comparison, whereas the other 2 trials were given at lunch and dinner. The 3 studies included in the 1000 mg MPFF group were given during breakfast. The 3 tests also used varied dosage forms of MPFF, with Kirienko 2016 being the most popular tablet, Carpentier 2017 being a bag suspension, and Mansilha 2022 being a chewable tablet. Despite using a standard dosage form for MPFF and a comparable placebo (experimental group and control group), the authors. But since we have not yet discovered any proof that changing dose forms will affect MPFF's efficacy, there may be some bias present.

Conclusion

This meta-analysis shows that taking MPFF 1000 mg orally once daily and taking it twice daily are both effective in reducing patients' limb discomfort and improving QoL scores, but there is no significant difference; there also was no significant difference in the occurrence of AEs and patient compliance between the 2 medication regimens. To produce more trustworthy results, more RCTs with longer treatment cycles and comparisons of various dosage forms are required.

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ORCID iD

Hong-Jie Cui https://orcid.org/0000-0002-5110-2301

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