

The Efficacy and Safety of *Euphorbia Prostrata* (100 mg) Versus Micronized Purified Flavonoid Fraction (500 mg) in the Management of Bleeding Hemorrhoids: A Prospective, Observer-Blind, Randomized, Comparative Study

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Abstract

Background: Hemorrhoids are very common with a prevalence of about 50% between the age of 45 to 65 years. Bleeding and pruritus are the most typical symptoms in patients with hemorrhoids and the reason why patients seek consultation from Colo-rectal surgeons. With availability of several therapies, there is a need to find comparative effectiveness of drugs prescribed in the management of presenting signs and symptoms. **Objective:** Compare the efficacy and safety of *Euphorbia Prostrata* (EP) dry extract with micronized purified flavonoid fraction (MPFF) in patients with bleeding hemorrhoids. **Methodology:** This observer-blind, randomized, comparative study included 60 (52M, 8F) patients with grade I/II hemorrhoids were randomized to receive EP dry extract (100mg one tablet daily for 14 days), or MPFF (500 mg two tablets three times per day for four days, then two tablets twice per day for three days, and finally two tablets once per day for seven days). All patients had per-rectal bleeding and pruritus and were followed up for symptom improvement on days five, ten and fourteen. Safety was evaluated based on adverse effects reported during the study period. The two groups were compared for difference for improvement in signs and symptoms using the chi-square test. **Results:** Sixty study participants completed the study, were assessed for safety and efficacy. On day 5, significantly greater number (55.3%) patients in EP group reported an average reduction (31-50%) in the amount of bleeding as compared to only 13.3% in MPFF group ($p=0.001$). On day 10 and 14, 36.7% and 100.0% patients in EP group respectively showed excellent reduction (71-100%) in bleeding as compared to 16.7% (day 10), 89.6% (day 14) in MPFF. However, these differences were non-significant ($p=0.291$ and 0.261 for day 10 and day 14 respectively). Complete improvement in pruritus was seen in 56.7% and 93.3% patients with EP, whereas with MPFF recovery was seen in 43.3% and 80.0% patients on days 5 and 10 respectively ($p>0.05$). None of the patients reported pruritus on day 14. No adverse effects were reported in the study. **Conclusion:** Oral administration of *Euphorbia Prostrata* dry extract provides significantly earlier and greater improvement in bleeding and pruritus as compared to micronized purified flavonoid fraction in patients with hemorrhoids.

Keywords: Euphorbia Prostrata, Micronized Purified Flavonoid Fraction, Hemorrhoids

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Introduction

Hemorrhoids or piles is a common condition that directs patients to go for consultation with a colon or rectal surgeon [1]. Its prevalence is high, with experts projecting that approximately 50% of the population would have hemorrhoids at some point in their life probably by the time they reach the age of 50 years, and not less than 5% would suffer from it at some point in their life [2]. Hemorrhoids being a multi-factorial condition makes it difficult to explain the pathophysiology in detail. From what we understand, sliding anal cushions, hyper perfusion of plexus, vascular abnormality, tissue inflammation, or internal rectal prolapse are the main pathological changes that takes place [3].

Patients usually visit the clinic with a major symptom of per-rectal bleeding followed by pain, pruritis, fecal seepage, prolapse, and

mucus discharge that is often debilitating and lowers the quality of life to a great extent [4] In internal hemorrhoids, bleeding is one of the most commonly problem, where blood occurs in bright red color and coats the stool at the end of defecation [5].

Flavonoids as a compound have shown promising result in increasing vascular tone, reducing venous capacity, decreasing capillary permeability, and facilitating lymphatic drainage [6,7]. These properties can help in the effective management and control of hemorrhoids. *Euphorbia Prostrata* (EP) dry extract contains flavonoids (Apigenin, Apigenin-7 glucoside, Luteolin and Luteolin-7 glucoside), phenolic compounds (Ellagic and Gallic acids) and tannins. EP has a proven hemostatic, anti-inflammatory, analgesic, antioxidant, anti-thrombotic, vasoprotective and astringent activities, and hence, is effective in the management of hemorrhoids [8]. Micronized Purified Flavonoid Fraction (MPFF) (Diosmin

and Hesperidin) has anti-inflammatory, antioxidant, and venoprotective actions [9]. Both of these drugs are commonly used in the management of hemorrhoids; wherein bleeding is one of the major complications requiring immediate attention. Thus, the objective of the study was to examine and compare the effectiveness and safety of *Euphorbia Prostrata* (EP) (100 mg) with Micronized Purified Flavonoid Fraction (MPFF) (500 mg) in the early stages of improvement of signs and symptoms for first 14 days from the onset of bleeding in hemorrhoids.

Methodology

Study design and setting

A Prospective, observer-blind, randomized comparative study carried out at general surgery department, Karnataka Lingayat Education Society (KLES) Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, Karnataka, India. Prior to enrolment, all patients provided written informed consent to participate in the study. The study protocol was approved by the Institutional Ethics and Research Committee, Jawaharlal Nehru Medical College, Belgaum, Karnataka, India. Following the principles of Good Clinical Practice (GCP), the study was carried out ethically.

According to the eligibility requirements for the study, sixty patients with grade-I and grade-II bleeding hemorrhoids between the ages of 19 and 75 were of either gender. Patients who had any aberrant findings on their vital signs or during a physical examination were not included in the study. Additional exclusions were nursing or pregnant women, patients who were already taking other medications or had undergone any type of surgical procedure to treat their hemorrhoids and associated anal fissure and/or infective anal pathology. A detailed medical history was obtained for each patient followed by a physical examination. Patients were assessed for bleeding per rectum and graded as blood-stained stools, slow flow of blood, drops of blood, or jet, as reported by them. Patients were subjected to proctoscopy examination to confirm the diagnosis and to assess the characteristics of bleeding hemorrhoids such as grade, position, and congestion.

Study medication were pre-packed in closed coded containers and patients in EP group were administered with one EP 100 mg tablet (Tablet Sitcom, manufactured by Panacea Biotec Ltd., India) once daily for 14 days, while MPFF group patients were administered with two tablets of MPFF 500 mg (Tab. Daflon, manufactured by Serdia Pharmaceuticals India Pvt. Ltd., India) three times per day for four days, then two tablets twice per day for three days, and finally two tablets once per day for seven days. Follow up assessments were done on days five, ten and fourteen. On follow-up, patients were assessed for per rectum bleeding and the end point of the study was determined as complete cessation of bleeding. The improvement in the bleeding severity during follow-up period was graded as excellent reduction (71 to 100%), good reduction (51 to 70%), average reduction (31 to 50%), and poor reduction (30% or less) reduction in bleeding. Patients were also assessed for presence/absence of pruritis during all visits. Clinical safety was evaluated based on the adverse effects reported by patients during the study period.

Statistical analysis

The data was expressed as numbers with percentages and comparisons between the two groups were analyzed using the chi-square test (χ^2 test). Continuous data was expressed as means with standard deviation (SD), and between group comparisons were done using two independent-sample 't' test. A 'p' value of ≤ 0.05

was considered as statistically significant.

Results

All 60 participants finished the study in accordance with the protocol and were included in the effectiveness and safety analyses.

Demography and profile of patients:

Table 1 and Figure 1 shows the demographics and distribution of patients participating in the study. Bleeding was reported by all the patients at baseline. The mean (SD) duration of bleeding in EP group was 14.6 (5.41) days compared to 12.4 (4.89) days in MPFF group ($p > 0.05$).

Rectal bleeding

Table 2 shows the number of patients along with reduction in amount of rectal bleeding after treatment with the EP group as compared to the MPFF group.

Pruritus

A total of 30 patients had complained of pruritis on the day of screening. Table 3 shows patients reporting pruritis at baseline and follow-up visits.

Clinical safety

None of the patients experienced any adverse effect during the study duration.

Discussion

Patients with hemorrhoids most frequently report bleeding as the presenting complaint, followed by pain, swelling, pruritis and congestion. From a pathological perspective, hemorrhoids cause vasodilatation, thrombosis, collagen fiber degeneration, and distortion associated with rupture of the anal sub-epithelial muscles [7]. Inflammatory reaction involving both the vascular part i.e., sinusoidal wall and the non-vascular part i.e., supportive tissue has been observed in hemorrhoids. The inflammatory process renders the blood vessels prone to erosion during defecation which results in hemorrhage. This bleeding presents as oozing when tiny arterioles of the lamina propria are eroded and as spurting when small arterioles are corroded [10]. The mucus discharge associated with prolapse causes itching and irritation [11]. Also, all these symptoms contribute to mental anguish and anxiety in patients that lowers their quality of life.

The treatment of hemorrhoids can vary to a great extent depending on its grade. But something that requires our utmost attention is the management of acute symptoms of hemorrhoids as it is responsible for bleeding, itching, irritation, and discomfort for the patient. The role of flavonoids comes into picture here as it has potent phlebotonic action [12].

In this study, it was found that on Day 5 of the follow-up, considerably more patients in the EP group (53.33%) than in the MPFF group (13.33%) showed an average reduction in the amount of bleeding. The number of patients in the EP group who had excellent bleeding decreased on Days 10 and 14 was higher than in the MPFF group. Hence, it shows that treatment with EP has significantly resulted in faster recovery from bleeding. However, the findings on day 10 and 14 were statistically non-significant. When we analyze the effect on pruritis, we find that the symptomatic relief is comparable in both the groups. Absence of adverse effects also points to the safety of this compound to the patients who require this for acute relief from symptoms. Patients

Table 1: Demographics and distribution of patients

Variables	EP (n=30)	MPFF (n=30)	P-value
	<i>Mean ± SD</i>	<i>Mean ± SD</i>	<i>(t- test)</i>
Age	39.60 ± 6.25	43.4 ± 10.11	0.092
• Pulse rate (bpm)	78.9 ± 2.91	77.5 ± 3.58	0.102
• Systolic BP (mm Hg)	117.4 ± 4.78	116.2 ± 8.45	0.502
• Diastolic BP (mm Hg)	76.8 ± 4.02	77.2 ± 5.25	0.750
	<i>No. (%)</i>	<i>No. (%)</i>	<i>Chi-square test</i>
Sex			
• Male	24 (80 %)	28 (93.33 %)	0.255
• Female	6 (20 %)	2 (6.67 %)	
Grade of Hemorrhoids			
Grade I	7 (23.33 %)	8 (26.67 %)	0.561
Grade II	23 (76.67 %)	22 (73.33 %)	
Duration of Bleeding			
• Up to 7 days	5 (16.67 %)	11 (36.67 %)	0.109
• 8 to 14	13 (43.33 %)	10 (33.33 %)	
• 15 to 21	10 (33.33 %)	9 (30.00 %)	
• > 21	2 (6.67 %)	0 (0.0 %)	
Bleeding (Volume)			
• Blood-stained stools	15 (50 %)	17 (56.67 %)	0.754
• Slow flow of blood	5 (16.67 %)	4 (13.33 %)	
• 5 drops	6 (20.00 %)	3 (10.00 %)	
• 10 drops	2 (6.67 %)	2 (6.67 %)	
• 15 drops	2 (6.67 %)	4 (13.33 %)	

SD: Standard Deviation, EP: Euphorbia Prostrata, MPFF: Micronized Purified Flavonoid Fraction, BP: Blood pressure, bpm: beats per minute

Table 2: Number (%) of patients with improvement in rectal bleeding

	Bleeding reduction	EP (n=30)		MPFF (n=30)		'p' (χ^2 test)
		No.	%	No.	%	
Day 5	Excellent	0	-	0	-	0.001
	Good	0	-	0	-	
	Average	16	53.3%	4	13.3%	
	Poor	14	46.7%	26	86.7%	
Day 10	Excellent	11	36.7%	5	16.7%	0.291
	Good	9	30.0%	11	36.7%	
	Average	10	33.3%	13	43.3%	
	Poor	0	-	1	3.3%	
Day 14	Excellent	30	100.0%	26	89.7	0.131
	Good	0	-	4	13.3	
	Average	0	-	0	-	
	Poor	0	-	0	-	

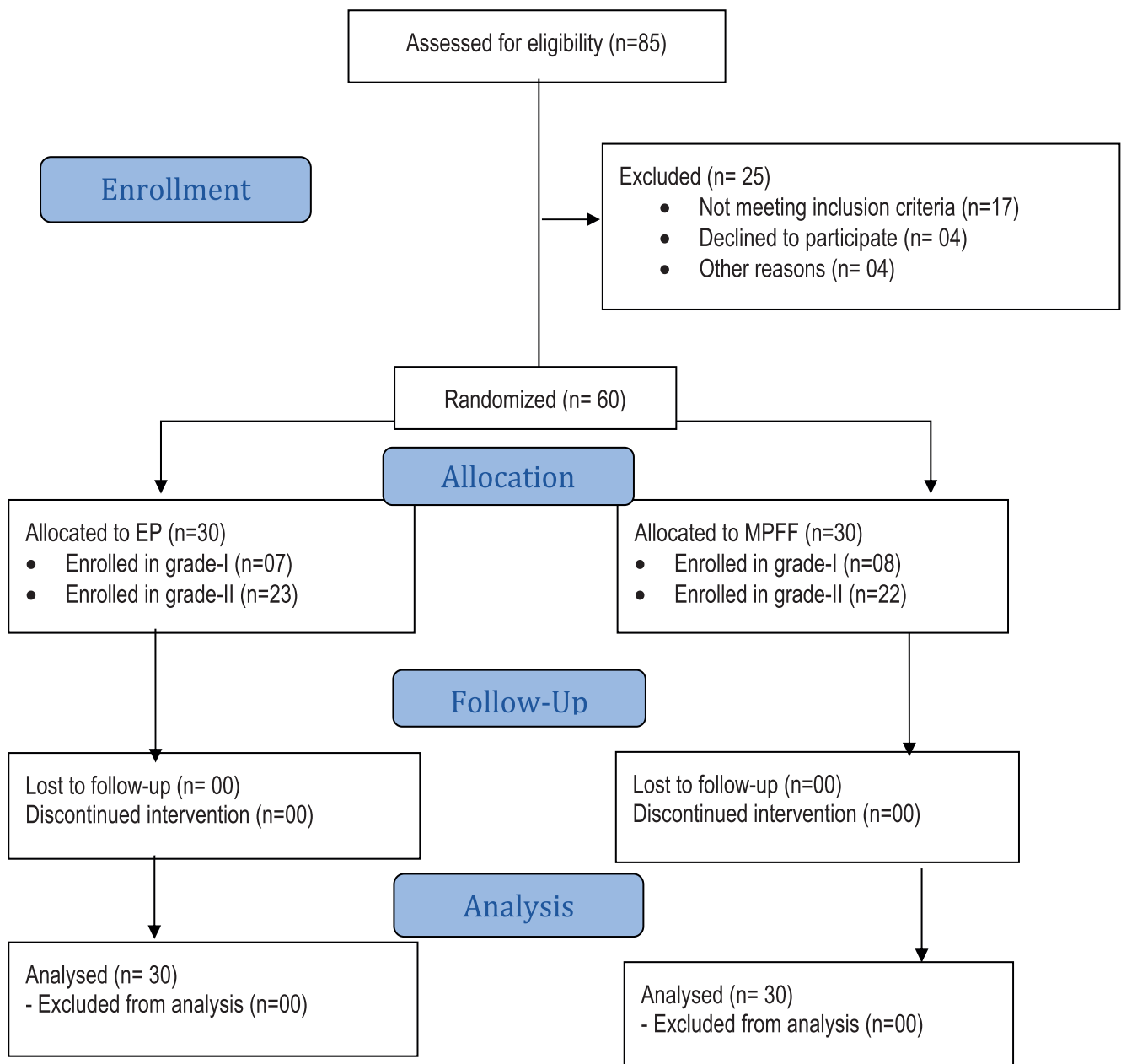


Figure 1: Flow Diagram of Patient Recruitment, Randomization and Follow-up.

Table 3: Number of patients with pruritis

	EP (n=30)		MPFF (n=30)		'p' ^{**} (χ^2 test)
	No.	%	No.	%	
Baseline	30	-	30	-	-
Day 5	13	43.33	17	56.67	0.302
Day 10	2	6.67	6	20.00	0.255
Day 14	0	0.00	0	0.00	1.000

in the EP group have to consume lesser number of tablets as compared to the MPFF group which could be a major factor leading to better compliance in them in a real-life setting, while MPFF have a high pill burden with low patient compliance.

This finding is like what has been shown in studies conducted before. A retrospective study by P.J. Gupta reported 82% of the patients had complete cessation of bleeding and pruritis was relieved in 73% of them at the end of two weeks. This study concluded that EP can be used as an effective and well-tolerated pharmaceutical agent in the treatment of early grades of hemorrhoids [13]. In another prospective, open-label, single arm, post marketing study, at day 3 bleeding was reported in 41% (n=752) of patients as compared to 89.3% (n=1640) at the baseline (p<0.0001), while at day 14 bleeding was reported only by 3.9% of these patients (p<0.0001) [14]. Hence, EP has shown significant early recovery and complete cessation of bleeding and pruritis in hemorrhoids patients.

The most important strength of this study is the comparative study design with blinded observer. Small sample size comes out to be one of the main limitations. This study can add to the pool of evidence we already have that has proven the efficacy of EP extract in achieving symptomatic relief in patients with hemorrhoids. Further studies with large sample size and for longer duration need to be conducted in comparison to the standard anti-hemorrhoidal therapy to get more information about long term impact of this treatment.

Conclusion

Euphorbia Prostrata (EP) 100 mg has shown significantly faster recovery from bleeding in patients with grade I/II hemorrhoids as compared to Micronized purified flavonoid fraction (MPFF) 500 mg. *Euphorbia Prostrata* also shows recovery from pruritis in all patients. EP extract at 100 mg dose with its anti-inflammatory, hemostatic, vasoprotective, analgesic, antioxidant, wound healing and astringent properties has hence proven to be an effective method to gain symptomatic relief in patients with hemorrhoids. With the benefit of patients having to consume a lesser number of tablets i.e., reduced pill burden, we can expect better patient compliance and outcomes.

Known About Subject

Hemorrhoid is the most common problem where in the patients visits clinician mostly with profound bleeding. Out of the drugs available in the market *Euphorbia Prostrata* & Micronized Purified Flavonoid Fraction are the most commonly used oral drugs in bleeding hemorrhoids and till date no head to head comparison have been done on these drugs in management of Hemorrhoids.

Study Literature

Study performed provides information on comparison in terms of efficacy and safety between the two most used drugs *Euphorbia Prostrata* & Micronized Purified Flavonoid Fraction in cessation of bleeding during Hemorrhoids.

Implication

The implications of results showed that *Euphorbia Prostrata* caused faster resolution of bleeding as compared to Micronized Purified Flavonoid Fraction. Which may provide directions for appropriate management of bleeding Hemorrhoids.

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Ethics:	There is no ethical violation as it is based on voluntary anonymous interviews
Funding:	No external funding
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