

Prospective, Open Label Study of Euphorbia Prostrata Extract 100 mg in the Treatment of Bleeding Haemorrhoids

Girish D Bakhshi*, Deepak G Langade**, Vidyadhar S Desai***

Abstract

Background: Haemorrhoidal disease is a common entity in the general population and usually associated with bleeding. Surgical techniques available for the treatment are associated with discomfort, hospital stay and some complications. So there is need for effective pharmacological treatment of bleeding haemorrhoids.

Objective: This study was done to evaluate the safety and efficacy of Euphorbia Prostrata dry extract in the treatment of bleeding haemorrhoids.

Methods: In this prospective, open label, single arm, post marketing study, a total of 1836 patients of bleeding haemorrhoids were given Euphorbia Prostrata dry extract 100 mg tablets for 14 days. Their symptoms like bleeding, pain, congestion, pruritus and prolapse were assessed during and at the end of study. Global assessment on a scale of 4 points was done by investigator and patient at the end of the study.

Results: At the end of the study, Bleeding was reported by 71 patients (3.9%) as compared to 1640 (89.3%) at the baseline ($p < 0.0001$). pain was reported by 86 patients (4.7%) as compared to 1470 (80.1%) at the baseline ($p < 0.0001$). Swelling was reported by 114 patients (6.2%) as compared to 1109 (60.4%) at the baseline ($p < 0.0001$). Congestion was reported by 77 patients (4.2%) as compared to 879 (47.9%) at the baseline ($p < 0.0001$). Global Assessment by the physician at the end of therapy showed total improvement in 505 patients (27.7%), moderate improvement in 1153 patients (63.2%). Global Assessment by the patient at the end of therapy showed total improvement in 501 patients (27.5%), moderate improvement in 1160 patients (63.6%).

Conclusion: Euphorbia Prostrata dry extract 100 mg tablets, given for 14 days in bleeding haemorrhoids patients showed maximum improvement during first 3 days of therapy and achieved total improvement in significant number of patients at the end of therapy.

Introduction

Haemorrhoidal disease is a common entity in the general population and in clinical

practice. In a study conducted in northern India, the reported prevalence of haemorrhoids as high as 17%, in the elderly population.¹ It affects male and female equally.²

They commonly occur in patients with chronic increased intra-abdominal pressure such as in chronic obstructive airway disease and in pregnancy. Symptoms of haemorrhoids include bleeding, mucosal or faecal soiling, itching and, occasionally, pain, which, if left

*Associate Professor, Dept. of Surgery, Grant Medical College and Sir J.J.Group of Hospitals, Byculla, Mumbai. **Associate Professor in Pharmacology, SUT Academy of Medical Sciences Vattapara, Thiruvananthapuram, Kerala.***Head – Strategic Medical Affairs, Panacea Biotec Ltd.7th Floor, Sagar Tech Plaza “A”, Sakinaka, Andheri (E), Mumbai 400 072.

untreated, continue to cause physical and social problems to patients.³

The basic pathological factor in haemorrhoids is the dilation of the anorectal venous plexuses. In the acute bleeding of internal haemorrhoids, one of the pathogenic processes implicated is the stagnation and stasis of blood in the vascular plexuses of the prolapsed anal cushions. It has also been demonstrated that stasis activates white blood cells to release inflammatory mediators and cause an inflammatory response leading to increased permeability, fragility and necrosis of the vessel wall. The anal cushions are therefore easily injured by the passage of stool and bleed.⁴

Numerous modalities and techniques have been developed to treat symptomatic haemorrhoids. Second and third degree haemorrhoids can be treated conveniently on an outpatient basis by means of sclerotherapy, photocoagulation, cryotherapy and rubber band ligation, while severe prolapsed or circumferential haemorrhoids can be treated using the Milligan-Morgan haemorrhoidectomy or stapled haemorrhoidectomy.⁵ But pain and discomfort, anal narrowing, tags, haemorrhage, faecal incontinence and residual piles are reported complications of surgical procedures.⁶ Therefore, any pharmacological agent leading to effective and rapid non-invasive control of signs and symptoms is of immense clinical value.

Euphorbia prostrata is a small prostrate, hispidly pubescent annual herb found all over India. This plant has traditionally been used to treat several ailments since time immemorial. The active principles in Euphorbia prostrata are chiefly flavonoids, phenolic acid and tannins. Flavonoids and phenolic acid have been reported to have anti-inflammatory, analgesic, antioxidant, haemostatic, antithrombotic and

vasoprotective actions. Tannins are known to possess astringent and haemostatic properties. Preclinical studies carried out on the extract have confirmed its wound healing and anti-haemorrhoidal activity.⁷⁻¹⁸

Euphorbia Prostrata dry extract is indicated for the treatment of bleeding haemorrhoids. Hence, this study was planned to evaluate safety and efficacy of Euphorbia Prostrata dry extract in the treatment of bleeding haemorrhoids.

Objectives

Primary objective of the study was to study efficacy of Euphorbia Prostrata dry extract in bleeding haemorrhoids patients, which was assessed by improvement of symptoms and signs like pain, pruritus, swelling, congestion and prolapse. Secondary objective was to study the safety of tablets which was assessed by monitoring of adverse events throughout the study.

Methods

This study was a prospective, open label, single arm, post-marketing study to evaluate safety and efficacy of Euphorbia Prostrata in the patients with bleeding haemorrhoids. About 478 surgeons and clinicians participated in the study at their respective clinics/hospitals and a total of 1836 patients were enrolled. Voluntary, written, informed consent was obtained from all patients prior to enrolment.

Patients

Patients of either sex between the ages of 12 and 75 years, who were diagnosed to have bleeding haemorrhoids, and had no abnormalities on physical examination and vital parameters, were included in the study. Pregnant and lactating women were excluded and females of child bearing potential who consented to use reliable measures of birth control were included. Patients who were

using other drugs or any surgical procedure for haemorrhoids were excluded. Patients who had given the history of or suggested the presence of any significant cardiac, gastro-intestinal, endocrine, neurological, liver, kidney or psychological disease were also excluded. Patients who were drug or alcohol dependent or having any clinically significant illness four weeks prior to the screening were excluded. Patients participating in any other clinical trial or using any other investigational drug within 30 days prior to the screening were also excluded.

Procedures

On the first visit (V1-Screening and enrolment), patients of bleeding haemorrhoids who were willing to participate in the study and provided informed consent, were allotted site specific subject study number. Medical history was recorded for each patient and full physical examination including height, weight, vital signs (blood pressure, pulse rate, temperature, and respiratory rate) was done. Vital signs were obtained after the subject was in supine position for 5 minutes. Tablets containing 100 mg Euphorbia Prostrata dry extract were dispensed to each subject and were advised to take 1 tablet daily for 14 days. Subjects were advised to return on day 3, 7 and 14; and also if they had any problem or their condition deteriorated.

On the next two visits (V2 and V3) i.e. on day 3 and day 7 of the study respectively, information about the general well being and adverse events (AE), if any were recorded. Investigator assessed the local symptoms in anal region like bleeding, pain, pruritus, swelling, congestion and prolapse at each visit.

On the last visit (V4) i.e. day 14 of the study, in addition to the assessment of AEs, global assessment was made by the investigator and the patient on a four-point

scale of '0' : no improvement, '1' : mild improvement, '2' : moderate improvement, and '3' : total improvement in sign and symptoms.

Statistical Analysis

Data is expressed as mean with Standard Deviation (S.D.) and numbers (No.) and percentages (%). Chi-Square test was applied for patients showing improvement /cure after therapy. Non-parametric data was analyzed using Wilcoxon Sign Rank Test (within group comparisons). For all statistical tests, the significance level is taken as $p < 0.05$.

Results

A total of 1836 patients of bleeding haemorrhoids were involved in the trial. There were no dropouts throughout the trial period. Mean age of the patients was 43.43 years (range, 14-90 years). Demographic data of the patients is shown in Table 1.

Mean duration of the symptoms for all the patients was 1.08 years (range, 3 days to 25 years). Bleeding was the most frequent complaint at the presentation (n=1640, 89%) followed by pain (n=1470, 80%). Other

Table 1 : Demographic data of the patients enrolled in the study

	No. of pts.	% of pts.
Gender (n=1816)		
• Male	1304	71.8
• Female	512	28.2
Type of Piles (n=105)		
• Internal Piles	74	70.5
• External Piles	22	21.0
• Internal + External Piles	9	8.6
Location of Piles (n=180)		
• 1 'O' Clock	7	3.9
• 3 'O' Clock	106	58.9
• 7 'O' Clock	103	57.2
• 11 'O' Clock	98	54.4

symptoms were swelling, congestion, pruritus and prolapse.

On the day 3 of the study, all of the symptoms were reduced in significant number of patients. Bleeding was reported in 41% (n = 752) of patients as compared to 89% (n = 1640) at the baseline (p < 0.0001). Pain was reported in 34.9% (n = 640) as compared to 80.1% (n = 1470) at the baseline (p < 0.0001). Likewise all the symptoms were reduced in most of the patients (Figs. 1-3).

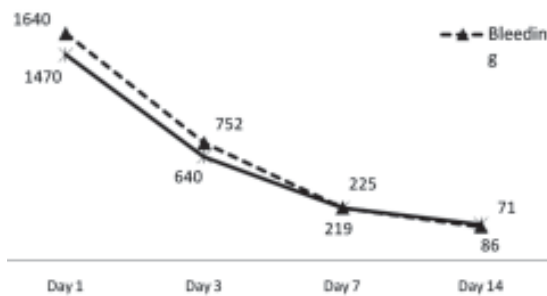


Fig. 1 : No. of patients with bleeding and pain.

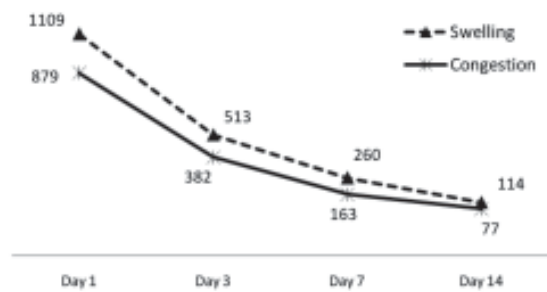


Fig. 2 : No. of swelling and congestion.

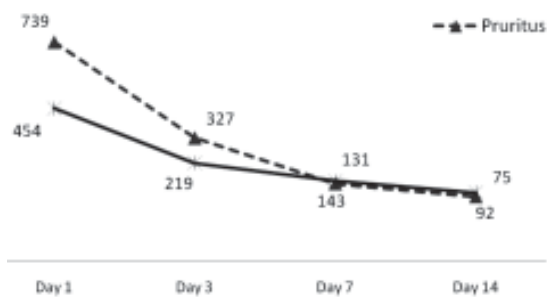


Fig. 3 : No. of patients with pruritus and prolapse.

At the completion of the study i.e. on day 14, Bleeding was reported by 71 patients (3.9%) as compared to 1640 (89.3%) at the baseline (p < 0.0001). Pain was reported by 86 patients (4.7%) as compared to 1470 (80.1%) at the baseline (p < 0.0001). swelling was reported by 114 patients (6.2%) as compared to 1109 (60.4%) at the baseline (p < 0.0001). Congestion was reported by 77 patients (4.2%) as compared to 879 (47.9%) at the baseline (p < 0.0001) (Figs. 1-3).

Global Assessment by the physician at the end of therapy showed total improvement in 505 patients (27.7%), moderate improvement in 1153 patients (63.2%) and mild improvement in 150 patients (8.2%). Only 17 patients (0.9%) showed no improvement at all (Fig.4).

Global Assessment by the patient at the end of therapy showed total improvement in 501 patients (27.5%), moderate improvement in 1160 patients (63.6%) and mild improvement in 146 patients (8.0%). Only 18 patients (1.0%) showed no improvement at all.

77 patients reported adverse events and total number of adverse events were 95. Of those, heart burn was the most frequent (25, 1.4%) followed by GI discomfort (17, 0.9%) and nausea (11, 0.6%) (Table 2).

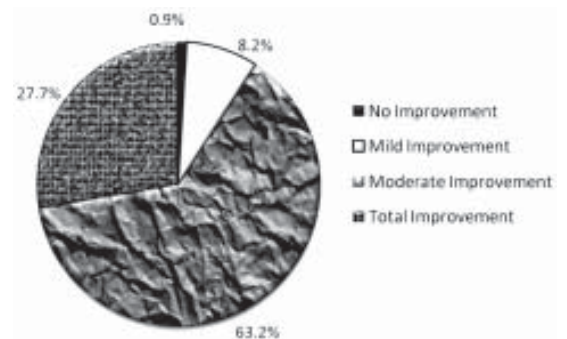


Fig. 4 : Global Assessment by Physician (% of patients).

Table 2 : Adverse events

Adverse Event	No. of Patients	% of Patients
Heartburn	25	1.4
GI Discomfort	17	0.9
Nausea	11	0.6
Headache	9	0.5
Diarrhoea	6	0.3
Dry Mouth	5	0.3
Vomiting	4	0.2
Giddiness	3	0.2
Pain	3	0.2
Constipation	2	0.1
Pruritus	2	0.1
Anorexia	1	0.1
Arrhythmia	1	0.1
Bleeding	1	0.1
Fever	1	0.1
Hiccough	1	0.1
Local Itching	1	0.1
Flushing	1	0.1
Palpitations	1	0.1

Discussion

In this study conducted by 476 investigators and enrolling 1836 patients, Euphorbia Prostrata dry extract 100 mg tablets were given to patients of bleeding hemorrhoids for 14 days. At the end of the study, it was found that symptoms of patients such as bleeding, pain, itching and prolapse were significantly reduced as compared to baseline.

According to Indian Folklore, the Euphorbia prostrata has anti-inflammatory properties and is also considered a blood purifier.⁷ Euphorbia prostrata is documented in the ancient medical science of India or Ayurveda for its various properties like in bronchial asthma.⁸

The active principles in Euphorbia prostrata are chiefly flavonoids (apigenin -7-glucoside, luteolin-7-glucoside), phenolic acid and tannins. Apigenin is a most potent

inhibitor of transcriptional activation of both COX-2 and iNOS enzyme in lipopolysaccharide activated RAW 264.7 macrophages. Such type of modulation of COX-2 and iNOS by apigenin may be important in the prevention of carcinogenesis and inflammation.⁹ Cholbi *et al*, reported that luteolin inhibits protein tyrosin phosphorylation, nuclear factor- κ B mediated gene expression and pro-inflammatory cytokine production in murine macrophages.¹⁰ Singla and Pathak also reported anti-inflammatory effects of Euphorbia prostrata in carrageenan, histamine, and bradykinin-induced pedal inflammation.¹¹ These flavonoids are well reported for analgesic, anti-inflammatory, antioxidant, antiangiogenic, anti-allergic, antiviral and antimutagenic activity.¹²⁻¹⁵ Ellagic acid is one of the major constituents of Euphorbia prostrata dry extract also reported to suppress histamine release mediated by histamine liberators (compound 48/80, dextran and polymyxin B sulphate) in vivo.¹⁶ Phenolic acids are reported to activate intrinsic blood coagulation by activation of Hageman factor and cause a state of hypercoagulability. Although the hypercoagulable state persists for as long as 4 hours after IV administration but no thrombotic phenomena has been reported.¹⁷ Tannins, a time tested astringent, toughens the mucosa by precipitating the surface proteins and has been used in bleeding haemorrhoids as suppositories due to its haemostatic properties.¹⁸

In a retrospective analysis, Euphorbia prostrata extract was administered in humans in the form of capsules and cream, over a period of 26 years (1970-1996) in approximately 32,000 patients of bleeding haemorrhoids and anal fissures.¹⁹ Retrospective analysis of the data generated from this population reveals that use of

Euphorbia prostrata provides excellent relief in symptoms like bleeding per rectum, pruritus, anal pain and discomfort. Overall, the product was well tolerated and the side effects, primarily gastrointestinal, were mild in intensity and transient in nature. In another study conducted by Arora *et al.*,²⁰ a total of 125 patients with first and second degree haemorrhoids were enrolled in a 10-day trial to determine the optimal dose, efficacy, safety and tolerability of the capsule formulation (50 mg and 100 mg) of Euphorbia prostrata extract. The reduction in signs and symptoms of acute haemorrhoidal attack (viz. bleeding, anal discomfort, anal discharge, pain at prolapse and proctitis) at day 10 was found to be significantly greater with 50 mg or 100 mg capsules as compared to placebo. A phase III trial across India,²¹ evaluated the efficacy of Euphorbia prostrata Dry Extract (100 mg tablets) in the treatment of internal haemorrhoids in first and second degree haemorrhoids. A total of 120 patients were enrolled in the trial and achievement of cessation of per rectal bleeding was assessed at the 14th day. There was a statistically ($p < 0.001$) and clinically significant improvement in cessation of bleeding from the baseline to the end of the therapy.

Beneficial effects of the Euphorbia prostrata in haemorrhoids have multiple mechanisms and are due to its active constituent flavonoids, tannins and phenolic acid.

Conclusion

Based on these findings it can be concluded that Euphorbia prostrata Dry Extract 100 mg tablets are effective and well tolerated in the treatment of bleeding haemorrhoids.

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