Original Research Article

Evaluation of Hilo® versus Daflon® in patients suffering from hemorrhoids: A randomized, controlled, open-labelled, multicentric study

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ABSTRACT

Aims: To evaluate and compare the efficacy of Hilo® and Daflon® 500 mg, in the treatment of hemorrhoids.
Study design: It is a multicentric, randomized, comparative clinical trial conducted for the period of 15 days.
Place and Duration of Study: Janta Hospital and Maternity Centre, Varanasi; King George Memorial Hospital, Lucknow; Vijan Hospital and Research Centre, Nasik and Santosh Hospital, Bangalore between May 2018 and December 2019.
Methodology: 201 patients were screened and 200 patients with hemorrhoids (proctoscopy proven Grade I to III) were randomly assigned to receive either Hilo® capsules (n = 99) or Daflon® 500 mg tablets (n = 101). Assessment of hemorrhoidal symptoms was carried out in all patients on Day 7 and Day 15. Proctoscopic examination was carried out before the start of treatment i.e. on day 0 and at the end of treatment duration i.e. on day 15
Results: The patients treated with Hilo® showed a statistically significant improvement in the clinical symptoms of bleeding, pain, itching, soiling, tenesmus, irritation after defecation and constipation on day 7 and day 15 as compared to baseline. The "mean total symptom score" reduced by 4.55 ± 2.07 vs 3.44 ± 2.00; $P < .0001$ on day 7 and 7.56 ± 2.40 vs 6.22 ± 2.55; $P < .0001$ on day 15 in the patients treated with Hilo® and Daflon® respectively. In Hilo® Group, 82.83% of patients assessed that the treatment with Hilo® made them 'A lot better' as compared to only 48.51% in Daflon® group. In the Hilo® group 20.2% of patients' treatment outcome was assessed as 'Excellent' by the investigators as compared to only 0.99% of patients in Daflon® group. No major adverse events were reported in the study with the use of either product.
Conclusion: Hilo® is found to provide better reduction in clinical symptoms of patients suffering from hemorrhoids as compared to Daflon®.

Keywords: Hemorrhoids, clinical study, phlebotonics, flavonoids, catechins

1. INTRODUCTION

Hemorrhoids are defined as the symptomatic enlargement and distal displacement of the normal anal cushions. The most common symptom of hemorrhoids is rectal bleeding associated with bowel movement. The abnormal dilatation and distortion of the vascular channel, together with destructive changes in the supporting connective tissue within the anal cushion, is a paramount finding of hemorrhoids [1].

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Approximately 40.7 million people in India are reported to suffer from hemorrhoids [2]. Hemorrhoidal symptoms are observed in about 60% of the patients suffering from hemorrhoids. The most common symptom of internal hemorrhoids is bleeding which can be painless and is bright red in color. The external hemorrhoids are more likely to be associated with pain, due to activation of perianal innervations associated with thrombosis. Patients typically describe a painful perianal mass that is tender to palpation. The other symptoms of hemorrhoids include: tenesmus, irritation of the skin surrounding the anus, soiling, itching, mucus discharge, sensation of tissue prolapse etc [3,4].

For the management of hemorrhoids, lifestyle changes and other non-operative measures have been recommended as first line therapy for management of hemorrhoids. These measures for hemorrhoids management are associated with significant improvement in the outcome scores reported by patients [5].

Various other options are available which are classified as surgical management such as Hemorrhoidectomy, Stapled hemorrhoidopexy, Doppler-guided hemorrhoid artery ligation. Non-surgical office procedures or minimally invasive procedures are also commonly used like Rubber band ligation, Sclerotherapy, Infrared coagulation, whereas the conservative management entailing treatment with phlebotonics, consumption of high fibre foods, psyllium husks, topical creams to relieve inflammation and pain, sitz bath, analgesics etc. is used for the symptomatic management of the hemorrhoids [3,6].

The medical and conservative management with high-fibre diets, stool softeners and laxatives are the preferred treatments for Grade I to Grade II hemorrhoids whereas surgical procedures are reserved for the more severe hemorrhoids [7].

Phlebotonics are a heterogeneous group of drugs which are indicated for the treatment of chronic vein insufficiency and also for the management of less severe hemorrhoids. These drugs are helpful in the management of Grade-I, Grade-II as well as thrombosed hemorrhoids. Phlebotonics act by strengthening the vascular walls which increases the venous tone and improves lymphatic drainage thus normalises the capillary permeability. Phlebotonics are mostly natural products; e.g.: flavonoids, sapsonides, etc. The synthetic phlebotonics include: calcium dobesilate, naftazone, aminaftone, chromocarbe [8].

Hilo® capsules are rich in flavonoid contents and act as phlebotonic with vascular-protecting properties. Hilo® reinforces venous tone, decreases venous capacitance, venous distensibility and venous emptying time. [9] Hilo® protects the microcirculation by fighting the venous inflammation via decreasing leukocyte activation, and as a consequence, by inhibiting the release of inflammatory mediators (Cytokines, IL 1-β & TNFα), free radicals (5-LOX, ROS & RNS) and prostaglandins**.** Thus, Hilo® normalizes capillary permeability and strengthens capillary resistance. [10]

Hilo® also acts on the lymphatic system and improves lymphatic drainage by increasing lymph flow and lymph oncotic pressure. [11] This action on the lymphatic system is associated with a venotonic and vasculoprotective effect thereby reducing edema. By virtue of its venotonic, vascular-protecting and anti-inflammatory action, Hilo® improves hemorrhoidal signs and symptoms e.g., anal discomfort, pain, redness, anal discharge, tenesmus, pruritus, erythema and bleeding. In addition to the above, it also significantly reduces the frequency, severity and duration of acute hemorrhoidal episodes and bleeding in all grades of hemorrhoids. [12]

Daflon® tablets are made from micronized purified flavonoid fraction consisting of 10% hesperidin and 90% diosmin. Daflon® also belongs to the phlebotonic category of drugs.

Daflon® exerts its effect by increasing the venous tone, protecting the microcirculation against inflammatory process and improving the lymphatic drainage [10]. It is indicated clinically for the treatment of venous insufficiency and hemorrhoids [13].

The present study was conducted to compare the efficacy and safety of Hilo® and Daflon® in the treatment of hemorrhoids.

2. MATERIAL AND METHODS

2.1 STUDY DESIGN

This was a multicentric, randomized, open labelled, comparative study. All the patients were randomly assigned in a 1:1 ratio that is 101 patients in Hilo® group and 99 in Daflon® group respectively. The study was conducted as per the ICH GCP guidelines [14] and Schedule-Y of Indian Drugs and Cosmetics Act [15]. The respective institutional ethics committees of the trial sites approved the study protocol and other relevant documents before the enrolment of patients.

2.2 PARTICIPANTS

For inclusion in the study, the patients had to qualify the inclusion and exclusion criteria as per the approved protocol (attached as appendix). Adult patients of either gender diagnosed with hemorrhoids confirmed by proctoscopy were included in the study. All the eligible patients were provided with all the necessary information regarding the study and the investigational products and were asked to sign the informed consent form before proceeding with the patient enrolment in the study.

Patients using other anti-hemorrhoidal drugs or planning to undergo any surgical procedure for hemorrhoids and pregnant women, or lactating mothers were not included in the study.

This study was conducted at four centers in India- Janta Hospital and Maternity Centre, Varanasi; King George Memorial Hospital, Lucknow; Vijan Hospital and Research Centre, Nasik and Santosh Hospital, Bangalore.

2.3 INTERVENTIONS

The enrolled patients were randomized to receive either of the two investigational products: Hilo® herbal capsules (2 caps twice daily), manufactured by Zuventus Healthcare Limited, India and Daflon® 500 mg (2 tablets daily), manufactured by Serdia Pharmaceuticals Private Limited, India.

Hilo® is a herbal preparation containing a mixture of four herbs, where each capsule contains Commiphora molmol (Heerabol) oleoresin (250mg), Gardenia gummifera (Naadihingu) gum-resin (83mg), and Tagates erecta (Genda) flowers (83.5mg), and Mesua ferrea (Nagakesar) stem (83.5). It is standardized to contain not less than 7% of total catechins and epicatechins. Each Daflon® 500 mg tablet contains micronized purified flavonoid extracts of rutaceae 500 mg, equivalent to 450 mg of diosmin and 50 mg of hesperidine per tablet.

At the end of treatment regimen (Day 15), study medication containers were retrieved from the patients and the remaining tablets were counted. Thus the compliance was ensured by

project staff through pill count. Any other anti-hemorrhoidal treatment or laxatives were not allowed during the trial period.

2.4 OUTCOMES

Primary outcome of the study was to evaluate an improvement in the intensity of hemorrhoidal symptoms and grades of hemorrhoids as observed with proctoscope on Day 15 by the investigator.

Secondary outcome was global assessment for overall improvement by patient and physician on Day 15 and number of adverse reactions reported by patients throughout the study duration.

2.5 SAMPLE SIZE

A sample size of the study was calculated using a level of significance of 5% and a power of 90%. Following parameters were considered-
Confidence level = 95%
Acceptable difference = 0.10
Assumed proportion = 0.50
Using WINPEPI software, it was found that required sample size is 97 in each group.
The present study enrolled 200 patients, 100 patients in each group.

2.6 RANDOMISATION

For allocation of the participants at various study centers, computer-generated randomization blocks were used. Participants were randomly assigned following a simple randomization procedure to either of the treatment groups. The randomization chart was prepared by a third party with no direct involvement in the study. Patients were screened and enrolled by the investigators based upon the eligibility criteria. Study medications were labelled and dispensed to trial patients by investigators as per the randomization chart.

2.7 STUDY ASSESMENTS

On day 0, screening and randomization of the patients was done. This involved signing of informed consent document and enrolment of patients as per the inclusion and exclusion criteria. Demographics and medical history including previous history of hemorrhoids or any other chronic diseases was assessed. The investigational products were dispensed to all eligible patients on day 0 as per the randomization scheme generated using SAS 9.1 software. The enrolled patients were given the investigational products for 15 days with instructions for drug administration.

Proctologic examination was performed to assess the hemorrhoidal conditions on day 0 and day 15 i.e. before the start of treatment and at the end of the study. Proctologic assessment was performed in the left-lateral position by inspection of the anal verge of the anal canal by using a proctoscope. Parameters namely, Grade (I, II, III, IV) and position of hemorrhoids (at one site, two sites or all three primary sites, i.e., 3'O clock, 7'O clock, 11'O clock position) were assessed. The severity of clinical symptoms of hemorrhoids (bleeding, pain, itching, soiling, tenesmus, irritation after defecation and constipation) was assessed using a 4-point scale: (0= absent, 1= mild, 2= moderate and 3= severe) on each visit i.e. day 0, day 7 and day 15. Additionally, on day 15, global assessment of the interventions was done subjectively by the patients as well as the investigators.

2.8 STATISTICAL ASSESMENT

The following null hypothesis was formulated:

Ho: There is no difference between the two treatment groups in improving the clinical symptoms of hemorrhoids

H1: There is a difference between the two treatment groups in improving the clinical symptoms of hemorrhoids

Analysis were performed using Stats Direct software (Version 3.1.22). The data are expressed as mean ± S.D. or percentage. Unpaired t-test was used to compare the demographic parameters of age, weight and height. Mann-Whitney U test was used for 'between the group' comparison while Wilcoxon's signed ranks test was used to compare the changes 'within the group' and McNemar and exact (Liddell) test was used to compare the proportions.

95% Confidence Interval (C.I.) for the true proportions were also calculated. All 'P values' were considered significant if less than .05.

3. RESULTS

In the present study, a total of 201 patients presenting with hemorrhoids were screened at 4 clinical trial sites. Out of the 201 patients screened, 200 fulfilled the eligibility criteria and were enrolled in the study. The patients were randomized to receive either Hilo® or Daflon® where the Hilo® group comprised of 99 patients while 101 patients were allotted in the Daflon® group. All 200 patients completed the study as per the approved protocol and their data was subjected to statistical analysis at the end of the study. A consort chart of trial participants is described in Figure 1. The first patient was enrolled on 18th May, 2017 at Janta Hospital, Varanasi and the last patient completed the study on 28th December, 2018 at Santosh Hospital, Bangalore.

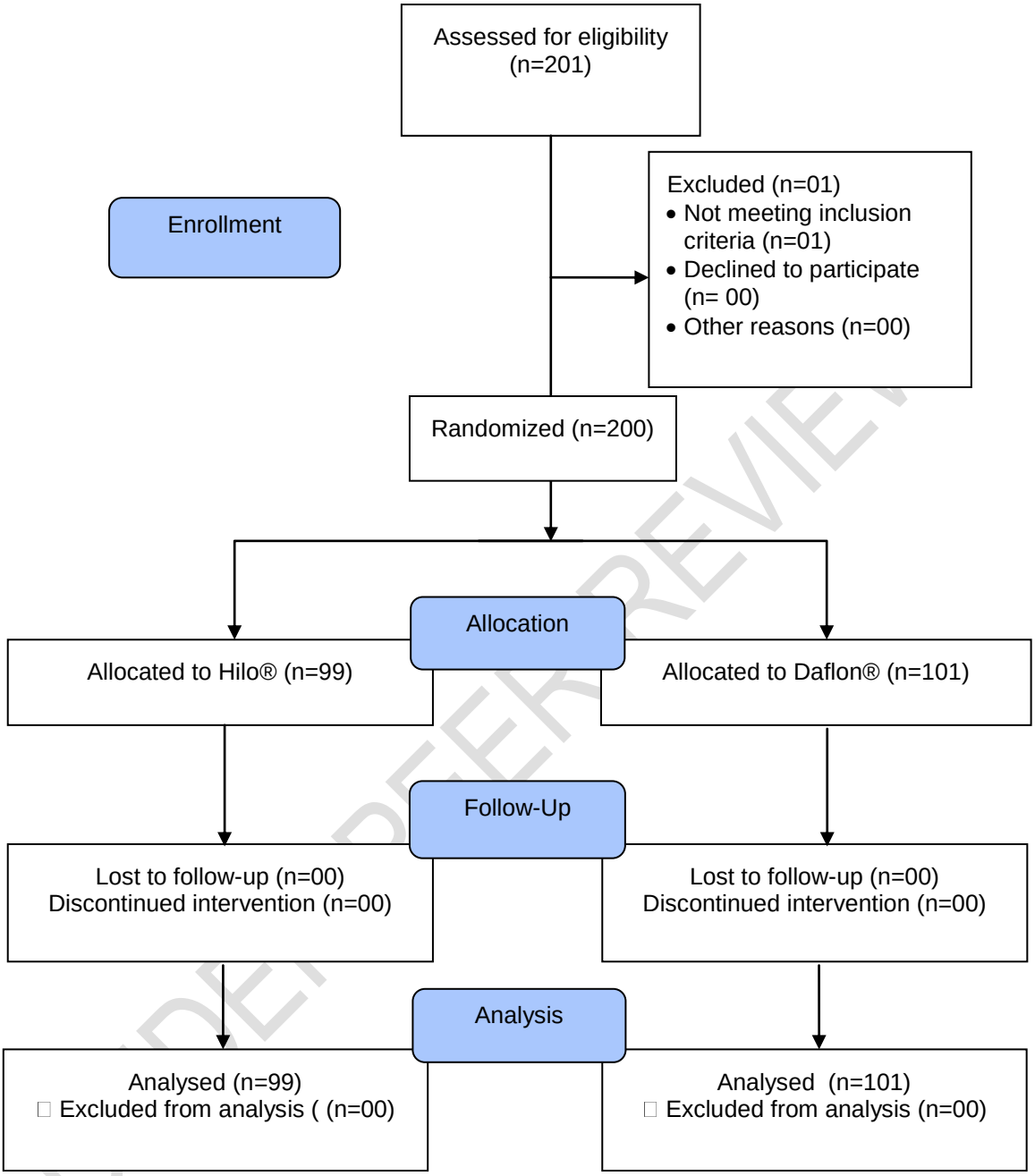

Fig. 1. Consort chart of trial participants.
n= number of patients

3.1 DEMOGRAPHICS

On Day 0, the demographic parameters like age, height and weight were documented. The means of demographic parameters of age, weight and height were compared using unpaired t-test. The baseline individual symptom scores of the two treatment groups were compared

using Mann-Whitney U test. No significant difference was observed between the two groups ($P > .05$) (Table 1).

Table 1. Comparative demographics using unpaired t-test and baseline scores of clinical symptoms using Mann-Whitney U Test

	Hilo® (n=99) Mean ± S.D.	Daflon® (n=101) Mean ± S.D.	*P*	95% C.I.
Age (years)	40.17 ± 13.67	38.31 ± 12.51	.32	Mean diff= 1.86 -1.79 to 5.52
Weight (kg)	61.07 ± 10.87	60.38 ± 8.29	.18	Mean diff= 0.69 0.34 to 0.53
Height (cm)	161.83 ± 7.51	161.46 ± 7.45	.61	Mean diff= 0.37 -1.71 to 2.46
Baseline scores of clinical symptoms				
Bleeding	1.45 ± 0.52	1.57 ± 0.64	.24	Mean diff= -0.12 0.41 to 0.57
Pain	1.75 0.52	1.72 ± 0.51	.73	Mean diff= 0.03 0.46 to 0.62
Itching	1.33 ± 0.64	1.29 ± 0.67	.83	Mean diff= 0.04 0.41 to 0.57
Soiling	1.27 ± 0.62	1.33 ± 0.60	.63	Mean diff= -0.06 0.44 to 0.59
Tenesmus	1.54 ± 0.63	1.51 ± 0.66	.99	Mean diff= 0.03 0.42 to 0.58
Irritation while defecation	1.24 ± 0.70	1.38 ± 0.75	.14	Mean diff= -0.14 0.47 to 0.63
Constipation	1.79 ± 0.67	1.71 ± 0.60	.33	Mean diff= 0.08 0.39 to 0.55

* Mean ± S.D.= Mean ± Standard Deviation, C.I.= Confidence Interval, kg = kilogram, cm= centimeter

3.2 Assessment of Total Symptom Score and Individual Clinical Symptom Score

The total symptom score was calculated by adding the individual symptom scores of bleeding, pain, itching, soiling, tenesmus, irritation after defecation, constipation for each patient. The individual symptom scores of bleeding, pain, itching, soiling, tenesmus, irritation after defecation, constipation were scored for their severity on Day 0, Day 7 and Day 15. The mean change in the total symptom score and the individual clinical symptom score from the baseline score of Day 0 was evaluated at Day 7 and Day 15 using Wilcoxon's signed ranks test for both the groups (Table 2).

Table 2 Improvement in the total symptom score and individual clinical symptom score of hemorrhoids before and after treatment with Hilo® and Daflon® using Wilcoxon's signed ranks test

	Hilo® (n=99)					**Daflon® (n=101)**				
	Day 0 (Visit 1) Mean ± S.D.	**Day 7 (Visit 2) Mean ± S.D.**	**Day 15 (Visit 3) Mean ± S.D.**	**Mean Change from Day 0 to Day 7 (95% C.I.)**	**Mean Change from Day 0 to Day 15 (95% C.I.)**	**Day 0 (Visit 1) Mean ± S.D.**	**Day 7 (Visit 2) Mean ± S.D.**	**Day 15 (Visit 3) Mean ± S.D.**	**Mean Change from Day 0 to Day 7 (95% C.I.)**	**Mean Change from Day 0 to Day 15 (95% C.I.)**
Bleeding	1.45 ± 0.73	0.69 ± 0.62	0.23 ± 0.47	0.77 ± 0.65* (0.5 to 1)	1.22 ± 0.72* (1.0 to 1.5)	1.57 ± 0.64	0.99 ± 0.56	0.43 ± 0.65	0.58 ± 0.55* (0.5 to 0.5)	1.15 ± 0.80* (0.99 to 1.31)
Pain	1.75 ± 0.52	0.94 ± 0.47	0.68 ± 0.68	0.81 ± 0.65* (0.5 to 1)	1.07 ± 0.92* (1.0 to 1.5)	1.72 ± 0.51	1.14 ± 0.58	0.86 ± 0.65	0.58 ± 0.53* (0.5 to 0.5)	0.86 ± 0.82* (0.5 to 1)

	Hilo® (n=99)					Daflon® (n=101)				
	Day 0 (Visit 1) Mean ± S.D.	**Day 7 (Visit 2) Mean ± S.D.**	**Day 15 (Visit 3) Mean ± S.D.**	**Mean Change from Day 0 to Day 7 (95% C.I.)**	**Mean Change from Day 0 to Day 15 (95% C.I.)**	**Day 0 (Visit 1) Mean ± S.D.**	**Day 7 (Visit 2) Mean ± S.D.**	**Day 15 (Visit 3) Mean ± S.D.**	**Mean Change from Day 0 to Day 7 (95% C.I.)**	**Mean Change from Day 0 to Day 15 (95% C.I.)**
Itching	1.33 ± 0.64	0.89 ± 0.50	0.64 ± 0.61	0.43 ± 0.66* (0.5 to 0.5)	0.69 ± 0.91* (0.5 to 1)	1.29 ± 0.67	1.00 ± 0.57	0.80 ± 0.55	0.29 ± 0.61* (0.0 to 0.5)	0.49 ± 0.74* (0.5 to 0.5)
Soiling	1.27 ± 0.62	0.54 ± 0.56	0.21 ± 0.41	0.74 ± 0.58* (0.5 to 1)	1.06 ± 0.62* (1.0 to 1.0)	1.33 ± 0.60	0.76 ± 0.59	0.39 ± 0.53	0.56 ± 0.59* (0.5 to 0.5)	0.94 ± 0.61* (1.0 to 1.0)
Tenesmus	1.54 ± 0.63	0.84 ± 0.63	0.75 ± 0.68	0.69 ± 0.54* (0.5 to 1)	0.79 ± 0.81* (0.5 to 1)	1.51 ± 0.66	0.99 ± 0.62	0.90 ± 0.61	0.52 ± 0.58* (0.5 to 0.5)	0.61 ± 0.71* (0.5 to 1)
Irritation after defecation	1.24 ± 0.70	0.81 ± 0.55	0.56 ± 0.59	0.43 ± 0.76* (0.28 to 0.59)	0.69 ± 0.85* (0.5 to 1)	1.38 ± 0.73	1.00 ± 0.65	0.79 ± 0.62	0.39 ± 0.75* (0.5 to 0.5)	0.59 ± 0.74* (0.5 to 1)

	Hilo® (n=99)					Daflon® (n=101)				
	Day 0 (Visit 1) Mean ± S.D.	**Day 7 (Visit 2) Mean ± S.D.**	**Day 15 (Visit 3) Mean ± S.D.**	**Mean Change from Day 0 to Day 7 (95% C.I.)**	**Mean Change from Day 0 to Day 15 (95% C.I.)**	**Day 0 (Visit 1) Mean ± S.D.**	**Day 7 (Visit 2) Mean ± S.D.**	**Day 15 (Visit 3) Mean ± S.D.**	**Mean Change from Day 0 to Day 7 (95% C.I.)**	**Mean Change from Day 0 to Day 15 (95% C.I.)**
Constipation	1.79 ± 0.67	1.06 ± 0.53	0.66 ± 0.48	0.73 ± 0.53* (0.5 to 1)	1.13 ± 0.69* (1.0 to 1.5)	1.71 ± 0.60	1.18 ± 0.65	0.82 ± 0.49	0.53 ± 0.61* (0.5 to 0.5)	0.89 ± 0.66* (1.0 to 1.0)
TOTAL SYMPTOM SCORE	10.75 ± 2.02	6.20 ± 1.71	3.19 ± 1.54	4.55 ± 2.07* (4.5 to 5)	7.56 ± 2.40* (7 to 8)	10.70 ± 2.40	7.26 ± 2.19	4.48 ± 2.05	3.44±2.00* (3 to 4)	6.22±2.55* (5.5 to 7)

200 *$P < .0001$

201 Mean changes in individual symptom scores from baseline to day 7 were statistically
202 significantly improved in Hilo® group as compared to Daflon® group viz. Bleeding (0.77 ±
203 0.65 vs 0.58 ± 0.55; $P < .0001$), Pain (0.81 ± 0.65 vs 0.58 ± 0.53; $P < .0001$), Itching (0.43 ±
204 0.66 vs 0.29 ± 0.61; $P < .0001$), Soiling (0.74 ± 0.58 vs 0.56 ± 0.59; $P < .0001$), Tenesmus
205 (0.69 ± 0.54 vs 0.52 ± 0.58; $P< .0001$), Irritation after defecation (0.43 ± 0.76 vs 0.39 ± 0.75;
206 $P< .0001$) and Constipation (0.73 ± 0.53 vs 1.13 ± 0.69; $P < .0001$).
207 Mean changes in individual symptom scores from baseline to day 15 were statistically
208 significantly improved in Hilo® group as compared to Daflon® group viz. Bleeding (1.22 ±
209 0.72 vs 1.15 ± 0.80; $P < .0001$), Pain (1.07 ± 0.92 vs 0.86 ± 0.82; $P < .0001$), Itching (0.69 ±
210 0.91 vs 0.49 ± 0.74; $P < .0001$), Soiling (1.06 ± 0.62 vs 0.94 ± 0.61; $P < .0001$), Tenesmus
211 (0.79 ± 0.81 vs 0.61 ± 0.71; $P < .0001$), Irritation after defecation (0.69 ± 0.85 vs 0.59 ± 0.74;
212 $P < .0001$) and Constipation (1.13 ± 0.69 vs 0.89 ± 0.66; $P< .0001$).
213 Mean change in total symptom score was found to be statistically significant from baseline to
214 day 7 (4.55 ± 2.07 vs 3.44 ± 2.00; $P < .0001$) and day 15 (7.56 ± 2.40 vs 6.22 ± 2.55; $P <$
215 .0001) in Hilo® group as compared to Daflon® group.

The patients treated with Hilo® capsules showed a significantly better improvement in total symptom score on both Day 7 & Day 15 when compared to Daflon® (*P* < .0001) (Table 3).

Table 3 Difference between Hilo® and Daflon® treatment groups in improvement of total symptom score of hemorrhoids using Mann-Whitney U test

Improvement in Total Symptom Score with Hilo® and Daflon®	
Improvement on Day 7	Mean diff = 1.10* 95% C.I. = 0.27 to 0.41
Improvement on Day 15	Mean diff = 0.23* 95% C.I. = 0.04 to 0.11

*$P < .0001$

3.3 Proportion of patients exhibiting reduction in total symptom score

The proportion of patients showing reduction of ≥ 50%, ≥ 75% and ≥ 80% in the total symptom score were evaluated and the two groups were compared using McNemar and exact (Liddell) test (Table 4).

In Hilo® treatment group, the scores of *89.89%* patients (89/99) was reduced to ≥ 50% on day 15. In the Daflon® treatment group, *74.26%* patients (75/101) exhibited ≥ 50% reductions in total symptom score on Day 15. *48.48%* patients from Hilo® group while only ***16.83%*** patients receiving Daflon® achieved ≥ 75% reduction in total symptom score. The total symptom score of ***32.32%*** patients from Hilo® group and ***13.86%*** patients from Daflon® group improved by ≥ 80% on Day 15.

The number of patients achieving ≥ 50%, ≥ 75% and ≥ 80% reduction in total symptom score on Day 15 was significantly higher in the Hilo® group when compared to Daflon® group (*P* < .0001).

Table 4. Number of patients showing ≥ 50%, ≥ 75% and ≥ 80% reduction in total symptom score on Day 15 as compared to Day 0 using McNemar and exact (Liddell) test

Improvement in hemorrhoid symptoms	**Hilo® group (n= 99)**	**Daflon® group (n=101)**	***P* value**
Number of patients with ≥ 50% reduction in total symptom score on	89	75	< .0001
Number of patients with ≥ 75% reduction in total symptom score on	48	17	< .0001

Number of patients with ≥ 80% reduction in total symptom score on	32	14	< .0001

3.4 Presence of clinical symptoms before and at the end of treatment period

At the baseline, the number of patients exhibiting the various clinical symptoms of hemorrhoids (bleeding, pain, itching, soiling, tenesmus, irritation after defecation, and constipation) were identified. At the end of the treatment (Day 15), the proportion of patients exhibiting the presence of these clinical symptoms were evaluated. The proportion of patients exhibiting clinical symptoms in the two groups were compared at the end of the treatment using McNemar and exact (Liddell) test (Table 5).

On comparing the two treatment groups, it was noted that a significantly less ($P < .01$) number of patients from Hilo® group exhibited the clinical symptoms of bleeding, pain, itching, soiling, tenesmus, irritation after defecation and constipation as compared to Daflon® on Day 7 as well as Day 15.

Table 5 Patients exhibiting clinical symptoms of hemorrhoids at baseline, day 7 and day 15 using McNemar and exact (Liddell) test

Clinical symptoms	Hilo® (n=99)			Daflon® (n=101)			Hilo® vs. Daflon® *P* value	
	Number of patients exhibiting clinical symptoms			Number of patients exhibiting clinical symptoms			Comparison of proportion of patients exhibiting clinical symptoms	
	Day 0	Day 7	Day 15	Day 0	Day 7	Day 15	Day 7	Day 15
Bleeding	87	61	21	94	86	34	< .0001	< .01
Pain	97	85	55	99	90	72	< .0001	< .01
Itching	91	81	56	89	85	68	< .0001	< .01
Soiling	90	50	21	95	69	37	< .01	< .01
Tenesmus	95	70	62	94	81	77	< .0001	< .0001
Irritation after defecation	85	73	50	88	80	69	< .0001	< .01
Constipation	96	88	65	100	89	78	< .0001	< .0001

3.5 Improvement in Hemorrhoidal Grades

Hemorrhoidal assessment was performed as described in the study assessment section. At the end of study (Day 15), the improvement in the stage of hemorrhoids was significantly higher in the Hilo® group (Grade I: 74.75% of patients) as compared to Daflon® group (Grade I: 55.45% of patients) (Table 6).

Table 6 Proportion of patients exhibiting various grades of hemorrhoids on proctoscopic examination on Day 0 and Day 15

	Hilo® (n=99)		Daflon® (n=101)	
	Day 0 n (%)	Day 15 n (%)	Day 0 n (%)	Day 15 n (%)
Grade IV	00 (0%)	00 (0%)	01 (0.99%)	00 (0%)
Grade III	16 (16.16%)	02 (2.02%)	25 (24.75%)	01 (0.99%)
Grade II	67 (67.68%)	21 (21.21%)	59 (58.42%)	43 (42.57%)
Grade I	16 (16.16%)	74 (74.75%)	16 (15.84%)	56 (55.45%)
No Hemorrhoids	00 (0%)	02 (2.02%)	00 (0%)	01 (0.99%)

At the end of the study, with Hilo® treatment 62 patients out of 83 (74.69%) from baseline of Grade II and Grade III combined exhibited improvement to Grade I. Similarly, with Daflon® treatment 44 patients out of 86 (total of Grade II and Grade III) improved to Grade I (51.16%). It was observed that a significantly a greater number of patients ($P < .01$) from Hilo® group showed improvement in hemorrhoidal grade as compared to Daflon® (Table 7).

Table 7 Difference between Hilo® and Daflon®: Proportion of patients showing improvement from Grade III & II (combined) III to Grade I using McNemar and exact (Liddell) test

	Visit 1 (Baseline)	Visit 3 (Day 15)	Success Rate	Hilo® vs. Daflon® *P* value
	Grade III & II (n)	Grade I (n)		
Hilo®	83	62	74.69 %	.006*

Daflon®	86	44	51.16 %	

*$P < .01$

3.6 Global Assessment of Therapy (Table 8)

In Hilo® Group, 82.83% of patients assessed that the treatment with Hilo® made them 'A lot better' as compared to only 48.51% in Daflon® group.

In the Hilo® group, 20.2% of patients' treatment outcome was assessed as 'Excellent' by the investigators while in Daflon® group only 0.99% patients showed 'Excellent' outcome as per the investigator. 5.94% of patients in Daflon® group showed 'Poor' outcome at the end of study.

Table 8 Assessment of therapy by patients and investigators

Assessment Of Therapy	Hilo® Group (n=99)	Daflon® Group (n=101)
By Patients		
The treatment made me a lot worse	0 (0%)	0 (0%)
The treatment made me slightly worse	0 (0%)	0 (0%)
The treatment made no change to my symptoms	01 (1.01%)	9 (8.91%)
The treatment made me slightly better	15 (15.15%)	43 (42.57%)
The treatment made me a lot better	82 (82.83%)	49 (48.51%)
The treatment completely relieved my symptoms	01 (1.01%)	0 (0%)
By Investigators		
Excellent	20 (20.20%)	1 (0.99%)
Good	67 (67.68%)	59 (58.42%)
Satisfactory	11 (11.11%)	35 (34.65%)
Poor	0 (0%)	6 (5.94%)

3.7 Adverse Events

There were no adverse events reported/observed in patients of either treatment groups during the course of the study.

4. DISCUSSION

A major component of a safe and effective therapy for hemorrhoids is the use of herbal products. Several herbal extracts containing flavonoids have been shown to improve microcirculation, capillary flow, and vascular tone, and strengthen connective tissue of the perivascular amorphous substrate. Flavonoid molecules also reduce inflammation by inhibiting prostaglandin and free radicals generated during the inflammatory response. The standard treatments for hemorrhoids are aimed toward removing the problem or palliating the disease.

Additionally, the low compliance associated with treatments such as hydrotherapy, mechanical compression therapy, and diet and lifestyle changes. This renders oral dietary supplementation an attractive option. The use of oral flavonoids offers an effective approach for the treatment of hemorrhoids. Early intervention with conservative therapies may prevent time-consuming and expensive complications of hemorrhoids [16,17].

Flavonoids are considered as phlebotonics and were first described in the treatment of chronic venous insufficiency and edema. They appeared to be capable of increasing vascular tone, reducing venous capacity, decreasing capillary permeability, and facilitating lymphatic drainage as well as having anti-inflammatory effects [1].

In an earlier study comparing Roidosanal® (standardized to contain not less than 7% of total catechins and epicatechins) and Daflon®, it was found that both the treatments are equally effective in improving anorectal conditions and the associated hemorrhoidal clinical symptoms. No major adverse events were reported in the study with the use of either product [18].

Daflon® tablets are a commercially available herbal medicine in India belonging to a similar category as that of Hilo®, hence it was used as comparator. In the present study, it was observed that patients treated with Hilo® showed a significant improvement in the clinical symptoms of bleeding, pain, itching, soiling, tenesmus, irritation after defecation and constipation ($P < .0001$) on day 7 as well as day 15 as compared to baseline. This is one of the most important aspect in the treatment of hemorrhoids when patient starts finding improvement in symptoms, the compliance towards prescribed drug increases and patient completes the full course of the medicine.

The mean total symptom score reduced by 4.55 on day 7 and by 7.56 on day 15 in the patients treated with Hilo®. The patients treated with Daflon® also showed a significant reduction in individual symptom score. The mean total symptom score reduced by 3.44 on day 7 and by 6.22 on day 15 in the patients treated with Daflon®. The improvement in total symptom score by both the treatments was compared using Mann-Whitney U test. Hilo® was found to be better in reducing the total symptom score on day 7 and day 15 as compared to Daflon® ($P < .0001$). These symptomatic improvement was corroborated by the proctoscopic findings of reduction in Grade of hemorrhoids.

Number of patients exhibiting clinical symptoms of hemorrhoids was significantly reduced in Hilo® group on Day 7 and day 15 as compared to Daflon® ($P < .01$). Proportion of patients exhibiting improvement in hemorhhoidal grades (from Grade II and Grade III to Grade I) was found to be greater in Hilo® group as compared to Daflon® ($P < .01$). This is an important aspect, as Grade III hemorrhoids, unlike Grade I and II hemorrhoids, do not usually present spontaneous improvement of the symptoms. These results are consistent with previously published data [18]. Thus a 15 days' course of Hilo can be recommended before proceeding for hemorrhoidectomy.

The current study has limitation of its smaller sample size. Further studies should be conducted to observe the impact of 15 days Hilo® therapy in avoiding the surgical intervention for the treatment of hemorrhoids.

5. CONCLUSION

In the present study, Hilo® was found to be better in improving the clinical symptoms of hemorrhoids as compared to Daflon®. Patients treated with Hilo® also showed improvement in the grades of hemorrhoids. There were no adverse events reported with either of the treatments. Hilo® is a safe and effective treatment for hemorrhoids.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Authors declare that written informed consent was obtained from all the patients who participated in this study. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

APPENDIX

Study Protocol.

REFERENCES

1. Lohsiriwat V. Hemorrhoids: From basic pathophysiology to clinical management. World J Gastroenterol 2012 May; 18(17): 2009-2017 [DOI:10.3748/wjg. v18.i17.2009]
2. Gupta A, Mitra SK. Role of piloherb tablets and ointment in the treatment of hemorrhoids. World J Pharm Pharm Sci 2015; 4(8): 1640-1647
3. Sun Z**,** Migaly J. Review of Hemorrhoid Disease: Presentation and Management. Clin Colon Rectal Surg 2016; 29:22–29 [PMCID: PMC4755769, PMID: 26929748, DOI: 10.1055/s-0035-1568144]
4. Mott T, Latimer K, Edwards C. Hemorrhoids: Diagnosis and Treatment Options. Am Fam Physician. 2018;97(3):172-179 [PMID:29431977]
5. Wilson MZ, Swarup A, Wilson LRT, Ivatury SJ. The Effect of Nonoperative Management of Chronic Anal Fissure and Hemorrhoid Disease on Bowel Function Patient-Reported Outcomes. Dis Colon Rectum 2018; 61: 1223–1227. [PMID: 30192331, DOI: 10.1097/DCR.0000000000001193]

6. Mayoclinic. Hemorrhoids. Accessed 30 April 2019 Available: https://www.mayoclinic.org/diseases-conditions/hemorrhoids/diagnosis-treatment/drc-20360280
7. Corsale I, Paolo Carrieri P, Martellucci J, Piccolomini A, Verre L, Rigutini M, et al. Flavonoid mixture (diosmin, troxerutin, rutin, hesperidin, quercetin) in the treatment of I–III degree hemorroidal disease: a double-blind multicenter prospective comparative study. Int J Colorectal Dis 2018; [DOI: https://doi.org/10.1007/s00384-018-3102-y]
8. Perera N, Liolitsa D, Iype S, Croxford A, Yassin M, Lang P, et al. Phlebotonics for hemorrhoids. Cochrane Database Syst Rev 2012, Issue 8. Art. No.: CD004322. [PMID:22895941, DOI: 10.1002/ 14651858. CD00 4322.pub3]
9. Danielsson G, Jungbeck C, Peterson K, Norgren L. A randomised controlled trial of micronised purified flavonoid fraction vs placebo in patients with chronic venous disease. Eur J Vasc Endovac Surg 2002 Jan 1;23(1):73-6. [PMID: 11748952, DOI: 10.1053/ejvs.2001.1531]
10. Lyseng-Williamson KA**,** Perry CM. Micronised purified flavonoid fraction. Drugs. 2003 Jan 1;63(1):71-100. [PMID:12487623, DOI: 10.2165/00003495-200363010-00005].
11. Demir A**,** Gökakın A, Üreyen O, Altınel Ö, Tezcan E, Gür A, et al. The efficacy of micronized flavonoid fraction (450 mg diosmin plus 50 mg hesperidin) in the treatment of lymphedema after axillary dissection. Cumhuriyet Medical Journal. 2011 Sep 16;33(3):312-7.
12. Jiang ZM, Cao JD. The impact of micronized purified flavonoid fraction on the treatment of acute haemorrhoidal episodes. Curr Med Res Opin. 2006 Jun 1;22(6):1141-7. [PMID: 16846547, DOI: 10.1185/030079906X104803]
13. Pascarella L, Lulic D, Penn AH, Alsaigh T, Lee J, Shin H, et al. Mechanisms in Experimental Venous Valve Failure and their Modification by Daflon® 500 mg. Eur J Vasc Endovasc Surg 2008; 35, 102e110 [PMID:17890112, DOI: 10.1016/j.ejvs.2007.08.011]
14. ICH Harmonised Guideline Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) Current Step 4 version dated 9 November 2016
15. Schedule Y (ammended version 2005) Drugs and Cosmetics Rules, 1945- CDSCO
16. MacKay D, Candidate ND. Hemorrhoids and Varicose Veins: A Review of Treatment Options. Altern Med Rev 2001; 6(2): 126-140 [PMID:11302778]
17. Mlakar B, Kosorok P. Flavonoids to reduce bleeding and pain after stapled hemorrhoidopoxy: a randomised controlled trial. Wien Klin Wochenchr 2005; 115/14-16: 558-560 [DOI: 10.1007/s00508-005-0420-1]
18. Aggrawal K, Satija N, Dasgupta G, Dasgupta P, Nain P, Sahu AR. Efficacy of a standardized herbal preparation (Roidosanal®) in the treatment of hemorrhoids: A randomized, controlled, open-label multicentre study. Journal of Ayurveda & Integrative Medicine 2014; 5(2): 117-14 [DOI: 10.4103/0975-9476.131732]