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AN OPEN LABELED, SINGLE CENTRE, PROSPECTIVE, CLINICAL STUDY TO EVALUATE EFFICACY AND SAFETY OF ARWL12 CAPSULE IN PATIENTS SUFFERING FROM INTERNAL HEMORRHOIDS

VIJAY PADMAKARRAO UKHALKAR[1], GOPAL RATHI[2], RAMESH JADAV[3] AND SANJAY TAMOLI*[4]

[1,2,3]Shlyatantra Department (Dept. of Surgery), Govt. Ayurved College, Vazirabad, Nanded, Maharashtra, India.
[4]Target Institute of Medical Education and Research, Dahisar (West), Mumbai, Maharashtra, India.*

ABSTRACT

Hemorrhoid is abnormal dilatation of venous plexus of anus, which causes bleeding per rectum, pain and itching at anus. 'ARWL12' capsule is a polyherbal formulation has been evaluated for efficacy and safety in patients of internal hemorrhoids. Thirty two patients received two 'ARWL12 capsules', twice daily orally after meals for 60 days. On day 60, reduction in proportion of patients showing bleeding per rectum was observed. The episodes and quantity of bleeding per rectum and piles mass decreased at the end of the study. The quality of life of patient also improved significantly. Global evaluation by physician and patient showed excellent improvement in reducing the symptoms of hemorrhoids. Almost all patients of the study showed excellent tolerability to study drug. No significant changes, in most of the safety laboratory parameters were observed. The study provided good evidence for potential efficacy and safety of 'ARWL12' capsule in patients with internal hemorrhoids.

KEY WORDS: Hemorrhoids, 'ARWL12' capsule, Efficacy, Safety, Bleeding per rectum, Quality of life.

SANJAY TAMOLI
Target Institute of Medical Education and Research, Dahisar (West), Mumbai, Maharashtra, India.

***Corresponding author**

INTRODUCTION

A hemorrhoid, also known as varicose veins, is a condition in which the veins around the anus, or in the anal canal, become swollen when stretched under pressure. Hemorrhoids (Greek; *Haima* = Blood, *Rhoo* = Flowing) are known as *Arsha* in *Ayurveda* and commonly known as Piles (Latin *pila* - a ball). They are usually of two types; external or internal, i.e., external or internal to anal orifice. More than half of men and women aged 50 years and older develop hemorrhoid symptoms during their lifetime[1-2]. Hemorrhoids are also commonly found among pregnant women and in patients with portal hypertension[1-2]. The main theories about the pathophysiology of hemorrhoidal disease are that they are abnormal dilatation of veins of the internal hemorrhoidal venous plexus, abnormal distension of the arteriovenous anastomosis, and prolapse of the cushions and the surrounding connective tissue[2]. Bleeding is the most common symptom experienced, and other less common symptoms include pain or discomfort, prolapse, itching, and mucous discharge[3]. The best treatment is prevention; by avoiding constipation, intake of high fibre diet and administration of bulk laxatives. Local symptoms can be alleviated by some soothing creams and suppositories, but long-term benefit is not often achieved. Nonsurgical treatment modalities such as rubber band ligation, injection sclerotherapy (using 5% phenol in almond oil), photocoagulation and cryotherapy are well established and acceptable to patients. However, they are not suitable for all grades of 'piles' and have recognized complications[4]. On the other hand, surgical haemorrhoidectomy is associated with a significant morbidity and may lead to delays in return to work[5]. Therefore, provision of a medical treatment that is easy to administer, free of any significant complications and reduces the likelihood of surgery would be attractive to patients and surgeons alike. *Ayurveda* offers a range of herbal and herbo-mineral combinations to control *Arsha* (piles or Hemorrhoids) successfully with minimum or no adverse effects. Many classical preparations are described in the *Ayurvedic* classical texts such as *Arsha Kuthar Rasa*, *Arshoghni Vati*, *Abhayarishta*, *Kasisadi Taila*, etc, for the management of hemorrhoids[6-7]. 'ARWL12' capsule is one such combination, prepared by Welex Laboratories Pvt. Ltd. Mumbai, for the effective management of hemorrhoids. Herbs present in 'ARWL12' capsule are known for their activity in relieving the symptoms of piles. Clinical trials are recommended by experts to establish the evidence base for the use of herbal formulations. Hence, a clinical trial to evaluate efficacy and safety of 'ARWL12' capsule in patients suffering from internal hemorrhoids (first and second grades) was planned.

METHODOLOGY

Subject Selection

Total 36 patients suffering from hemorrhoids were screened during the study period. Out of 36 screened patients, 32 patients were recruited in the study. Four patients were not recruited in the study because they did not meet inclusion and exclusion criteria. Out of 32 recruited patients, 30 patients completed the study and 2 patients dropped out of the study due to loss of follow up. Subjects of both sexes of age group between 20-60 years (both inclusive), willing to follow study procedures mentioned in protocol and voluntarily sign the informed consent forms were included in study. Subjects with symptomatic internal hemorrhoids of Grade I & II (small haemorrhoids without prolapse and medium size that prolapses and returns spontaneously, respectively) by direct proctoscopic visualization and having bleeding from hemorrhoids for at least two days prior to randomization were included in study. Subjects having BMI of ≥ 18.5 to ≤ 36 kg/m^2 were included in study. Subjects of female gender and/or non-pregnant, non-lactating at least six weeks postpartum were included in study. Female of child bearing potential, agreed to use contraception, with negative urine pregnancy test, or with known history of hysterectomy, tubal ligation, or was > 2 years postmenopausal was included in study. Pregnant and lactating females were excluded from the trial. Subjects with protruding or irreducible hemorrhoids (Grade IV), anal fistulas, periproctitis or

hemorrhagic diathesis was excluded. Subjects having Type I or Type II diabetes mellitus, severe hepatic, renal or cardiovascular disorders, infectious disease, cancer and known alcohol and drug abuse were excluded. Subject who had been involved with another experimental trial and who is using anticoagulants within the past 30 days from date of recruitment drug was excluded. Subjects using over the counter or prescription anti-hemorrhoid agents (Allopathic, Herbal, Homeopathic, *Ayurveda*, *Unani*, *Siddha* medicines) within past 14 days from date of recruitment were excluded. Subjects using suppositories, anti-platelet agents, low dose aspirin and who had known hypersensitivity to any ingredient of study drug were excluded. Subjects with abnormal blood or urine laboratory values were excluded.

Investigational Drug

The investigational product i.e. 'ARWL12' capsule was manufactured by the Sponsor following GMP and all applicable regulatory guidelines. The composition of the drug is given in (Table I).

Procedures

It was an open labeled, single-center, prospective, interventional, phase II clinical trial. Primary objectives of the study were to evaluate proportion of subjects achieving cessation of per rectal bleeding at the end of the treatment and also to evaluate post treatment reduction in severity of bleeding per rectum. Secondary objectives were to evaluate post treatment reduction in pile mass, reduction in other symptoms of hemorrhoids, global assessment of overall improvement of patient and physician, improvement in quality of life (QOL) of patients and assessment of pre and post treatment changes in laboratory investigations at the end of the treatment. On a screening visit (Day -3), subject's voluntary written informed consent was taken. The study was conducted at Government Ayurved College, Vazirabad, Nanded-431601, Maharashtra, India. On screening visit, detailed medical history along with the current medications (if any) was noted. Subject's general and systemic examinations were done. Subject's body constitution as per *Ayurveda* i.e. *Prakriti* was evaluated. Subject's proctoscopic examination was done and position and size of hemorrhoids were assessed. Subject was evaluated on WHO quality of life assessment questionnaire to judge subject's quality of life. Subject's symptom i.e. bleeding per rectum episodes, bleeding per rectum quantity, abdominal pain/discomfort (assessment on VAS), constipation (frequency of stool per day), straining on defecation (assessment on VAS), mucus discharge, pruritis [score ranging from 0 (no symptom) to 100 (severe symptom)] and pain in the anal region/perineum (assessment on VAS) were assessed. Subject then underwent investigations i.e. fasting blood sugar, CBC, ESR, Hb%, liver function tests (LFTs), renal function tests (RFTs), lipid profile, urine routine and microscopic, stool routine and microscopic, urine pregnancy test (only if the subject is female of child bearing potential), HIV test (I & II), X- ray chest (PA View) and ECG. A wash out period of 3 days was advised during which patients were advised to refrain from any medication that would have effected in the digestive system as well as hemorrhoids (Allopathic /Herbal /Homeopathic, etc.). All subjects were advised to continue their routine, diet and exercise regimen (which they had been already following) during the entire study. Subjects were provided with a diary card to record daily symptoms of hemorrhoids. Patients were advised to come to hospital for a baseline visit on third day after screening visit. All the activities and findings were documented in the source document and the CRF. On a baseline visit (Day 0), totally 32 patients were enrolled, who met inclusion and exclusion criteria. All subjects were asked for any AE/SAE occurred during wash-out period. If subject had AE/SAE, the details of the incidence were documented in the source document and CRF. SAE, if any, was reported to the IEC in an SAE reporting form. Rescue medication used, if required, from baseline visit to end of the study and detail was recorded in the CRF. After baseline visit, all subjects were called for follow up visits on day 15 (Visit 1), day 30 (Visit 2), day 45 (Visit 3) and day 60 (Visit 4). On baseline visit and on each follow-up visit, subject's general and systemic examinations were done. Subjects were asked

for AE/SAE if any. Subject's symptom i.e. bleeding episodes, bleeding quantity, abdominal pain/discomfort, constipation, straining on defecation, mucus discharge, pruritis and pain in the anal region/perineum were assessed. Filled diary cards were collected from patients. Diary cards, to record daily symptoms of hemorrhoids during next 15 days, were provided to patients on baseline visit and each follow-up visit (except visit 4). On baseline visit and on each follow-up visit (except visit 4), a container containing 72 capsules of 'ARWL12' was given to every subject (60 capsules for 15 days + additional 12 capsules, if follow-up was delayed maximum by three days). All subjects were advised to take 2 capsules twice daily orally after meals for 60 days. Subjects were advised to return empty containers after 15 days when they come for next follow-up to check the drug compliance. All the activities and findings were documented in the source document and the CRF. On every follow-up visit, subject's general and systemic physical examinations were done. Subject's proctoscopic examination was done and position and size of hemorrhoids were assessed. On every follow up visit, the container provided to the subject on previous visit was collected and remaining medicine was counted to check missed dosage. If 80% study medication was consumed over 80% time, the patient was considered compliant. If < 80% of study medication was consumed over 80% of time, the patient was considered as non-compliant. On visit 2 (Day 30) and at the end of the study, subject was evaluated on WHO quality of life assessment questionnaire to judge subject's quality of life. At the end of the study (day 60), global assessment of overall improvement had done by the investigator and by the patient. Subjects underwent for investigations viz. CBC, ESR, Hb%, liver function tests (LFTs), renal function tests (RFTs), lipid profile, urine routine and microscopic, stool routine and microscopic. Also, subject's ECG was done. Drug tolerability was assessed by the patient and by the investigator on day 60. At the end of the study, all subjects were asked to stop the trial drug and were advised to meet physician for further course of treatment. All the activities and findings were documented in the source document and CRF.

Ethics

Before initiation of the study, the study protocol and related documents were reviewed and approved by IEC at Govt. Ayurved College, Vazirabad, Nanded-431601, India. The study was conducted in accordance with Schedule Y of Drugs and Cosmetics Act of 1945, India, amended in 2005 and ICMR ethical guidelines for biomedical research on human participants, which are originated from WMA Declaration of Helsinki. Also, the clinical trial was registered prospectively on website of Clinical Trial Registry of India (CTRI), on 28/01/2013. The CTRI number for the trial is CTRI/2013/01/003329.

Statistics

An in-house statistician performed the analysis of the data using statistical software SPSS 10.0. Data describing quantitative measures were expressed as median or mean ± SD or SE or the mean with range. Qualitative variables were presented as counts and percentage. Comparison of variables representing categorical data like improvement in clinical symptoms, assessment of number of episodes of bleeding per rectum, quality of life, overall global improvement assessed by patients and investigators were performed using Chi-square test of Fisher's exact test. Mean differences of continuous variables were examined by Student's' test and comparison between two groups by independent t test. All p-values were reported based on two-sided significance test and all the statistical tests were interpreted at 5% level of significance.

RESULTS AND OBSERVATIONS

Subject's Characteristics

Thirty six subjects suffering from haemorrhoids were screened during the study period. Four out of 36 subjects did not meet the inclusion criteria, hence not recruited in study. Out of 32 recruited subjects, 28 (93.33%) were males, while 2 (6.66 %) were females. The age-wise and *Prakriti-wise* distribution of patients is

mentioned in (Table II and Graph I) and (Table III and Graph II), respectively.

Changes in Vital Parameters

No statistically significant changes in pre and post treatment values of pulse, blood pressure, temperature and respiratory rate were observed. Also, no statistically significant change in pre and post of body weight was observed.

Assessment of Efficacy of Drug

1. Effect of trial drugs on bleeding per rectum

Bleeding per rectum was evaluated on proportion of patients showing cessation of bleeding per rectum, number or episodes (frequency) of bleeding per rectum and quantity of bleeding per rectum at the end of the trial period.

A. Proportion of patients showing cessation of bleeding per rectum

At screening visit, all 30 patients complained of bleeding per rectum. On evaluation at 30 days follow up it was observed that 22 patients did not have any bleeding while 8 patients still complained of bleeding. At the end of the trial i.e. 60 days it was observed that 26 patients did not complain of bleeding while only 4 patients still had bleeding per rectum. The details are presented in (Table IV and Graph III).

B. Number or episodes (frequency) of bleeding per rectum

The frequency of bleeding per rectum was evaluated by the number of episodes that the patient experienced over the last week. At the beginning of the trial, 11 patients had one episode of bleeding per rectum, 14 patients had 2 episodes, 4 patients had 3 episodes while one patient complained of 8 episodes of bleeding in the last week at the initial visit. On evaluation of day 30, 24 patients had one episode of bleeding per rectum, 5 patients had 2 episodes while one patient had 3 episodes of bleeding per rectum over the last week. At the end of the trial period (60 days), no bleeding episode was reported by 26 patients, while 4 patients experienced one episode of bleeding over the last week. The details are presented in (Table V and Graph III).

C. Quantity of bleeding per rectum

The quantity of bleeding was evaluated by grading on VAS scale of 0 to 100, where 0 denoted no bleeding and 100 denoted maximum bleeding. It was observed that the mean VAS score at the beginning of the trial was 26 ± 18.86 which reduced to 8.60 ± 13.57 (statistically significant) at the end of 15 days of the trial. After 30 days the mean VAS score was observed to be 6 ± 10.37, at 45 days it was 4.60 ± 9.73 and at the end of the trial it was 3.33 ± 8.84. The reduction in the mean VAS score at the end of the study was statistically significant. The details are presented (Table VI and Graph IV).

2. Effect of trial drugs on pile mass

Pile mass assessment was done by proctoscopic examination. Gradation of Pile mass was done on a scale of 0 to 4. It was observed that the average grade score of pile mass in 30 patients was 2.10 ± 0.31 at the beginning of the trial which reduced to 1.92 ± 0.37 at 15 days, 1.53 ± 0.50 at 30 days and 1.40 ± 0.50 at 45 days. At the end of the trial i.e. 60 days the average of gradation of pile mass was 1.42 ± 0.50. The details are presented in (Table VII and Graph V). Also, at the beginning of the trial, 2 patients were in grade 1, 24 patients in grade 2, while 4 patients in grade 3. At follow up visit after 30 days, it was observed that 14 patients were in grade 2 while 16 patients in grade 1. None of the patient was in grade 3. At the end of the trial i.e. 60 days, it was observed that 17 patients remained in grade 1 while 13 patients were in grade 2. The details are presented in (Table VIII).

3. Effect of Trial drugs on other symptoms of haemorrhoids

Other symptoms that were evaluated included - constipation, straining on defecation, pruritis in the anal region and pain in the anal region.

A. Constipation

Constipation was evaluated by grading it on a scale of 0 to 3. It was observed that at the initial visit the average grade score for constipation

was 1.85 ± 0.80 which was reduced to 1.64 ± 0.67 at 30 days and 1.60 ± 0.67 at the end of 60 days of the trial. The details are presented in (Table IX and Graph VI).

B. Straining on defecation

Straining on defecation was evaluated by grading it on VAS scale of 0 to 100, where 0 denoted no straining required and 100 denoted maximum straining required. It was observed that the average score for straining on defecation at the initial visit was 26 ± 26.60 which reduced to 22 ± 23.40 after 15 days. The mean score at 30 days was found to be 18.16 ± 21.67 and 15.50 ± 21.26 at the end of 45 days of treatment with the trial drug. The mean score at the end of the trial i.e. 60 days was found to be 13 ± 18.22. The reduction in the mean score of straining on defecation at the end of the trial was statistically significant. The details are presented in (Table X and Graph VII).

C. Pruritis, pain in the anal region and mucus discharge

Symptoms like pruritis, pain in the anal region and mucus discharge were not reported by any patient at screening i.e. initial visit. It was observed that none of the patients developed these symptoms over the period of 60 days of the trial duration.

4. Effect of trial drug on laboratory parameters

No statistically significant changes in any of the laboratory parameters were observed at the end of the study. Also, no statistically significant difference was observed between the groups at the end of the study (Table XI and XII). ECG examination was also done pre and post-trial and it was observed that at both times the ECG was within normal limits showing no change occurred on this parameter by the trial drug.

Table I
Composition of 'ARWL12' capsule
Each Capsule Contains

Sr. No.	Botanical Name	Ingredients	Quantity
1	*Mimosa pudica* extract	Lajwanti	30 mg
2	*Nymphaea rubra*	Nilophar	30 mg
3	*Azadirachta indica seed* extract	Neem beej	30 mg
4	*Amorphophallus campanulatus*	Suran	30 mg
5	*Plantago ovate*	Isabgol	30 mg
6	*Shorea robusta*	Sal	30 mg
7	*Corriandrum sativum* extract	Dhania	30 mg
8	*Terminalia chebula* extract	Harde	25 mg
9	*Emblica officinalis* extract	Avla	25 mg
10	*Mesua ferrea*	Nagkeshar	25 mg
11	*Commiphora myrrha*	Raktabol	25 mg
12	*Holarrhena antidysenterica*	Kutaj	25 mg
13	*Salmalia malabarica*	Mochras	25 mg
14	*Aegle marmelos*	Beal Phal	25 mg
15	*Caesalpinia crista*	Karanj	20 mg
16.	-	Excipients	QS

Table II
Age wise distribution in patients

Sr. No.	Age in years (both inclusive)	Number of patients	Percentage of patients
1	21-30	14	46.67%
2	31-40	11	36.67%
3	41-50	4	13.33%
5	51-60	1	3.33%
5	61-70	0	0.00%
	Total	30	100%

Table III
***Prakriti*-wise distribution in patients**

Sr. No.	*Prakriti*	Number of Patients	Percentage of patients
1	*Vata-Pitta*	14	46.67 %
2	*Pitta-Vata*	4	13.33 %
3	*Vata*	7	23.33 %
4	*Kapha*	1	3.33 %
5	*Pitta*	2	6.66 %
6	*Vata Kapha*	2	6.66 %
	Total	30	100 %

Table IV
Assessment of incidence of bleeding per rectum in 30 patients

Sr. No	Visit	Number of Patients with Bleeding per Rectum	Number of Patients with Cessation of Bleeding per Rectum
1	Baseline Visit on Day 0	30 (100%)	0
2	Visit-1 on Day 15	15 (50%)	15 (50%)
3	Visit-2 on Day 30	8 (26.66%)	22 (73.33%)
4	Visi-3 on Day 45	6 (20%)	24 (80%)
5	Visit-4 on Day 60	4 (13.33%)	26 (86.66%)

Table V
Frequency of bleeding per rectum during the trial duration of 60 days

Sr. No.	No Bleeding Episode	1 Episode	2 Episodes	3 Episodes	More than 3 Episodes
No. of Patients at Baseline Visit	Nil	11	14	4	1
No. of Patients on Visit-2 (Day 30)	Nil	24	5	1	Nil
No. of Patients on Visit-4 (Day 60)	26	4	Nil	Nil	Nil

Table VI
Mean VAS score of quantity of bleeding per rectum

Sr. No.	Duration	Mean VAS Score ±SD	T Value (as compared to baseline visit)
1	Quantity of Bleeding on VAS scale at Baseline Visit	26 ± 18.86	-
2	Quantity of Bleeding on VAS scale on Day 15	8.60 ± 13.57	3.12 (p<0.01 HS)
3	Quantity of Bleeding on VAS scale on Day 30	6 ±10.37	3.37 (p<0.01 HS)
4	Quantity of Bleeding on VAS scale on Day 45	4.60 ± 9.73	3.50 (p<0.01 HS)
5	Quantity of Bleeding on VAS scale on Day 60	3.33 ± 8.84	3.62 (p<0.01 HS)

Table VII
Mean grade score of pile mass evaluated by proctoscopic examination

Sr. No	Grade Score of Pile Mass on Visit	Mean Grade Score ±SD	T Value (as compared to baseline visit)
1	Baseline Visit	2.10 ± 0.31	-
2	Day 15	1.92 ± 0.37	2.40 (p<0.01 HS)
3	Day 30	1.53 ± 0.50	5.75 (p<0.01 HS)
4	Day 45	1.40 ± 0.50	6.60 (p<0.01 HS)
5	Day 60	1.42 ± 0.50	7.07 (p<0.01 HS)

Table VIII
Assessment of gradation of pile mass in number of patients

Sr. No	Visit	Grade 1 Pile mass	Grade 2 Pile Mass	Grade 3 Pile Mass
1	Baseline Visit (Day 0)	2	24	4
2	Visit-2 (Day 30)	16	14	Nil
3	Visit-4 (Day 60)	17	13	Nil

Table IX
Mean grade score of constipation

Sr. No	Duration	Mean Grade Score ±SD	T Value (as compared to baseline visit)
1	Grade Score of constipation at Baseline Visit	1.85 ± 0.80	--
2	Grade Score of constipation at Day 30	1.64 ± 0.67	2.26 (p<0.05 S)
3	Grade Score of constipation at Day 60	1.60 ± 0.67	2.53 (p<0.01 HS)

Table X
Mean Grade score of straining on defecation

Sr. No.	Duration	Mean Grade Score ±SD	T Value (as compared to baseline visit)
1	Grade Score of straining on defecation at Baseline Visit	26 ± 26.60	-
2	Grade Score of straining on defecation at Day 15	22 ± 23.40	1.36 (p>0.05 NS)
3	Grade Score of straining on defecation at Day 30	18.16 ± 21.67	2.93 (p<0.01 HS)
4	Grade Score of straining on defecation at Day 45	15.50 ± 21.26	3.46 (p<0.01 HS)
5	Grade Score of straining on defecation at Day 60	13 ±18.22	3.35 (p<0.01 HS)

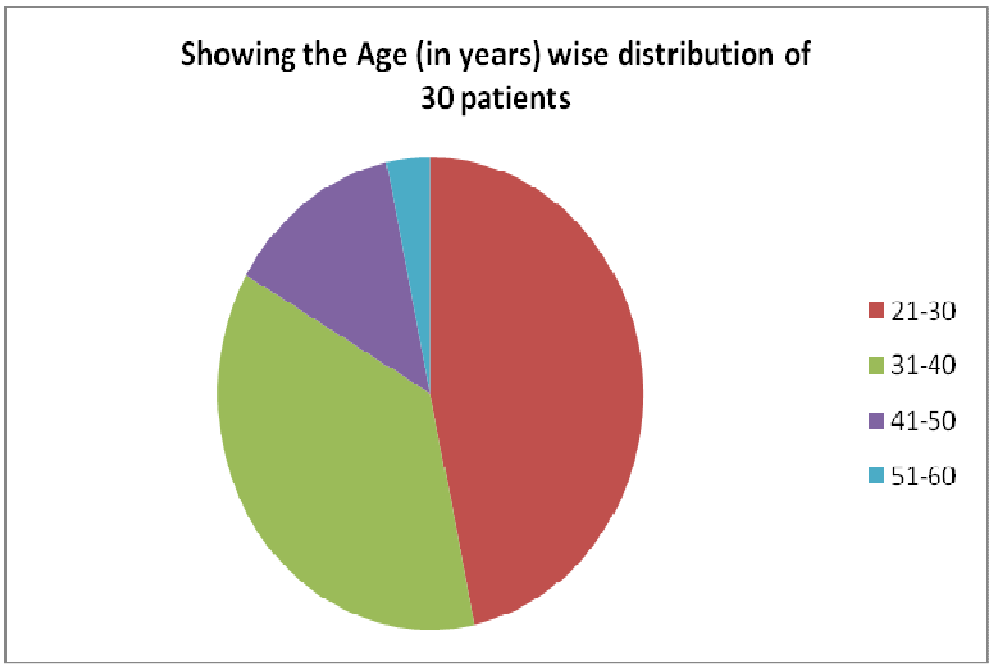
Table XI
Effect of trial drug on Hb % levels after 60 days of treatment

Sr. No	Duration	Mean Grade Score ±SD	T Value (as compared to baseline visit)
1	Hb% at Baseline Visit	11.20 ± 2.06	-
2	Hb% at Final Visit	11.75 ± 1.75	0.55 (p>0.1- NS)

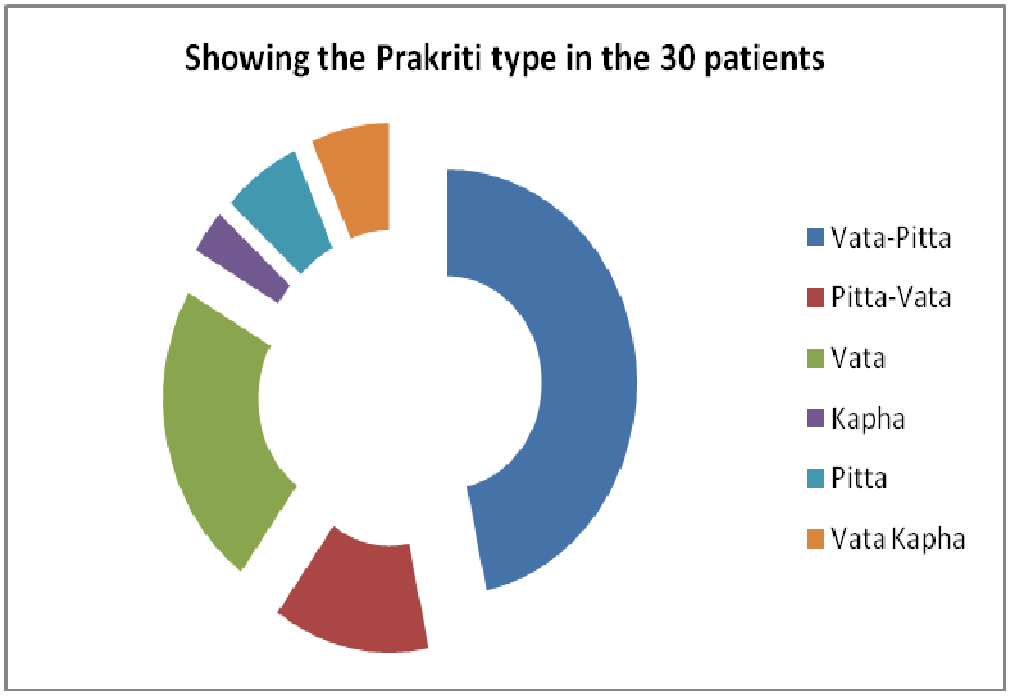
Table XII
Effect of trial drug on blood parameters after 60 days of treatment

Sr. No.	Investigations	Initial Visit	Final Visit
1	Total Cholesterol	177.17 mg% ± 36.15	180.58mg% ± 29.13
2	Triglycerides	115.39 mg% ± 50.27	123.67mg% ± 55.17
3	Bilirubin Total	0.7975 mg/dl ± 0.33	0.8333mg/dl ± 0.31
4	Bilirubin Direct	0.215 mg/dl ± 0.10	0.2991mg/dl ± 0.21
5	SGOT	26.565 ± 8.52	26.7 ± 10.51
6	SGPT	54.425 ± 21.12	50.39 ± 19.50
7	Serum Albumin	4.8944gm/dl ± 1.26	4.5gm/dl ± 1.08
8	BUN	29.975 mg/dl ± 9.60	26.962mg/dl ± 8.11
9	Serum Creatnine	1.0043 mg% ± 0.24	1.08mg% ± 0.26

Graph I
Age-wise distribution in patients

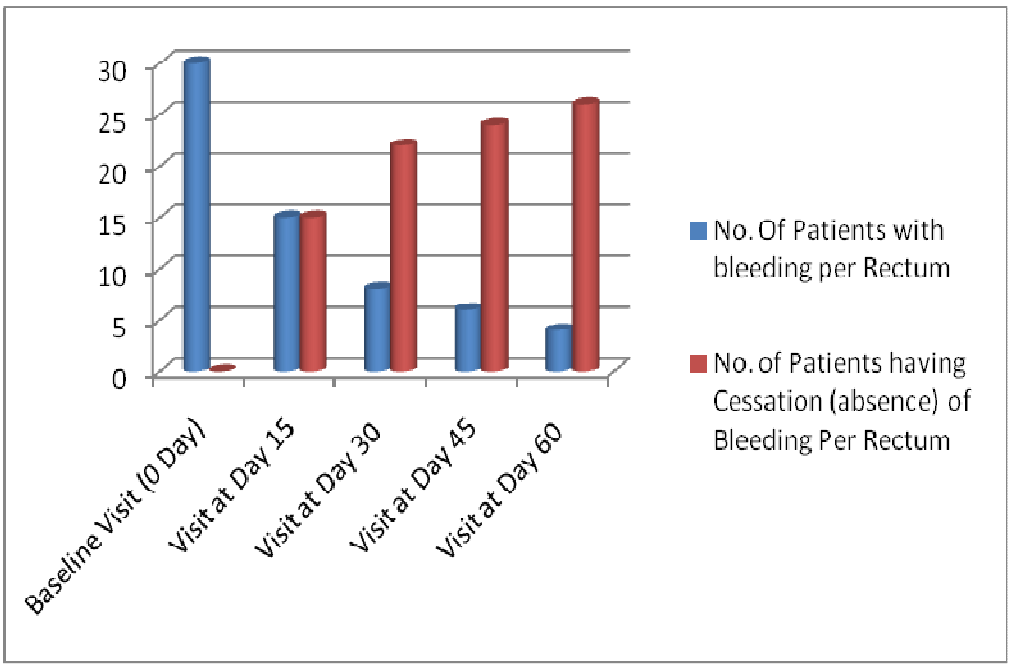


Graph II
Prakriti-wise distribution in patients



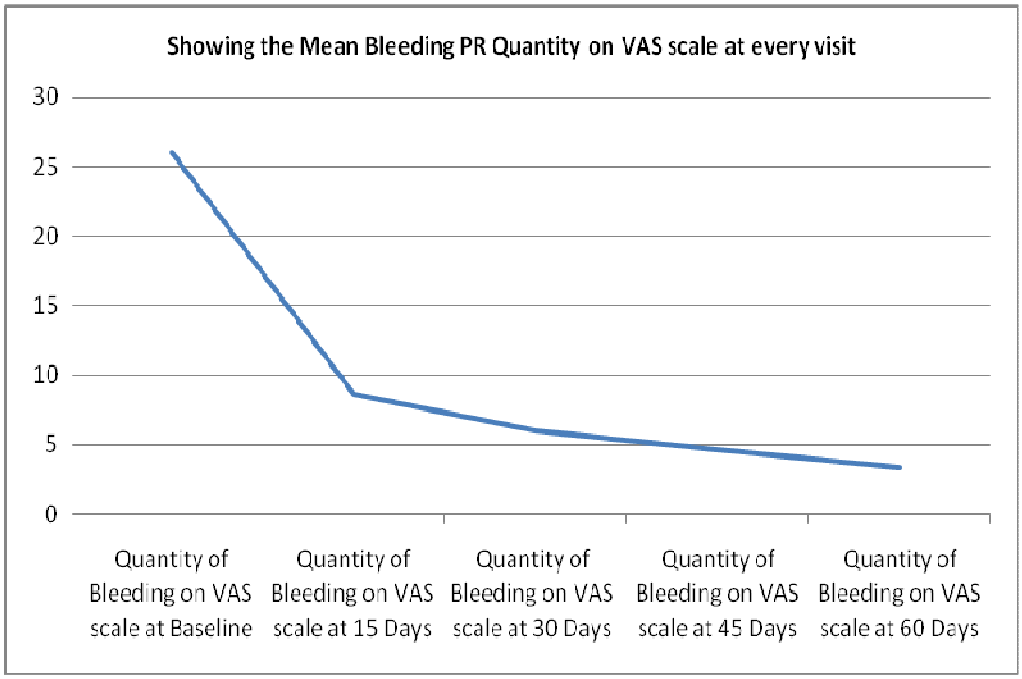
Graph III

Assessment of incidence of bleeding per rectum in 30 patients



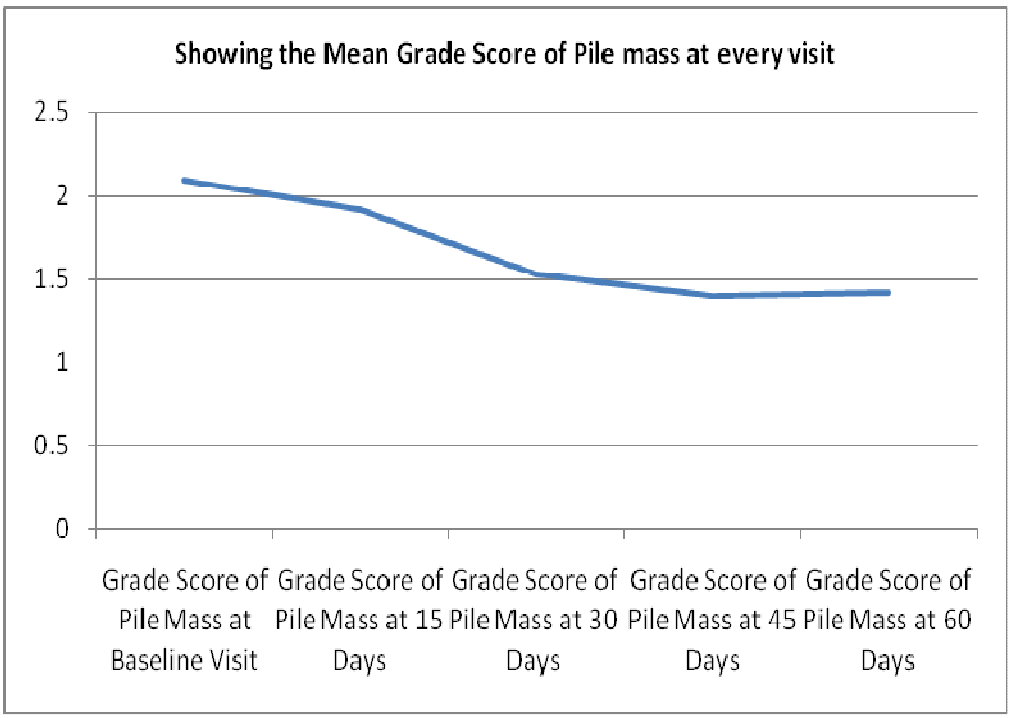
Graph IV

Mean VAS score of quantity of bleeding per rectum



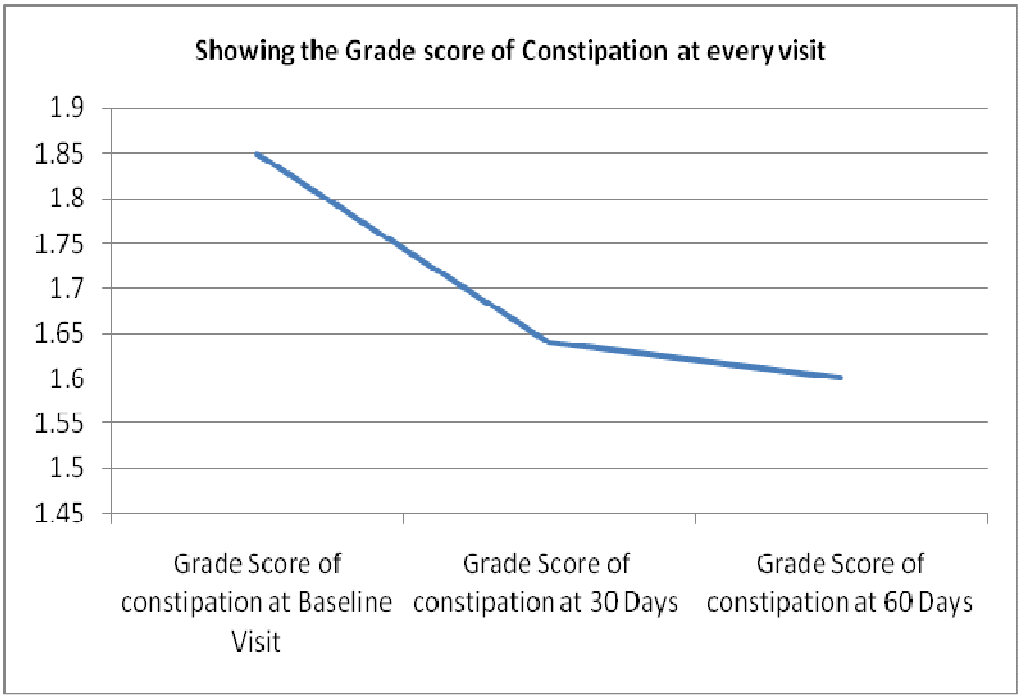
Graph V

Mean grade score of pile mass evaluated by proctoscopic examination

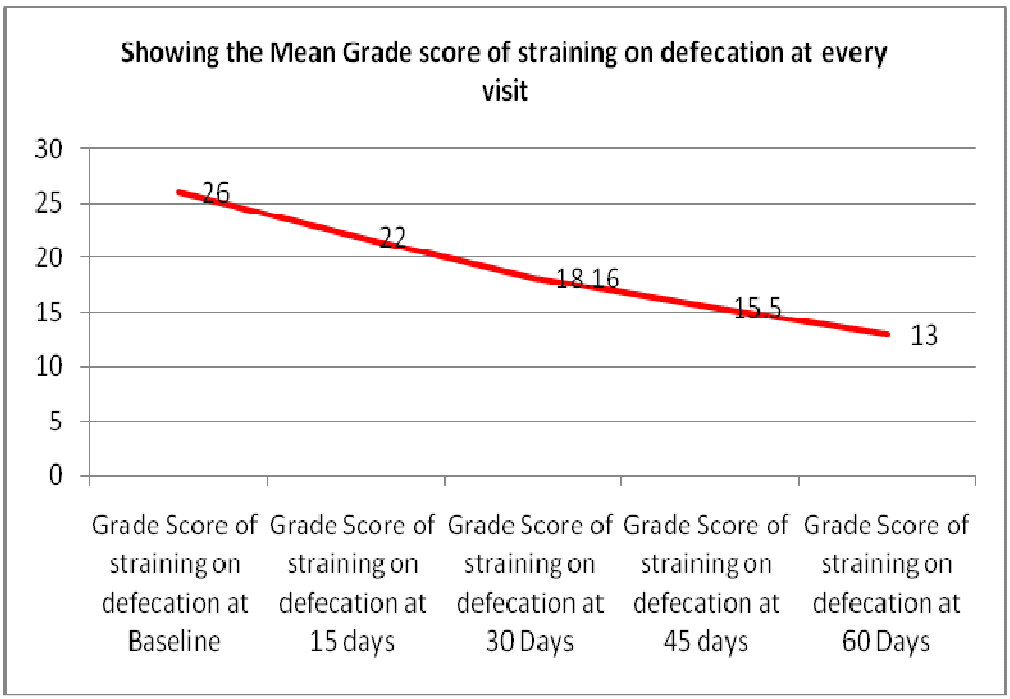


Graph VI

Mean grade score of constipation



Graph VII
Mean grade score of straining on defecation



DISCUSSION

The present study was done with the aim to evaluate proportion of subjects achieving cessation of per rectal bleeding at the end of the treatment and also to evaluate post treatment reduction in severity of bleeding per rectum. The efficacy of the study drug was also done to evaluate post treatment reduction in pile mass, post treatment reduction in other symptoms of hemorrhoids, improvement in Quality of Life of patient, global assessment for overall improvement by patient and by physician and pre and post treatment changes in laboratory investigations at the end of the study. Thirty six patients suffering from hemorrhoids were screened during the study period. Out of 36 screened patients, 32 patients were recruited in the study. Four patients were not recruited in the study because they did not meet inclusion and exclusion criteria. The primary reasons behind screen failure were higher degree of hemorrhoids and bleeding. Out of 32 recruited patients, 30 patients completed the study and 2 patients dropped out of the study due to loss to follow up. Out of 30 patients who completed the trial, there were 28 (93.33%) males and 2 (6.66 %) females. The higher incidence of male patients in this trial could be due to the predominant male population attending the site and the higher incidence of the disease in males in the region, lack of female patients being aware or not reporting of the disease. It was observed in the current study that the incidence of hemorrhoids was high amongst the young population between 21 to 30 years (46.66%) and 31 to 40 years (36.66%). This probably signals towards the role of food and life style habits in this age group. In terms of incidence of the disease with respect to body constitution (*Prakriti*), it was observed that about half the study population (46.67 %) was having *Vata-Pita Prakriti*. This signifies the higher incidence of the disease condition in this *Prakriti* type. Assessment of efficacy of the trial drug was done by evaluating the difference in mean, percentage change and the rate of shift of grades in the VAS score and in the grade/severity of the various symptoms by comparing the baseline score and scores at every follow up. Mean, Standard deviation, t values and percentage changes from base line at every follow up were calculated to arrive to conclusions. It was observed that there was a

statistically significant reduction in symptoms like bleeding per rectum, straining on defecation, and reduction in the pile mass. Assessment of study drug on the incidence of bleeding PR revealed that 86.66 % of study population showed cessation of bleeding after treatment for 60 days. Evaluation of the quantity of bleeding PR revealed that a statistically highly significant reduction was observed within 15 days of starting the trial drug which continued to be highly significant ($p<0.01$) at every follow up till the last follow up of 60 days. Assessment of study drug for its effect on the pile mass was also done which was evaluated by proctoscopic examination at every follow up of 15 days. It was observed that a highly significant reduction was observed in the pile mass ($p<0.01$) after 15 days which further continued and was observed at every follow up till the final visit of the patient. In the present study, it was also observed that there was a significant reduction in the other main symptoms of hemorrhoids viz. constipation and straining on defecation. While constipation showed a significant improvement $p<0.05$) at the end of 30 days it further improved to being highly significant ($p<0.01$) at the end of 60 days. Straining on defecation showed significant improvement after 15 days which further continued till 60 days. It was observed that there were no significant changes in the laboratory parameters like CBC, Hb%, ESR, LFTs, RFTs, lipid profile, urine and stool examinations and ECG. These parameters remained within the normal limits both at the initial and final visit of the patients during the trial. Global evaluation by the physician and patient showed excellent improvement in reducing the symptoms of hemorrhoids. Subjects also showed excellent tolerability and good compliance to study drugs. There was no evidence of any adverse event or severe adverse event during the study period. It was observed from results of the present clinical study that the synergistic effect of the herbs present in 'ARWL12' capsule has helped to reduce symptoms of piles significantly. Ingredients such as *Lajjalu*, *Nagkeshar* and *Neem* possess astringent and styptic properties thus helped to stop bleeding from pile mass. *Lajjalu* possesses vasoconstrictor, anti-inflammatory and anti-biotic effects thus helped to reduce pile mass in patients. Ingredients like *Isabgol* and *Haritaki* helped to relieve constipation in the patients. Thus, 'ARWL12' capsule is a unique combination of herbs useful in the management of piles. The results of the present clinical study are highly encouraging. A randomized, double blind, active comparative, multi-centric clinical study with large sample size is needed to further validate safety and efficacy of 'ARWL12' capsule in the management of piles.

CONCLUSION

The present study confirms the efficacy and safety of 'ARWL12' capsule in relieving symptoms of hemorrhoids. Symptoms such as bleeding pile mass, straining on defecation and constipation was significantly reduced at the end of the study. Hence, it can be concluded that 'ARWL12' capsule can be used safely and effectively in the treatment of internal hemorrhoids.

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