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A CLINICAL STUDY TO EVALUATE EFFICACY AND SAFETY OF PILOSET TABLET + PILOSET CREAM IN PATIENTS SUFFERING FROM INTERNAL HEMORRHOIDS.

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ABSTRACT

Objectives: The main objective of study was to assess the efficacy and safety of Piloset tablet + Piloset cream (polyherbal formulations) in subjects suffering from internal hemorrhoids. **Methods**: It was an open label, single-center, prospective, interventional, phase II clinical trial. Total 32 subjects were completed the study. All subjects were advised to take two Piloset tablets twice daily orally after meals and to apply sufficient amount of Piloset cream on piles mass twice daily for 60 days. After baseline visit, all subjects were called for follow-up on day 15, 30, 45 and day 60. Data describing quantitative measures were expressed as mean ± SD. Comparison of variables representing categorical data was performed using Chi-square test or Fisher's exact test. **Results:** Episodes of bleeding per rectum were completely stopped in all 32 patients. At the end of the treatment, a significant reduction in abdominal pain & discomfort, straining on defecation, mucus discharge, pain at anal region (assessed on VAS scale) and pruritus has been observed. No significant change in vital parameters and safety laboratory parameters were observed at the end of the study. Global evaluation by the physician and patient showed excellent improvement in the symptoms of hemorrhoids. Almost all patients showed excellent tolerability to the study drugs. **Conclusion:** The study provides good evidence in support of the efficacy and safety of Piloset tablet + Piloset cream in hemorrhoids.

KEYWORDS: Piloset tablet + Piloset cream, hemorrhoids, VAS.

INTRODUCTION

Hemorrhoids 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. The external variety is covered by skin, while internal variety lies beneath anal mucous membrane.[1]

More than half of men and women aged 50 years and older develop hemorrhoid symptoms during their lifetime.[1] Haemorrhoids are also common among pregnant women. The pressure of the fetus in the abdomen, as well as hormonal changes causes hemorrhoidal vessels to enlarge. Anorectal varices are commonly found in patients with portal hypertension also.[1-2]

Abnormal dilatation of veins of the internal hemorrhoidal venous plexus, abnormal distension of the arteriovenous anastomosis, prolapse of the cushions and the surrounding connective tissue leads to hemorrhoids. Elevated anal sphincter pressure is also presumed as one of the etiologic factors contributing to the disease.[2]

Bleeding is the most common symptom of hemorrhoids, and other less common symptoms include pain or discomfort, prolapse, itching, and mucous discharge.[3]

Internal hemorrhoids originate from the internal hemorrhoidal venous plexus above the dentate line; external haemorrhoids originate from the external plexus below the dentate line. Internal hemorrhoids can be classified according to the degree of prolapse, although this may not reflect the severity of a patient's symptoms. First-degree haemorrhoids bleed but do not prolapse. Second-degree haemorrhoids prolapse on straining and reduce spontaneously. Third degree haemorrhoids prolapse on straining and require manual reduction. Fourth degree haemorrhoids are prolapsed and incarcerated.

The treatment includes intake of high fiber 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 smodalities 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 are associated with complications. On the other hand, surgical haemorrhoidectomy is associated with a significant morbidity and may lead to delay in recovery. Therefore patients are looking for a medical treatment which is easy to administer and devoid of significant side effects.[4]

Arsha in Ayurvedic texts can be correlated to Piles described in modern era. It irritates person like enemy (Ari) hence it is called as Arsha.[5] According to Ayurveda, *Arsha* is a mass which occurs in *Gudvalli* (layers of anus).[5] Several pathogenic factors such as improper diet, low digestive fire (Mandagni) excessive straining during defecation, excessive riding of horses can lead to *Arsha* formation in *Guda* (anus).[6] Theses causes lead to vitiation of *Dosha* (*Vata*, *Pitta* and *Kapha*) and these *Dosha* vitiate *Twaka* (skin), *Rakta* (blood), *Mamsa* (muscles) and *Meda* (fat) at *Guda* (anal) region and cause *Masankur* (lump) formation. This lump is called as *Arsha.*[7] *Mandagni* (improper digestion) has been considered as main cause of *Arsha* (piles).

Arsha causes *Kila vat Pida* (pricking pain), *Kandu* (itching sensation), *Rakta Srava* (bleeding), *Ruja* (pain) at anal region and also causes *Avarodha* (obstruction) during defecation[8]. Four types of treatments of *Arsha* have been described in Ayurveda viz. *Aushadha Prayoga* (use of medicines), *Shastra Karma* (surgery), *Kshara Karma* (burning by alkalis) and *Agni Karma* (burning of Arsha using fire). In all four types of treatment methodologies, *Aushadha Prayoga* (use of medicines) has been preferred by many physicians due to fewer side effects. *Aushadha Chikitsa* is also divided in two parts viz. *Shodhana* (purification) and *Shamana* (conservative). *Shodhana* (purification) includes use of *Basti* (enemas), *Virechana* (laxative), etc. In *Shamana*, Ayurveda offers a range of herbal and herbo-mineral combinations to treat *Arsha* successfully. Many classical preparations are described in the Ayurvedic classical texts such as *Arshakuthar Rasa*, *Arshoghni Vati*, *Abhayarishta*, *Kasisadi Taila*, etc., for the management of hemorrhoids. Also, individual plants such as *Devadaru*, *Bilva*, *Eranda*, *Nimba*, *Lajjalu*, *Nagkeshar*, *Apamarga*, etc., have been used in the treatment of *Arsha*.[9]

Piloset Tablet is one such combination, developed by Arjun Healthcare for the effective management of hemorrhoids. The ingredients of Piloset tablet possess astringent and styptic properties thus help to stop bleeding from pile mass. The ingredients also have vasoconstrictor, anti-inflammatory and anti-biotic effects thus useful to reduce pile mass. The ingredients are also helpful in relieving symptoms like pruritus ani, discomfort at anal region, constipation, flatulence and also abdominal pain. Also, Piloset cream has been developed by Arjun Healthcare for local application on affected area. It helps to control bleeding, reduces inflammation, pain, pruritus ani and other associated symptoms of hemorrhoids.

Clinical Trials were recommended by experts to establish the evidence base for the use of herbal formulations. Hence, a clinical trial to evaluate efficacy and safety of Piloset Tablet + Piloset Cream in patients suffering from Internal Hemorrhoids was planned.

METHODOLOGY

1. Study Design

The study was an open labeled, single-center, prospective, interventional, phase II clinical study.

2. IEC Approval

Before the initiation of the study, the study protocol and related documents were reviewed and approved by IEC of Seth Tarachand Ramnath Ayurvedic Charitable Hospital, 580/2, Rasta Peth, Pune-11. The study was conducted in accordance with this protocol and AYUSH GCP guidelines (issued by AYUSH in March 2013). No changes in study plan or protocol were implemented during the trial.

3. CTRI Registration

The clinical study was registered prospectively on CTRI. The trial was registered on 08.01.2014. The CTRI No. for the trial is CTRI/2014/01/004300.

4. Study Objectives

Primary objectives were to evaluate efficacy of Piloset tablet + Piloset cream in patients suffering from internal hemorrhoids by assessing proportion of subjects achieving cessation of per rectal bleeding at the end of the treatment and by assessing post-treatment reduction in severity of bleeding per rectum.

Secondary objectives were to evaluate the efficacy of Piloset tablet + Piloset cream by assessing post treatment reduction in pile mass, post treatment reduction in other symptoms of hemorrhoids, improvement in Quality of Life at the end of the treatment, global assessment for overall improvement by patient at the end of the treatment, global assessment for overall improvement by physician at the end of the treatment and pre & post treatment changes in laboratory investigations like Liver function tests (LFT), Renal function tests (RFT), Lipid profile, Complete Blood Count (CBC), ESR, Urine Examination, Stool Examination and ECG.

5. Sample Size

Sample size calculation was based on the assumption that a sample size of 30 evaluable cases would have provided 80% power to estimate the reduction in pile mass. Considering 20% dropout, 36 patients were enrolled.

6. Subject Selection

Male and female subjects between 21-60 years of age were selected for the study. Subjects, who were suffering from first and second degree internal hemorrhoids, and attending the outpatient department (OPD) of department of Shalya Tantra, at Seth Tarachand Ramnath Ayurvedic Charitable Hospital, 580/2, Rasta Peth, Pune-411011 and meeting the inclusion criteria were recruited in the trial. Subjects willing to follow study procedures mentioned in protocol and voluntarily signed the informed consent form were included in study. Subjects who were suffering from symptomatic internal hemorrhoids (grades I & II by direct proctoscopic visualization) and having bleeding from hemorrhoids for at least two days prior to randomization were included in study. Subjects, who were ready to refrain from any allopathic, Ayurvedic, homeopathic, Siddha, Unani drug(s) or any other traditional or folklore medicine for hemorrhoids or for constipation during washout period (3 days) were included in study. Females of child bearing potential who agree to use contraception were included in study. Subjects who were having body mass index of $\geq$ 18.5 to $\leq$ 36 kg/m^2 were included in study. Precautions were taken not to recruit subjects belonging to possible vulnerable groups. Pregnant and lactating women were excluded from the study. Subjects with known hypersensitivity to trial medicines or its components were excluded from the study. Subjects with protruding or irreducible hemorrhoids (grade III & IV), anal fistulas, periproctitis or hemorrhagic diathesis, current history of Type I or Type II diabetes mellitus, severe hepatic, renal or cardiovascular disorders, any type of infectious disease and presently diagnosed with cancer were excluded from the study. Patients who were using suppositories, anticoagulants within 30 days prior to recruitment and those using anti-platelet agents or low dose aspirin and over the counter or prescription anti-hemorrhoid agents (allopathic, herbal, homeopathic, Unani, Siddha medicines) within 14 days prior to recruitment were excluded from the trial. Subjects known to have alcohol and drug abuse were excluded from the study. Patients who had been involved with another experimental drug trial within the past 30 days form the day of recruitment and subjects with blood or urine laboratory values outside the normal limits or those with values considered abnormal in the opinion of the investigator were excluded from the study.

7. Investigational Drug

The investigational products i.e. Piloset tablet and Piloset cream were manufactured by the Sponsor i.e. Arjun Healthcare Pvt. Ltd., following GMP and all applicable regulatory guidelines. The compositions of the drugs are given in Table 1 and Table 2.

8. Study Procedure

On screening visit, patient's voluntary written informed consent was taken & general and systemic examinations were done. Vital signs including pulse rate, respiratory rate, body temperature and blood pressure were assessed. Subject's Prakriti, detailed medical history along with the current medications (if any) were noted. Subject was evaluated on WHO quality of life assessment questionnaire to judge subject's quality of life. Subjects presenting with bleeding per rectum and or other symptoms of hemorrhoids were subjected to proctoscopic examination to confirm the diagnosis of hemorrhoids, position of hemorrhoids and size of hemorrhoids (each pile mass was graded on a scale of 1 to 4, for size and inflammation. Grade 0 size denotes no internal haemorrhoid or flat mucosa. Grade 1 - small haemorrhoids, without prolapse. Grade 2 - medium size that prolapses and returns spontaneously Grade 3 - large internal haemorrhoids that prolapses but can still be manually reduced. Grade 4- very large internal haemorrhoids and cannot be manually reduced).

On screening visit, subject's symptoms i.e. bleeding (severity of bleeding was assessed by the number of bleeding episodes per day over a given week before treatment, at each follow up visit and after treatment) was considered severe if it occurred more than five times a week, moderate if three to five times per week and mild if less than three times per week. Also, the quantity of bleeding at each episode of bleeding was measured. The quantity of bleeding was measured on 0 to 100 scales, wherein 0 indicates no bleeding and 100 indicate maximum bleeding). Symptoms such as abdominal pain/discomfort (assessment on VAS), constipation (frequency of stool per day), straining on defecation (assessment on VAS), mucus discharge, pruritus [score ranging from 0 (no symptom) to 100 (itching all the time and causing severe interruption in routine activities)] and pain in the anal region/perineum (assessment on VAS) were assessed. On screening visit, subject undergone investigations viz. fasting blood sugar, CBC, ESR, Hb%, Liver function tests, Renal function tests, Lipid profile, Urine routine and microscopic, Stool Routine and microscopic, Urine pregnancy test (only if the subject was female of child bearing potential), HIV test (I& II), X- ray chest (PA View) and ECG. Subjects were provided with diary card to record daily symptoms of hemorrhoids. After screening visit, subjects were called at study site for follow-up visits viz. Baseline Visit (day 0), Visit-I (day 15), Visit-II (day 30), Visit-III (day 45) and Visit-IV (day 60).

On baseline visit, subject was recruited, if he/she met all the inclusion criteria. Subject was asked for any AE/SAE occurred. If subject had AE/SAE, the details of the incidence were documented and reported to the IEC. Rescue medication used, if any, was recorded in the CRF. On baseline visit and every follow-up visit, subject's general and systemic examinations were done. Vital signs including pulse rate, respiratory rate, body temperature and blood pressure were assessed. Subject's bleeding episodes, severity of bleeding and quantity of bleeding at each episode were measured. Symptoms such as abdominal pain/discomfort, constipation, straining on defecation, mucus discharge, pruritus and pain in the

anal region/perineum were also assessed. On every follow-up visit, filled diary card was collected from subjects. On baseline visit and every follow-up visit except last follow-up visit, subjects were provided with new diary card to record daily symptoms of hemorrhoids. On baseline visit, visit 2 and visit 4, subject was evaluated on WHO quality of life assessment questionnaire to judge subject's quality of life. On baseline visit and every follow-up visit except last follow-up visit, subjects were given 1 HDPE container of Piloset tablet (60 tablets) + 2 tubes of Piloset cream. Subjects were advised to take 2 tablets of given medicine twice daily orally after meals for next 15 days. Also, subjects were advised to apply sufficient amount of given cream on piles twice daily for 15 days. Subjects were advised to return empty container after 15 days when they come for next follow up to check the drug compliance. The container provided to the subject on the previous visit was collected and remaining medicine was counted (tablets) and weighed (cream) 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 4 (day 60), subject's global assessment and investigator's global assessment for overall improvement were done. Tolerability of the trial drugs was assessed on global assessment scale by the investigator and by patient. Subjects had undergone investigations viz. CBC, ESR, Hb%, liver function tests, renal function tests, lipid profile, urine routine and microscopic, stool routine and microscopic. Also, subject's ECG was done. Safety analysis was done by clinical review of all safety parameters, including the laboratory investigations (if required), adverse events and vital signs. All the study activities and findings were documented in the source document and CRF. Subjects were asked to stop the trial drugs and were advised to meet physician for further course of treatment.

9. Statistical Analysis

Consultant statistician performed the analysis of the data using statistical software SPSS 10.0. Data describing quantitative measures are expressed as median or mean ± SD or SE or the mean with range. Qualitative variables are 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 was performed using Chi-square test or Fisher's exact test. Mean differences of continuous variables were examined by Student t test and comparison between two groups by independent t test or Group means of dependent sample was compared by means of ANOVA (repeated-measures design, GLM procedure). All p-values were reported based on two-sided significance test and all the statistical tests were interpreted at 5% level of significance.

RESULTS

A total of 45 subjects were screened for recruitment, out of which 36 subjects suffering from internal haemorrhoids were recruited in the study. The reasons for screen failure were third or fourth degree piles, fissures etc. Four subjects, out of 36 subjects dropped out prematurely. The reason for drop outs was lost to follow up. Out of 32 subjects included in the trial, 23 (71.87%) were males while 9 (28.12%) were females. There were 9 (28.12%) subjects of 21-30 years of age, 8 (25%) subjects of 31-40 years of age, 6 (18.75%) subjects of 41-50 years of age and 9 (28.12%) subjects of 51-60 years of age. Among the 32 recruited subjects, 17 (53.12%) subjects were having *Pitta-Vata Prakriti*, 13 (40.62%) subjects were having *Vata-Pitta Prakriti*, 1 (3.12%) subject was having *Pitta-Kapha Prakriti* and 1 (3.12%) subject was having *Pitta Prakriti*. No significant change from baseline to end of therapy values in any of the vital signs i.e. pulse rate, body temperature, respiratory rate, systolic and diastolic BP was observed.

Among the 32 recruited subjects, 26 (81.25%) subjects were having sound sleep, 5 (15.62%) subjects had interrupted sleep and 1 (3.12%) subject had disturbed sleep on day 0 (baseline visit). On day 15 (visit 1), 30 (93.75%) subjects were having sound sleep and 2 (6.25%) subjects had interrupted sleep. On day 30 (visit 2), 30 (93.75%) subjects were having sound sleep and 2 (6.25%) subjects had interrupted sleep. On day 45 (visit 3) and day 60 (visit 4), all 32 (100%) subjects had sound sleep. Among the 32 recruited subjects, 16 (50%) subjects were having normal appetite, 1 (3.12%) subject had increased appetite and 15 (46.87%) subjects had decreased appetite on day 0 (baseline visit). On day 15 (visit 1), 27 (84.37%) subjects were having normal appetite, 2 (6.25%) subjects had increased appetite and 3 (9.37%) subjects had decreased appetite. On day 30 (visit 2), 30 (93.75%) subjects were having normal appetite and 2 (6.25%) subjects had increased appetite. On day 45 (visit 3), all 32 (100%) subjects had normal appetite. On day 60 (visit 4), 29 (90.62%) subjects were having normal appetite and 3 (9.37%) subjects had increased appetite. Among the 32 recruited subjects, 6 (18.75%) subjects were having regular bowel movements, 25 (78.12%) subject had constipation and 1 (3.12%) subject had loose bowel movements on day 0 (baseline visit). On day 15 (visit 1), 26 (81.25%) subjects were having regular bowel movements and 6 (18.75%) subjects had constipation. On day 30 (visit 2), 30 (93.75%) subjects were having regular bowel movements and 2 (6.25%) subjects had constipation. On day 45 (visit 3) and day 60 (visit 4), all 32 (100%) subjects had regular bowel movements.

Among the 32 recruited subjects, 12 (37.50%) subjects were having 1 piles mass, 18 (56.25%) subjects had 2 piles mass and 2 (6.25%) subjects had 3 piles mass on day 0 (baseline visit). On day 15 (visit 1), day 30 (visit 2) and day 45 (visit 3), 11 (34.37%) subjects were having 1 piles mass, 19 (59.37%) subjects had 2 piles and 2 (6.25%) subjects had 3 piles mass. On day 60 (visit 4),

14 (43.75%) subjects were having 1 piles mass, 16 (50%) subjects had 2 piles and 2 (6.25%) subjects had 3 piles mass. The details are given in Table 3 and Figure 1.

Among the 32 recruited subjects, 7 (21.87%) subjects were having grade 1 piles mass and 25 (78.12%) subjects had grade 2 piles mass on day 0 (baseline visit). On day 15 (visit 1),day 30 (visit 2), day 45 (visit 3) and day 60 (visit 4), 6 (18.75%) subjects were having grade 1 piles mass and 26 (81.25%) subjects had grade 2 piles mass. The details are given in Table 4 and Figure 2.

Among the 32 recruited subjects, all 32 (100%) subjects were having bleeding per rectum on day 0 (baseline visit). On day 15 (visit 1), 4 (12.5%) subjects were having bleeding per rectum and 28 (87.5%) subjects had no bleeding. On day 45 (visit 3), and day 60 (visit 4), no subject had bleeding per rectum. The details are given in Table 5 and Figure 3.

Among the 32 recruited subjects, 1 (3.12%) subject had 1 episode of bleeding per rectum, 9 (28.12%) subjects had 2 episodes, 5 (15.62%) subjects had 3 episodes, 7 (21.87%) subjects had 4 episodes, 7 (21.87%) subjects had 4 episodes, 9 (28.12%) subjects had 5 episodes and 1 (3.12%) subject had 6 episodes of bleeding per rectum on day 0 (baseline visit).On day 15 (visit 1), 28 (87.5%) subject had 1 episode of bleeding per rectum, 1 (3.12%) subject had 2 episodes and 3 (9.37%) subjects had 3 episodes of bleeding per rectum. On day 30 (visit 2), 31 (96.87%) subject had 1 episode of bleeding per rectum and 1 (3.12%) subject had 3 episodes of bleeding per rectum. On day 45 (visit 3) and day 60 (visit 4), no subject had bleeding per rectum. The details are given in Table 6 and Figure 4.

Among the 32 recruited subjects, 25 (78.12%) subjects had VAS score from 50-80 and 7 (21.88%) subjects had VAS score from 10-40 on day 0 (baseline visit). On day 15 (visit 1), 4 (12.5%) subjects had VAS score from 10-40 and 28 (87.5%) subjects had VAS score 0 i.e. no sever bleeding. On day 30 (visit 3), 2 (6.25%) subjects had VAS score from 10-20 and 30 (93.75%) subjects had VAS score 0 i.e. no sever bleeding. On day 45 (visit 3) and day 60 (visit 4), all 32 (100%) subjects had VAS score 0 i.e. no sever bleeding. The details are given in Table 7 and Figure 5.

On day 0 (baseline visit), the VAS score (for quantity of bleeding per rectum) was 56.56 ± 16.18. The VAS score decreased to 6.25 ± 19.13 on day 15 (visit 1). On day 30, the VAS score decreased to 1.56 ±6.27. When compared, the differences were significant between VAS score on day 0 and VAS score on day 15 and day 30. The details are given in following table. VAS Score was 0 on day 45 and day 60. The details are given in Table 8 and Figure 6.

On day 0 (baseline visit), 13 (40.62%) subjects were having VAS score (abdominal pain and discomfort) 0, 2 (6.25%) subjects were having VAS score 20, 1 (3.12%) had VAS score 30, 4 (12.5%)subjects had VAS Score 50, 2 (6.25%)subjects had VAS Score 60, 5 (15.62%) subjects had VAS score 70, 1 (3.12%) subject had VAS score 80, 3 (9.37%) subjects had VAS score 90 and 1 (3.12%) subject had VAS score 100, On day 15, 27 (84.37%) had VAS score 0, 2 (6.25%) subjects had VAS score 10, 1(3.12%) subject had VAS score 20 , 1(3.12%) subject had VAS score 30 and 1(3.12%) subject had VAS score 70. ON day 30, day 45 and day 60 all the subjects had VAS score 0. The details are given in Table 9 and Figure 7.

On day 0 (baseline visit), the mean abdominal pain assessed on VAS was 37.18 ± 35.85, which reduced significantly to 4.37 ± 13.66 on day 15. On day 30, 45 and 60 day the mean abdominal pain assessed on VAS was 0. The details are given in Table 10 and Figure 8.

On day 0 (baseline visit), the mean VAS score of straining on defecation was 45.93 ± 29.82, which reduced significantly to 2.5 ± 9.15 on day 15. On day 30, 45 and 60 day the mean VAS score of straining on defecation was 0. The details are given in Table 11 and Figure 9.

On day 0 (baseline visit), the mean VAS score of mucus discharge was 31.25 ± 29.26, which reduced significantly to 1.25 ± 3.36 on day 15. On day 30, 45 and 60 day the mean VAS score of mucus discharge was 0. The details are given in Table 12 and Figure 10.

On day 0 (baseline visit), the mean VAS score of pruritus was 49.37 ± 34.72, which reduced significantly to 23.43 ± 28.23 on day 15. On day 30, the mean VAS score of pruritus reduced to 16.87 ± 25.83. On day 45, the mean VAS score of pruritus reduced to 9.06 ± 17.66 and on day 60, the mean VAS score of pruritus significantly reduced to 2.5 ± 9.5. The details are given in Table 13 and Figure 11.

On day 0 (baseline visit), the mean VAS score of pain in anal region was 50 ± 36.10, which reduced significantly to 6.25 ± 16.80on day 15. On day 30, the mean VAS score of pain in anal region reduced to 0.31 ± 1.76. On day 45 and day 60, the mean VAS score of pain in anal region was 0. The details are given in Table 14 and Figure 12.

On day -3 (screening visit), 3 subjects (9.37%) were having blood in their stool and 29 (90.62%) patients were not having blood in their stool. On day 60, all the 32 subjects were not having blood in their stool. The details are given in Table 15 and Figure 13.

No statistically significant difference was observed in Hb% and RBC count post treatment. Post treatment statistically significant decreased in ESR was observed. It was clinically insignificant. The details are given in Table 16 and Figure 14. No significant change in any of

the parameters of lipid profile was observed after treatment. The details are given in Table 17 and Figure 15. No significant change in any of the parameters of liver profile was observed after treatment. The details are given in Table 18 and Figure 16. No significant change in any of the parameters of renal profile was observed after treatment. The details are given in Table 19 and Figure 17.

As per assessment of physician, excellent response was observed in 11 (34.37%) subjects, while good response was observed in 21 (65.62%) subjects. As per subject's assessment, excellent response was observed in 14 (43.75 %) subjects, while good response was observed in 18 (56.25%) subjects. The details are given in Table 20. As per physician and subject, 100% subjects had over all excellent tolerability to the study drugs administered. The details are given in Table 21.

Both the study drugs were well tolerated by all the study subjects. No adverse event or adverse drug reaction was observed in any subject.

Table-1: Composition of Piloset Tablet

Each Film Coated Tablet Contains

S. No.	***Ingredients***	***Botanical Name***	***Quantity(mg)***
1	Lajjalu Powder	*Mimosa pudica*	120
2	Nagkesar Powder	*Mesua ferrea*	120
3	Aralu Extract	*Ailanthus excels*	100
4	Senna Extract	*Cassia angustifolia*	100
5	Chitrak Extract	*Plumbago zeylanica*	50
6	Daruharidra Extract	*Berberis aristata*	50
7	Nimba Extract	*Azadirachta indica*	45
	Approved colors used for film coating		

Table-2: Composition of Piloset Cream

Each gm of Cream Contains % of Ingredients

S. No.	***Ingredients***	***Botanical Name***	***Quantity***
1	Lajjalu Extract	*Mimosa pudica*	2
2	Daruharidra Extract	*Berberis aristata*	1
3	Nagkeshar Extract	*Mesua ferrea*	2
4	Haridra Extract	*Curcuma longa*	2
5	Kasisadi Taila	Ayurvedic Classical Formulation	5
6	Jatyadi Taila	Ayurvedic Classical Formulation	5
7	Nimba Taila	Ayurvedic Classical Formulation	2
8	Kshara (Ksharodaka)	Ayurvedic Classical Formulation	2
	Apararg kshaar	*Achyranthus aspera*	
	Powders of		
9	Yashada Bhasma	Ayurvedic Classical Formulation	1
10	Tankan Bhasma	Ayurvedic Classical Formulation	1
11	Shuddha Gandhaka	Ayurvedic Classical Formulation	2
	Cream base to make 100%		

Table 3: Showing no of subjects having 1, 2 or 3 pile mass over 60 days

No. of Piles mass	**No. of Patients**				
	Day 0	Day 15	Day 30	Day 45	Day 60
1	12 (37.5%	11 (34.37%)	11(34.37%)	11(34.37%)	14(43.75%)
2	18 (56.25%)	19 (59.37%)	19(59.37%)	19(59.37%)	16 (50%)
3	2 (6.25%)	2(6.25%)	2(6.25%)	2(6.25%)	2(6.25%)
Total	32	32	32	32	32

Table 4: Showing grade wise distribution of pile mass over 60 days in the subjects

	No. of Patients				
Grade of Pile Mass	**Day 0**	**Day 15**	**Day 30**	**Day 45**	**Day 60**
1	7 (21.87%)	6 (18.75%)	6(18.75%)	6(18.75%)	6(18.75%)
2	25 (78.12%)	26 (81.25%)	26(81.25%)	26(81.25%)	26(81.25%)
3	0	0	0	0	0
Total	32	32	32	32	32

Table 5: Showing the incidence of bleeding per rectum over 60 days in subjects

Bleeding per rectum	No. of Patients				
	Day 0	Day 15	Day 30	Day 45	Day 60
Present	32 (100%)	4 (12.5%)	0	0	0
Absent (No Bleeding)	0	28 (87.5%)	32 (100%)	32(100%)	32(100%)

Table 6: Showing the episodes of bleeding in one week over 60 days in subjects

	No. of Patients				
No. of Bleeding Episodes Over last Week	**Day 0**	**Day 15**	**Day 30**	**Day 45**	**Day 60**
0	0	28 (87.5%)	31 (96.87%)	32 (100%)	32 (100 %)
1	1 (3.12%)	0	0	0	0
2	9 (28.12%)	1 (3.12%)	0	0	0
3	5 (15.62%)	3 (9.37%)	1 (3.12%)	0	0
4	7 (21.87%)	0	0	0	0
5	9 (28.12%)	0	0	0	0
6	1 (3.12%)	0	0	0	0
Total	32 (100%)	32 (100%)	32(100%)	32(100%)	32(100%)

Table 7: Showing the severity of bleeding on VAS scale (0 to100) over 60 days

Severity of Bleeding on VAS	No. of Patient				
	Day 0	**Day 15**	**Day 30**	**Day 45**	**Day 60**
0	0	28	30	32 (100%)	32(100%)
10	0	1(3.12%)	1(3.12%)	0	0
20	1(3.12%)	1(3.12%)	1(3.12%)	0	0
30	4(12.5%)	1(3.12%)	0	0	0
40	2(5.25%)	1(3.12%)	0	0	0
50	4(12.5%)	0	0	0	0
60	12(37.5%)	0	0	0	0
70	5(15.62%)	0	0	0	0
80	4(12.5%)	0	0	0	0
90	0	0	0	0	0
100	0	0	0	0	0
Total	32	32	32	32	32

Table 8: Showing Mean VAS score of Quantity of Bleeding per Rectum during the trial period

Sr. No.	Duration (Quantity of Bleeding on)	Mean VAS Score ±SD	T Value (as compared to baseline visit)
1	VAS scale at Baseline Visit	56.56 ± 16.18	-
2	VAS scale at 15 Days	6.25 ± 19.13	11.35($p<0.01$ HS)
3	VAS scale at 30 Days	1.56 ±6.27	17.92($p<0.01$ HS)
4	VAS scale at 45 Days	0	19.76($p<0.01$ HS)
5	VAS scale at 60 Days	0	19.76($p<0.01$ HS)

Table 9: Showing the distribution of Abdominal Pain & Discomfort assessed on VAS scale over 60 days

	No. of Patient				
Abdominal Pain & Discomfort (VAS)	**Day 0**	**Day 15**	**Day 30**	**Day 45**	**Day 60**
0	13(40.62%)	27 (84.37%)	32 (100%)	32(100%)	32(100%)
10	0	2 (6.25%)	0	0	0
20	2 (6.25%)	1(3.12%)	0	0	0
30	1 (3.12%)	1(3.12%)	0	0	0
40	0	0	0	0	0
50	4 (12.5%)	0	0	0	0
60	2 (6.25%)	0	0	0	0

70	5 (15.62%)	1(3.12%)	0	0	0
80	1(3.12%)	0	0	0	0
90	3 (9.37%)	0	0	0	0
100	1(3.12%)	0	0	0	0
Total	32	32	32	32	32

Table 10: Showing Mean VAS score of Abdominal Pain during the trial period

Sr. No.	Duration	Mean VAS Score ±SD	T Value (as compared to baseline visit)
1	Abdominal Pain on VAS scale at Baseline Visit	37.18 ± 35.85	-
2	Abdominal Pain on VAS scale at 15 Days	4.37 ± 13.66	4.83 (p<0.01 HS)
3	Abdominal Pain on VAS scale at 30 Days	0	5.86 (p<0.01 HS)
4	Abdominal Pain on VAS scale at 45 Days	0	5.86 (p<0.01 HS)
5	Abdominal Pain on VAS scale at 60 Days	0	5.86 (p<0.01 HS)

Table 11: Showing Mean VAS score of Straining on defecation during the trial period

Sr. No.	Duration	Mean VAS Score ±SD	T Value (as compared to baseline visit)
1	Straining on defecation on VAS scale at Baseline Visit	45.93 ± 29.82	-
2	Straining on defecation on VAS scale at day 15 Visit	2.5 ±9.15	7.87 (p<0.01 HS)
3	Straining on defecation on VAS scale at day 30 Visit	0	8.71 (p<0.01 HS)
4	Straining on defecation on VAS scale at day 45 Visit	0	8.71 (p<0.01 HS)
5	Straining on defecation on VAS scale at day 60 Visit	0	8.71 (p<0.01 HS)

Table 12: Showing Mean VAS score of Mucus discharge during the trial period

Sr. No.	Duration	Mean VAS Score ±SD	T Value (as compared to baseline visit)
1	Mucus Discharge on VAS scale at Baseline Visit	31.25 ± 29.26	-
2	Mucus Discharge on VAS scale at day 15 Visit	1.25 ±3.36	5.76 (p<0.01 HS)
3	Mucus Discharge on VAS scale at day 30 Visit	0	6.04 (p<0.01 HS)
4	Mucus Discharge on VAS scale at day 45 Visit	0	6.04 (p<0.01 HS)
5	Mucus Discharge on VAS scale at day 60 Visit	0	6.04 (p<0.01 HS)

Table 13: Showing Mean VAS score of Pruritus during the trial period

Sr. No.	Duration	Mean VAS Score ±SD	T Value (as compared to baseline visit)
1	Pruritus on VAS scale at Baseline Visit	49.37 ±34.72	-
2	Pruritus on VAS scale at day 15 Visit	23.43 ±28.23	3.27 (p<0.01 HS)
3	Pruritus on VAS scale at day 30 Visit	16.87 ±25.83	4.24 (p<0.01 HS)
4	Pruritus on VAS scale at day 45	9.06 ±17.66	5.85

	Visit		(p<0.01 HS)
5	Pruritus on VAS scale at day 60 Visit	2.5 ±9.5	7.36 (p<0.01 HS)

Table 14: Showing Mean VAS score of Pain in Anal region during the trial period

Sr. No.	Duration	Mean VAS Score ±SD	T Value (as compared to baseline visit)
1	Pain in Anal region on VAS scale at Baseline Visit	50 ±36.10	-
2	Pain in Anal region on VAS scale at day 15 Visit	6.25 ±16.80	6.21 (p<0.01 HS)
3	Pain in Anal region on VAS scale at day 30 Visit	0.31 ±1.76	7.77 (p<0.01 HS)
4	Pain in Anal region on VAS scale at day 45 Visit	0	7.83 (p<0.01 HS)
5	Pain in Anal region on VAS scale at day 60 Visit	0	7.83 (p<0.01 HS)

Table 15: Showing the incidence of Blood in stool before and after treatment

	No. of Patient	
Blood in stool	**Day -3**	**Day 60**
Present	3 (9.37%)	0
Absent	29(90.62%)	32 (100%)

Table 16: Showing the effect of trial medicines on Hb%, ESR and RBC count

	Hb%		ESR		RBC	
	Day 0	**Day 60**	**Day 0**	**Day 60**	**Day 0**	**Day 60**
Mean	12.82	13.41	19.68	13.45	4.27	4.44
SD	±1.66	±1.64	±12.62	±5.42	±0.59	±0.68
t		1.44		2.41		1.02
p		0.07 p>0.01 (NS)		0.009 P<0.01 (HS)		0.15 p>0.01 (NS)

Table 17: Showing the effect of trial medicines on Lipid Profile over 60 days

	Total Cholesterol		HDL		Triglycerides		LDL		VLDL	
	Day 0	Day 60	Day 0	Day 60	Day 0	Day 60	Day 0	Day 60	Day 0	Day 60
Mean	145.25	144.31	50.1	42.72	81.65	81.06	89.5	90.45	17.04	18.31
SD	±34.56	±35.5	±18.13	±18.05	±44.45	±33.93	±26.94	±27.33	8.56	±10.15
t		0.1		0.01		0.059		0.14		1.01
p		0.45 p>0.01 (NS)		0.49 p>0.01 (NS)		0.47 p>0.01 (NS)		0.44 p>0.01 (NS)		0.15 p>0.01 (NS)

Table 18: Showing the effect of trial medicines on Liver Profile over 60 days

	Bilirubin Total		SGOT		SGPT		Alkaline phosphatase		Total Protein	
	Day 0	Day 60	Day 0	Day 60	Day 0	Day 60	Day 0	Day 60	Day 0	Day 60
Mean	0.8	0.77	27.18	31.16	28.44	29.33	68.58	60.28	6.58	6.68
SD	±0.11	±0.11	±10.98	±17.07	±11.98	±17.47	±19.92	±20.92	±0.82	±1.12
T		1.06		1.1		0.0065		1.62		0.24
P		0.14 p>0.01 (NS)		0.12 p>0.01 (NS)		0.49 p>0.01 (NS)		0.05 p>0.01 (NS)		0.4 p>0.01 (NS)

Table 19: Showing the effect of trial medicines on Renal Profile over 60 days

	BUN		Sr. Creatinine	
	Day 0	Day 60	Day 0	Day 60
Mean	25.36	25.13	0.92	0.94
SD	±5.17	±7.13	±0.21	±0.21
t		0.15		0.39
p		0.44 [p>0.01 (NS)]		0.34 [p>0.01 (NS)]

Table 20: Global assessment of overall efficacy assessed by the physician and subject

Sr. No.	Global assessment of overall efficacy assessed by the investigator	Global assessment of overall efficacy assessed by the subject
Grade 1	11 (34.37%)	14 (43.75 %)
Grade 2	21 (65.62%)	18 (56.25%)

Table 21: Global assessment of overall safety assessed by the physician and subject

Sr. No	Global assessment of overall safety assessed by the Investigator	Global assessment of overall safety assessed by the Subject
Grade 1	32 (100%)	32(100%)

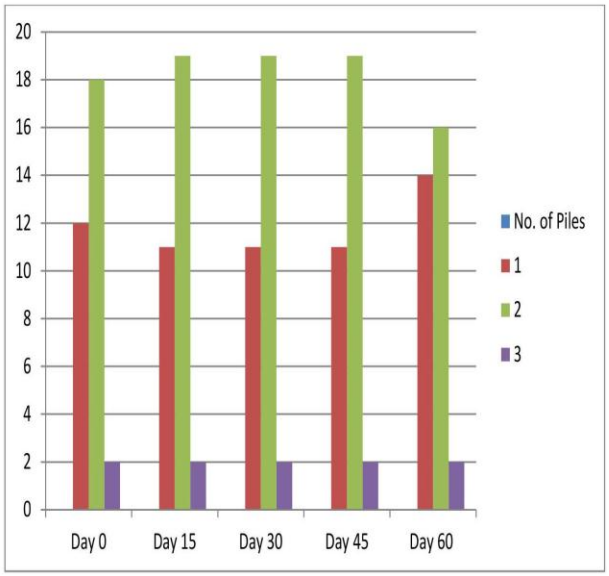


Figure-1: Showing no of subjects having 1, 2 or 3 pile mass over 60 days

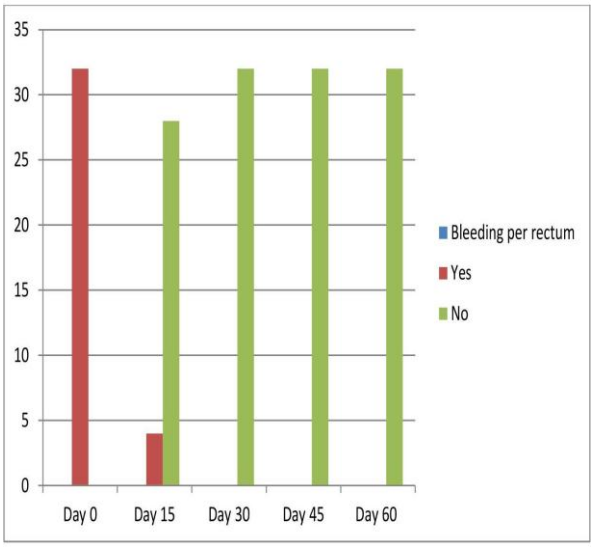


Figure-3: Showing the incidence of bleeding per rectum over 60 days

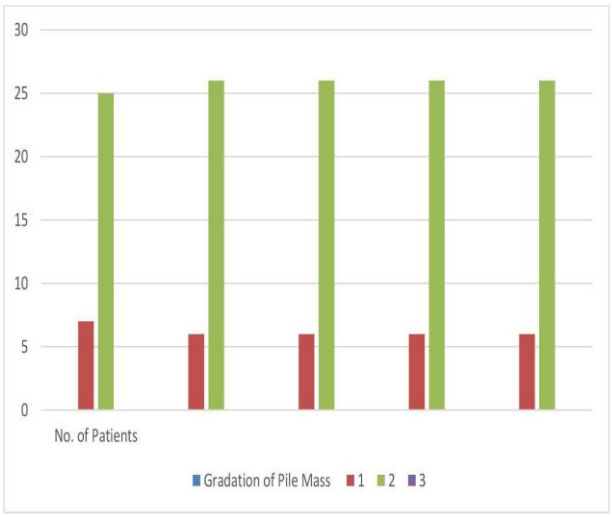


Figure-2: Showing grade wise distribution of pile mass over 60 days

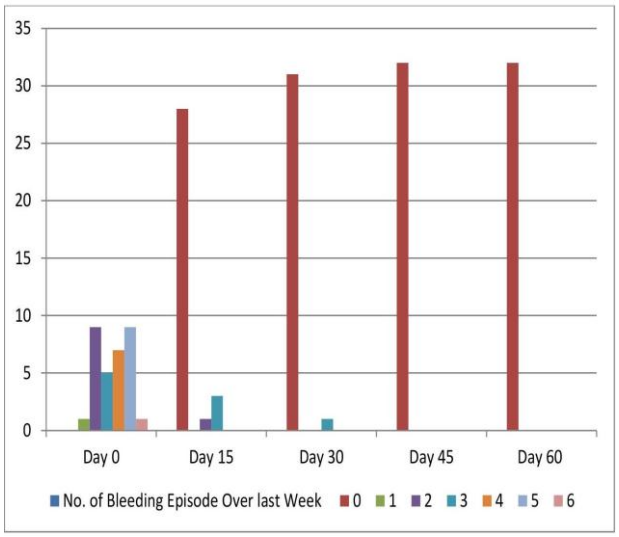


Figure 4: Showing episodes of bleeding in one week over 60 days

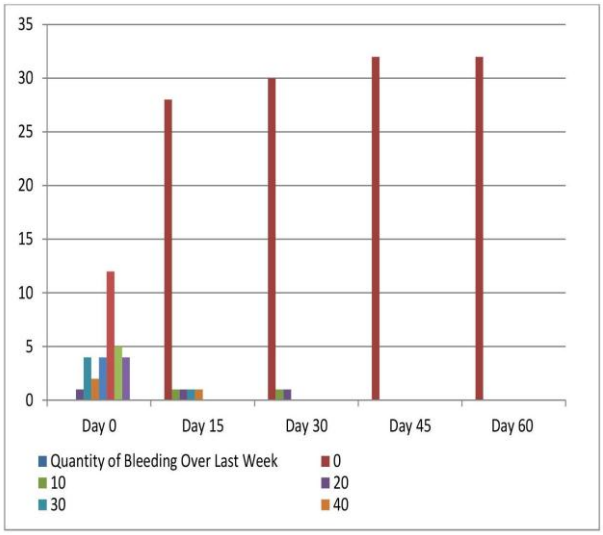


Figure 5: Showing the severity of bleeding on VAS scale (0 to100) over 60 days

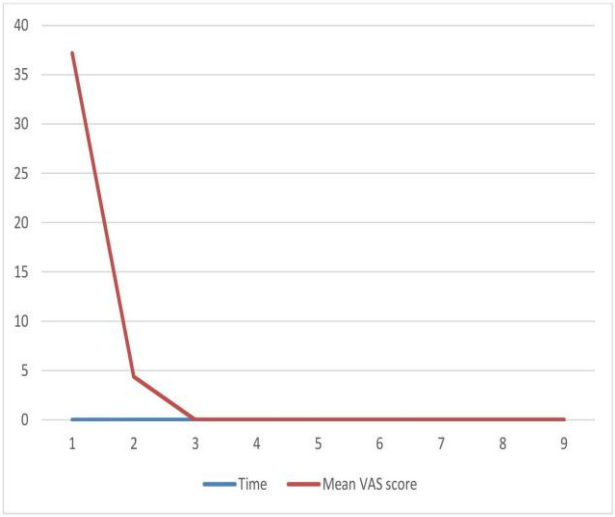


Figure 8: Showing Mean VAS score of Abdominal Pain and discomfort during the trial period

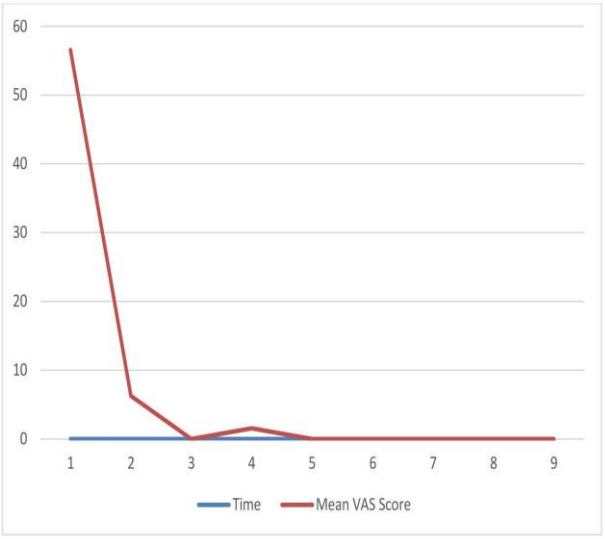


Figure 6: Showing Mean VAS score of Quantity of Bleeding per Rectum during the trial period

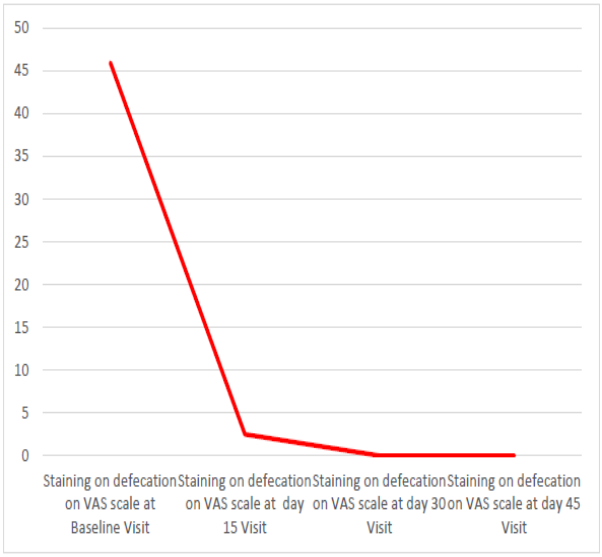


Figure 9: Showing Mean VAS score of Straining on Defecation during the trial period

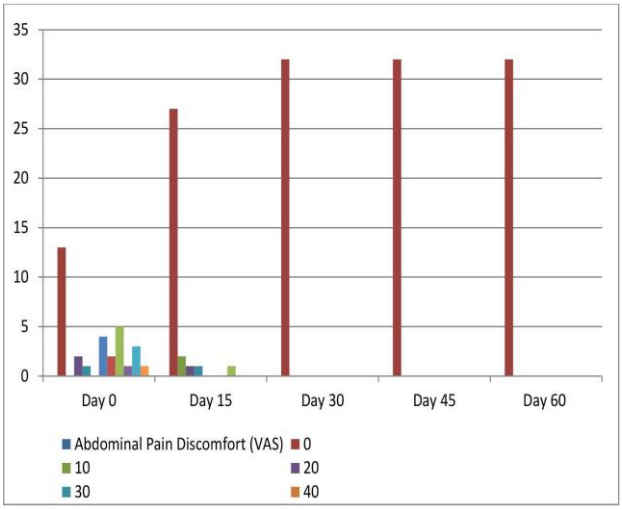


Figure 7: Showing the distribution of Abdominal Pain & Discomfort assessed on VAS scale over 60 days

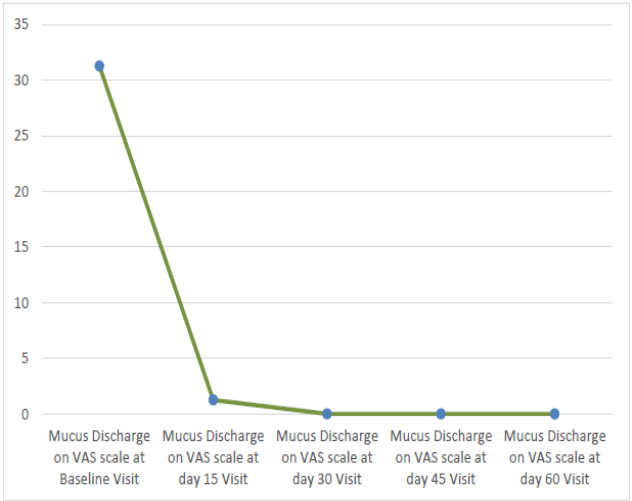


Figure 10: Showing Mean VAS score of Mucus discharge during the trial period

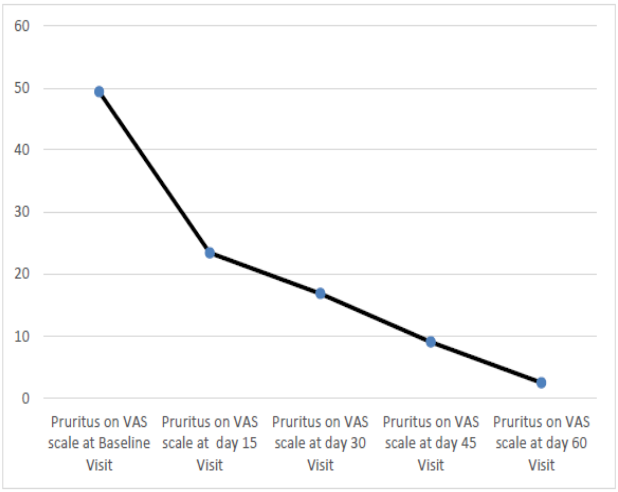


Figure 11: Showing Mean VAS score of Pruritus during the trial period

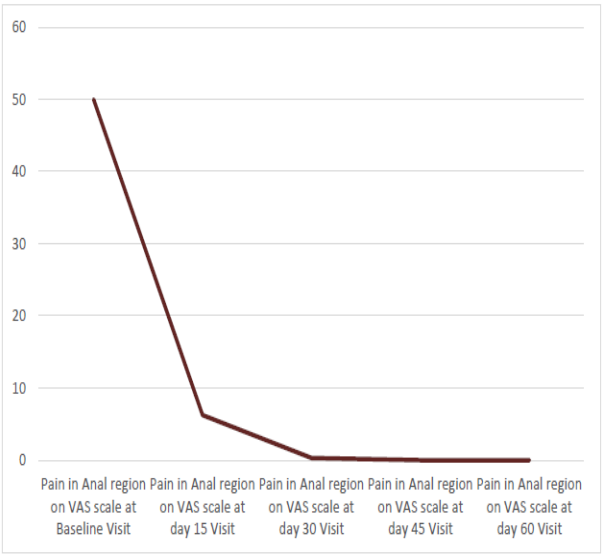


Figure 12: Showing Mean VAS score of Pain in Anal region during the trial period

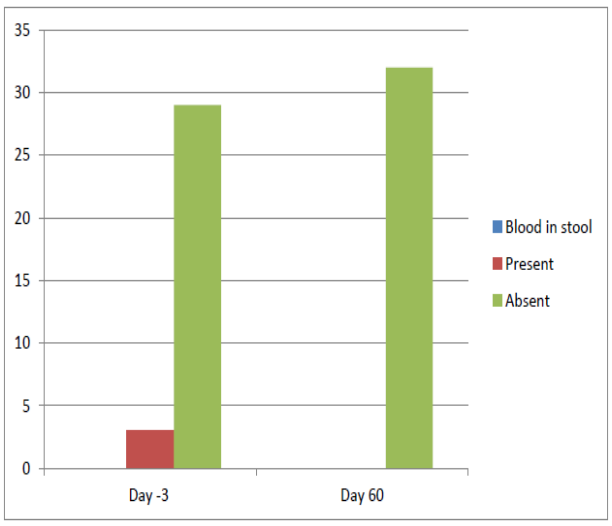


Figure 13: Showing the incidence of Blood in stool before and after treatment

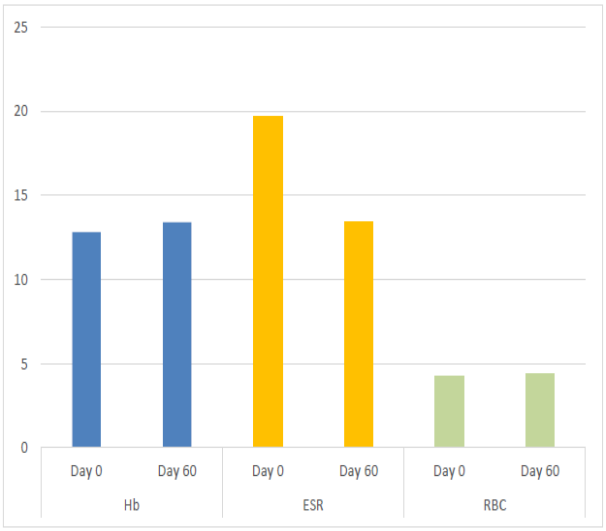
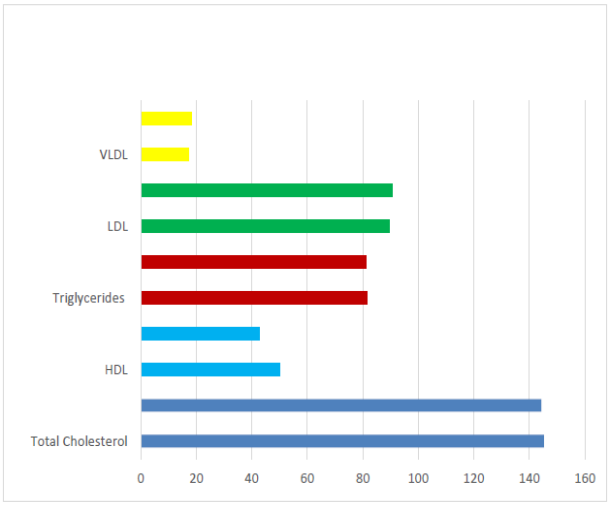
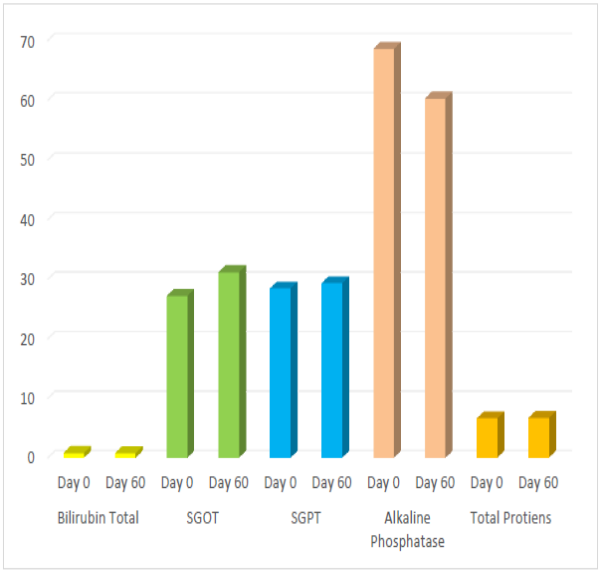


Figure 14: Showing the effect of trial medicines on Hb%, ESR and RBC count



Graph 15: Showing the effect of trial medicines on Lipid Profile over 60 days



Graph 16: Showing the effect of trial medicines on Liver Profile over 60 days

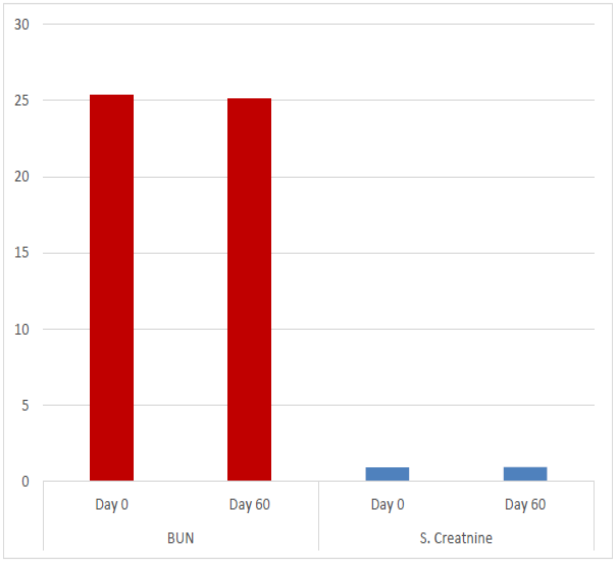


Figure 17: Showing the effect of trial medicines on Renal Profile over 60 days

DISCUSSION

The present study was conducted to evaluate the efficacy and safety of Piloset tablet + Piloset cream in patients suffering from internal hemorrhoids. All the subjects were advised to take Piloset tablet in a dose of 2 tablets twice daily orally after meals with lukewarm water and advised to apply sufficient amount of Piloset cream on affected area twice daily for 60 days. 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. Assessment of post treatment reduction in pile mass, post treatment reduction in other symptoms of hemorrhoids, global assessment for overall improvement by patient and by physician and post treatment changes in laboratory investigations were done.

A total of 45 subjects were screened for recruitment, out of which 36 subjects suffering from internal haemorrhoids were recruited in the study. 9 patients were not recruited in the study because they did not meet the inclusion criteria. Most of the screened failed patients had third or fourth degree piles. Also few patients had fissures. Four out of 36 recruited subjects dropped out prematurely. The reason for drop outs was lost to follow up. Out of 32 patients, there were 23 (71.87%) males and 9 (28.12%) females. There was higher incidence of piles in male patients as compared to female patients, which is in line with the incidence reported by many research studies.

53.12% patients were from age group of 21 to 40 years. 53. 12% patients had Pitta Vata Prakriti and 40.62% patients had Vata Pitta Prakriti. This indicates that the disease is dominant in young age and Pitta dominated prakriti.

In all study subjects no statistically significant change was observed in any of the vital signs (viz. heart rate, respiratory rate, blood pressure) during the study period and at the end of the study. Sleep pattern was improved on day 45. All the 32 patients had sound sleep from day 45 onwards till the completion of the study. This could be because of reduction in abdominal pain and discomfort, relief from pruritus ani and other associated symptoms of hemorrhoids.

After 15 days of treatment with drugs, constipation was relieved in maximum number of patients and on day 45 all the subjects had normal bowel movements. The effect of the drugs continued till the end of the study. Piloset tablet contains extract of Senna (*Cassia angustifolia*), which has got stimulant laxative activity. Because of the stimulant laxative activity constipation could have relieved.

Number of Pile mass was counted and also the size of pile mass was evaluated on graded scale. It was observed that number of pile mass and the size of pile mass reduced at the end of the study. The reduction in the number of pile mass and the size of pile mass was not statistically significant.

Bleeding per rectum is very important symptom of hemorrhoids; almost every patient had bleeding per rectum at the beginning of the trial. It was observed that from initiation of the study treatment gradually quantity of bleeding per rectum reduced. On day 30, bleeding per rectum was completely stopped in almost all the patients. Till the completion of the study, no patient had bleeding per rectum. The ingredients of Piloset tablet such as Nagkesar, Nimba, Lajjalu, Daruharidra possess astringent property. Astringent property of these ingredients helps to stop bleeding per rectum. Also ingredients of Piloset Cream such as Jatyadi Oil, Nimba Taila, Haridra extract, Yashda Bhasma possess astringent, anti-inflammatory and wound healing properties. These ingredients help in local vasoconstriction and subsequently bleeding per rectum was stopped. The combination of oral and local medications has helped patients in faster and sustained relief from bleeding per rectum.

A significant reduction in other main symptoms of hemorrhoids viz. abdominal pain & discomfort, straining on defecation, mucus discharge and pain at anal region assessed on VAS scale has been observed from day 15 and the results continued till the end of study period. Pruritus was relieved in all the subjects from day 15 and remained subsided till the end of the study period.

It was observed that post treatment 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.

Global evaluation by the physician and patient showed excellent improvement in 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.

Thus combination of oral (Piloset tablet) and local (Piloset Cream) treatments helped in decreasing bleeding tendency. The combination also helped in prolonging the bleeding time. Vasoconstrictor and anti-inflammatory effects of ingredients present in Piloset Tablet and Piloset Cream helped in reduction of pile mass. Symptoms such as itching and discomfort were relieved because of the anti-histaminic property present in ingredients of Piloset tablet and Piloset cream. Ingredients of Piloset tablet also helped in relieving constipation, flatulence and abdominal pain.

CONCLUSION

The present study confirms the efficacy and safety of 'Piloset Tablet + Piloset Cream' in relieving symptoms of internal hemorrhoids. Symptoms such as bleeding per rectum, pile mass, abdominal pain & discomfort, straining on defecation, mucus discharge, pruritus and pain at anal region were significantly reduced at the end of the study. Hence, it can be concluded that 'Piloset Tablet + Piloset Cream' can be used safely and effectively in the treatment of internal as well as external hemorrhoids.

Source(s) of support: Arjun Healthcare Pvt. Ltd.

Presentation at a meeting: Nil.

Conflicting Interest

All authors have substantially contributed in the concept, design, literature search and analysis & interpretation of the study data. All the authors have substantially contributed in preparation, editing & review of the manuscript. Dr. Arjun K Kohli is a director of Arjun Healthcare, 11, Krypton towers, Prabhadevi, Mumbai. Investigational products are manufactured by Arjun Healthcare. Dr. N Borse, Dr. S Indore, Dr. R Bhise and Dr. S Tamoli do not have any conflict of interest.

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7. Ashtanga Hrudaya Nidana Sthana, Adhyaya 7; Shloka 2.
8. Charaka Chikitsa Sthana, Adhyaya 14; Shloka 21-22.
9. Charaka Chikitsa Sthana, Adhyaya 14; Shloka 33-37.