








ORIGINAL PAPER

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Randomized, open-label, controlled, comparative clinical study to evaluate the safety and efficacy of Pilex Forte tablets in combination with Pilex Ointment application for the effective management of common ano-rectal conditions

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ABSTRACT

Introduction. Haemorrhoids and anal fissures are considered as the most common ano-rectal conditions.

Aim. To evaluate the safety and efficacy of Pilex Forte tablets in combination with Pilex Ointment as compared to the Standard of Care in common ano-rectal conditions

Material and methods. Randomized, open-label, controlled comparative clinical study conducted on 162 patients of either sex, aged between 18-50 years, confirmed with common ano-rectal conditions. As per randomization, patients received either standard of care or Pilex Forte tablet along with Pilex Ointment at a recommended dose of two tablets twice daily and twice daily local application (anal) for a period of 4 weeks. Clinical safety and efficacy assessments were carried out at study specific scheduled visits. Laboratory assessments were carried out only at screening and at the end of the study.

Results. Patients who completed the study were considered for statistical analysis. Significant clinical improvement was observed in patients with ano-rectal conditions who received Pilex Forte tablet and Pilex Ointment than to those who received standards of care. No abnormal lab values were recorded and there were no adverse events reported during the study period.

Conclusion. Pilex Forte tablet along with Pilex Ointment at recommended dose is safe and effective in the management of ano-rectal conditions like haemorrhoids and fissure-in-ano.

Keywords. ano-rectal, fissure-in-ano, haemorrhoids

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

Received: 28.04.2021 | Accepted: 8.07.2021

Publication date: September 2021

Kumar S, Selvarajan S, Lakshmi P, Paramesh R, Kumawat R, Palaniyamma D, Srikrishna HA. *Randomized, open-label, controlled, comparative clinical study to evaluate the safety and efficacy of Pilex Forte tablets in combination with Pilex Ointment application for the effective management of common ano-rectal conditions.* Eur J Clin Exp Med. 2021;19(3):221–232. doi: 10.15584/ejcem.2021.3.3.



Introduction

Haemorrhoids and anal fissures (fissure – in – ano) are considered as the most common anorectal conditions. Although; they are not life threatening, they can detrimentally impact patients' quality of life and daily living activities.¹ Anorectal disorders are commonly seen by both primary and specialty health care providers such as gastroenterologists. Nonsurgical anorectal management has become an increasingly emphasized portion of the core curriculum for many gastroenterology training programs.²

Haemorrhoids are abnormalities of submucosal, venous structures in the anorectum resulting in symptoms.³ The prevalence of symptomatic haemorrhoidal disease is difficult to evaluate due to a high percentage of people with symptomatic haemorrhoids who avoid evaluation or those who successfully use lifestyle modifications, non-pharmacological therapies, or over the counter agents for their symptom relief. It has been estimated that up to 75% of individuals have symptomatic haemorrhoids at least once in their lifetime.⁴ The exact prevalence is unknown because most patients are asymptomatic and do not seek care from a physician. A study shown that patients undergoing routine colorectal cancer screening found 39% prevalence of haemorrhoids, with 55% of those patients reporting no symptoms.⁵

Haemorrhoids usually develop when the venous drainage of the anus is changed, causing the venous plexus and connecting tissue to dilate, producing an outgrowth of anal mucosa from the rectal wall. Haemorrhoids are classified depending on their location. Haemorrhoids which are distal to the dentate line are considered external and are covered by sensate squamous epithelium. Internal haemorrhoids are situated proximal to the dentate line and are covered by insensate columnar epithelium. As per Goligher classification, internal haemorrhoids are classified into four degrees: First-degree internal haemorrhoids do not prolapse into the anorectum; second-degree haemorrhoids prolapse into the anorectum and spontaneously reduce; third-degree haemorrhoids prolapse into the anorectum and require manual reduction; and fourth-degree are unable to be reduced manually.⁴

Symptoms depend upon the location of haemorrhoids. External haemorrhoids are characteristically asymptomatic but may cause pain due to their overlying sensate squamous mucosa, predominantly when thrombosis occurs. The most common symptom of internal haemorrhoids is painless rectal bleeding.⁶ The treatment of haemorrhoids involves lifestyle modification, medical, and surgical approaches⁷⁻⁸. First-line conservative treatment of haemorrhoids consists of a high-fiber diet, (sitz) baths, increased water intake, warm water, and stool softeners.⁹⁻¹⁰ Non-operative treatment includes

Sclerotherapy, Rubber band ligation, Cryotherapy, Infrared coagulation, Radiofrequency ablation.¹¹

Anal fissures are tears that occur beneath the dentate line in the anal canal. Anal fissures are classified as acute or chronic depending on their time course with those lasting 6 weeks or longer being classified as chronic.¹² The etiopathogenesis of anal fissures is multifactorial. Manometric studies have revealed that augmented resting anal pressure is common in patients diagnosed with anal fissures. Majority of fissures occur in the posterior midline and are solitary. Fissures occurring away from the midline or fissures that fail to heal should prompt additional evaluation for alternative etiologies such as Crohn's disease, tuberculosis, HIV, other sexually transmitted diseases or malignancy.¹³ Over half of simple, acute anal fissures resolve without specific medical therapy. Fissures that fail to resolve spontaneously should receive medical therapy. Dietary and lifestyle changes are the important aspects of the non-surgical care of anal fissures. The primary goal of medical therapy is to relax the anal sphincter and allow the fissure to heal through interruption of the sphincter spasm and tearing cycle. Warm sitz baths are also recommended based on studies that have revealed that they can help to briefly decrease internal and external sphincter spasticity and decrease pain.¹⁴ Bulking agents has been revealed in well-designed studies to be beneficial in this ailment.¹⁵ Among the variety of agents that have been investigated to chemically relax the anal sphincter, topical nitroglycerin Ointment has been most extensively studied in the treatment of anal fissure with success rate of 80%.¹⁵

Pilex Forte tablet is a polyherbal formulation consisting of principal ingredients like *Balsamodendron mukul* (Purified), *Shilajeet* (Purified), *Melia azadirachta*, *Berberis aristata*, *Emblica officinalis*, *Terminalia chebula*, *Terminalia belerica*, *Cassia fistula*, *Bauhinia variegata*, and *Mesua ferrea*. Pilex Ointment is a herbo-mineral formulation consisting extracts of *Mimosa pudica*, *Eclipta alba*, *Vitex negundo*, *Calendula officinalis*, *Mimosa pudica*, *Eclipta alba*, *Vitex negundo*, *Calendula officinalis*, *Cinnamomum camphora*, *Tankana*, *Yashada bhasma* which have anti-inflammatory, analgesic, wound healing, membrane stabilizing, anti-microbial and antioxidant actions. Therefore, a safety and efficacy study was planned to further evaluate the role of Pilex Forte along with local application of Pilex Ointment as compared to standard of care in the management of common ano-rectal conditions like haemorrhoids and fissure-in-ano.

Aim

To evaluate the safety and efficacy of Pilex Forte tablets along with Pilex Ointment in the treatment of common ano-rectal conditions in comparison with the standard of care.

Material and methods

This study was a Randomized, Prospective, Interventional, Open-label, Controlled Comparative clinical study conducted at State Indian System of Medicine (ISM) Department, Department of Surgery and Department of Clinical Pharmacology, JIPMER, Puducherry. All essential study documents were submitted to the JIPMER Institutional Ethics committee for review and approval with the vide approval number JIP/IEC/2018/050. All the patients gave their informed consent for their active participation in the study.

This was a randomized, prospective, interventional, open-label, controlled comparative clinical study conducted on 162 patients of either sex, aged between ≥18 to ≤50 years clinically confirmed with the history of common anorectal conditions like haemorrhoids and Fissure-in-Ano. Common ano-rectal conditions include; Haemorrhoids (symptoms of Grade I and Grade II Haemorrhoids, i.e, Haemorrhoids which may protrude out of anal canal during defecation, but reduce spontaneously) with symptoms like Pain, Itching, Bleeding, protruding mass per anus, difficulty in passing stools and constipation. Fissure-in ano [Chronic or recurrent fissures (>4 months)] with symptoms of pain, itching and irritation were included in the study. While patients with haemorrhoidal complications like swelling, thrombosis, prolapsed and/or ulcers, patients with any serious systemic illness requiring long term medications, women who are pregnant, attempting to conceive,

or nursing an infant were excluded from the study. As per randomization, all patients received either the routine standard of care (Syrup Liquid paraffin 30 ml HS oral with lignocaine gel for local application for 4 weeks, along with high fibre diet with plenty of oral fluids and Sitz bath twice a day in both the groups) or Pilex Forte tablet along with Pilex Ointment for a period of 4 weeks at a recommended dose of two tablets twice daily and twice daily local application. Clinical Safety and efficacy assessments were carried out at entry, at the end of 1st week, 2nd week and at the end of 4th week. Laboratory assessments (Haemoglobin, Total Leukocyte Count, Differential Leukocyte Count, Random Blood Sugar, Serum Creatinine and Serum Glutamic Pyruvic Transaminase) were carried out only at screening and at the end of the study. Grading of symptoms were carried out based on VAS scale from 0-10 for pain (0= no pain, 1-3= mild pain, 4-6= moderate, 7-10= Severe pain), constipation/Painful defecation. For bleeding, itching, burning sensation. scoring was based on 5-point Likert scale (0- Nil, 1- Mild, 2- Moderate, 3- Severe and 4- Very severe). Adverse events either reported or observed during the study period were recorded in the case report form. Figure 1 represents the consort study flow.

All patients who completed the study were considered for statistical analysis. Friedman test Followed by Dunnett’s multiple comparisons test was used for within group comparisons, Mann Whitney test was used to compare the difference between participants receiving Pilex

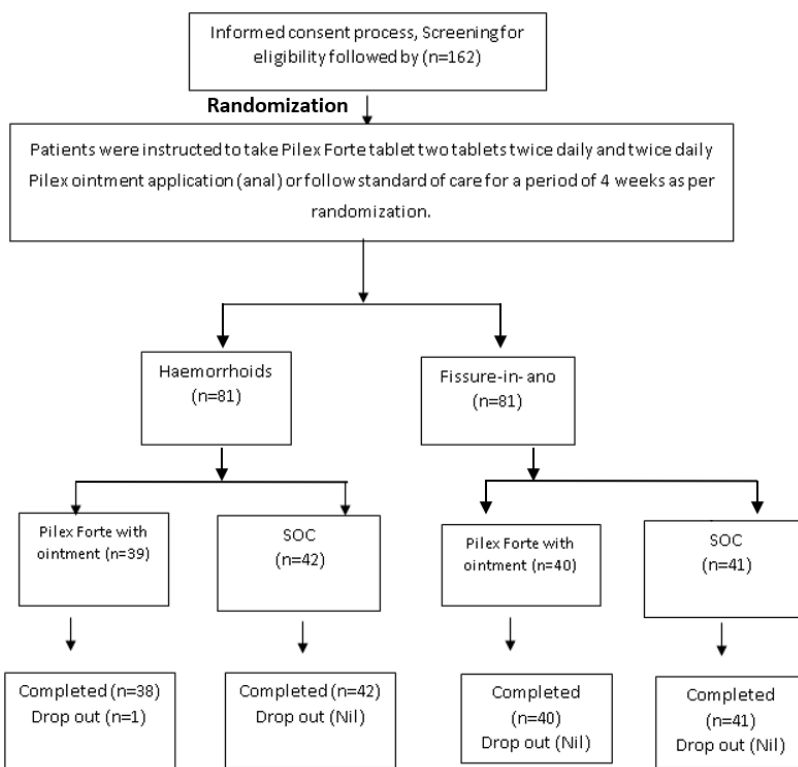


Fig. 1. Consort Study Flow Diagram

Forte and Ointment vs. Standard of care. These tests were performed with a significance level of 0.05 (two-sided). Descriptive statistics was provided for all parameters, Values were represented in Mean ± SD, number of patients and percentages. All statistical analyses were carried out using GraphPad prism software Version 6.07 for Windows, GraphPad Software, San Diego, California, USA.

Results

Total 162 patients were enrolled into the study. 79 patients received Pilex Forte tablets with Pilex Ointment local application and 83 patients received Standard of Care treatment for 4 weeks, 1 patient was not considered for analysis due to lost to follow up and rest all patients completed the study and were considered for statistical evaluation. Table 1 elicits the demographic data of the study.

In haemorrhoid group, 39 patients who received Pilex Forte tablet along with local application of Pilex Ointment were with the mean age of 37.15±9.72 and 42 patients who received Standard of Care treatment were with the mean age of 36.48±9.25.

In fissure-in ano group, 40 patients who received Pilex Forte Tablet along with local application of Pilex Ointment were with the mean age of 37.10±10.07 and 41 patients who received Standard of Care treatment were with the mean age of 38.39±8.78.

From overall 162 patients randomized, 81 patients were included for the assessment of Haemorrhoids (39 patients received Pilex Forte tablets with local application of Pilex Ointment and 42 patients received Standard of Care treatment) and 81 patients were included for the assessment of Fissure-in-ano, out of which 40 patients received Pilex Forte tablet with local application of Pilex Ointment and 41 patients received standard of care treatment alone.

Table 1. Demographics data of patients

	Haemorrhoids group		Fissure-in-ano group	
	Pilex Forte	Standard of Care	Pilex Forte	Standard of Care
Number of patients	39	42	40	41
Age in years	37.15 9.72	36.48 9.25	37.1 10.07	38.39 8.78
Gender				
Male	20	27	25	24
Female	19	15	15	17

Clinical Assessment of Pilex Forte Tablet with local application of Pilex Ointment in Haemorrhoid Group
Effect on Pain

Figure 2 elicits the effect of Pilex Forte tablets along with local application of Pilex Ointment on pain in haemorrhoids group.

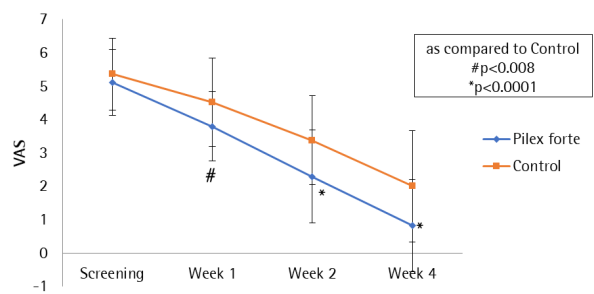


Fig. 2. Effect of Pilex Forte tablets along with local application of Pilex Ointment on pain in haemorrhoids group

Table 2. Clinical Assessment of Pilex Forte tablets with local application of Pilex Ointment in Haemorrhoids Group [Mean±SD]

Parameters	Visits	Pilex Forte	Standard of care
Pain	Screening	5.11±0.98	5.36±1.08
		3.79±1.04	4.52±1.33
	Week 1	b:p<0.0048	b:p<0.0264
		c:p<0.0088	
	Week 2	2.29±1.39	3.38±1.34
		b:p<0.0001	b:p<0.0001
		c:p<0.0001	
	Week 4	0.82±1.39	2±1.67
		b:p<0.0001	b:p<0.0001
		c:p<0.0001	
Constipation/ painful defecation	Screening	5.71±1.18	5.86±1.24
		4.24±1.17	4.95±1.29
	Week 1	b:p<0.0056	b:p<0.0337
		c:p<0.0177	
	Week 2	2.66±1.19	3.69±1.46
		b:p<0.0001	b:p<0.0001
		c:p<0.0007	
	Week 4	1.11±1.56	2.38±1.64
		b:p<0.0001	b:p<0.0001
		c:p<0.0001	

Within the group analysis: Statistical test: Friedman test Followed by Dunnett's multiple comparisons test. Significance level was fixed at 0.05; b: as compared to Screening. **Between the group analysis:** Statistical test: Mann Whitney test; c: as compared to Standard of care. Two sided p value; Software: GraphPad Prism 6.07

The mean value of Pain at screening was 5.11±0.98 in Pilex Forte group, it was reduced to 3.79±1.04 at the end of week 1 with a significance of p<0.0048 as compared to screening and p<0.0088 as compared to standard of care which further reduced to 2.29±1.39 at the end of the week 2 with a significance of p<0.0001 as compared to screening and p<0.0001 as compared to standard of care and it reduced to 0.82±1.39 at the end of the week 4 with a significance of p<0.0001 as compared to screening and p<0.0001 as compared to standard of care. In Standard of Care group, the mean value of Pain at screening was 5.36±1.08, it was reduced to 4.52±1.33 at the end of week 1 with a significance of

$p < 0.0264$ as compared to screening, which further reduced to 3.38 ± 1.34 at the end of the week 2 with a significance of $p < 0.0001$ as compared to screening. It was further reduced to 2 ± 1.67 at the end of the week 4 with a significance of $p < 0.0001$ as compared to screening (Table 2).

Effect on constipation/painful defecation

Figure 3 elicits the effect of Pilex Forte tablets along with local application of Pilex Ointment on constipation/painful defecation in haemorrhoids group.

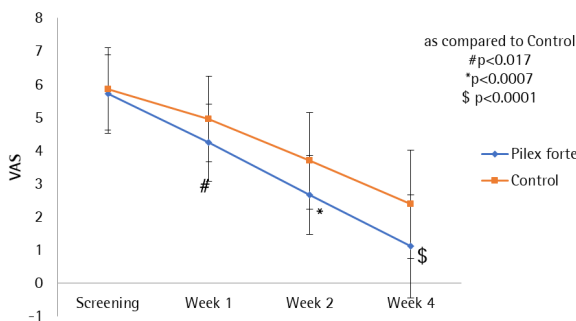


Fig. 3. Effect of Pilex Forte tablets along with local application of Pilex Ointment on constipation/painful defecation in haemorrhoids group

The mean value of constipation/ painful defecation at screening was 5.71 ± 1.18 in Pilex Forte group, it was reduced to 4.24 ± 1.17 at the end of week 1 with a significance of $p < 0.0056$ as compared to screening and $p < 0.0177$ as compared to standard of care which further reduced to 2.66 ± 1.19 at the end of the week 2 with a significance of $p < 0.0001$ as compared to screening and $p < 0.0007$ as compared to standard of care and it reduced to 1.11 ± 1.56 at the end of the week 4 with a significance of $p < 0.0001$ as compared to screen-

ing and $p < 0.0001$ as compared to standard of care. In Standard of Care group, the mean value of constipation/ painful defecation at screening was 5.86 ± 1.24 , it was reduced to 4.95 ± 1.29 at the end of week 1 with a significance of $p < 0.0337$ as compared to screening, which further reduced to 3.69 ± 1.46 at the end of the week 2 with a significance of $p < 0.0001$ as compared to screening and it was reduced to 2.38 ± 1.64 at the end of the week 4 with a significance of $p < 0.0001$ as compared to screening.

Effect on Itching

Table 2a and Table 2b elicits the effect of Pilex Forte tablets along with local application of Pilex Ointment on the symptoms like itching, bleeding, burning sensation in haemorrhoids group.

In Pilex Forte group, 9 patients presented severe itching, 21 showed moderate itching and 8 patients showed mild itching at screening; however after treatment, 1 patient improved to moderate itching, 1 patient improved to mild itching and 36 patients showed no symptoms of itching at the end of week 4.

In standard of care group, 2 patients had very severe itching, 9 patients presented severe itching, 27 patients showed moderate itching and 4 patients showed mild itching at screening, while after treatment 1 patient showed severe itching, 1 patient showed moderate itching, 9 patients showed mild itching and 31 patients showed no symptoms of itching at end of week 4.

Effect on Bleeding

In Pilex Forte group, 14 patients presented very severe bleeding/streaks, 22 showed severe, 2 showed moderate bleeding/streaks at screening, while after treatment, 1 patient showed very severe bleeding/streaks, 11 patients showed mild bleeding/streaks and 26 patients showed no symptoms of bleeding/streaks at end of week 4.

Table 2a. Clinical assessment of Pilex Forte tablets with local application of Pilex Ointment in haemorrhoids group Pilex Forte group (n=38)

Parameters	Scale	Screening	Week 1	Week 2	Week 4
Itching	Nil	0 (0)	4 (10.53)	25 (65.79)	36 (94.74)
	Mild	8 (21.05)	18 (47.37)	10 (26.32)	1 (2.63)
	Moderate	21 (55.26)	14 (36.84)	2 (5.26)	1 (2.63)
	Severe	9 (23.68)	2 (5.26)	1 (2.63)	0 (0)
	Very severe	0 (0)	0 (0)	0 (0)	0 (0)
Bleeding/ Streaks	Nil	0 (0)	0 (0)	7 (18.42)	26 (68.42)
	Mild	0 (0)	5 (13.16)	15 (39.47)	11 (28.95)
	Moderate	2 (5.26)	13 (34.21)	14 (36.84)	0 (0)
	Severe	22 (57.89)	17 (44.74)	1 (2.63)	0 (0)
	Very severe	14 (36.84)	3 (7.89)	1 (2.63)	1 (2.63)
Burning sensation	Nil	0 (0)	2 (5.26)	19 (50)	36 (94.74)
	Mild	3 (7.89)	16 (42.11)	14 (36.84)	1 (2.63)
	Moderate	26 (68.42)	17 (44.74)	4 (10.53)	1 (2.63)
	Severe	9 (23.68)	3 (7.89)	1 (2.63)	0 (0)
	Very severe	0 (0)	0 (0)	0 (0)	0 (0)

Scale: 0- Nil, 1- Mild, 2- Moderate, 3- Severe, 4- Very severe.

Table 2b. Clinical assessment of Pilex Forte tablets with local application of Pilex Ointment in haemorrhoids group standard of care group (n=42) [N (%)]

Parameters	Scale	Screening	Week 1	Week 2	Week 4
Itching	Nil	0 (0)	1 (2.38)	13 (30.95)	31 (73.81)
	Mild	4 (9.52)	9 (21.43)	24 (57.14)	9 (21.43)
	Moderate	27 (64.29)	29 (69.05)	3 (7.14)	1 (2.38)
	Severe	9 (21.43)	2 (4.76)	1 (2.38)	1 (2.38)
	Very severe	2 (4.76)	1 (2.38)	1 (2.38)	0 (0)
Bleeding/ Streaks	Nil	0 (0)	0 (0)	1 (2.38)	10 (23.81)
	Mild	0 (0)	2 (4.76)	8 (19.05)	16 (38.1)
	Moderate	3 (7.14)	12 (28.57)	16 (38.1)	9 (21.43)
	Severe	16 (38.1)	12 (28.57)	16 (38.1)	7 (16.67)
Burning sensation	Very severe	23 (54.76)	16 (38.1)	1 (2.38)	0 (0)
	Nil	0 (0)	1 (2.38)	8 (19.05)	29 (69.05)
	Mild	4 (9.52)	9 (21.43)	20 (47.62)	6 (14.29)
	Moderate	26 (61.9)	27 (64.29)	13 (30.95)	7 (16.67)
	Severe	10 (23.81)	4 (9.52)	0 (0)	0 (0)
Very severe	2 (4.76)	1 (2.38)	1 (2.38)	0 (0)	

Scale: 0- Nil, 1- Mild, 2- Moderate, 3- Severe, 4- Very severe.

In standard of care group, 23 patients presented very severe bleeding/streaks, 16 patients showed severe and 3 patients showed moderate bleeding/streaks at screening, while after treatment, 7 patients showed severe bleeding/streaks, 9 patients showed moderate bleeding/streaks, 16 patients showed mild bleeding/streaks and 10 patients showed no symptoms of bleeding/streaks at end of week 4.

Table 3. Clinical assessment of Pilex Forte tablets with local application of Pilex Ointment in fissure-in-ano group [Mean±SD]

Parameters	Visits	Pilex Forte	Standard of care
Pain	Screening	7.15±0.89	6.9±0.97
		5.03±1.03	5.71±1.03
	Week 1	b:p<0.0014 c:p<0.0015	b:p<0.004
		2.9±1.08	4.15±1.22
	Week 2	b:p<0.0001 c:p<0.0001	b:p<0.0001
		0.9±1.24	2.76±1.59
	Week 4	b:p<0.0001 c:p<0.0001	b:p<0.0001
		7.2±0.99	6.83±1.14
Constipation/ painful defecation	Screening	4.83±1.08	5.71±1.06
		b:p<0.0016 c:p<0.0004	b:p<0.0062
	Week 1	2.78±1.05	4.22±1.28
		b:p<0.0001 c:p<0.0001	b:p<0.0001
	Week 2	0.88±1.09	2.73±1.58
		b:p<0.0001 c:p<0.0001	b:p<0.0001
	Week 4	b:p<0.0001 c:p<0.0001	b:p<0.0001
		0.88±1.09	2.73±1.58

Within the group analysis: Statistical test: Friedman test Followed by Dunnett’s multiple comparisons test. Significance level was fixed at 0.05; b: as compared to Screening. **Between the group analysis:** Statistical test: Mann Whitney test; c: as compared to Standard of care. Two-sided p value; Software: GraphPad Prism 6.07

Effect on Burning sensation

In Pilex Forte group; 9 patients presented severe burning sensation, 26 patients showed moderate burning sensation and 3 patients showed mild burning sensation at screening, while after treatment, 1 patient showed moderate burning sensation, 1 patient showed mild burning sensation and 36 patients showed no symptoms of burning sensation at end of week 4.

In standard of care group; 2 patients presented very severe burning sensation, 10 patients showed severe burning sensation and 26 patients showed moderate burning sensation at screening, while after treatment, 7 patients showed moderate burning sensation, 6 patients showed mild burning sensation and 29 patients showed no symptoms of burning sensation at end of week 4.

Clinical assessment of Pilex Forte tablet with local application of Pilex Ointment in fissure-in-ano group (Table 3)

Effect on Pain

Figure 4 elicits the effect of Pilex Forte tablets along with local application of Pilex Ointment on pain in fissure-in-ano Group.

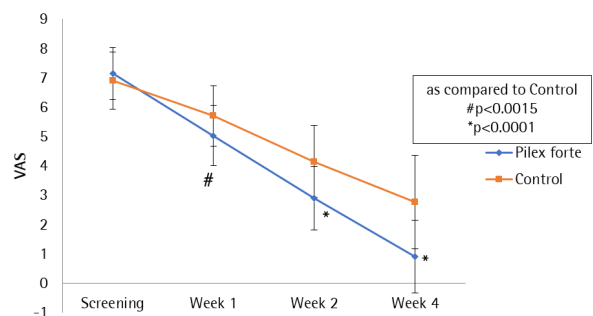


Fig. 4. Effect of Pilex Forte tablets along with local application of Pilex Ointment on pain in fissure-in-ano group

The mean value of pain at screening was 7.15 ± 0.89 in Pilex Forte group, it was reduced to 5.03 ± 1.03 at the end of week 1 with a significance of $p < 0.0014$ as compared to screening and $p < 0.0015$ as compared to standard of care, which further reduced to 2.9 ± 1.08 at the end of the week 2 with a significance of $p < 0.0001$ as compared to screening and $p < 0.0001$ as compared to standard of care and it further reduced to 0.9 ± 1.24 at the end of the week 4 with a significance of $p < 0.0001$ as compared to screening and standard of care.

In Standard of Care group, the mean value of Pain at screening was 6.9 ± 0.97 , it was reduced to 5.71 ± 1.03 at the end of week 1 with a significance of $p < 0.004$ as compared to screening which further reduced to 4.15 ± 1.22 at the end of the week 2 with a significance of $p < 0.0001$ as compared to screening and it reduced to 2.76 ± 1.59 at the end of the week 4 with a significance of $p < 0.0001$ as compared to screening.

Effect on constipation/painful defecation

Figure 5 elicits the effect of Pilex Forte tablets along with local application of Pilex Ointment on constipation/painful defecation in fissure-in-ano group.

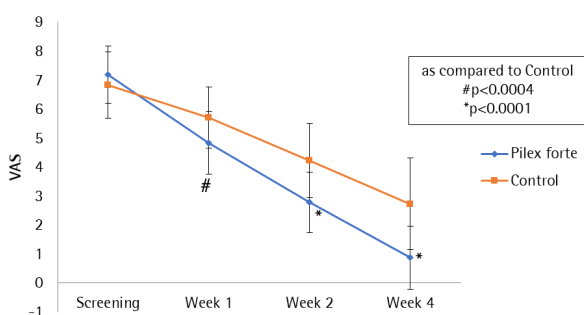


Fig 5. Effect of Pilex Forte tablets along with local application of Pilex Ointment on constipation/painful defecation in fissure-in-ano group.

The mean value of constipation/ painful defecation at screening was 7.2 ± 0.99 in Pilex Forte group, it was reduced to 4.83 ± 1.08 at the end of week 1 with a significance of $p < 0.0016$ as compared to screening and $p < 0.0004$ as compared to standard of care, which further reduced to 2.78 ± 1.05 at the end of the week 2 with a significance of $p < 0.0001$ as compared to screening and standard of care. It further reduced to 0.88 ± 1.09 at the end of the week 4 with a significance of $p < 0.0001$ as compared to screening and standard of care. In Standard of Care group, the mean value of constipation/painful defecation at screening was 6.83 ± 1.14 , it was reduced to 5.71 ± 1.06 at the end of week 1 with a significance of $p < 0.0062$ as compared to screening which further reduced to 4.22 ± 1.28 at the end of the week 2 with a significance of $p < 0.0001$ as compared to screen-

ing. It further reduced to 2.73 ± 1.58 at the end of the week 4 with a significance of $p < 0.0001$ as compared to screening.

Table 3a and Table 3b elicits the effect of Pilex Forte tablets along with local application of Pilex Ointment on the symptoms like itching, bleeding, burning sensation in fissure-in-ano group.

Table 3a. Clinical assessment of Pilex Forte tablets with local application of Pilex Ointment in fissure-in-ano group, Pilex Forte Group (n=40) [N (%)]

Parameters	Scale	Screening	Week 1	Week 2	Week 4
Itching	Nil	0 (0)	0 (0)	10 (25)	36 (90)
	Mild	0 (0)	7 (17.5)	24 (60)	2 (5)
	Moderate	3 (7.5)	26 (65)	6 (15)	2 (5)
	Severe	33 (82.5)	6 (15)	0 (0)	0 (0)
	Very severe	4 (10)	1 (2.5)	0 (0)	0 (0)
Bleeding/Streaks	Nil	0 (0)	0 (0)	13 (32.5)	38 (95)
	Mild	0 (0)	12 (30)	22 (55)	0 (0)
	Moderate	8 (20)	23 (57.5)	4 (10)	1 (2.5)
	Severe	32 (80)	5 (12.5)	1 (2.5)	1 (2.5)
	Very severe	0 (0)	0 (0)	0 (0)	0 (0)
Burning sensation	Nil	0 (0)	0 (0)	15 (37.5)	37 (92.5)
	Mild	0 (0)	13 (32.5)	19 (47.5)	1 (2.5)
	Moderate	5 (12.5)	23 (57.5)	5 (12.5)	1 (2.5)
	Severe	30 (75)	4 (10)	1 (2.5)	1 (2.5)
	Very severe	5 (12.5)	0 (0)	0 (0)	0 (0)

Scale: 0- Nil, 1- Mild, 2- Moderate, 3- Severe, 4- Very severe.

Effect on Itching

In Pilex Forte group; 4 patients presented very severe itching, 33 patients showed severe itching and 3 patients showed moderate itching at screening, while after treatment 2 patients showed moderate itching, 2 patients showed mild itching and 36 patients showed no symptoms of itching at end of week 4. In standard of care group; 4 patients had very severe itching, 32 patients presented severe itching and 5 patients showed moderate itching at screening, while after treatment, 2 patients showed severe itching, 10 patients showed moderate itching, 10 patients showed mild itching and 19 patients showed no symptoms of itching at end of week 4.

Table 3b. Clinical assessment of Pilex Forte tablets with local application of Pilex Ointment in fissure-in-ano group, standard of care group (n=41) [N (%)]

Parameters	Scale	Screening	Week 1	Week 2	Week 4
Itching	Nil	0 (0)	0 (0)	3 (7.32)	19 (46.34)
	Mild	0 (0)	3 (7.32)	13 (31.71)	10 (24.39)
	Moderate	5 (12.2)	20 (48.78)	19 (46.34)	10 (24.39)
	Severe	32 (78.05)	17 (41.46)	6 (14.63)	2 (4.88)
	Very severe	4 (9.76)	1 (2.44)	0 (0)	0 (0)
Bleeding/ Streaks	Nil	0 (0)	0 (0)	3 (7.32)	20 (48.78)
	Mild	0 (0)	2 (4.88)	15 (36.59)	10 (24.39)
	Moderate	6 (14.63)	20 (48.78)	17 (41.46)	10 (24.39)
	Severe	35 (85.37)	19 (46.34)	6 (14.63)	1 (2.44)
	Very severe	0 (0)	0 (0)	0 (0)	0 (0)
Burning sensation	Nil	0 (0)	0 (0)	1 (2.44)	16 (39.02)
	Mild	1 (2.44)	1 (2.44)	13 (31.71)	11 (26.83)
	Moderate	5 (12.2)	21 (51.22)	19 (46.34)	10 (24.39)
	Severe	33 (80.49)	18 (43.9)	8 (19.51)	4 (9.76)
	Very severe	2 (4.88)	1 (2.44)	0 (0)	0 (0)

Scale: 0- Nil, 1- Mild, 2- Moderate, 3- Severe, 4- Very severe.

Effect on Bleeding

In Pilex Forte group; 32 patients presented severe bleeding/streaks and 8 patients showed severe bleeding/streaks at screening, while after treatment, 1 patient showed very severe bleeding/streaks, 1 patient showed moderate bleeding/streaks and 38 patients showed no symptoms of bleeding/streaks at end of week 4. In standard of care group; 35 patients presented severe bleeding/streaks and 6 patients showed moderate bleeding/streaks at screening, while after treatment, 1 patient showed severe bleeding/streaks, 10 patients showed moderate bleeding/streaks, 10 patients showed mild bleeding/streaks and 20 patients showed no symptoms of bleeding/streaks at end of week 4.

Effect on Burning sensation

In Pilex Forte group, 5 patients presented very severe burning sensation, 30 patients showed severe and 5 patients showed moderate burning sensation at screening, while after treatment 1 patient showed severe burning sensation, 1 patient showed moderate burning sensa-

tion, 1 patient showed mild burning sensation and 37 patients showed no symptoms of burning sensation at end of week 4. In standard of care group; 2 patients presented very severe burning sensation, 33 patients showed severe and 5 patients showed moderate burning sensation and 1 patient showed mild burning sensation at screening, while after treatment, 4 patients showed severe burning sensation, 10 patients showed moderate burning sensation, 11 patients showed mild burning sensation and 16 patients showed no symptoms of burning sensation at end of week 4.

Overall Comparative Assessment of Pilex Forte with Standard of Care

Table 4a and 4b elicits the overall comparative assessment of Pilex Forte tablets along with local application of Pilex Ointment with standard of care alone by patient & by investigator as assessed at the end of the study (graphically represented in figure 6 and 7).

Table 4a. Overall comparative assessment of Pilex Forte tablets with local application of Pilex Ointment in haemorrhoids Group

Scale	Pilex Forte N (%)		Standard of care N (%)	
	By patient	By investigator	By patient	By investigator
Cured	13 (34.21)	13 (34.21)	4 (9.52)	4 (9.52)
Marked improvement	21 (55.26)	21 (55.26)	12 (28.57)	11 (26.19)
Moderate improvement	3 (7.89)	3 (7.89)	13 (30.95)	14 (33.33)
Slight improvement	1 (2.63)	1 (2.63)	11 (26.19)	11 (26.19)
No change	0 (0)	0 (0)	1 (2.38)	1 (2.38)
Symptoms became worse	0 (0)	0 (0)	1 (2.38)	1 (2.38)

Table 4b. Overall comparative assessment of Pilex Forte tablets with local application of Pilex Ointment in fissure-in-ano group

Scale	Pilex Forte N (%)		Standard of care N (%)	
	By patient	By investigator	By patient	By investigator
Cured	16 (40)	20 (50)	1 (2.5)	1 (2.5)
Marked improvement	20 (50)	17 (42.5)	5 (12.5)	6 (15)
Moderate improvement	3 (7.5)	1 (2.5)	22 (55)	21 (52.5)
Slight improvement	1 (2.5)	2 (5)	12 (30)	12 (30)
No change	0 (0)	0 (0)	0 (0)	0 (0)
Symptoms became worse	0 (0)	0 (0)	0 (0)	0 (0)

In Haemorrhoid group; who received Pilex tablets along with local application of Pilex Ointment, 13 (34.32%) patients out of 38 patients were completely symptom free at the end of 4 week as compared to only 04 (9.52%) patients out of 42 patients who received standard of care alone.

In Fissure-in-ano group; who received Pilex tablets along with local application of Pilex Ointment, 16 (40%) patients out of 40 patients were completely symptom free at the end of 4 week as compared to only 01 (2.5%) patients out of 40 patients who received standard of care alone.

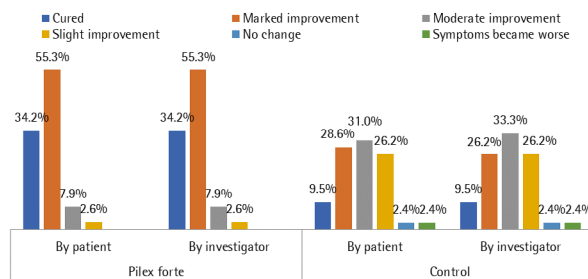


Fig. 6. Overall effect of Pilex Forte tablets with local application of Pilex Ointment in haemorrhoids Group

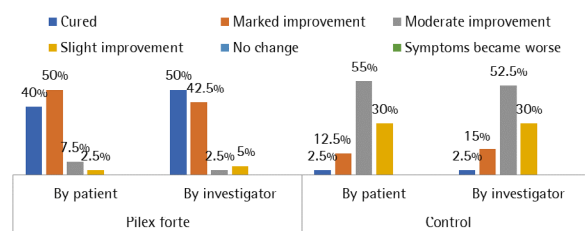


Fig. 7. Overall effect of Pilex Forte tablets with local application of Pilex Ointment in fissure-in-ano group

Discussion

Anorectal disorders are a common reason for visits to both primary care physicians and gastroenterologists/surgeons. These disorders are varied and include benign conditions such as haemorrhoids to more serious conditions such as malignancy; thus, it is important for the clinician to be familiar with these disorders as well and know how to obtain an appropriate history and conduct physical examination. Some of the most common anorectal disorders, including haemorrhoids are anal fissures, fecal incontinence (FI), proctalgia fugax, excessive perineal descent, and pruritus ani.

Pilex Forte tablet and Pilex Ointment for local application is specially formulated for the treatment of various anorectal conditions like Haemorrhoids and fissure-in-ano.

The laxative property of Pilex Forte tablet corrects chronic constipation associated with haemorrhoids. The therapeutic effects of various ingredients in Pilex Ointment are also stated to be anti-inflammatory, lax-

ative and styptic. Pilex Forte tablet contains ingredients such as *Balsamodendron mukul* (Purified), *Shilajeet* (Purified), *Melia azadirachta*, *Berberis aristata*, *Emblica officinalis*, *Terminalia chebula*, *Terminalia belerica*, *Cassia fistula*, *Bauhinia variegata*, *Mesua férrea* with the following pharmacological actions which might possibly be responsible for their synergistic action in bringing about significant clinical improvement in both haemorrhoidal and fissure-in-ano group as appreciated in the present study. The individual herbal actives and its actions with few anecdotal references are detailed as follows,

Balsamodendron mukul (Syn. *Commiphora mukul*)

The guggulsterone fraction of gum Guggul exhibited anti-inflammatory activity in the models of acute inflammation, which was comparable to approximately one-fifth that of hydrocortisone and equal to phenylbutazone and ibuprofen.¹⁶

Shilajeet (Purified)

Shilajit (Purified) have been used as anti-inflammatory agents for ages. There are reported results of clinical use of Shilajeet(Purified) in diabetes, fever, anemia, anorexia, spasmodic pain, obesity, abdominal disorders, and skin diseases. It also has cardiotoxic activities.¹⁷⁻¹⁸

Melia azadirachta (Syn. *Azadirachta indica*)

The leaf & bark has antimicrobial, antifungal, anthelmintic, insecticidal, antiviral, antipyretic, anti-inflammatory activities. The same is used in inflammatory gum diseases, boils, sores, measles, small pox, and other cutaneous infections.¹⁹⁻²⁰

Berberis aristata

The extract has bitter, cholagogue, antidiarrhoeal, stomachic, laxative, antipyretic, antiseptic activities. The same also has anti-inflammatory, hypotensive, and anti-tamoebic activities.²¹ The decoction is used for gastric disorders, piles, and other allied complaints. It gives good relief in senile pruritus. It has laxative activity too that is helpful in managing haemorrhoids.²²

Emblica officinalis

It has antiviral, antibacterial and antiallergy activities. It is rich in phenols. Aqueous extract showed antibacterial activity against *S. aureus*.²³ Its varied therapeutic activity leads its use in viral hepatitis, premature atherosclerosis, and managing anemia, pimples, fistula etc.²⁴

Terminalia chebula

It has shown antibacterial, antifungal activity against number of dermatophytes, and improves the immunity to protect from viral growth and infections. Additional antispasmodic and potent wound healing activity by improved rates of contraction and decreased period of ep-

ithelialization were also established. Purgative action of *Terminalia chebula* is also noted. It's widely prescribed in constipation, ulcer, gastroenteritis, cough, haemorrhoids and other skin diseases.²⁵

Terminalia belerica

It shows hepatoprotective action against other common hepatotoxic agents.²⁶ It shows gastroprotective, laxative activity being one of the ingredients of Triphala.²⁷

Cassia fistula

In traditional medicines, the same is used in haematemesis, pruritus, leucoderma, and diabetes and other commonly dermatological infestations, inflammatory disorders, and constipation.²⁸ *C. fistula* pod infusion could be safely utilized as laxative drugs and as a substitute for the official Senna.²⁹

Bauhinia variegata

It's widely used in constipation as laxative, antibacterial and blood purifier activities, antioxidant activity and tumours, anti-tumour property and hepatoprotective activity.³¹

Mesua ferrea

Mesua ferrea have potent broad-spectrum antimicrobial actions and prevent secondary microbial infections.³² It also have astringent and styptic actions that are useful in bleeding piles.³³

Pilex Ointment and its pharmacology

Pilex Ointment is a herbo-mineral formulation consisting extracts of *Mimosa pudica*, *Eclipta alba*, *Vitex negundo*, *Calendula officinalis*, *Mimosa pudica*, *Eclipta alba*, *Vitex negundo*, *Calendula officinalis*, *Cinnamomum camphora*, *Tankana*, *Yashada bhasma* which have anti-inflammatory, analgesic, wound healing, membrane stabilizing, anti-microbial and antioxidant actions. Synergistic actions of these potent herbs might possibly bring about localized reduction of varicosities of venous plexus in common ano-rectal conditions like haemorrhoids and fissure-in-ano. The individual herbal actives and its actions with few anecdotal references are detailed as follows,

Mimosa pudica

Mimosa pudica has astringent and styptic actions that are useful in bleeding piles.³⁴

Eclipta alba

Eclipta alba has anti-inflammatory and analgesic activities.³⁵ These actions are mediated via prostaglandin synthesis inhibition and cell membrane stabilizing activities.

Vitex nigundo

This has potent broad-spectrum antimicrobial action; and prevents secondary microbial infections.³⁶ This also

has potent analgesic³⁷, significant and directly dose-dependent analgesic activity.³⁸ *Vitex negundo* has strong antihistaminic activity, which helps to control associated itching and also membrane stabilizing and antioxidant activities.³⁸ Additionally, anti-inflammatory activity due to presence of triterpenoids and anti-histamine activity were also evident.³⁹

Calendula officinalis

Calendula officinalis has anti-inflammatory and analgesic activities. *Calendula officinalis* accelerates the wound healing by the epithelial regeneration.⁴⁰ Pilex Ointment improves the network of basal membrane collagenous substance, which leads to renormalization of the capillary membranes resistance and subsequently, it induces reduction in the hemorrhoidal mass of the dilated veins of hemorrhoidal plexus.⁴⁰ *Calendula officinalis* have potent free radical scavenging activities.⁴¹

Cinnamomum camphora

Cinnamomum camphora has analgesic activity. It relieves or soothes pain by reducing the sensitivity of the brain or nervous system to pain.⁴² It accelerates wound-healing by epithelial regeneration and have potent broad-spectrum antimicrobial actions and prevent secondary microbial infections.⁴³ It also has potent free radical scavenging activities.⁴⁴

Tankana

Tankana has potent broad-spectrum antimicrobial actions and prevent secondary microbial infections.⁴⁵

Yashada Bhasma

Yashada bhasma, have potent anti-inflammatory and analgesic actions. It accelerates wound-healing by epithelial regeneration.⁴⁶

Conclusion

Based on the results of the present clinical study, it was clearly evidential that Pilex Forte tablets along with the local application of Pilex Ointment showed significant clinical improvement with reduced clinical signs and symptoms in both Haemorrhoids and fissure-in-ano as compared to Standard of care alone. No serious or non-serious adverse events were reported or observed throughout the study period. It can be concluded that Pilex Forte tablet along with the local application of Pilex Ointment is safe and effective in the treatment of anorectal conditions like haemorrhoids and fissure-in-ano.

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