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Original Research Article

A phase 3, randomized, open-label, multicentre study to evaluate the efficacy and safety of diltiazem plus lidocaine fixed-dose combination gel versus diltiazem gel in Indian patients with anal fissure

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ABSTRACT

Background: Anal fissures cause significant pain and morbidity, requiring prompt and effective treatment. This study aims to evaluate the efficacy and safety of a fixed-dose combination (FDC) gel containing diltiazem and lidocaine compared to diltiazem gel alone in the treatment of anal fissures.
Methods: In this randomized, open-label, phase 3 study, eligible Indian patients (n=326) of either sex, aged 18 to 64 years, were randomly allocated (1:1) to the test (FDC diltiazem and lidocaine) or reference (diltiazem) group. Patients were asked to apply ~1 g of test or reference product, intra-anally, thrice-a-day, for 40±2 days. The assessment time points were day 1, 5, 10, 25, and 40.
Results: There was a significant reduction in pain scores between the test group and the reference group at the assessment time points. The least-squares mean difference in the mean anal pain intensity reduction from Baseline to day 10 between test and reference groups was −.1 (95% confidence interval: −9.18, −3.02; p=0.0001). More patients in the test versus reference group had pain relief at 0.5 hours after first treatment application on day 1 (60.7% versus 48.8%; p=0.0302). Proportion of patients with partial healing of anal fissure was significantly higher at day 5 (64.2% versus 46.5%; p=0.0015) and day 10 (92.5% versus 81.5%; p=0.0036) in the test versus reference group) treatment-emergent adverse events occurred in four patients in the test group and in eight patients in the reference group.
Conclusions: In this large, phase 3 multicentric study, the FDC of diltiazem and lidocaine demonstrated superior pain intensity reduction and early onset of pain relief with an acceptable safety profile as compared with diltiazem gel alone in Indian patients with anal fissure.

Keywords: Anal fissures, Diltiazem, Fixed-dose combination, Lidocaine, Pain relief

INTRODUCTION

Anal fissure is a linear or oval shaped tear in the lining of the distal anal canal below the dentate line.[1,2] It can be acute or chronic (>6 weeks), with a tendency for recurrence.[2,3] Anal fissures are a common ailment, although there are no available published population-level data.[4] It can occur in all age groups but most commonly

affects young healthy adults of either sex.[5] In India, various studies have reported anal fissure prevalence in the range of 11% to 54% among those with anorectal complaints; it was most common in the younger age group and in males.[6-11] Anal fissures are caused due to trauma to the anal canal. Symptoms include bleeding, itching, constipation, and anal pain typically induced or aggravated during defecation, all of which cause considerable discomfort and reduction in quality of life.[12-14] In patients with anal fissure, the resting pressure in the internal anal sphincter is increased, which causes the pain and spasm experienced during defecation and leads to decreased blood flow to the traumatized anoderm resulting in delayed wound healing.[2]

First-line therapy in the treatment of anal fissure is high fiber diet, medications to regulate bowel movements, and topical agents and analgesics.[4,5] The goal of medical treatment is to achieve a temporary reduction of anal canal pressure and to facilitate fissure healing.[15] Chemical sphincterotomy using a variety of pharmacological agents including topical glyceryl trinitrate, topical calcium channel blockers (nifedipine or diltiazem) and botulinum toxin have been found to be effective in improving symptoms, healing anal fissures, and reducing the need for surgical interventions.[13,16,17] In Indian patients with chronic anal fissure, topical treatment with a combination of diltiazem gel and lidocaine gel was observed to provide significantly better pain relief compared with either diltiazem gel alone or lidocaine gel alone.[11,18] Using a fixed-dose combination (FDC) rather than individual combination of treatments with synergistic mechanism of action is expected to enhance efficacy, reduce side effects, lower costs, and increase patient compliance.[19,20]

This study was conducted to assess the efficacy and safety of an FDC gel of diltiazem hydrochloride 2% w/w and lidocaine hydrochloride 2% w/w (test product) versus diltiazem hydrochloride 2% w/w gel (reference product, CremaGel®, Abbott India Ltd.) in the treatment of anal fissure in Indian patients. The primary objective of this study was to compare the effectiveness of a fixed-dose combination gel of diltiazem and lidocaine versus diltiazem gel alone in reducing anal pain intensity from baseline (prior to application) to day-10 in patients with anal fissure. Secondary objectives included comparing the two treatments in reducing anal pain, relieving itching symptoms, and promoting fissure healing over multiple time points (day 5, day 10, day 25, and day 40). Additionally, the study assessed time to complete healing and evaluated the safety and tolerability profiles of both treatments.

METHODS

Study design

This randomized, open-label, phase 3, comparative study was conducted at 12 centres across India from March to November 2021.

Ethical considerations

Ethical approval was obtained from the institutional or independent ethics committees of all 12 participating hospitals. The study was conducted in accordance with international ethical standards, including the guidelines of the Indian Council of Medical Research (ICMR) and the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment. The trial was registered with the Clinical Trials Registry of India (CTRI/2021/02/030971)

Study population

The study population included patients diagnosed with anal fissure experiencing moderate to severe anal pain.

Sample size

Based on the difference in anal pain intensity visual analogue score (VAS) scores between treatments in the Mital et al a sample size of 130 patients per arm was required to show superiority of the test product versus reference product at 80% power.[21] Considering a 20% dropout rate, a total of 326 patients (163 patients in each arm) were planned to be enrolled.

Selection criteria

Inclusion criteria

Patients of either sex, aged 18 to 64 years (inclusive), diagnosed with anal fissure (up to 6 weeks acute) and experiencing moderate to severe anal pain (defined as a score ≥45 mm on a 100 mm VAS were included in the study. Eligible patients were required to discontinue the use of any other concomitant topical preparations applied to the perianal area and to be willing to comply with all study procedures and requirements.

Exclusion criteria

The exclusion criteria included patients with anal fistulas or fissures secondary to conditions such as Crohn's disease, anal suppuration, anal abscess, or fixed anal stenosis/fibrosis. Patients with anal fissures associated with other underlying conditions or with active gastrointestinal disorders within four weeks prior to screening defined as two or fewer bowel movements per week accompanied by straining or the passage of hard stools were also excluded. Additional exclusions included a history of neoplastic disease within the past five years, acute hemorrhoidal attacks, anal or perianal cancer, previous surgical interventions involving the anal canal or perianal region (e.g., lateral sphincterotomy or anal stretch), prior pelvic radiation therapy, and the use of diltiazem hydrochloride gel, other topical calcium channel blockers, or any medicated topical ointments within three days prior to screening.

Study treatment/intervention

At baseline (day 1), eligible patients were randomized in a 1:1 ratio to receive either the test product (fixed-dose combination diltiazem and lidocaine, 2% gel) or the reference product (diltiazem gel) using a computer-generated (4 block) randomization list.

Patients were instructed to apply approximately 1 g of the assigned gel peri-anally—equivalent to 2 cm of gel in the syringe provided for the test product, or 1 g measured using the scale provided with the reference product. Randomization codes were kept strictly confidential, securely and accessed only by authorized personnel in accordance with the standard operating procedures until study completion.

The first application on day 1 was carried out at the study centers when patients were trained on the method of application by the investigator or designated personnel. Patients were then instructed to continue applying the test or reference product perianally thrice a day (morning, afternoon/evening, and at bedtime) for 40±2 days.

Patients received 8 tubes of the test or reference product, and the gel tubes were dispensed to each patient at visits 1 to 4 (days 1, 5, 10, and 24). All patients were permitted at investigator discretion to use laxatives/stool softeners/ fiber supplements during the entire study.

Efficacy measurements

Anal pain intensity and pain relief

The anal pain intensity was measured using a 100-mm VAS as a patient-reported measure. Anal pain intensity was evaluated prior to treatment application at 0.5, 1, 2, 4, and 8 hours post treatment application on day 1, and on days 5, 10, 25, and 40. Patients were asked to rate pain relief on a 5-point scale where 1=no relief, 2=some relief, 3=partial relief, 4=significant relief, and 5=complete relief.

The intensity of anal pain and pain relief at 0.5-, 1-, and 2-hours was recorded at the study site, and at 4- and 8-hours was recorded by the patient in the patient diary.

Peri-anal itching

The intensity of peri-anal itching was rated by patients on a 5-point scale, as 1=not present, 2=mild, 3=moderate, 4=severe, and 5=unbearable.[21] The itching intensity was measured prior to treatment application on day 1, and on days 5, 10, 25, and 40.

Peri-anal bleeding

Participants were instructed to use a standardized toilet paper roll given by the study staff after each bowel movement. They were advised to lightly swab the anal region and check the tissue for blood. Any visible bleeding was promptly noted in a patient diary, noting the date, time, and approximate amount.

The grade of peri-anal bleeding was calculated as the sum of the frequency score and the amount score.[22] The frequency of peri-anal bleeding was rated on a 5-point scale as 1= <1 episode per 2 weeks, 2=1 to 2 episodes per 2 weeks, 3=1 to 2 episodes per week, 4=3 to 4 episodes per week, and 5= >5 bleeding episodes per week. The amount of peri-anal bleeding was rated on a 4-point scale as 1=non-existent, 2=mild (blood spot on toilet paper), 3=moderate (blood streak on toilet paper), and 4=severe (blood visible on stool). The scores were measured prior to treatment application on day 1 and on days 5, 10, 25, and 40.

Partial/complete healing of anal fissure

Partial healing was defined as persistence of fissure but with improvement in symptoms (pain relief and/or control of bleeding). Pain relief was defined as at least a 20-point reduction in anal pain intensity VAS scores and/or at least a single point reduction on bleeding score from baseline. Complete healing of anal fissures was defined as the presence of scar on physical examination.

Safety measurements

Vital signs and physical examinations, including local examination of anal area, were conducted at each scheduled visit on days 0 (baseline), 5, 10, 25, and 40. Electrocardiograms, body weight measurements, treatment compliance evaluations, and laboratory tests—including haematology and biochemistry were performed at baseline and day 40. Treatment-emergent adverse events (TEAEs) and serious TEAEs were recorded throughout the study, and safety follow-up was conducted telephonically three days post end of treatment.

Study endpoints

The primary efficacy endpoint was the difference in mean reduction in anal pain intensity from baseline (prior to treatment application) to day 10 between test and reference groups.

The secondary efficacy endpoints were: mean reduction in anal pain intensity from baseline (prior to treatment application) to day 10 within test and reference group; mean reduction in anal pain intensity from baseline (prior to treatment application) to 0.5-, 1-, 2-, 4- and 8-hours post application on day 1, and on days 5, 25, and 40 within and between treatment groups; onset of pain relief on day 1; reduction in itching and bleeding (recorded as peri-anal bleeding score) from baseline (prior to treatment application) to days 5, 25, and 40 within and between treatment groups; proportion of patients with partial/complete healing of anal fissure on days 5, 25, and 40; and mean time to complete healing of anal fissure.

Statistical analysis

Efficacy data were presented for the full analysis set that included patients who received at least one treatment application and had at least one post-baseline efficacy assessment data. The safety patient sample included all randomized patients who received at least one treatment application.

The primary endpoint was assessed using analysis of variance (ANOVA) with treatment as factor. Test was carried out as 2-sided on a 5% level of significance. Point estimates and 2-sided 95% confidence intervals (CIs) for the difference in mean was estimated, and superiority was claimed if the upper bound of the 2-sided 95% CI was <0 for difference between treatment groups in mean anal pain intensity reduction from baseline to day 10.

Paired t-test at a 2-sided 5% level of significance was used to analyse mean reduction in anal pain intensity within each treatment group from baseline to day 10, and from baseline to 0.5-, 1-, 2-, 4-, and 8-hours (post treatment application) on day 1, and on days 5, 25, and 40. Point estimates and 2-sided 95% CI for the difference in mean were estimated. Difference between test and reference groups for mean reduction in anal pain intensity from baseline at each of the timepoints (other than day 10) was analysed using ANOVA. Reduction in perianal bleeding was analysed using the ANOVA for between-group comparison and using paired t-test for within group comparison. Missing values were imputed using last observation carried forward method. Log-rank test was used to compare the time to onset of some/partial/ significant/complete relief in pain between test and reference groups separately and overall. Two-sided p value from the log-rank test at 5% level of significance was presented. Two-sided chi-squared test/Fisher exact test at 5% level of significance was performed to test the difference between the two treatments in proportion of patients with partial or complete healing of anal fissure. Two-sample t-test was used to compare mean time for complete healing of anal fissure between test and reference groups, and log-rank test was used to compare the median time. Safety results were summarized descriptively. Statistical analysis was carried out using SAS version 9.4 (SAS® Institute Inc., United States).

RESULTS

Demographics and baseline characteristics

A total of 334 patients were screened, and 326 patients were enrolled, of whom 311 completed the study (Figure 1). The demographic and baseline characteristics are comparable between treatment groups (Table 1).

Mean reduction in anal pain intensity

The least-squares mean difference in the mean anal pain intensity reduction from baseline to day 10 between test and reference group was ─6.1 (95% CI: ─9.18, ─3.02; p=0.0001 (primary endpoint)). The upper bound of the two-sided 95% CI was less than 0, demonstrating superiority of test product to reference product. In both treatment groups, there was a significant reduction in mean (SD) anal pain intensity from baseline (prior to treatment application) to day 10. A significant reduction from baseline was also observed at all time points tested on day 1 and on days 5, 25 and 40, in both treatment groups; the between-group difference at all timepoints was significantly in favour of the test product (Table 2 and Figure 2).

Table 1: Demographic and baseline characteristics – safety patient sample.

Characteristics	Test group (n=163)	Reference group (n=162)
Age (years), mean (SD)	36.7 (11.9)	37.8 (11.5)
Male sex, n (%)	99 (60.7)	95 (58.6)
BMI (kg/m^2), mean (SD)	24.7 (3.71)	23.7 (2.98)
Supine systolic blood pressure (mmHg), mean (SD)	122.8 (6.44)	124.1 (6.90)
Supine diastolic blood pressure (mmHg), mean (SD)	79.2 (5.22)	78.5 (5.04)

BMI=body mass index; SD=standard deviation

Onset of pain relief

A significantly higher proportion of patients in test group versus reference group had pain relief at 0.5 hours after first treatment application on day 1 (60.7% versus 48.8%, p=0.0302). The proportion of patients with overall pain relief increased from 0.5 hours to 8 hours on day 1 post treatment application in both treatment groups. At 8 hours post-treatment application, more patients in the test group (51.5%) versus reference group (39.5%) experienced complete pain relief. Median time to onset of pain relief was 0.5 hour in test group and 1.0 hour in reference group.

Partial/complete healing of anal fissure

Partial healing of anal fissures was observed in significantly more patients in test group than in reference group on days 5 and 10 (Figure 3). Complete healing of anal fissure was observed in more patients in test group than reference group on days 25 and 40, but the between-group difference was not significant. Mean (SD) time to complete healing of anal fissure was 37.9 (7.67) days in test group and 37.8 (8.05) days in reference group. The between-group difference was not significant (─0.627 (─2.22, 0.97), p=0.4395 by 2-sample t test).

Reduction in perianal itching and bleeding

There was a significant reduction in peri-anal itching and bleeding scores from baseline to days 5, 10, 25, and 40 in both treatment groups; the between-group difference was not statistically significant (Table 3).

Safety

Five TEAEs were reported in 4 (2.5%) patients in the test group and 8 TEAEs were reported in 5 (3.1%) patients in the reference group (Table 4). All TEAEs were mild or moderate in intensity and considered by the investigator to be not treatment related. One serious TEAE of anal spasm was reported in the test group, which led to study discontinuation. This serious TEAE was moderate in intensity, resolved with treatment and was considered by the investigator to be not treatment related. There were no deaths reported in the study. There were no major changes in vital signs, physical examination findings, electrocardiogram, and laboratory findings during the study.

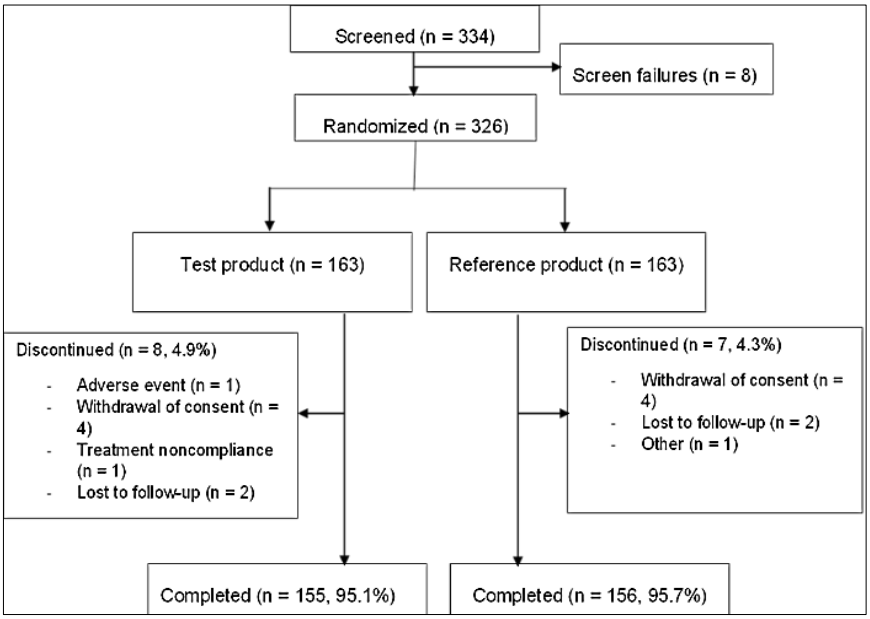

Figure 1: Patient disposition.

Table 2: The mean reduction in anal pain intensity from baseline to day 1 (8 hour), and on day 5, day 10, day 25, and day 40 within and between test group and reference group.

Visits	Test group (n=163)	Reference group (n=162)	LSM difference (95% CI) between treatment groups)	P value[2]
Pain score				
Baseline, mean (SD)	71.1 (10.35)	71.4 (10.10)		
Day 1 (8 hour), mean (SD)	37.5 (20.44)	43.2 (18.93)		
Change from baseline, mean (SD)	-33.6 (17.72)	-28.2 (17.93)	-5.4 (-9.28, -1.50)	<0.0001
P value	<0.0001	<0.0001		
Day 5, mean (SD)	51.6 (14.60)	56.9 (12.27)		
Change from baseline, mean (SD)	-19.6 (12.85)	-14.3 (10.63)	-5.3 (-7.94, -2.75)	<0.0001
P value[1]	<0.0001	<0.0001		
Day 10, mean (SD)	39.8 (13.06)	45.9 (13.86)		
Change from baseline, mean (SD)	-31.5 (13.19)	-25.4 (14.81)	-6.1 (-9.18, -3.02)	<0.0001
P value[1]	<0.0001	<0.0001		
Day 25, mean (SD)	25.0 (12.89)	33.7 (15.28)		
Change from baseline, mean (SD)	-46.3 (14.61)	-37.6 (17.37)	-8.7 (-12.22, -5.13)	<0.0001
P value[1]	0.0001	<0.0001		
Day 40, mean (SD)	9.8 (11.15)	18.2 (15.66)		
Change from baseline, mean (SD)	-61.6 (13.02)	-53.3 (18.14)	-8.3 (-11.80, -4.76)	<0.0001
P value[1]	<0.0001	<0.0001		

P value[1] for within-group comparison by paired t-test; P value[2] for between-group comparison by ANOVA treatment group, ANOVA=analysis of variance; CI=confidence interval; LSM=least square mean; SD=standard deviation

Table 3: Reduction in perianal itching and bleeding from baseline to day 40.

Visits	Test group (n=163)	Reference group (n=162)	LSM difference (95% CI)	P value[2]
Itching scores				
Baseline, mean (SD)	2.2 (0.80)	2.4 (0.88)		
Day 5	n=162	n=159		
Change from baseline, mean (SD)	−0.3 (0.62)	−0.3 (0.60)	0.0 (−0.13, 0.13)	0.9918
P value[1]	<0.0001	<0.0001		
Day 10	n=159	n=162		
Change from baseline, mean (SD)	−0.6 (0.70)	−0.6 (0.74)	0.0 (−0.17, 0.15)	0.8950
P value[1]	<0.0001	<0.0001		
Day 25	n=158	n=159		
Change from baseline, mean (SD)	−0.8 (0.79)	−0.7 (0.79)	−0.1 (−0.28, 0.07)	0.2328
P value[1]	0.0001	<0.0001		
Day 40	n=156	n=156		
Change from baseline, mean (SD)	−1.1 (0.81)	−1.2 (0.85)		
P value[1]	<0.0001	p<0.0001	0.1 (−0.13, 0.24)	0.5414
Bleeding scores				
Baseline, mean (SD)	5.0 (1.97)	5.1 (2.13)		
Day 5	n=162	n=159		
Change from baseline, mean (SD)	−0.6 (1.53)	−0.3 (1.70)	−0.3 (−0.68, 0.03)	0.0692
P value[1]	<0.0001	0.0463		
Day 10	n=159	n=162		
Change from baseline, mean (SD)	−1.0 (1.34)	−0.7 (1.40)	−0.3 (−0.60, 0.00)	0.0537
P value[1]	<0.0001	<0.0001		
Day 25	n=158	n=159		
Change from baseline, mean (SD)	−1.6 (1.71)	−1.2 (1.67)	−0.3 (−0.70, 0.05)	0.0889
P value[1]	<0.0001	<0.0001		
Day 40	n=156	n=156		
Change from baseline, mean (SD)	−2.2 (1.92)	−2.0 (1.98)	−0.2 (−0.63, 0.24)	0.3851
P value[1]	<0.0001	<0.0001		

P value[1] for within-group comparison by paired t-test; P value[2] for between-group comparison by ANOVA treatment group; ANOVA=analysis of variance; CI=confidence interval; LSM=least square mean; SD=standard deviation

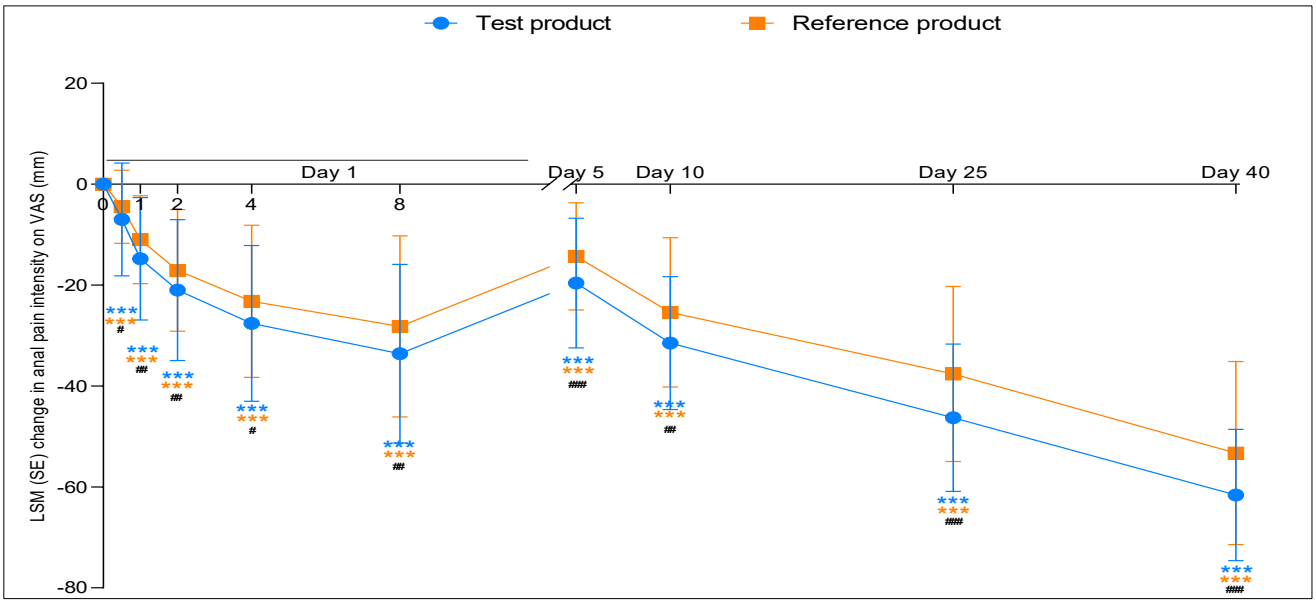

Figure 2: Mean anal pain intensity reduction from baseline to day 40.

***P<0.0001 for within group comparison by paired t-test; #p<0.05, ##p<0.01 and ###p<0.0001 for between group comparisons by ANOVA

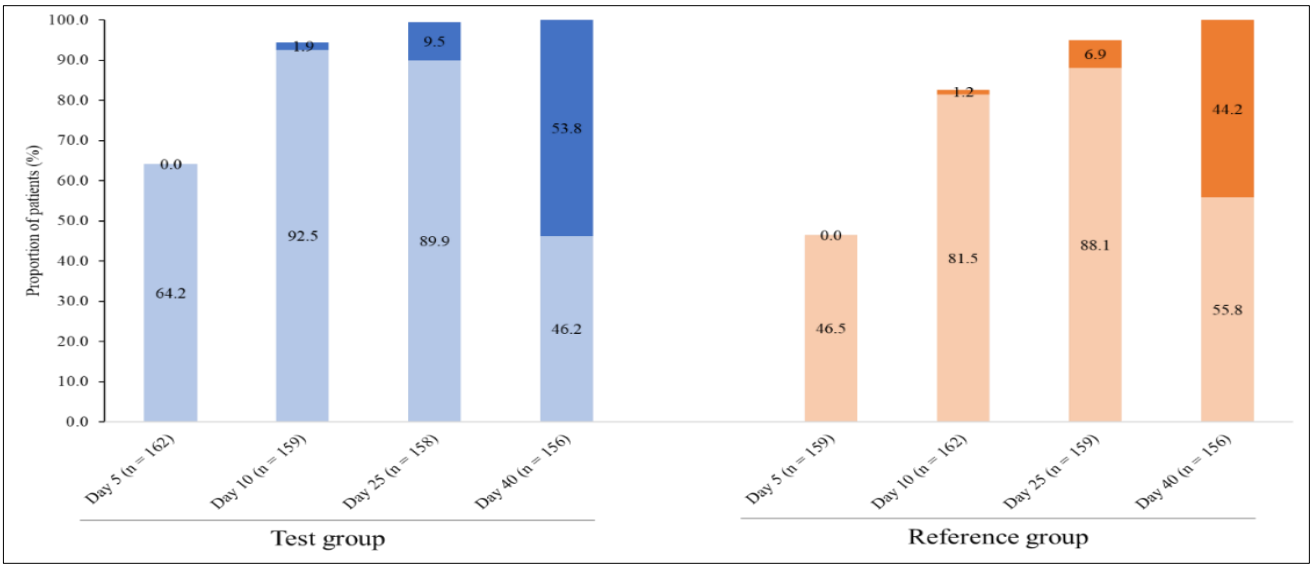

Figure 3: Proportion of patients with partial/complete healing of anal fissures from baseline to day 40.

Light bars indicate partial healing and dark bars indicate complete healing. Between-group difference in partial healing of anal fissures was significantly in favor of test group on day 5 (p=0.0015) and on day 10 (p=0.0036). There was no significant difference between groups in complete healing of anal fissures on all days. P value by chi-squared/Fisher exact test

Table 4: Treatment-emergent adverse events reported during the study.

TEAEs, n (%)	Test group (n=163)	Reference group (n=162)
At least one TEAE	4 (2.5)	5 (3.1)
Headache	2 (1.2)	1 (0.6)
Anal inflammation	1 (0.6)	0
Anal spasm	1 (0.6)	0
Anal pruritus	0	1 (0.6)
Anorectal discomfort	0	2 (1.2)
Diarrhea	0	2 (1.2)
Asthenia	0	1 (0.6)
Pyrexia	0	1 (0.6)

TEAE=treatment-emergent adverse event, adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24. Events are presented in descending order of occurrence in the test group

DISCUSSION

The key finding of this research demonstrated that the FDC of diltiazem hydrochloride 2% w/w and lidocaine hydrochloride 2% w/w gel had beneficial effects in terms of greater reduction in anal pain intensity and faster onset of pain relief compared to diltiazem hydrochloride 2% w/w gel alone in Indian patients with anal fissure. Currently, pharmacological therapies based on topical application have been preferred in the management of anal fissures. Topical delivery of calcium channel blockers is preferred over oral treatment considering the better healing and fewer systemic side effects.[5,23] Topical diltiazem as first-line therapy effectively heals anal fissures by increasing blood flow to the area via smooth muscle relaxation and vascular dilatation and leads to improvement in health-related quality of life.[14,24-27] Topical diltiazem also causes significantly less headaches than topical nitrates.[5] Addition of a local anaesthetic to diltiazem is expected to produce faster pain relief and healing. Lidocaine, a topical anaesthetic agent, is indicated for anaesthesia of mucous membranes in anal conditions such as fissures, and has been shown to be safe following repeated anorectal administration.[28,29] Several studies have shown the benefits of combined topical treatment with calcium channel blockers plus lidocaine for anal fissures.[11,30]

Mital et al compared diltiazem plus lidocaine versus diltiazem alone in Indian patients with chronic anal fissure. They observed similar reduction in mean anal resting pressure with the two treatments, but significantly higher pain relief with diltiazem plus lidocaine.[18] Kujur et al compared diltiazem plus lidocaine and nifedipine plus lidocaine versus lidocaine alone in Indian patients with chronic anal fissure.[11] They observed a significant reduction in anal pain intensity and bleeding and significantly higher healing rates with both nifedipine plus lidocaine and diltiazem plus lidocaine compared with lidocaine alone after four weeks of treatment.

Interestingly, anal pain reduction, improvement in bleeding and healing rates were similar between nifedipine and diltiazem.

Results from our phase 3 trial confirmed the superior efficacy and comparable safety of an FDC gel of diltiazem plus lidocaine versus diltiazem gel alone in the treatment of anal fissure in Indian patients. The mean anal pain intensity decreased significantly from baseline to day 10 with both the FDC gel and diltiazem gel. Moreover, there was a significant between-group difference in favour of the FDC gel, and the upper bound of the two-sided 95% CI was less than 0, demonstrating superiority of the FDC gel in providing pain intensity reduction. This finding is consistent with the finding of superior efficacy of diltiazem plus lidocaine reported by Mital et al and Kujur et al mean pain intensity reduction from baseline at all other timepoints tested until end of study was also significantly higher with the FDC gel.[11,18] Similarly, significant to complete pain relief by day 40 was observed in more patients applying FDC gel versus diltiazem gel alone.

In addition, in this study significantly higher percentage of patients applying FDC gel versus diltiazem gel experienced pain relief at 0.5 hours post-application on day 1 (the first timepoint assessed), demonstrating early onset of pain relief with the FDC gel. It is however possible that patients experienced pain relief even earlier than 0.5 hours with the FDC gel (although not assessed), considering lidocaine onset of action occurs within 3 to 5 minutes of topical application.[28] The mean (SD) time to complete healing of anal fissure and reduction in peri-anal itching and bleeding, which are related to the mechanism of action of diltiazem, were similar with FDC gel and diltiazem gel. The demographics of patients with anal fissure included in this study were consistent with those observed in previous studies in Indian patients, in that patients were generally young and of male sex.[6-11] Treatment-emergent adverse events were few with both treatments (5 in test group and 8 in reference group), all were mild or moderate in intensity and considered by the investigator to be not treatment related. There were no deaths, and the one serious event reported in a patient who applied the FDC gel was moderate in intensity, resolved with treatment and considered by the investigator to be not treatment related.

A limitation of the study is its open-label nature. Earliest timepoint for measurement of onset of pain relief was 30 min; considering the fast onset of action at lidocaine, evaluation at earlier time points could have resulted in detection of earlier onset of pain relief in the test versus reference group.

CONCLUSION

In this large phase 3 multicentre study, the FDC of diltiazem and lidocaine gel demonstrated significantly greater reduction in anal pain intensity and a faster onset of pain relief compared to diltiazem gel alone in Indian patients with anal fissure. The FDC combination was well tolerated and exhibited an acceptable safety profile, supporting its potential as an effective treatment option for healing with good patient reported outcome.

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