

Original Research Article

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A prospective non-comparative study to assess the effectiveness and safety of combination laxative therapy containing milk of magnesia, liquid paraffin and sodium picosulphate (Cremaffin-Plus®) in the management of constipation in patients with anal fissure/hemorrhoids/obstructive defecation syndrome

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ABSTRACT

Background: Assess the effectiveness and safety of combination laxative therapy containing milk of magnesia, liquid paraffin and sodium picosulphate (Cremaffin-Plus®) in management of constipation, in patients with anal fissure/haemorrhoids/obstructive defecation syndrome (ODS).

Methods: Patients visiting study site with complaints of constipation secondary to anal fissures/haemorrhoids/ODS, intended to receive combination laxative therapy (as per physicians' discretion), were enrolled. Primary objectives were to assess the change in number of bowel movements per day and stool consistency; secondary objectives were to assess change in straining, physician global efficacy assessment, quality of life (PAC-QOL score), Constipation Symptoms (CSS), Fecal Incontinence Score (FIS), Patient Assessment of Constipation Symptoms (PAC-SYM) score, along with the Modified Longo Score (MODS) for ODS from baseline to end of 4 weeks. Safety, tolerability and treatment adherence were also assessed.

Results: About 32 patients (anal fissure:19, haemorrhoids:5, ODS:8) met inclusion criteria. Significant improvement in stool frequency was observed in all patients pooled together ($p=0.016$); group wise, statistical significance was noted in patients of anal fissures. Stool consistency was improved in all patients pooled together ($p<0.001$); group wise, significant improvement was seen in patients of anal fissure and ODS. There was a significant improvement in straining noted in all patients pooled together ($p=0.002$). Significant reduction ($p<0.001$) was noted in all the symptom scores (CSS, FIS, PAC-SYM and PAC-QOL) from baseline to 4 weeks in all patients. About 51.44% reduction in MODS score was noted in patients with ODS.

Conclusions: Improvement in stool frequency, consistency and straining was noted in all patients with constipation (with fissure/haemorrhoids/ODS) treated with Cremaffin-plus for 4-weeks, improving the quality of life. All patients showed good therapy adherence with better safety and tolerability profile.

Keywords: Anal fissure, Constipation, Hemorrhoids, Milk of magnesia, Obstructive defecation syndrome, PAC-QoL, Sodium picosulphate

INTRODUCTION

Chronic constipation is a common disorder that affects 2–30% of people in the western world. Most patients define constipation by one or more symptoms: hard stools, infrequent stools (typically fewer than three per week), the need for excessive straining, a sense of incomplete bowel evacuation, and excessive time spent in the toilet or in unsuccessful defecation. It has a considerable impact on health costs and quality of life (QoL). It is estimated that about 25% of constipated patients may have obstructed defecation.^{1,2}

The treatment of constipation is aimed at treating the underlying cause, if known. In chronic constipation of unknown cause, the main treatment involves increased water and fiber intake in diet.³ Apart from these nonpharmacological measures, laxatives are the integral part of constipation management which include bulk (psyllium, wheat bran), lubricant (liquid paraffin), osmotic laxatives (milk of magnesia, lactulose, polyethylene glycol) and stimulants (bisacodyl, sodium picosulphate). In addition to appropriate laxative, patients with ODS will also need biofeedback therapy.⁴

Milk of magnesia is an osmotic laxative which acts by increasing the water content of the stool and making the stool softer and easier to pass. In 1987, Kinnunen O. et al. conducted a study in 64 elderly patients with constipation, treated with milk of magnesia and bulk laxatives. An improved stool consistency and frequency was reported in milk of magnesia treated group as compared to bulk laxatives group ($p<0.001$).⁵ Liquid paraffin is an emollient laxative which acts by lubricating the passage of stool, thereby reducing the resistance to passage of stools.⁶

Sodium picosulphate is a commonly used oral laxative which gets activated to bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM) by the colonic bacteria, thereby stimulating the colonic nerve endings, resulting in enhanced peristalsis and bowel evacuation. In an earlier 4-week study with bisacodyl (5-10 mg daily; n=70) and sodium picosulphate (5-10 mg daily; n=74), in patients with chronic constipation (N=144), a significant improvement in physicians' global assessment was observed in 74.6% patients treated with bisacodyl and 79.2% patients treated with sodium picosulphate.^{7,8}

However, though these data are existing for individual laxatives, there is no literature available on the combination laxative therapy containing milk of magnesia, liquid paraffin and sodium picosulphate for the management of constipation. Hence the objective of this study was to assess the effectiveness and safety of combination laxative therapy containing milk of magnesia, liquid paraffin and sodium picosulphate in the management of constipation in patients with anal fissure/hemorrhoids/ODS, over the period of 4-weeks.

METHODS

This prospective, single-arm, non-comparative, single-centre study was carried out after obtaining approval from the Institutional Ethics Committee, in accordance with the principles of Declaration of Helsinki (World Medical Association) and Good Clinical Practice guidelines issued by the ICMR and DCG(I), Govt. of India.^{9,10} All the patients were explained about the study in details and were provided opportunity to raise any queries/doubts about the study. Informed written consent was obtained from all patients before enrolment. The study is registered in the clinical trials registry of India (CTRI/2016/10/007403; Registered on: 24/10/2016).

Study participants

Patients of either gender, between 18 and 65 years of age, those suffering from constipation secondary to anal fissures, hemorrhoids, or ODS were enrolled after obtaining written informed consent. Patients with primary idiopathic constipation, history of organic disease of the colon, ileus, any acute surgical abdominal conditions, presence of active gastrointestinal disease, obstruction or dehydration, as well as ingestion of any drug affecting gastrointestinal motility or known hypersensitivity were excluded. Also, patients with any severe cardiac, hepatic, neurological and renal diseases, pregnant or lactating women, patients on any investigational therapy within 30 days prior to enrolment and patients not willing to provide written informed consent were also excluded.

Study treatment

All the enrolled patients were administered 15 ml of combination laxative therapy (Cremaffin-Plus® Abbott India Ltd.) for 4 weeks, as per the physicians' discretion, and in accordance with locally approved package insert. All patients continued to receive their co-medications for other medical conditions.

Study outcomes

Primary outcome was change in bowel movements and stool consistency at the end of the 4 weeks. The average daily number of stools was determined at baseline and then during different study periods. A 5-point scale was adopted for stool consistency, corresponding to liquid= 1, soft= 2, well-formed= 3, moderately hard= 4, hard= 5. The daily stool consistency score was obtained as the number of stools of each consistency class multiplied by the appropriate score and divided by the total number of stools for that day.

Secondary outcomes were change in straining during defecation (scored as 0= absent, no straining, 1= mild straining, 2= moderate straining, 3= severe straining) and changes in physicians' global efficacy assessment (assessed using 4-point rating scale as 1= worsened, 2= unchanged, 3= somewhat improved, 4= significantly

improved) from baseline to the end of 4 weeks. Changes in the Wexner's constipation scoring system (CSS), Wexner's fecal incontinence score (FIS), PAC-SYM (Patient's assessment of stool frequency and severity of constipation), PAC-QoL (Quality of life), and Modified Longo Score (MODS) for ODS from baseline to 4 weeks were also assessed.

Statistical analysis

Based on an average prevalence rate of 10% for constipation, the estimated sample size was 138 for the primary outcome.¹¹ Assuming a dropout rate of 10%, it was planned to enroll 150 patients. However, due to poor patient accrual, only 45 patients were screened of which 1 failed study eligibility criteria and 44 patients were enrolled. Continuous variables were summarized with the descriptive statistics (number of observations), mean, and standard deviation, median, minimum and maximum values.

A summary of categorical data was done through numbers and percentages. Efficacy analysis was done on the Per-Protocol Set (PPS) which included the subset of patients from full analysis set (FAS). The PPS included

all patients who satisfied the study criteria and completed the study as per the study protocol. The FAS was as close as possible to the intention-to-treat (ITT) data set and included all patients screened and enrolled. That is, all patients who had taken at least one dose of study medication and had no major protocol violations were included in FAS. All safety and tolerability analysis were done on the FAS.

RESULTS

Demographics and patient characteristics

A total of 44 out of 45 screened patients were enrolled; one patient failed study eligibility criteria. A total of 12 patients were excluded from the efficacy analysis dataset (PPS) due to major protocol violation (had primary constipation). Hence, a total of 32 patients were included in the PPS; safety analysis was done on all 44 patients who participated in the study (FAS). Of the 44 patients (FAS), 19 had constipation secondary to anal fissure, 8 had constipation associated with ODS, and 5 patients had constipation secondary to hemorrhoids. The patients were between 21 to 64 years of age (mean [SD]: 42.84 [12.24] years).

Table 1: Average number of stools passed daily at baseline and at 4 weeks (Per-Protocol Set).

	ODS (n=8)		Fissure (n=19)		Hemorrhoids (n=5)		Total (n=32)	
	No.	%	No.	%	No.	%	No.	%
Baseline								
One	3	37.50	4	21.05	1	20.00	8	25.00
Two	3	37.50	7	36.84	0	0.00	10	31.25
Three	2	25.00	3	15.79	2	40.00	7	21.88
Four	0	0.00	0	0.00	0	0.00	0	0.00
More than 4	0	0.00	1	5.26	1	20.00	2	6.25
Once on two days	0	0.00	4	21.05	0	0.00	4	12.50
Once in three days	0	0.00	0	0.00	1	20.00	1	3.13
4 weeks								
One	3	37.50	7	36.84	2	40.00	12	37.50
Two	2	25.00	9	47.37	3	60.00	14	43.75
Three	3	37.50	1	5.26	0	0.00	4	12.50
Four	0	0.00	0	0.00	0	0.00	0	0.00
More than 4 times	0	0.00	0	0.00	0	0.00	0	0.00
Once on two days	0	0.00	2	10.53	0	0.00	2	6.25
Once in three days	0	0.00	0	0.00	0	0.00	0	0.00
Chi-square test (p)		0.783		0.016		0.182		0.016

About 21 (47.73%) patients had normal weight while 23 (52.27%) were overweight or obese. Majority of the patients had moderate physical activity (52.27%); 25% patients followed a sedentary lifestyle. Tea consumption was reported in majority of the patients (72.73%); about 15.91% patients consumed coffee.

About 81.25% patients reported using squatting position for defecation; 18.75% patients were using western toilet seat for defecation.

Vital parameters were normal for all patients before and after surgery.

Primary outcomes: Bowel movement and stool consistency

Table 1 shows the data for the number of stools passed daily at baseline and after 4 weeks in PPS patients. There was a significant improvement in stool frequency after 4 weeks in all patients, when pooled together (n=32; p=0.016); however, group wise, statistical significance was noted in patients of constipation associated with anal

fissures (p=0.016). Stool consistency (Table 2) was improved in all patients, when pooled together (p<0.001); however, group wise, significant improvement was seen in patients of constipation associated with ODS (p=0.040) and anal fissure (p=0.001). Improvement in stool consistency after 4 weeks from baseline was observed in 75.0% patients with ODS, 73.68% patients with fissure and 80.0% patients with hemorrhoids; overall improvement was observed in 75% patients.

Table 2: Stool consistency at baseline and at 4 weeks (Per-Protocol Set).

ODS (n=8)		Fissure (n=19)		Hemorrhoids (n=5)		Total (n=32)							
No.	%	No.	%	No.	%	No.	%						
Baseline													
Liquid stools	0	0.00	0	0.00	0	0	0.00						
Soft	2	25.00	1	5.26	0	0.00	3	9.38					
Well formed	2	25.00	4	21.05	0	0.00	6	18.75					
Moderately hard	0	0.00	9	47.37	2	40.00	11	34.38					
Hard stools	4	50.00	5	26.32	3	60.00	12	37.50					
4 weeks													
Liquid stools	0	0.00	0	0.00	0	0.00	0	0.00					
Soft	6	75.00	7	36.84	0	0.00	13	40.63					
Well formed	2	25.00	10	52.63	3	60.00	15	46.88					
Moderately hard	0	0.00	1	5.26	2	40.00	3	9.38					
Hard stools	0	0.00	1	5.26	0	0.00	1	3.13					
Chi-square test (p)	0.040		0.001		0.151		<0.0001						
Change in stool consistency after 4 weeks from baseline													
Stool consistency													
Improvement	6	75.00	14	73.68	4	80.00	24	75.00					
No change	1	12.50	3	15.79	1	20.00	5	15.63					
Worsening	1	12.50	2	10.53	0	0.00	3	9.38					

Table 3: Straining during defecation at baseline and at 4 weeks (Per-Protocol Set).

ODS (n=8)		Fissure (n=19)		Hemorrhoids (n=5)		Total (n=32)		
No.	%	No.	%	No.	%	No.	%	
Baseline								
No straining	1	12.50	2	10.53	0	0.00	3	9.38
Mild	2	25.00	8	42.11	2	40.00	12	37.50
Moderate	2	25.00	5	26.32	2	40.00	9	28.13
Severe	2	25.00	3	15.79	1	20.00	6	18.75
Very Severe	1	12.50	1	5.26	0	0.00	2	6.25
4 weeks								
No straining	4	50.00	5	26.32	1	20.00	10	31.25
Mild	1	12.50	11	57.89	4	80.00	16	50.00
Moderate	3	37.50	2	10.53	0	0.00	5	15.63
Severe	0	0.00	1	5.26	0	0.00	1	3.13
Very Severe	0	0.00	0	0.00	0	0.00	0	0.00
Chi-square test (p)	0.121		0.034		0.965		0.002	
Change in straining during defecation after 4 weeks from baseline								
Improvement	5	62.50	10	52.63	4	80.00	19	59.38
No change	1	12.50	7	36.84	1	20.00	9	28.13
Worsening	2	25.00	2	10.53	0	0.00	4	12.50

Secondary outcomes

There was a significant improvement in straining during defecation after 4-weeks in all patients, when pooled together ($p=0.002$; Table 3). Group wise, significant improvement was seen only in patients of constipation associated with fissure ($p=0.034$). Mean score (SD) for straining during defecation at baseline was 2.75 (1.08), and 1.91 (0.78) after 4 weeks ($p=0.003$). That is, a reduction by 27.89% in the scores for straining during defecation was noted from baseline to 4 weeks. A total of 59.38% (19/32) patients reported improvement in

straining at defecation after therapy, only 28.13% (9/32) patients had no change in straining; 12.50% (4/32) patients had worsening in straining during defecation. In patients with ODS, 62.50% patients showed improvement; 12.50% had no change and 25.00% had worsening in straining during defecation. Similarly, in patients with fissure, 52.63% patients showed improvement, 36.84% had no change and only 10.53% had worsening in straining during defecation. In patients with hemorrhoids, about 80% patients reported improvement in straining.

Table 4: Physician's global efficacy assessment (Per-Protocol Set).

	ODS (n=8)		Fissure (n=19)		Hemorrhoids (n=5)		Total (n=32)	
	No.	%	No.	%	No.	%	No.	%
Assessment outcome								
Worsened	0	0.00	0	0.00	0	0.00	0	0.00
Unchanged	0	0.00	0	0.00	0	0.00	0	0.00
Somewhat improved	6	75.00	8	42.11	2	40.00	16	50.00
Significantly improved	2	25.00	11	57.89	3	60.00	16	50.00

Table 5: Symptom scores at baseline and after 4 weeks.

	Baseline		4 weeks		Percent change from baseline		Wilcoxon test	
	Mean	SD	Mean	SD	Mean	SD	Z	P
All patients (n=32)								
Wexner's CSS [#]	9.16	2.44	5.91	2.41	-33.63	27.26	-4.617	<0.0001
Wexner's FIS*	4.13	2.54	2.59	1.29	-19.50	59.98	-3.238	0.001
PAC-SYM Score	16.44	4.68	7.94	4.44	-48.44	30.16	-4.707	<0.0001
PAC-QOL Score	31.03	8.63	17.28	8.58	-43.13	24.30	-4.798	<0.0001
ODS (n=8)								
Wexner's CSS [#]	10.63	2.83	6.88	2.80	-37.03	16.71	-2.530	0.011
Wexner's FIS*	4.88	3.60	2.50	1.20	-38.37	29.75	-2.214	0.027
PAC-SYM Score	18.75	6.30	8.38	2.97	-50.03	25.61	-2.521	0.012
PAC-QOL Score	32.25	10.79	20.13	11.37	-39.03	18.80	-2.524	0.012
MODS Score	11.63	3.70	5.88	4.09	-51.44	23.42	-2.527	0.012
Fissure (n=19)								
Wexner's CSS [#]	8.63	2.09	5.74	2.08	-29.37	30.99	-3.237	0.001
Wexner's FIS*	3.79	2.23	2.68	1.45	-7.92	72.47	-1.969	0.049
PAC-SYM Score	15.68	4.01	7.47	4.05	-48.62	30.72	-3.524	<0.0001
PAC-QOL Score	29.58	7.31	15.58	7.67	-44.47	29.02	-3.623	<0.0001
Hemorrhoids (n=5)								
Wexner's CSS [#]	8.80	2.59	5.00	3.00	-44.39	26.41	-2.032	0.042
Wexner's FIS*	4.20	1.79	2.40	0.89	-33.33	33.34	-1.633	0.102
PAC-SYM Score	15.60	3.65	9.00	7.78	-45.19	40.43	-2.032	0.042
PAC-QOL Score	34.60	10.21	19.20	6.69	-44.60	11.21	-2.023	0.043

Constipation symptom score; * Fecal incontinence score.

Overall, 50% patients showed significant improvement while rest 50% patients showed somewhat improvement during physician's global efficacy assessment (Table 4). None of the patient was assessed worsened/unchanged of his symptoms of constipation by physicians, after the course of study medication. Table 5 present the symptom

scores (Wexner's CSS, Wexner's FIS, PAC-SYM and PAC-QOL) at baseline and at 4 weeks. A significant reduction ($p<0.001$) in all the symptom scores was noted after 4 weeks from baseline. There was a reduction in constipation CSS by 33.63% ($p<0.0001$), FIS by 19.50% ($p=0.001$), PAC-SYM score by 48.44% ($p<0.0001$) and

PAC-QOL score by 43.13% ($p<0.0001$). About 51.44% reduction in MODS score ($p<0.012$) from baseline to 4 weeks was noted in patients with ODS.

Safety and tolerability

No adverse events were reported by any of the patients during this period. All patients completed the 4 weeks' treatment period.

DISCUSSION

Constipation has many definitions and is often described differently depending on the population queried.¹² Physicians may define constipation as a reduction in the frequency of bowel movements to fewer than three times per week while patients identify more with the symptoms associated with constipation such as difficulty passing stool, hard stool consistency, feelings of abdominal cramping, and feelings of incomplete stool passage.¹³ Causes of constipation may be primary (functional) or secondary to other factors such as medications, medical (diabetes, hypothyroidism), organic (stricture, carcinoma, obstruction) and anorectal (anal fissures, hemorrhoids) conditions.¹⁴ Constipation, if untreated, can lead to complications like hemorrhoids, anal fissure, faecal impaction and rectal prolapse, causing a considerable impact on the health costs and QoL.^{3,15} It is very important to note that anorectal disorders like anal fissures and hemorrhoids are not only the etiology but also the complications of untreated constipation.^{15,16} To address this vicious cycle, timely intervention is of utmost importance. Early treatment with laxatives relieves the straining at stools and helps patients in improving their QoL.^{15,17}

Although data is available for individual laxatives like milk of magnesia, liquid paraffin and sodium picosulphate in constipation management, there is no data available on this combination for the same indication. A liquid oral formulation containing milk of magnesia, liquid paraffin and sodium picosulphate is available in India (Cremaffin-Plus®, Abbott India Ltd.) and is indicated for management of constipation.

In the current study, 32 patients with constipation secondary to anal fissure, ODS and hemorrhoids were treated with the combination study laxative as per the approved dosage for a period of 4 weeks. The results demonstrated that there was a significant improvement in stool frequency (average number of stool passed daily after 4 weeks) in all patients pooled together ($p=0.016$) however, group wise, statistical significance was noted only in patients of constipation associated with anal fissures. We also found that there was an improvement in stool consistency after 4 weeks in all patients pooled together ($P<0.001$); group wise, significant improvement was seen in patients of constipation associated with ODS and anal fissure. Improvement in stool consistency was observed in 75.0% patients with ODS, 73.68% patients

with fissure and 80.0% patients with hemorrhoids. Kinnunen et.al. had demonstrated that milk of magnesia improved stool frequency and normalized the stool consistency in elderly patients with constipation.⁵ Wulkow R et al in their study had demonstrated significant improvement in stool frequency and reduction of straining with sodium picosulphate, in patients of constipation, compared to placebo ($p=0.01$).¹⁸

Further, our findings showed that there was a significant improvement in the straining during defecation after 4 weeks in all patients pooled together ($p=0.002$). Significant improvement was seen in patients of constipation associated with fissure. There was ~28% reduction in the mean scores for straining during defecation with the use of study medication from baseline to 4 weeks. Straining during defecation is a key risk factor for the development of complications like anal fissures and hemorrhoids. In patients who had already developed these complications, straining further increases the risk of worsening of symptoms with bleeding and pain during defecation which lead to poor QoL.^{15,16} Therapy with milk of magnesia, liquid paraffin and sodium picosulphate showed significant improvement in stool frequency, stool consistency and straining, which translated into an improvement in QoL in these patients (reduction in PAC-QOL score by 43.13%, $p<0.0001$ compared to baseline).

Frequency and severity of constipation is commonly assessed by CSS and PAC-SYM scores. Our study demonstrated that therapy with combination laxatives resulted in a reduction in CSS by 33.63% ($p<0.0001$ compared to baseline) and PAC-SYM score by 48.44% ($p<0.0001$ compared to baseline), indicating superior efficacy of the study medication in addressing constipation symptoms.

The ODS is characterized by the urge to defecate but an impaired ability to expel the fecal bolus. Symptoms include unsuccessful fecal evacuation attempts, excessive straining, pain, bleeding after defecation, and a sense of incomplete fecal evacuation, which is also an important cause of constipation.^{18,19} The MODS is the most commonly used scoring system to evaluate the treatment strategy for ODS patients and to assess the percent and total change in ODS symptom score from baseline after intervention in short term and long-term follow-up trials of various intervals. A cut-off of nine for surgical intervention is preferred by many authors. Our results showed that the combination therapy with milk of magnesia, liquid paraffin and sodium picosulphate reduced mean MODS score from 11.63 to 5.88 (51.44% reduction, $p<0.012$ vs baseline), indicating towards the role of Cremaffin plus in the medical management of ODS.²⁰

Fecal incontinence is seen in patients of ODS as a small amount of stool is retained in the rectum at the end of defecation and is not perceived due to impaired rectal

sensation. Subsequently this small amount of stool may leak out of the anus unconsciously, because of the impairment of conscious contraction of the anal sphincter.²¹ The FIS is commonly used to assess the continence. Our study demonstrated a significant reduction (38.37%) in FIS score in patients of constipation with ODS after therapy with combination laxative therapy which could be attributed to the overall improvement in straining, consistency and frequency of defecation.

Physician global efficacy assessment demonstrated that overall, 50% patients had 'significant improvement' and the rest 50% had 'somewhat improvement'. Worsened/unchanged of his symptoms of constipation after the course of study medication was not reported by physician for any of the patient. In patients with constipation associated with ODS (n=8), 75% patients showed somewhat improvement while 25% showed significant improvement.

In patients with constipation associated with fissure (n=19), 57.89% patients showed significant improvement. In patients of constipation with hemorrhoids (n=5), 60% of them showed significant improvement in physician global efficacy assessment. This demonstrated the superior efficacy profile of Cremaffin Plus in constipation management, across multiple etiologies.

Adverse events like abdominal pain, nausea, vomiting, diarrhoea are reported with sodium picosulphate, while anal seepage, granulomatous reactions are seen with liquid paraffin usage in earlier published literature.^{6,8,18} In our study, the tolerability with combination laxatives were considered as good as none of the patients reported any adverse events during the 4-week study period. Present study has several strengths.

Firstly, this is a first of its kind study which uses the combination laxative therapy containing sodium picosulphate, liquid paraffin and milk of magnesia for the treatment of constipation associated with anal fissure/hemorrhoids/ODS. Secondly, study had used validated scales/scores to evaluate the primary and secondary objectives which establishes the precision of results. However, this being a non-comparative study, was restricted to a small number of patients from a single clinical set-up, thus the possibility of selection bias, warranting further large-scale studies.

CONCLUSION

Improvement in stool frequency, consistency and straining during defecation was noted in all patients with constipation (due to fissure/hemorrhoids/ODS) treated with Cremaffin-plus for 4-weeks, thereby improving the overall quality of life. All patients showed complete therapy adherence (4 weeks), with good safety and tolerability profile.

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Conflict of interest: None declared

Ethical approval: The study was approved by Suraksha Ethics Committee, Asian Institute of Medical Sciences (AIMS), Dombivali, Mumbai vide letter. (CTRI/2016/10/007403)

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