AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Topical Diltiazem Alone Versus Diltiazem With Lidocaine for the Treatment of Chronic Anal Fissure: A Prospective, Randomized Controlled Clinical Trial

Kushal Mital[1], Sanjay Kumar Maroo[2]*, Ketan Patel[2], Rakesh Ojha[2]

1.Department of general surgery, Medicare Hospital, Mumbai, India

2.Medical Services Department, Troikaa Pharmaceuticals Limited, Commerce House 1, Bodakdev, Ahmedabad Gujarat

ABSTRACT

Increase in anal resting pressure (ARP) is considered as the primary cause of chronic anal fissure (CAF). Reduction in ARP is the primary objective in treatment of CAF. Topical diltiazem is considered as first-line treatment option in CAF as surgical treatment may be associated with several post operative complications including permanent incontinence in some cases. Few studies have reported that lidocaine alone is inferior to anal dilators for pain relief in CAF which suggest that relief of internal anal sphincter is required for effective symptomatic management. The aim of this study was to evaluate whether combined treatment with diltiazem and lidocaine has any significant advantage over diltiazem monotherapy in patients with CAF. To evaluate this, 150 patients were enrolled and randomized to either treatment group. ARP, pain intensity and adverse events were recorded at various time points over 20 days study period. Fall in the mean ARP from baseline was comparable in both the study groups. However, significantly greater fall in pain intensity from baseline was observed with combined treatment with diltiazem and lidocaine, which can be attributed to the additional local anesthetic effects of lidocaine with combination treatment. No patient had any systemic or local adverse effects. Global assessment by patients and investigator was also favourable for combination treatment. We conclude that combined treatment with topical diltiazem and lidocaine is safe and effective option for pharmacological treatment of CAF, and addition of lidocaine to diltiazem significantly increases the pain relief achieved with diltiazem alone.

Keywords: Chronic anal fissure, diltiazem, lidocaine, anal resting pressure

*Corresponding Author Email: medicalservices@troikaapharma.com

Received 12 September 2013, Accepted 20 September 2013

Please cite this article in press as: Maroo S. *et al.*, Topical Diltiazem Alone Versus Diltiazem With Lidocaine for the Treatment of Chronic Anal Fissure: A Prospective, Randomized Controlled Clinical Trial. American Journal of PharmTech Research 2013.

INTRODUCTION

Chronic Anal Fissure (CAF) is a painful perineal condition. Increased anal resting pressure (ARP) is considered as the primary cause of CAF. Treatment of CAF is based on reducing the spasm of the internal anal sphincter, either with the use of pharmacological agents (chemical sphincterotomy) or by surgical sphincterotomy [1]. Internal anal sphincterotomy is the gold standard surgical treatment which lowers the ARP and effectively treats the anal fissures. However, the post operative period may be associated with many complications including incontinence which may be permanent in some cases. These complications have led to the search for alternative mode of therapies for the treatment of CAF [2].

Chemical sphincterotomy using a variety of pharmacological agents including topical glyceryl trinitrate (GTN), topical calcium channel blockers (CCBs) such as nifedipine or diltiazem and botulinum toxin (Btx) have been found to be effective in reducing ARP and healing the anal fissures [2]. It has been recommended that conservative treatment with topical CCBs, topical GTN, or Btx is effective method that may reduce the need for surgical interventions [3].

Several lines of evidence suggest that topical diltiazem; a CCB is safe and effective in the management of CAF including fissures which do not respond to topical nitrates. It acts by relaxing the anal sphincter and thereby decreasing internal anal sphincter pressure. Topical diltiazem is preferred over topical GTN in the treatment of CAF, as it is associated with a fewer adverse effects particularly headache. Hence, diltiazem may be considered as the first-line treatment option for CAF [4, 5].

Lidocaine is a local anesthetic that has been used topically for symptomatic improvement in patients with anal fissures from the long time. It has been postulated that, lidocaine being a local anesthetic can provide additional benefits if added to anal dilators like diltiazem, nifedipine, GTN and minoxidil for the treatment of anal fissures. It has been reported that the ointment for topical application containing combination of nifedipine 0.3% and lidocaine 1.5% resulted in healing in 94.5% of the patients with CAF after 6 weeks of therapy with no significant adverse effects [6]. In addition to this, Muthukumarassamy et al. have reported that topical formulation containing combination of minoxidil 0.5% and lidocaine 5% produces better symptomatic relief as compared to either agent alone [7]. In few clinical studies lidocaine was also compared with anal dilators for symptomatic improvement in CAF. Bacher et al. have reported that the pain relief with topical lidocaine was significantly inferior to topical GTN [8], this suggest that local anesthetic property alone may be ineffective for treatment of CAF and relief of spasm may be

needed to effectively heal fissure which can be achieved with anal dilators.

Effect of addition of lidocaine to diltiazem for treatment of CAF has not been studied. Hence, the present study was conducted to evaluate whether addition of lidocaine to diltiazem provide any significant improvement in management of CAF as compared to diltiazem monotherapy.

MATERIALS AND METHODS

Patients of either gender, between 18 to 60 years diagnosed with CAF were considered eligible for enrollment in this study between August 2009 to August, 2011. All the subjects were explained about the study and written informed consent was obtained from every subject before their participation.

At the time of screening, medical history was obtained; physical examination and laboratory investigations were performed. Patients having anal fistulas, or anal fissure of various causes such as Crohn's disease, anal suppuration, abscesses and, anal or perianal malignancies were excluded. Patients with HIV infection and patients with past history of hypersensitivity to amide type local anesthetics or diltiazem were also excluded during screening. Patients who have been previously treated surgically and patients taking oral CCBs, nitrates, or any other vasodilators were also excluded. The women of child bearing age underwent the urine pregnancy test; the pregnant and lactating women were excluded in this study.

This randomized, parallel, open label, active controlled study was conducted at Department of General Surgery, Medicare hospital, Mumbai, India. The study was conducted according to the ethics committee approved protocol, and in compliance with the ethical standards laid down in the Declaration of Helsinki, 1964 and its later amendments; Good Clinical Practice (GCP) guidelines issued by the Central Drugs Standard Control Organization (CDSCO), Ministry of Health, Government of India. The study was registered at clinical trial registry-India (CTRI Reg.No CTRI/2009/091/000356). Total 150 patients diagnosed with CAF were recruited in this study as per eligibility criteria. The enrolled patients were identified only by randomization number, not by name or initials during the conduct of study. Study participants were divided into two groups as per computer generated randomization sheet. One group received topical diltiazem 2% gel, and other group received lidocaine 2% gel in addition to diltiazem 2% gel.

Each patient was instructed to apply 2.5 cm strip of gel(s) to the anal margin twice daily for 20 days at regular interval. Follow up visits were scheduled on day 5, 10 and 20 at study site. Each patient underwent anal manometry using a spinctometer, a cordless hand held anal manometer to record ARP. Anal manometry was performed at baseline (0 hrs) i.e. prior to application, and at

15, 30 and 60 minutes after application of study treatment on day 1. Anal manometry was repeated on day 5, 10 and 20 after initiation of treatment. Intensity of pain was also recorded on day 1 at baseline (0 hrs) i.e. prior to application, and on day 5, 10 and 20 using 10 point Visual Analogue Scale (VAS) where 0 represents no pain and 10 represents worst possible pain. At the end of the study (day 20), both investigator and patient rated their global assessment of treatment based on safety and efficacy of study treatments.

During study period, patients who did not experience adequate pain relief as per the judgment of investigator were additionally treated with oral analgesic (diclofenac 50 mg, to a maximum of 150 mg/day) as a rescue medication. The number of rescue medications administered was recorded in case record forms of respective patient.

Each patient was enquired about the adverse events experienced during study period at every follow up visit. The only medications, considered necessary for the patient's welfare and which do not interfere with the study medication were allowed during the study period.

Sample size calculation and statistical analysis

Sample size calculation was performed using software PS Power and Sample Size Calculations (version no.3). Based on a power of 80% and a Type I error rate of $\alpha = 0.05_{2\text{-tailed}}$, a sample size of 65 participants per group was required to detect an estimated difference of 6.25 mmHg in ARP between the treatment arms with standard deviation (SD) of 12.4 [6]. Assuming dropout rate of 15%, a total sample size of 150 participants (75 per treatment group) was considered in this study. All statistical analyses were performed on intention-to-treat basis with last observation carried forward method. All statistical analyses were performed using software, GraphPad prism, version no.5. Unpaired t test or Mann Whitney test was used to compare the continuous data and Chi-square test was used to compare the categorical data of study groups. *P* value of less than 0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

Total 139 patients completed the study and were included in intention to treat analysis. There was no statistically significant difference in the demographic characteristics between the study groups (Table 1). Number of patients in different age group between both the treatment groups was described in figure 1.

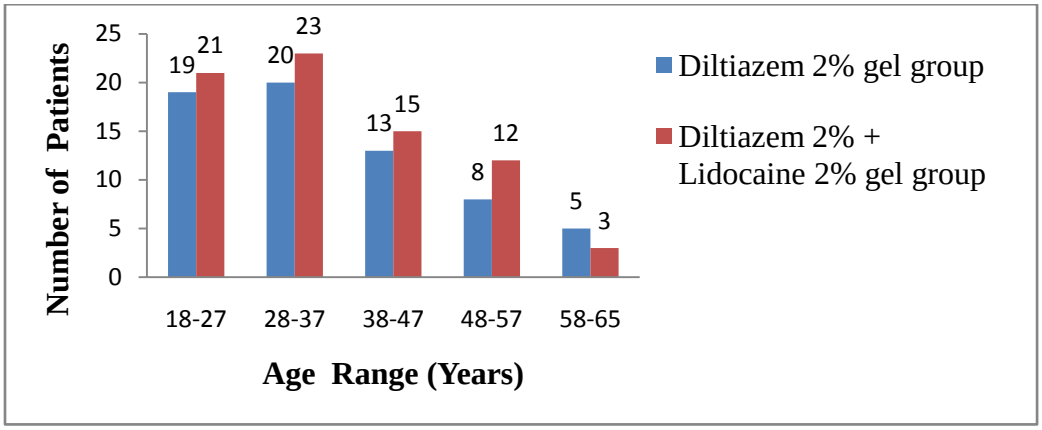

Figure 1: Number of patients in different age group

Table 1. Demographic characteristics

Characteristics	Diltiazem 2% gel group (N=65)	Diltiazem 2% + Lidocaine 2% gel group(N=74)	*P* value
Age (Years)	35.98 ± 12.54	35.94 ± 11.43	0.8262*
Weight (Kg)	65.32± 9.69	65.48±8.58	0.9922*
Height (Cms)	158± 7.84	159.16± 7.313	0.5363*
Gender (Male/Female)	35 /30	32 /42	0.2810#

Values are expressed in Mean ± SD for age, weight, height and absolute numbers for gender, N = number of subjects. *Data were analyzed by Unpaired t test; # Data were analyzed by Chi-Square test.

The mean baseline ARP was 49.98 ± 23.56 mmHg (mean ± SD) in diltiazem 2% gel group and 51.97 ± 14.19 mmHg in diltiazem 2% plus lidocaine 2% gel group. The change in mean ARP at 15, 30 and 60 minutes after study drug application on day 1 in relation to baseline mean ARP was comparable in both the study groups (Table 2). Similarly, the change in mean ARP on day 5, 10 and 20 of treatment in relation to baseline mean ARP was comparable in both the study groups (Table 2). This results suggested that addition of lidocaine with diltiazem did not show significantly additional reduction in ARP compared to diltiazem alone. It is well documented that lidocaine does not have significant effect in reducing ARP in patients with anal fissure [8]. Perrotti et al., have evaluated the effects of topical nifedipine and lidocaine in comparison to topical lidocaine and hydrocortisone for reduction in mean ARP in patients with CAF. There was significant reduction (11%) in mean ARP from baseline at 3 weeks of therapy with topical nifedipine and lidocaine group while no change in mean ARP from baseline was reported in topical lidocaine and hydrocortisone group [6]. The results of this study conclude that fall in ARP was attributed to nifedipine alone; and lidocaine, a local anesthetic is ineffective in reducing ARP. Similarly, in our study, mean fall in ARP from baseline at various time points can be attributed to topical diltiazem in both the study treatments.

Table 2. Change in Anal Resting Pressure after treatment

Duration	Difference in mean ARP from baseline		*P* value
	Diltiazem 2% gel group (N=65)	Diltiazem 2% + Lidocaine 2% gel group(N=74)	
15 minutes**	7.015 ± 12.62	10.43 ± 15.29	0.2682
30 minutes**	9.308 ± 12.38	10.51 ± 17.40	0.7040
60 minutes**	8.708 ± 13.13	10.85 ± 17.76	0.5478
Day 5	6.400 ± 16.01	10.05 ± 15.37	0.3164
Day 10	7.462 ± 14.97	11.20 ± 15.25	0.2839
Day 20	7.908 ± 15.94	11.65 ± 15.22	0.2391

Values are expressed in Mean ± SD, N = Number of subjects, ARP = Anal Resting Pressure. ** Duration after topical application of study treatment on day 1. Data were analyzed by Mann Whitney test.

The mean baseline pain intensity experienced by the patients (as per VAS score) was 6.32 ± 3.27 in diltiazem 2% gel group and 7.59 ± 3.00 in diltiazem 2% plus lidocaine 2% gel group. The mean change in the VAS score for pain intensity at day 5, 10 and 20 of treatment in relation to baseline VAS score for pain intensity was significantly higher in diltiazem 2% plus lidocaine 2% gel group as compared to diltiazem 2% gel group (Table 3). Based on the observation of reduction in ARP, it is evident that patients in both the groups have experienced reduction in the tone of internal anal sphincter, which is generally considered as the primary cause of CAF. Numerous clinical studies have shown that anal dilators i.e., nifedipine and GTN are superior to lidocaine for pain relief in patients with CAF [9-12]. Results of these studies suggest that reduction in ARP is the primary mechanism of pain relief in CAF. However, in our study significantly greater fall in pain intensity from baseline was observed with combined treatment with diltiazem and lidocaine as compared to diltiazem alone. These results suggest that combination of anal dilator with lidocaine, a local anesthetic may have additional pain relief effects as compared to that achieved with anal dilator alone.

Table 3. Change in pain intensity (VAS score) after treatment

Duration	Difference in VAS score for pain intensity from baseline		*P* value
	Diltiazem 2% gel group(N=65)	Diltiazem 2% + Lidocaine 2% gel group (N=74)	
Day 5	2.12 ± 2.19	2.92 ± 2.59	0.0363
Day 10	3.65 ± 2.42	4.55 ± 2.72	0.0278
Day 20	4.65 ± 2.66	5.59 ± 2.58	0.0196

Values are expressed in Mean ± SD, N = Number of subjects, VAS = Visual Analogue Scale. Data were analyzed by Mann Whitney test.

No cases of any adverse events were observed and reported during study period. Upon local examination of site, no cases of any undesirable local dermatological effects were observed in

both the study groups. None of patients from diltiazem 2% plus lidocaine 2% gel group required any rescue medication, while only one patient from diltiazem 2% gel group required oral analgesic as a rescue medication during study period.

Global assessment of treatment by patients and investigator was favourable for diltiazem 2% plus lidocaine 2% gel group (Table 4). This finding can be attributed to significantly higher degree of pain relief achieved with combined treatment of diltiazem and lidocaine, which in most instances is the primary concern in patients with CAF.

Table 4. Global assessment of treatment

Grade	**Global assessment of treatment by patients**		**Global assessment of treatment by investigator**	
	Diltiazem 2% gel group (N=65)	**Diltiazem 2% + Lidocaine 2% gel group(N=74)**	**Diltiazem 2% gel group (N=65)**	**Diltiazem 2% + Lidocaine 2% gel group(N=74)**
Excellent	18	31	41	57
Good	34	39	15	15
Fair	10	3	9	2
Poor	3	1	0	0
***P* value**	0.0458		0.0386	

Values are expressed as absolute numbers, N = Number of subjects. Data were analyzed by Chi square test

CONCLUSION:

Based on the results of our study, *we conclude that* combined treatment with topical diltiazem and lidocaine is safe and effective option for pharmacological treatment of CAF, and addition of lidocaine to diltiazem significantly increases the pain relief achieved with diltiazem alone.

ACKNOWLEDGMENT

This study was sponsored by Troikaa Pharmaceuticals Ltd., India and all the study related materials including study drugs were provided by Troikaa Pharmaceuticals Ltd., India. Authors would like to thank all the study subjects for their valuable participation in this study.

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