DOI: 10.14260/jemds/2014/3644

ORIGINAL ARTICLE

STUDY ON USE OF TOPICAL DILTIAZEM VERSUS TOPICAL GLYCERYL TRINITRATE (GTN) IN THE TREATMENT OF CHRONIC ANAL FISSURE: A RETROSPECTIVE STUDY

Madhu Lata Rana[1], Narayan Jeet Singh[2], Avtar Singh Bansal[3], Neetu Swain[4], Navpreet Singh[5]

HOW TO CITE THIS ARTICLE:
Madhu Lata Rana, Narayan Jeet Singh, Avtar Singh Bansal, Neetu Swain, Navpreet Singh. "Study on use of Topical Diltiazem Versus Topical Glyceryl Trinitrate (GTN) in the Treatment of Chronic Anal Fissure: A Retrospective study". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 54, October 20; Page: 12418-12428, DOI: 10.14260/jemds/2014/3644

ABSTRACT: OBJECTIVE: To compare the efficacy, associated side effects in short term as well as long term use of topical Diltiazem and topical GTN in the management of chronic anal fissure. **MATERIAL AND METHODS:** Out patients records of 231 patients with chronic anal fissure who reported to hospital from August 2011 to August 2014 and treated were randomly selected for both types of management of which 118 patients had received topical 2% diltiazem and 113 were treated with 0.2% glyceryl trinitrate topical ointment thrice daily for 6 weeks. They were assessed at the time of presentation, then at the end of 1st week, 3rd week and at the end of 6th week of treatment. Records of patients with anal fissure due to other diseases like inflammatory bowel disease, malignancy, sexually transmitted diseases, previous treatment with local ointment or surgery, patients who required anal surgery for any concurrent disease like hemorrhoids, pregnant women, patients with significant cardiovascular conditions and patients who did not turned up for follow up were excluded. Signs and symptoms and side-effects were noted at the given time. **RESULTS:** The study results are comparable to national figures and other studies. **CONCLUSION**: Topical application of both the ointments, 2% Diltiazem and 0.2% Glyceryl trinitrate observed to be quite effective in treatment of chronic fissure in Ano. However, topical Diltiazem is preferred to topical glyceryl trinitrate due to its lesser side effects and long term better control.

KEYWORDS: Anal fissure, Diltiazem, Glyceryl trinitrate.

INTRODUCTION: Anal fissure is a break or tear in the mucosa or skin in the anal canal. Anal fissures are commonly encountered in surgical OPD. They may be confused with hemorrhoids. Typically it presents with severe pain during or after defecation, may be lasting for few hours.[1] Patient may notice bright red blood on toilet paper or on stool. Anal fissure is usually associated with constipation. Development of newer drugs has resulted in preference of conservative treatment than surgical treatment.

Early fissures can be treated by simple measures. Most chronic and acute anal fissures are associated with raised internal anal sphincter pressure and vascular perfusion is low at the base. Initially anal fissure is treated with conservative management. An acute anal fissure may heal spontaneously with sitz bath, stool softener, analgesics and serratiopeptidases along with local application of anesthetics.[2] High fiber diet is helpful in long-term control and low recurrence in anal fissure.[3]

Glyceryl trinitrate (GTN) causes increase in the local blood flow secondary to the vasodilatation of the vessels of anal muscles and also causes reduction in the intra anal pressure which aid in healing of anal fissure, but there is evidence that it has limited duration of action[4] and

DOI: 10.14260/jemds/2014/3644

may be ineffective altogether.[5] It has also been noticed that chronic fissure for greater than six months and which are associated with sentinel pile are more likely to refractory to treatment.[6]

CALCIUM ANTAGONISTS: Diltiazem is a commonly used calcium channel blocker. It causes the dilatation and relaxation of muscular smooth muscle. Use of topical 2% diltiazem ointment in anal fissure reduces maximum resting pressure (MRP) by approximately 28%, which last for 3 – 5 hours after application.[7]

Topical diltiazem causes minimal side effects like peri–anal dermatitis. Oral diltiazem has also known to heal anal fissure, however side effects are significant.[8] Topical diltiazem is effective alternative to GTN with similar reduction in MRP and better improvement, low recurrence rate and fewer side effects than GTN.[9-12] Topical diltiazem also has lead to healing of GTN resistant fissure.[13]

The present study was undertaken to compare the efficacy and associated side effects in short term as well as long term use of topical Diltiazem and topical GTN in the management of chronic anal fissure.

MATERIAL AND METHODS: The retrospective study conducted in AIMSR, Bathinda, Punjab from August 2011 to August 2014. The study was carried out randomly in 231 patients with chronic anal fissure. Clearance from the local ethical committee was obtained for the study.

INCLUSION CRITERIA: Patient of both gender male and female aged between ≥18 years to ≤ 60 years, presence of anal fissure for < 6 weeks that has failed with other conservative management like stool softener, high fibre diet, local lignocaine application.

EXCLUSION CRITERIA: Patients records of anal fissure due to other diseases like anorectal malignancy, sexually transmitted disease, crohn's disease, ulcerative colitis, tuberculosis and other inflammatory disease, previous anorectal surgeries, anorectal trauma due to child birth, patients with associated hemorrhoids, fistula in ano, pregnant/lactating women, patients with significant cardiovascular conditions and if the patients did not comply with the treatment and follow up as advised were excluded. All patients selected for study were on outpatient basis.

As per records the detailed history of each patient was studied and clinical examination findings including inspection, palpation, digital rectal and proctoscopic examination performed were noted, where examination revealed features of chronicity like sentinel pile, indurated edges which were painful on examination were noted.

For the purpose of study the medical records of two groups were named as Topical DTZ Group and Topical GTN Group. 118 patients were studied in DTZ group and 113 patients were studied in GTN group and were randomized by sequential order as follows (DTZ, GTN) As per records, DTZ group was treated with 2% DTZ ointment locally while GTN group was to instruct to use 0.2% GTN ointment locally along with sitz bath, analgesics, serratiopeptidases and laxatives for 6 consecutive weeks.

Records show that they were assessed in surgical OPDs at presentation, at the end of 1st week then at 3rd week and finally at the end of 6th week of treatment. Follow up was done monthly for a year. At each visit signs and symptoms of pain relief, bleeding while defecation, healing of fissure, side effects and recurrence record were noted.

DOI: 10.14260/jemds/2014/3644

Intensity of pain was assessed based on Likert's, where every patient was asked to mark the pain score chart given to him or her at each visit. These charts were graded from 0 to 5 where 0 stands for no pain and 5 stands for worst pain.

Healing was defined as complete disappearance of fissure on examination, which the surgeon assessed from visual analogue score. Healing Likert's score was marked from 0 to 5, where 0 stands for complete healing and 5 stood for deep fissure for initial presentation.

Patient was also given a peri anal itching score ranging from 0 to 5, where 0 stood for no itching and 5 stood for worst itching.

The disease was termed as recurrent if the fissure appeared at the same site within one month after 6 weeks course of topical application.

Data Analysis: Data was collected and was analyzed statistically. The P values were calculated using Chi square test and were considered significant below 0.001.

RESULTS: In both the groups there was male predominance. Ages of patients were similar in both the groups (Table 1). Pain was the main presenting symptom which was present in 99% of patients in DTZ group and 98% in GTN group, followed by bleeding per rectum while defecation which was present in 89% in DTZ group and 84% in GTN group, most of the patient had constipation at presentation which was present in 60% patient in DTZ group and 63% patient in GTN group. Perianal itching was present in 18% in DTZ group and 16% in GTN group.

CHARACTERISTICS	DTZ Group (n=118)	GTN Group (n=113)
Male	86	83
Females	32	30
Age in years (range)	18 - 65	18 – 60
Duration of symptoms	< 6 months	< 6 months
SYMPTOMS:		
Pain	99%	98%
Bleeding P/R on defecation	89%	84%
Constipation	60%	63%
Perianal itching	18%	16%
LOCAL FINDINGS:		
Posterior midline AF	64%	67%
Anterior midline AF	42%	55.7%
Anterior and posterior midline AF	**1.69%**	**3.38%**
Sentinel pile	63.5%	54%
Sphincter spasm	100%	100%

Table1: Clinical details of the subjects on initial presentation

Most common location of fissure in ano was posterior midline, which was present in 64% patient in DTZ group and in 67% patient in GTN group. Fissure was located in anterior midline in 42% patients in DTZ group and 55.7% patients in GTN group, whereas in 1.69% patients, fissure was present in both positions, i.e. anterior midline and posterior mid line in DTZ group and in 3.38%

DOI: 10.14260/jemds/2014/3644

patients in GTN group. Almost all the cases had sphincter spasm. Sentinel pile was present in 63.5% patients in DTZ group and in 54% patients in GTN group. Cases were assessed at presentation, at the end of 1st week, 3rd week, and 6th week and findings were recorded.

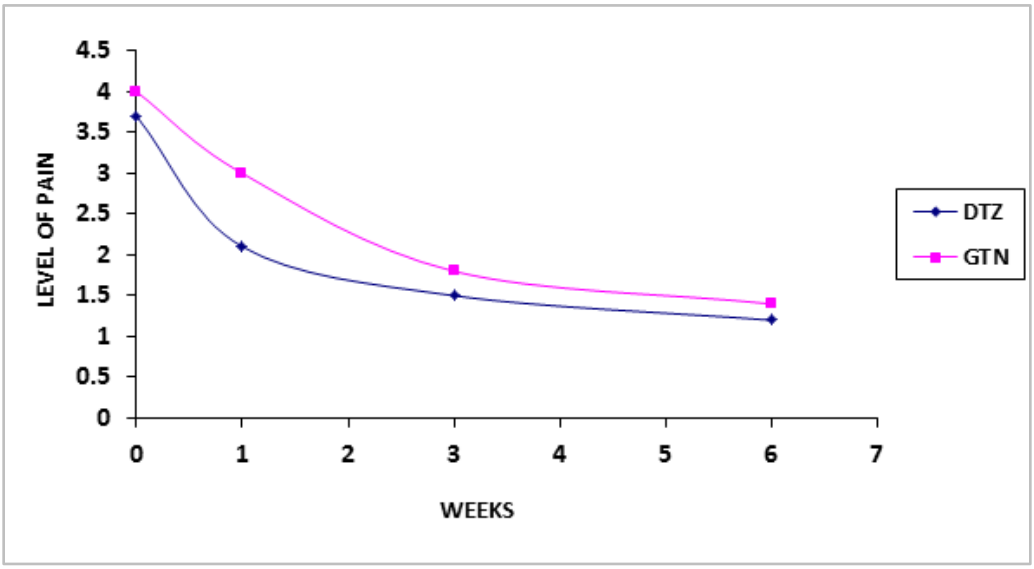

Figure: 1 Level of pain in DTZ group and GTN group at presentation, 1st weekend, 3rd weekend and 6th weekend

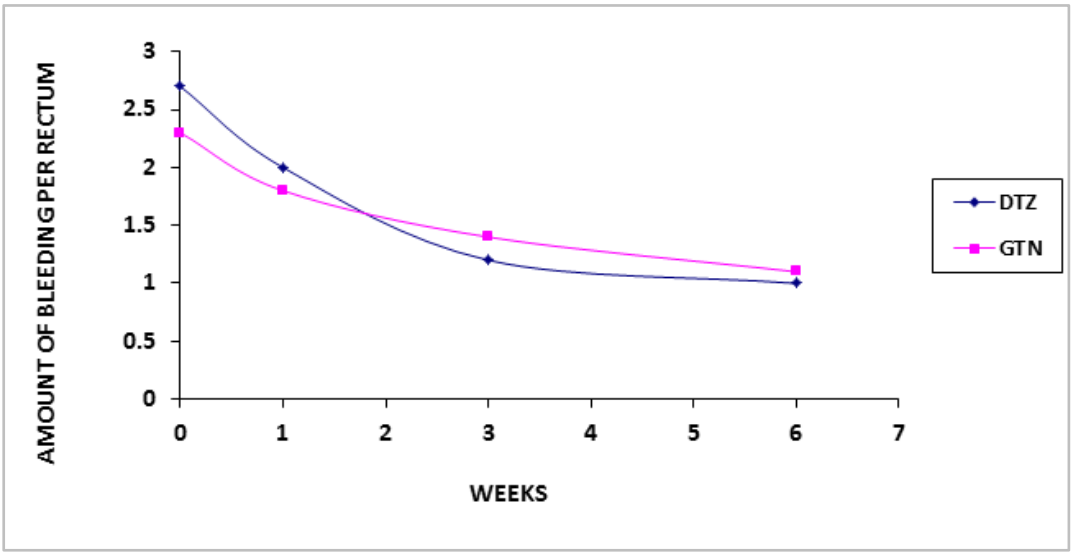

Figure 2: Amount of bleeding in DTZ group and GTN group at presentation, 1st weekend, 3rd weekend and 6th weekend

DOI: 10.14260/jemds/2014/3644

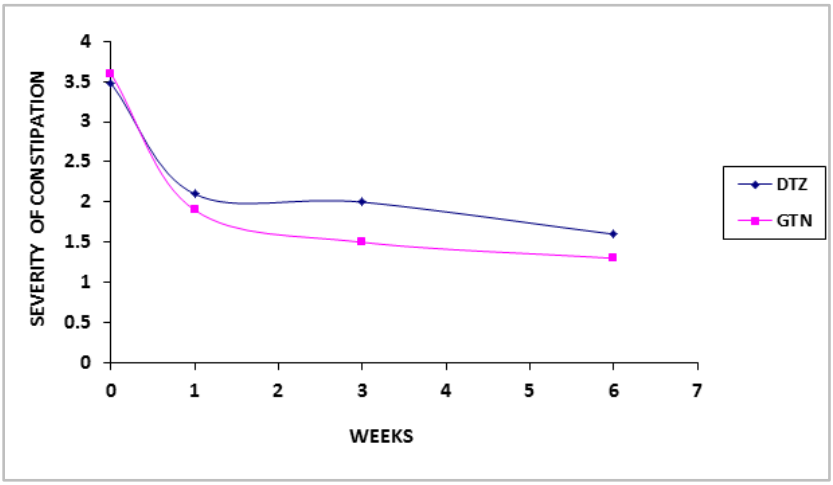

Figure 3: Severity of constipation at presentation, 1st weekend, 3rd weekend and 6th weekend

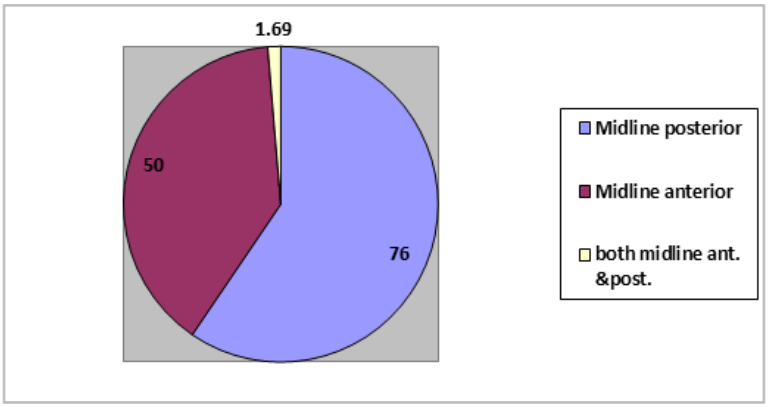

Figure 4: Position of fissure in DTZ group

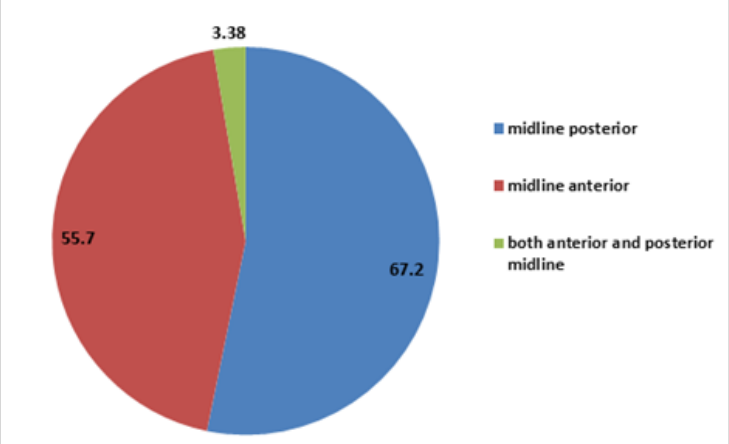

Figure 5: Position of fissure in GTN group

DOI: 10.14260/jemds/2014/3644

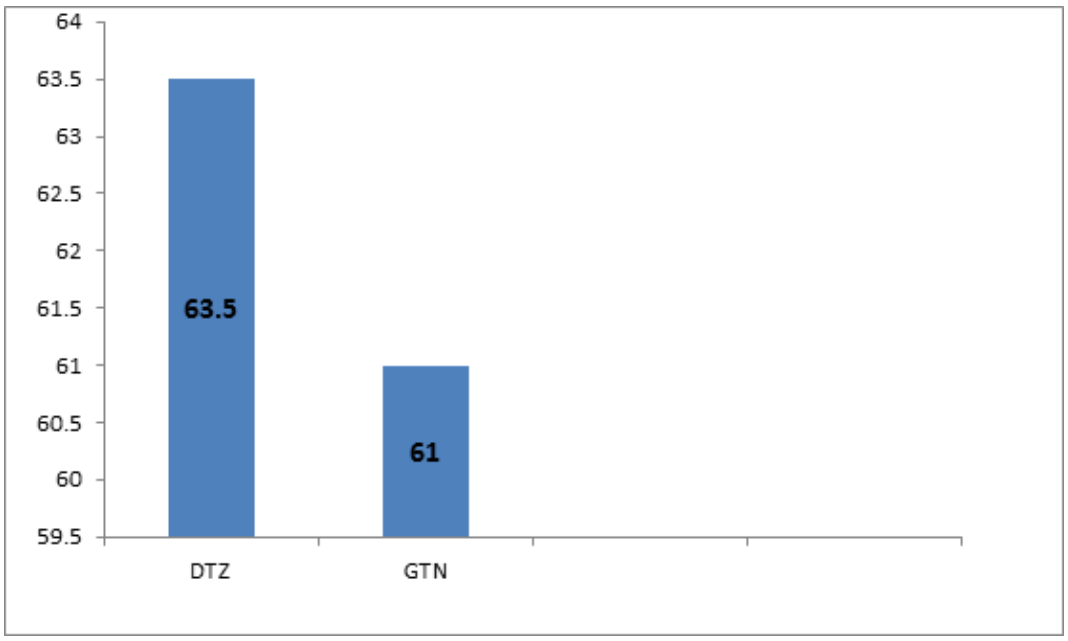

Figure 6: Percentage of sentinel pile in DTZ is 63.5% and in GTN it is 61%

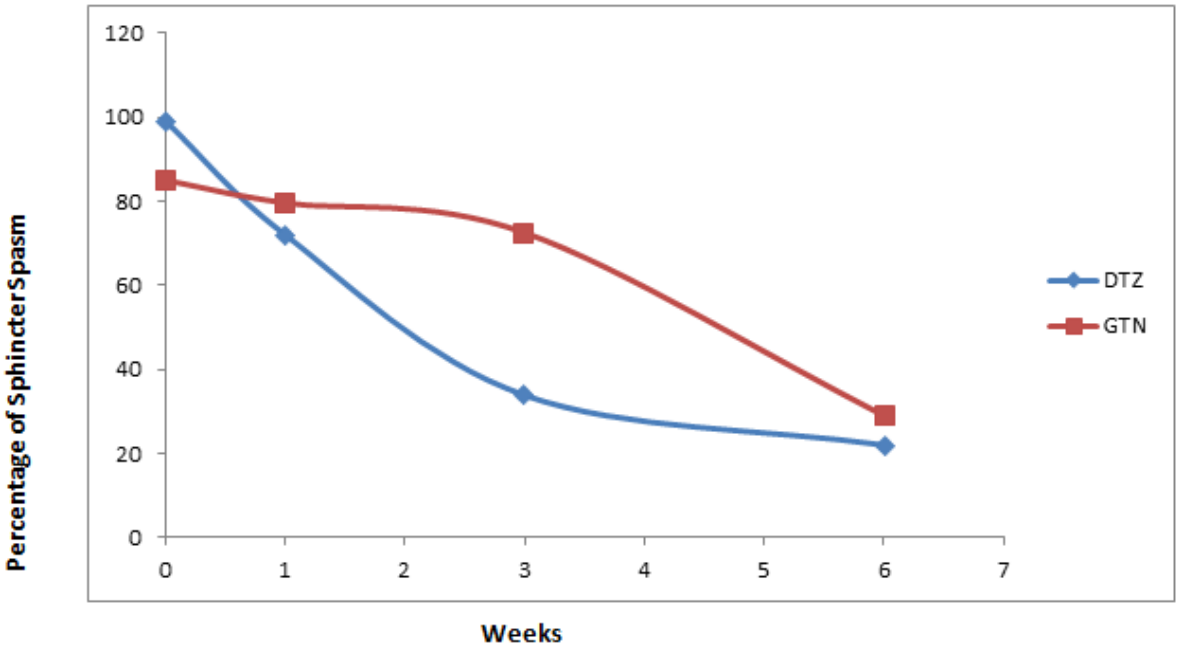

Figure 7: Percentage of sphincter spasm at presentation, 1st weekend, 3rd weekend and 6th weekend

DOI: 10.14260/jemds/2014/3644

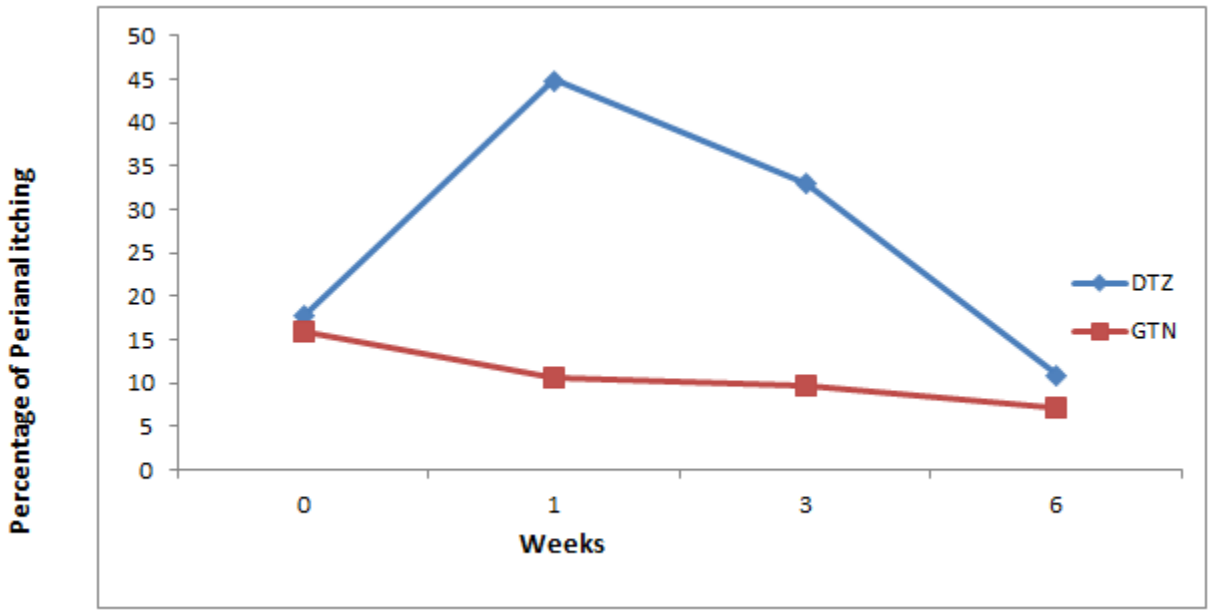

Figure 8: Percentage of perianal itching in DTZ group and GTN group at presentation, 1st weekend, 3rd weekend and 6th weekend

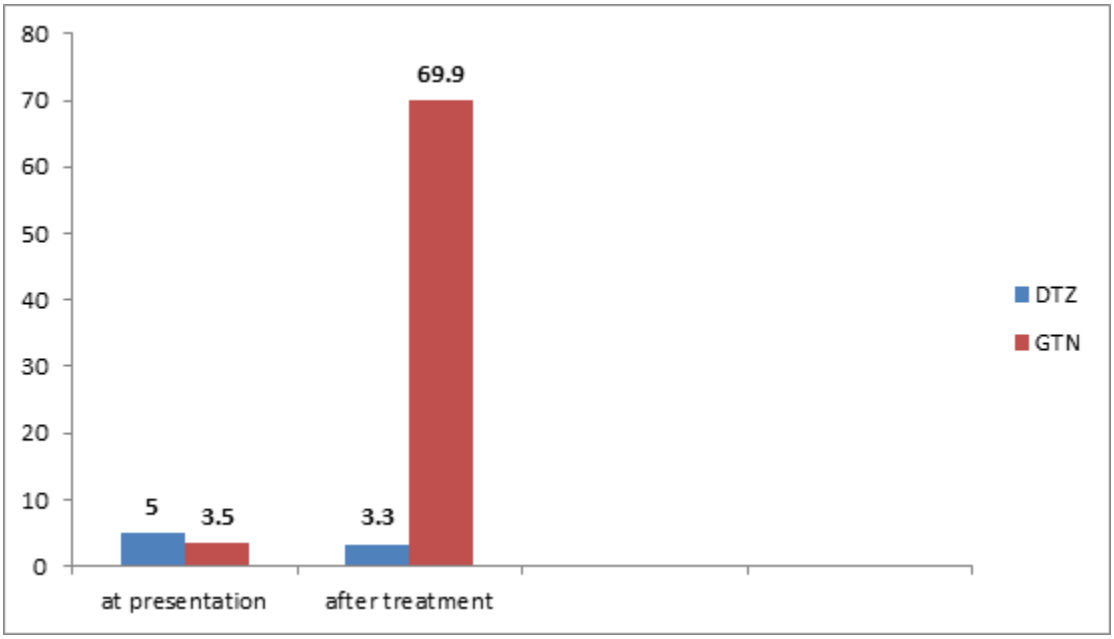

Figure 9: Percentage of headache at presentation and after treatment in DTZ and GTN group

DOI: 10.14260/jemds/2014/3644

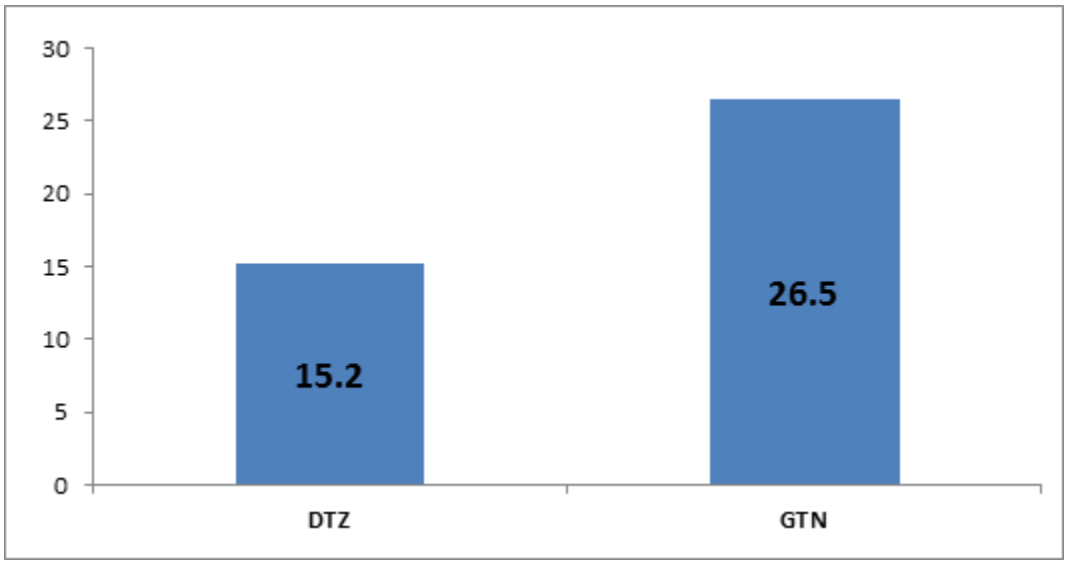

Figure 10: Percentage of recurrence after treatment in DTZ and GTN group

	DTZ (n=118)	GTN (n=113)	Chi-square	P VALUE
Perianal itching	13 (11%)	8 (7.07%)	1.083	0.298
headache	4 (3.3%)	79(69.9%)	110.95	<0.0001

Table 2: Side effects of DTZ and GTN

Table no. 2 shows that 69.9% of subjects from GTN group developed headache compared with 3.3% in DTZ (P value <0.001). The difference in headache observed between the two groups was statistically significant (df=1, Chi –square – 110.95 and p < 0.0001) 11% of subjects developed perianal itching from DTZ group, whereas 7.07% subjects from GTN group developed perianal itching.

The difference in perianal itching observed between the two groups was statistically insignificant (df=1, Chi- square = 1.083, p=0.298).

No. of patients with recurrences	DTZ (n=118)	GTN (n=113)	Chi- Square	P Value
	18(15.2%)	30(26.5%)	4.473	0.034

Table 3: Incidence of recurrence with DTZ and GTN

The difference in recurrence rate observed between two groups was statistically insignificant at p< 0.001 (df=1, Chi- square = 4.473, p=0.034).

DISCUSSION: Anal fissure is a split in the anoderm. It is a common disease, which affects both genders man and woman and affects all age group particularly young adults.[14].Most of the fissures occur posterior midline and a few occur in anteriorly. Less than 1% of patient present with fissure in ano both anteriorly and posteriorly.[15]

DOI: 10.14260/jemds/2014/3644

Most commonly presenting symptom of anal fissure is pain while defecation, which may be associated with bright red fresh blood per rectum.[16] Acute anal fissure, may heal spontaneously with simple conservative measures including dietary fibre, stool softener, plenty of water intake along with sitz bath and local anesthetic ointment.[17]

However, chronic anal fissure usually required either conservative management or surgical management.[16] Treatment of chronic anal fissure is mainly based on to reduce the spasm of internal sphincter, [18] which is considered as the primary pathology of anal fissure.[19]

Lateral sphincterotomy is the surgical procedure to reduce the sphincter hypertonia, thus healing of ulcer.[15] Lateral sphicterotomy may cause permanent incontinence, [20] so non-conservative measures are gaining popularity. Non-conservative measures in the treatment of anal fissure are Botulinum toxin injection given in the internal sphincter muscle, which reduces the spasm of internal sphincter (chemical sphincterotomy).[21]

Topical Diltiazem and GTN (Glyceryl trinitrate) are other pharmacological agents from which chemical sphincterotomy can be achieved.[22-23] Glyceryl trinitrate (GTN) causes an increase in local blood flow by vasodilatation of vessels supplying anal musculature and by reducing spasm of internal sphincter by reducing the intra anal pressure. Whilst GTN is effective in treating anal fissures but evidences are there that it is ineffective altogether.[5] There is also limitation of its duration and have been noticed that fissure greater than 6 – 8 weeks duration or those associated with sentinel piles are more likely to failure of treatment.[6]

Diltiazem is non-hydro pyridine calcium channel blocker. Topical 2% diltiazem in anal fissures causes smooth muscle relaxation and thus reducing internal sphincter spasm. Besides that it causes vasodilatation of vessels supplying anal musculature thus promoting healing.[24] It is superior to topical glyceryl trinitrate as it has lesser side effects and low recurrence rate then GTN. There are evidences that 2% diltiazem heals GTN resistant anal fissures.[13]

In our study also anal fissure was present in both the genders, especially affecting young adults. Most common site was posterior midline, followed by anterior midline and occasional was both anterior and posterior midline. In our study most common symptom was pain while defecation with almost all the patients had anal musculature spasm, followed by bleeding per rectum. Most of the patients had associated constipation.

Carapeti et al. reported that healing rate of anal fissure was 67%[25], and Knight et al. reported healing rate of anal fissure to be 73%[24] in patients using 2% topical diltiazem.

While in our study healing rate of anal fissure with the use of topical 2% diltiazem is 68%. Lund JN et al. reported that 0.2% glyceryl trinitrate has cured 68 – 80% of chronic anal fissures, [26] whereas in our study it has cured 65%.

Lock and Thomsom reported that 44% of anal fissure recurred after treatment with topical 0.2% GTN, [27] whereas in our study recurrence rate after treatment with topical 0.2% GTN is 26.5%. According to Lund JN et al. headache occurred in 58% of patients with the use of topical 0.2% GTN, whereas in our study it is 69.9%.[26]

Jonas et al reported recurrence rate of 4% with topical 2% DTZ, whereas in our study it is 15.2%.[8] 5.6% patients reported perinanal dermatitis with the use 2% DTZ by Knight JS et al whereas in our study it is 11%. Knight JS et al also reported 1.4% patient developed headache with DTZ whereas in our study it is 3.3%.[24]

DOI: 10.14260/jemds/2014/3644

CONCLUSION: Topical application of both the ointment 2% Diltiazem and 0.2% Glyceryl trinitrate are quite effective in treatment of chronic fissure in Ano. However, topical Diltiazem is preferred to topical glyceryl trinitrate due to its lesser side effects and better tolerance by the patient and better long term control.

BIBLIOGRAPHY:

1. Gott MD, Peter H. (5 March 1998). "New Therapy coming for Anal Fissures." The Fresno Bee (Fresno.CA: Mc Clatchy Co).P.E2, "Life" section.
2. Sharp FR. Patient selection and treatment modalities for chronic anal fissure. Am J Surg. 1996; 171: 512–5.
3. Jensen SL. Maintenance therapy with unprocessed bran in the prevention of acute anal fissure recurrence. J R Soc Med. 1987; 80: 296–8.
4. Jonas M, Amin S, Wright JW, Neal KR, Scholefield JH. Topical 0.2 percent glyceryl trinitrate ointment has a short-lived effect on resting anal pressure. Dis Colon Rectum. 2001; 44: 1640–3.
5. Thornton MJ, Kennedy ML, King DW. Prospective manometric assessment of botulinum toxin and its correlation with healing of chronic anal fissure. Dis Colon Rectum. 2005; 48: 1424–31.
6. Pitt J, Williams S, Dawson PM. Reasons for failure of glyceryl trinitrate treatment of chronic fissure-in-ano**:** a multivariate analysis. Dis Colon Rectum. 2001; 44: 846–7.
7. Carapeti EA, Kamm MA, Evans DE, Phillips RKS. Diltiazem lowers resting anal sphincter pressure– a potential low side-effect alternative to glyceryl trinitrate for fissures. Gastroenterology. 1998; 114: A7.
8. Jonas M, Neal KR, Abercrombie JF, Scholefield JH. A randomized trial of oral vs. topical diltiazem for chronic anal fissures. Dis Colon Rectum. 2001; 44: 1074–8.
9. Kocher HM, Steward M, Leather AJ, Cullen PT. Randomized clinical trial assessing the side-effects of glyceryl trinitrate and diltiazem hydrochloride in the treatment of chronic anal fissure. Br J Surg. 2002; 89: 413–7.
10. Das Gupta R, Franklin I, Pitt J, Dawson PM. Successful treatment of chronic anal fissure with diltiazem gel. Colorect Dis. 2002;4:20–2.
11. Griffin N, Acheson AG, Jonas M, Scholefield JH. Long-term follow up of trial patients treated with diltiazem for anal fissure. Colorect Dis. 2002; 2002 (Suppl 1): 20.
12. Bielecki K, Kolodziejczak M. A prospective randomized trial of diltiazem and glyceryl trinitrate ointment in the treatment of chronic anal fissure. Colorect Dis. 2003; 5: 256–7.
13. Jonas M, Speake W, Scholefield JH. Diltiazem heals glyceryl trinitrate-resistant chronic anal fissures: a prospective study. Dis Colon Rectum. 2002; 45: 1091–5.
14. Gui D, Rossi S, Runfola M, Magalini SC. Botulinum toxin in the therapy of gastrointestinal motility disorders. Aliment Pharmacol Ther. 2003; 18: 1–16.
15. Kodner IJ, Fry RD, Fleshman JW, Birnbaum EH, Read TE. Colon, Rectum and Anus. In: Schwartz Seymour I, et al., editors. Principles of Surgery. 7th ed. Mac Grow-Hill: 1999. pp. 1265–1382.
16. Lund JN, Scholefield JH. Aetiology and treatment of anal fissure. Br J Surg. 1996; 83: 1335–1344.
17. Beck DE, Timmcke AE. Pruritus ani and fissure-in-ano. In: Beck DE, editor. Handbook of Colorectal Surgery. 2nd ed. New York: Marcel Dekker; 2003. p. 367.

DOI: 10.14260/jemds/2014/3644

18. Farouk R, Duthie GS, MacGregor AB, Bartolo DC. Sustained internal sphincter hypertonia in patients with chronic anal fissure. Dis Colon Rectum. 1994; 37 (5): 424–429.
19. Cook TA, Brading AF, Mortensen NJ. The pharmacology of the internal anal sphincter and new treatments of anorectal disorders. Aliment Pharmacol Ther. 2001; 15: 887–898.
20. Jost WH. Ten years' experience with botulin toxin in anal fissure. Int J Colorectal Dis.2002; 17: 298–302.
21. Jost WH, Schimrigh K. Use of Botulinum toxin in anal fissure. Dis Colon Rectum.1993; 36:974.
22. Schouten WR, Briel JW, Boerma MO, Auwerda JJ, Wilms EB, Graatsma BH. Pathophysiological aspects and clinical outcome of intra-anal application of isosorbide dinitrate in patients with chronic anal fissure. Gut. 1996; 39: 465–469.
23. Gorfine SR. Topical nitroglycerin therapy for anal fissures and ulcers. N Engl J Med.1995; 333: 1156–1157.
24. Knight JS, Birks M, Farouk R. Topical diltiazem ointment in the treatment of chronic anal fissure. Br J Surg. 2001; 88: 553–6.
25. Carapeti EA, Kamm MA, Phillips RK. Topical diltiazem and bethanecol decrease anal sphincter pressure and heal anal fissures without side effects. Dis Colon Rectum. 2000; 43: 1359–62.
26. Lund JN, Scholefield JH. A randomised, prospective, double-blind, Placebo- controlled trial of glyceryl trinitrate ointment in the treatment of chronic anal fissure. Lancet 1997;349: 11-14
27. Lock MR, Thomson JP. Fissure-in-ano: the initial management and prognosis. Br J Surg 1977; 64: 355–8.

AUTHORS:

1. Madhu Lata Rana
2. Narayan Jeet Singh
3. Avtar Singh Bansal
4. Neetu Swain
5. Navpreet Singh

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of General Surgery, Adesh Institute of Medical Research and Sciences , Barnala Road, Bathinda, Punjab.
2. Assistant Professor, Department of General Medicine, Adesh Institute of Medical Research and Sciences , Barnala Road, Bathinda, Punjab.
3. Professor, Department of Community Medicine, Adesh Institute of Medical Research and Sciences , Barnala Road, Bathinda, Punjab.
4. Statistician, Department of Community Medicine, Adesh Institute of Medical Research and Sciences , Barnala Road, Bathinda, Punjab.
5. Intern, M.B.B.S, Adesh Institute of Medical Research and Sciences, Barnala Road, Bathinda, Punjab.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Madhu Lata Rana,
Assistant Professor,
Department of General Surgery,
Adesh Institute of Medical
Research and Sciences,
Barnala Road, Bathinda-151101,
Punjab.
Email: drmadhulata@gmail.com

Date of Submission: 03/10/2014.
Date of Peer Review: 06/10/2014.
Date of Acceptance: 14/10/2014.
Date of Publishing: 17/10/2014.