Establishing the Superiority of Topical Diltiazem over Glyceryl Trinitrate in the Treatment of Chronic Anal Fissure: a Prospective Analytical Study

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Abstract
Introduction: Anal fissure is a common ailment of young age group, affecting males and females alike. Traditionally surgery has been the 1st line of treatment but recently the topical agents such as Glyceryl Trinitrate and Diltiazem are replacing the surgical treatment as preferred modality. Objective: The present study was conducted to compare the topical GTN and DTZ in terms of effectiveness, side effects and patient satisfaction. Material and methods: The study was conducted on 50 patients who were divided into 2 groups- Group I and Group II. Group I patients were treated with topical 2% DTZ while Group II patients were put on topical 0.2% GTN. Cases were kept in follow up for 6 weeks and data thus gathered was analyzed. Results: No significant difference was noted in both groups in term of relief in pain, bleeding and fissure healing. However group II patients reported a higher incidence of headache associated with Topical GTN usage, when compared with the Group II patients (p <0.05). Conclusion: Topical Diltiazem is preferred to topical Glyceryl trinitrate as it is better tolerated with a fewer side effects. Hence 2% DTZ should be considered as 1st line of therapy for the treatment of chronic anal fissure.

Keywords: chronic anal fissure, Diltiazem, Glyceryl trinitrate, chemical sphincterotomy


1. Introduction

An anal fissure is nothing but a tear in the vertical axis of squamous lining of the anal canal between the anal verge and dentate line. [1] It is a painful condition characterized by pain on defecation, bleeding per anum and spasm of anal sphincter. [2,3] Anal fissure is a very common problem across the world, particularly affecting the young and otherwise healthy adults with equal incidence across both sexes. [1] Estimate of the incident of this condition is difficult as many patients with acute fissures do not seek medical advice due to embarrassing nature of the problem. It causes considerable morbidity and adversely affects the quality of life, and therefore appropriate treatment is mandatory.

Majority of anal fissures are probably acute and relatively short lived, resolving, spontaneously or with dietary modification. Fissures failing to heal within 6 weeks despite straight for dietary measures are designated as chronic. [4] Although a proportion (10-30%) of fissures will eventually resolve with conservative measures, most require intervention in order to heal. [5] Traditionally surgical treatments such as manual anal dilatation and an internal sphincterotomy have been used for this ailment. [6] These methods work by causing a fall in anal canal pressure and allowing fissure healing. But due to the possibility of fecal incontinence after surgical treatment [7], alternative treatment in the form of pharmacological agents is worth trying. These agents are less invasive and the effects of treatment are reversible.

Various pharmacological agents have been used to treat fissure so far. Out of these topical hydrocortisone and local anesthetics are found to confer no added benefit over dietary bran. [8] Topical steroids are thought to precipitate extensive anal herpes and therefore abandoned. The discovery of agents, that produce reversible relaxation of anal sphincters, has brought a paradigm shift in the medical management of anal fissure. Out of such agents, Glyceryl Trinitrate (GTN) and Diltiazem (DTZ) are the forerunners. [9] These drugs have become the first line treatment for anal fissure, reserving the surgery for failures or recurrences. [10] These drugs heal the fissure so effectively that the pharmacological treatment of anal fissure has been termed as ‘Chemical sphincterotomy’.

Topical Glyceryltrinitrate (GTN) acts by releasing nitric oxide, a neuro-transmitter which mediates the relaxation of internal anal sphincter. This relaxation of sphincter facilitates the optimal healing of fissure. [11] Approximately two-third of patients using GTN ointment or patch develop headache as a side effect, which may be severe enough to warrant cessation of treatment [12].
Toxapical Diltiazem (DTZ) on the other hand is a calcium channel blocker which works by preventing the influx of calcium into the smooth muscle cell, decreasing intracellular calcium concentration, thus hindering the smooth muscle contraction. In addition to relax the smooth muscles of internal sphincter, they also dilate the blood vessels of the ano derm, leading to an increased blood flow resulting in a faster recovery [13]. Keeping these facts in mind, the present study was conducted to compare the effectiveness and side effects of both the drugs and to determine the topical agent of choice for the treatment of chronic anal fissure.

2. Aims and Objectives

1. To compare the results of topical Diltiazem (DTZ) and Glyceryltrinitrate (GTN) in the treatment of chronic anal fissure.
2. To determine the topical agent of choice for the treatment of anal fissure that, imparts good healing and has lesser side effects and recurrence rate.

3. Materials and Methods

This was a prospective comparative study conducted in a government run tertiary care hospital, catering the suburban and rural population. The study was carried out on 50 patients presenting with chronic anal fissure between May, 2011 and June, 2012. Informed written consent was taken from all the patients. Clearance from the local ethical committee was obtained for the study.

Inclusion criteria for the study was as follows:
- Presence of chronic anal fissure for more than 8 weeks that had failed to resolve with simple measures such as laxatives & high fiber diet.
- Examination revealing features of chronicity such as induration at the edges, external skin tag, and exposure of the horizontal fibers of the internal anal sphincter on the floor.

Following patients were excluded from the study:
- Those having anal fissure due to other diseases such as inflammatory bowel disease, tuberculosis, malignancy, or STD.
- Those who had taken prior course of topical agents.
- Those who had undergone surgery for anal fissure in past.
- Those having associated hemorrhoids or fistula.
- Pregnant or lactating women.
- Patients with significant cardiovascular conditions.

The subjects were treated as outpatients. Clinical examination, including digital rectal & proctoscopic examination, was performed on all the subjects. Sigmoidoscopy & colonoscopy were performed as & when necessary.

Subjects were divided into two groups, Group I & Group II. 25 patients were allotted to each group after randomized by sequential order. Subjects in Group I were treated with 2% Diltiazem ointment while Group II subjects were instructed to use 0.2% Glyceryl Trinitrate (GTN) ointment twice daily for 6 consecutive weeks.

Both groups were advised to apply their respective ointment 1.5 to 2 cm deep into the anal canal. The application was to be done either with clean index finger or by taking the gel on a clean piece of gauge/cotton and gently pushing it into the anus. The subjects were instructed to apply ointment before and after every defecation. Application of ointment at bedtime was compulsory.

The subjects were assessed on 2nd, 4th and 6th weekend during the course of the treatment & then onwards bimonthly up to six months. At each visit, fissure healing, pain relief, any side effects & recurrence were recorded. The treatment protocol was considered violated if a patient didn't comply with the treatment as advised. Symptomatic relief in terms of pain and bleeding was assessed on follow up. Healing of the fissure was assessed visually and results were compiled as Very good (complete), Good (partial) and Poor (no healing). The disease was termed recurrent if the fissure reappeared at the same site one month after 6 weeks course of topical application.

Data was collected and was analyzed statistically. The P values were calculated using chi-square test and were considered significant below a value of 0.05.

4. Results

A total number of 50 cases of chronic anal fissure were included in this prospective comparative study. The cases were divided into two groups, Group I and Group II, comprising of 25 cases each. Group I was put on 2% DTZ ointment, while Group II on 0.2% GTN ointment.

A detailed history and examination of each patient was recorded on admission and again when the patients came for follow up. Then the results were evaluated on each visit in terms of symptomatic relief, healing and any recurrences and complications on further follow up. Results thus obtained are described in tabulated and graphical forms.

Mean age in two groups was fairly similar. DTZ group had a mean age of 40.32 years while GTN group had mean age of 38.52 years. Both groups showed male predominance. 60% of patients in DTZ group and 52% in GTN group were males.

Main presenting complaints were pain while defecation and bleeding per anum. Other minor complaints were Mucoid discharge per anum, anal tag, constipation and Pruritus. Almost all cases complained of pain during defecation. Only 8% patients in DTZ group and 4% in GTN group did not give history of any pain during defecation. On the other hand, only 28% of patients in DTZ group and 20% in GTN group reported having pain after defecation. One patient complained of continuous pain, both during and after defecation.

Most of the cases (80% in each group) presented with complaint of bleeding while passing stools. While only 3 cases out of 25 in DTZ group and none in GTN group had complaint of bleeding after stool passage. None of the patients reported of having episodes of bleeding between two motions.

12% of cases in DTZ group and 8% in GTN group had complaint of mucoid discharge per anum. 32% of patients in DTZ group and 48% of case in GTN group complained of presence of an anal tag. Constipation was reported by 60% of patients in DTZ group and 56% of patients in
cases in DTZ group and 59.09% in GTN group had no complaint of pain. After 4 weeks and 6 weeks however, 95.66% cases in DTZ group and 81.82% cases GTN group after 2 weeks of treatment. After 4 weeks of 86.95% of patients in DTZ group and 77.27% of cases in GTN group were relieved of pain.

Healing of fissure was noted in 4.34% of patients in DTZ group and 4.54% of cases in GTN group after 2 weeks of treatment. After 4 weeks, 56.52% of fissures in DTZ group and 90.91% cases in GTN group were not bleeding at all (Graph 1).

Main complications observed during the study period were headache, perianal itching and recurrence. 8.69% of cases from DTZ group developed headache during the course of treatment, as compared with 50% of cases in GTN group (p < 0.05). Perianal itching was reported by 4.34% of cases in DTZ group and 9.09% of cases in GTN group. Recurrence was seen in 8.69% of cases in DTZ group, as compared to 18.18% in GTN group (Graph 4).

Overall, slightly better results in terms of patient satisfaction were shown by DTZ group (Graph 5).

- Ages of the patients were fairly similar in both groups.
- In both groups, there was a slight male predominance.
- Pain was the main presenting symptom especially during defecation followed by the bleeding per rectum.
- Majority of the cases had constipation.
- Posterior midline was the most common location and majority of fissures were associated with sentinel piles.
- 3 cases from GTN group & 2 cases from DTZ group failed to complete the study due to headaches and cooperation problems. Those subjects were not considered in the final statistical analysis.
- Main complaints (pain and bleeding) were resolved after 6 weeks of treatment in majority of patients (Graph 1 & 2), with no significant difference between two groups (p >0.05).
- No significant difference in both groups was seen in terms of fissure healing after 6 weeks of treatment. (Graph 3) (p >0.05).

5. Discussion

Anal fissure is a slit in the lining of the distal anal canal [14] & is the most common cause of severe anal pain. [15] Posterior midline is the commonest site, but anterior midline fissures are not infrequent, especially in females. [16,17] Constipation & passage of hard stool have been known to be the initiating factors of fissure. In females, it is usually triggered during pregnancy and following childbirth. [15] They can be associated with inflammatory bowel disease & tuberculosis.

There is no agreement in the literature on the criteria to define chronic anal fissure, so we used the time of duration of symptoms and the signs of chronicity seen on exploration. Most authors arbitrarily use a 6 week time of evolution as a selection criterion. [4] Following Nelson’s directives in his review of Cochrane, [19] we have used both evolution and morphological data to select chronic anal fissure. We considered the ailment as chronic when there was a history of pain of more than 6 weeks duration or pain of less duration, but with similar episodes in the past, or with signs of chronicity.

The exposed internal sphincter muscle underneath the fissure goes into spasm resulting in severe pain. Besides, the spasm pulls the edges of the fissure apart, which impairs healing of the wound. The typical symptoms of anal fissure are anal pain during defecation associated with the passage of bright red blood per rectum. The pain may be so severe that patients may postpone defecation for days together until it becomes inevitable. This leads to hardening of the stools, which further worsens the condition. The fissures can be either acute or chronic. Acute fissure is of short duration (less than a month) and has fresh mucosal edges. They usually heal spontaneously or with simple measures like high fibre diet, adequate water intake, and warm sitz baths. Chronic fissures generally have indurated edges. External skin tag (sentinel pile) is commonly observed. Horizontal fibers of the internal sphincter are usually exposed on the floor of the well developed fissure, which leads to spasm due to irritation [14,15].

Acute anal fissures tend to cure with simple conservative measures, whereas chronic fissures usually need other forms of definitive therapy, either medical or surgical. [18] Various treatment modalities have been described which may be grouped into non-operative and operative measures.

Non-operative methods include Injection of Botulinum toxin, oral nifedipine, topical application of glyceril...
trinitrate (GTN) and topical diltiazem ointment. Botulinum toxin is effective in treating fissures that have failed to heal with topical agents. Botulinum toxin can also be combined with surgical modalities. Lindsey et al. [20] showed that, following injection of 25 U of Botox into the internal sphincter combined with fissurectomy in 30 patients (19 of whom had failed both GTN and botulinum toxin injection), 28 (93%) had healed after a median of 16.4 weeks' follow-up. Dysport is an alternative tolerable commercial formulation of botulinum toxin to Botox; however, the change in dose needs attention as, in one study by Brisinda et al. [21] patients with fissures were randomised to receive 50 U of Botox formulation or 150 U of Dysport.

Topical GTN has been the most extensively used nonsurgical treatment for chronic anal fissure. [22] It is a potent nitric oxide donor [23] & it has been believed that nitric oxide is a neurotransmitter mediating the relaxation of the internal sphincter. [14] GTN ointment or patch applied to the anal verge results in the healing of approximately two-thirds of chronic anal fissures. [16,24,25] But headache and dizziness are its main drawbacks. [16] The headache is dose-related and was found to be occurring in around 50% of patients in a study by Bailey et al. [26]. Danish et al have shown that GTN-associated headache sometimes became so severe and intractable that the treatment has to be abandoned. [12] Besides, tolerance to nitrates is a well-documented fact. [16] Another drawback associated with GTN therapy is high recurrence rate [22,27].

Isosorbide dinitrate (ISDN) is an alternative nitric oxide donor that has been used successfully in the treatment of anal fissures. The problems encountered are similar to those with GTN but long-term effectiveness has been questioned [28,29].

Nifedipine and Diltiazem are calcium channel blockers which act by blocking slow L-type calcium channels in smooth muscle causing relaxation. [14] Topical Diltiazem has been reported to result in the healing of chronic anal fissure in 60% to 75% of cases. [1,13,16] In a study, Carapeti et al reported fissure healing in 67% of patients treated with GTN [24], while headache was observed in 72% of cases. In another study, Knight et al from UK observed 75% of their cases had fissure healed with topical Diltiazem. Only 1 of 71 cases had headache [13].

Topical Diltiazem, a non-dihydropyridine calcium-channel blocker also has been tried successfully in the treatment of chronic anal fissure that have failed to respond to GTN. [1,17] Diltiazem ointment has been known to cause less headache & a fewer side effects than GTN ointment without a significant difference in healing rates between the two agents. [13,30] Also, recurrence rate has been known to be lower with topical Diltiazem [1,30,31,32].

Fissures which refuse to heal or recur with this conservative topical regimen should be treated with internal sphincterotomy, which is the currently accepted gold standard treatment [33].

6. Summary & Conclusion

Both Diltiazem ointment (2%) and Glyceryl trinitrate ointment (0.2%) are quite effective in the treatment of chronic anal fissure. However, topical Diltiazem is preferred to topical Glyceryl trinitrate as it is better tolerated with a fewer side effects. Therefore, 2% diltiazem should be considered the first line therapy for the treatment of chronic anal fissure. Surgical intervention should be reserved for the failure or recurrence after the trial of chemical sphincterotomy.

References

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