Comparison of Observational and Controlled Clinical Trials of Diltiazem in the Treatment of Chronic Anal Fissure

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Abstract Diltiazem has been extensively studied in the treatment of chronic anal fissures, but efficacy in clinical practice is not fully established. The aim of the present study was to evaluate the safety and efficacy of topical application diltiazem in observational studies as well as in controlled clinical trials in the treatment of chronic anal fissures. A systematic literature search was carried out from 1966 to 31 December, 2007 on PubMed, Medline, Embase and Cochrane database, using the appropriate search words. We found six observational studies with 392 patients and five controlled clinical trials with 289 patients in which topical diltiazem treatment was given. Efficacy was found

to be very high in observational studies (56.88%), whereas it was found to be modest in controlled clinical trials (29.41%). In observational studies, most of the patients reported complete healing of fissures within 6–12 weeks, whereas in controlled trials healing was reported within 8 weeks, with tolerable adverse effects of diltiazem. On the basis of the above studies, it can be concluded that topical application of diltiazem is useful in the treatment of chronic anal fissure, but to fully establish its efficacy, larger prospective double-blind study is required in the near future.

Keywords Diltiazem · Chronic anal fissure · Clinical trial

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Introduction

Occurrence of anal fissures is a common medical problem that affects both sexes equally. Anal fissures are longitudinal or elliptical tears or ulcers in the distal anal canal, extending below the dentate line to the anal verge [1]. Anal fissures are common in people of all ages especially in teenagers and young adults. Some studies suggest that as many as one in five persons develop fissure during their lifetime. Anal fissures occur predominantly in the midline and most commonly 90% are located posteriorly and 10% anteriorly. After childbirth, women tend to develop anterior fissure; less than 1% of patients have fissures both in anterior and posterior positions [2]. Most anal fissures are acute and resolve spontaneously or with conservative medical management in 10–14 days. It takes 6–8 weeks for actual tear to heal. Fissures which fail to heal become chronic. A fissure is said to be chronic if it is present for more than 6 weeks. Patients usually need further treatment or intervention, when fissure becomes large and deep, forming chronic anal fissure

[3]. When multiple fissures are located in atypical locations and fail to heal following treatment, other conditions such as inflammatory bowel disease, neoplasm, leukemia, syphilis, tuberculosis or HIV have to be ruled out [4–6].

The aim of the treatment is to eliminate constipation, soften stool and reduce anal sphincter spasm. This medical treatment is effective in patients with acute anal fissures. Chronic anal fissures require surgical or pharmacological intervention. Drugs tried in the treatment of anal fissures include glyceryl trinitrate (GTN), isosorbide dinitrate, botulinum toxin, calcium channel antagonist such as nifedipine, diltiazem, lignocaine, cholinomimetic bethanechol, alpha-adrenoceptor antagonist such as indoramine and potassium channel opener such as minoxidil.

Calcium channel antagonists are effective in causing smooth muscle relaxation [7]. Nifedipine was evaluated for the treatment of anal fissures. With 0.2% nifedipine ointment a mean reduction of 30% was observed in maximum resting pressure (MRP) [8]. Total remission of 95% was observed by 3 weeks and 60% after 8 weeks. It was well tolerated except for flushing and mild headache. There was no episode of postural hypotension or incontinence. A calcium-dependent mechanism is required to maintain internal sphincter muscle tone. Calcium channel blockers cause relaxation of gastrointestinal smooth muscles [1, 4]; oral diltiazem has been shown to reduce the resting anal pressure [5]. Several observational and controlled clinical trials with different results have already been conducted to prove the safety and efficacy of topical diltiazem in chronic anal fissures. The purpose of the present study was to evaluate efficacy and safety of diltiazem in chronic anal fissures based on earlier observational and controlled clinical trials.

Materials and Methods

A systematic literature search was carried out from 1966 to December 2007 on PubMed, Medline, Embase and Cochrane database, using the following search words: chronic anal fissure, topical diltiazem, topical therapy, gel, ointment, generic name of drugs, pain relief, clinical trial and randomized controlled trial. Reference list of original reports and review articles were searched for finding desired studies. Related journals in the National Medical Library (New Delhi), library of the institute and conference abstracts for 2003–2006 of international societies of surgical discipline were also searched manually.

Inclusion and Exclusion Criteria

We included observational and randomized controlled clinical trials, comparing any topical therapy (diltiazem or

others) with placebo or vehicle or other active drugs. Studies satisfying the following criteria were selected:

1. Patients suffering from chronic anal fissure
2. Study duration either 4 weeks or more
3. Primary efficacy end point decrease in anal pain score and healing of chronic anal fissure

Studies were excluded in the following cases:

1. Patients with anal fistula
2. Mixed patient population such as patients with chronic anal fissure and other anal pathology
3. Patients using any other therapies along with topical diltiazem therapy except for rescue medication

Data Extraction, Outcome Measure and Statistical Analysis

Data were extracted in a specially designed format. The only outcome measure was anal pain score and healing at final scheduled follow-up. The percentage of healing was calculated from pooled data from observational studies as well from controlled clinical trials. From individual studies, number of patients in treatment and control groups, mean and standard deviation (SD) of the final anal pain scores and healing fissures were obtained.

Results

Of the 185 citations, 65 were duplications. We identified six observational (Table 1) and five randomized controlled clinical trials (Table 2) among the relevant publications. Another five studies were excluded as per inclusion criteria. Eleven studies fulfilled all the specified criteria (Table 3). All the studies were in English language and published in index journals.

An observational study by Knight et al. [9] showed treatment with 2% topical diltiazem in 71 patients. It was observed that 75% experienced healing in 2–3 months and in further 2 months 88% experienced healing. Minor side effects were perianal dermatitis, headache (in one patient) and recurrent fissures (in seven patients); six of them were successfully treated by repeat chemical sphincterotomy. Another study by Jonas et al. [10] showed efficacy of diltiazem for fissures that failed to heal with GTN. Thirty-nine patients with chronic anal fissures received GTN therapy, of which 27 patients completed the GTN course, and 12 patients discontinued. Of the 27 patients who completed the course and presented with resistant chronic anal fissures, 44% were healed with topical diltiazem, whereas in 56% of the patients the fissures persisted and

Table 1 Summary of observational studies of topical application of diltiazem in treatment of chronic anal fissures

S. no.	References	Total patients	Treatment group (diltiazem)	Remarks	Duration of study period
1.	Knight et al. [9]	71	71/71	83% showed efficacy	9 weeks
2.	Jonas et al. [10]	39	39/39	48% showed healing	8 weeks
3.	Dasgupta et al. [11]	23	11/23	48% healing	3 years
4.	Griffin et al. [12] (2002)	47	47/47	48% showed healing	8 weeks
5.	Nash et al. [13]	112	2% diltiazem cream	41% Safe for long term use	6 weeks
6.	Placer et al. [14]	100	Topical diltiazem 2% topical gel	Cure 62% with 5% morbidity	8 weeks

they had to undergo surgical sphincterotomy. In this trial, 12 patients discontinued GTN therapy and 58% were healed with topical diltiazem. Dasgupta et al. [11] found that fissures healed in 48% patients, including the 75% who previously failed to heal with GTN therapy. No recurrences or adverse effects were reported. Griffin et al. [12] concluded that topical 2% diltiazem is an effective and safe treatment for patients who fail topical 0.2% GTN therapy. Sphincterotomy can be avoided in 70% of the patients with chronic anal fissure. Nash et al. [13] evaluated long-term outcome (up to 2 years) of topical diltiazem in chronic anal fissures. A total of 112 patients treated for 6 weeks with 2% diltiazem cream (twice-daily topical application) showed benefits over two-thirds. Nearly 80% of the patients reported no adverse effects. Placer et al. [14] showed that cure was achieved in 62%, with morbidity of 5% (mild headache in 2%, and pruritus in 3%) within 8 weeks. No significant differences were found between the groups with and without response to diltiazem 2% in terms of age, sex, localization, bleeding or pruritus (Tables 1 and 3).

In a controlled clinical trial, Carapeti et al. [15] found that a single dose of 60 mg diltiazem lowered MRP by a mean of 21%. Once-daily diltiazem produced clinically insignificant effect, but twice-daily regimen reduced anal pressure by a mean of 17%. Study reported that 2% diltiazem gel produced a maximal 28% reduction and effect

lasted for 3–5 h. In addition intervention produced potential low side effects alternative to topical nitrates for the treatment of anal fissure. Jonas et al. [16] assessed the effectiveness of oral and topical diltiazem in healing chronic anal fissure. MRP fell by 15% and 23% in oral and topical groups, respectively. Fissure healing was 38% in oral and 65% in topically treated groups by 8 weeks. Oral diltiazem caused side effects such as rash, headache, nausea, vomiting, decreased smell and taste, whereas topically treated groups showed no side effects. Kocher et al. [17] showed adverse effects of GTN and diltiazem in the treatment of chronic anal fissure. Diltiazem therapy was shown to cause less headache than GTN therapy [$P=0.01$]. There was no significant difference in healing and symptomatic improvement rates between the two groups. Bielecki et al. [18] concluded that diltiazem and GTN therapy are equally effective in healing anal fissures. But diltiazem reported in few adverse effects. Shrivastava et al. [19] showed comparative evaluations of the three groups regarding an improvement in symptoms, progress in healing, appearance of side effects, and recurrence using diltiazem 2%, GTN and control. Study showed diltiazem ointment to be superior (Tables 2, 3).

Observational studies that included a total of 392 patients showed topical diltiazem to be highly efficacious. The pooled percentage of healing was 56.88%. Patients reported complete healing within 6–12 weeks; more than

Table 2 Summary of controlled clinical trials of topical application of diltiazem in chronic anal fissure healing

S no.	References	No of patients	Diltiazem treated group	Control	Remarks	Duration of study period
1.	Carapeti et al. [15]	30	2% diltiazem topical—28%	Oral diltiazem (60 mg)—21%; 0.1% bethanechol—24%	Comparable	8 weeks
2.	Jonas et al. [16]	50	26/50	24/50 (60 mg oral diltiazem)	Effective than control	8 weeks
3.	Kocher et al. [17]	60	31/60. 41% healing	29/60. 46% healing (GTN)	Comparable	8 weeks
4.	Bielecki et al. [18]	43	22/43. 86% healing	21/43. 85% healing (GTN)	Comparable	8 weeks
5.	Shrivastava et al. [19]	90	Diltiazem ointment (2%)	GTN ointment (0.2%)	Effective than GTN	Assessed monthly and then after 3 months

Table 3 Characteristics of observational and randomized clinical trials using topical diltiazem in patients with chronic anal fissure

S. no.	References	Total patients	Treatment group (diltiazem)		Age and anal pain at baseline		Duration of study period	Remarks
1.	Knight et al. [9]	71	71/71	Open trial	39 ^a	Severe	9 weeks	83% showed efficacy
2.	Jonas et al. [10]	39	39/39		42 ^a	Severe	8 weeks	48% showed healing
3.	Dasgupta et al. [11]	23	11/23		45 ^a	Severe	3 years	48% healing
4.	Griffin et al. [12]	47	47/47		38 ^a	Severe	8 weeks	48% showed healing
5.	Nash et al. [13]	112	2% diltiazem cream		NM	Severe	6 weeks	41% Safe for long term use
6.	Placer et al. [14]	100	Topical diltiazem 2% topical gel		43 ^b	Severe	8 weeks	Cured 62%, morbidity in 5%
7.	Carapeti et al. [15]	30	2% diltiazem topical—28%	Oral diltiazem (60 mg)—21%; 0.1% bethanechol—24%	37 ^a	Severe	8 weeks	Comparable.
8.	Jonas et al. [16]	50	26/50 Topical diltiazem	24/50 (60 mg oral diltiazem)	35 ^a	Severe	8 weeks	Effective than control
9.	Kocher et al. [17]	60	31/60. 41% healing	29/60. 46% healing (GTN)	39 ^a	Severe	8 weeks	Comparable
10.	Bielecki et al. [18]	43	22/43. 86% healing	21/43. 85% healing (GTN)	49.1 ^b	Severe	8 weeks	Comparable
11.	Shrivastava et al. [19]	90	Diltiazem ointment (2%)	GTN ointment (0.2%)	35.93 ^b	Severe	Assessed monthly and then after 3 months	Effective than GTN

^a Median^b Mean

57% patients showed improvement in term of chronic anal fissure healing (Table 1), whereas controlled clinical trials showed modest efficacy of 29.4% as compared with that of the control group (25.6%); duration of healing was 8 weeks, a total of 289 patients were included in five randomized controlled clinical trials (Table 2). In the control group, patients were treated with GTN, nifedipine and bethanechol, etc.

In the studies included in the present analysis, none of the patients withdrew from the study because of adverse drug reactions, only minor adverse drug reactions were reported (Table 4).

Discussion

The aim of pharmacological treatment for chronic anal fissures is to reduce the resting anal fissure and improve anal mucosal blood flow so as to promote healing of the fissure without damaging the anal sphincter. Earlier, GTN was the standard therapy. Clinical trials show that healing can be achieved in 45–80% patients with GTN therapy, but significant adverse effects such as headache, tachyphylaxis and occasional loss of flatus control have also been reported. Some studies report poor long-term outcome of GTN therapy; only 6% of patients healed in 12 months [10, 20–23].

Table 4 Adverse drug reactions and withdrawals in observational and controlled clinical trials

S. no.	References	Group	Adverse drug reaction		Total withdrawals	
			Control	Treatment (Topical)	Control	Treatment
1.	Knight et al. [9]	2% diltiazem ointment	Open trial	1,2	Nil	Nil
2.	Jonas et al. [10]	2% diltiazem ointment.		1,2 (less)	Nil	Nil
3.	Dasgupta et al. [11]	2% diltiazem Oint.		Nil	Nil	Nil
4.	Griffin et al. [12]	2% diltiazem ointment		Nil	Nil	Nil
5.	Nash et al. [13]	2% diltiazem ointment.		1,2	Nil	Nil
6.	Placer et al. [14]	2% diltiazem ointment		Nil	Nil	Nil
7.	Carapeti et al. [15]	2% diltiazem ointment/oral Dil/Beth.	Nil	Nil	Nil	Nil
8.	Jonas et al. [16]	Topical diltiazem/Oral diltiazem	1, 2, 3, 4	Nil	Nil	Nil
9.	Kocher et al. [17]	Topical diltiazem/GTN	1,2,3	Less in diltiazem	Nil	Nil
10.	Bielecki et al. [18]	Topical diltiazem/GTN	2	Nil	Nil	Nil
11.	Shrivastava et al. [19]	Topical diltiazem/GTN	2	Nil	Nil	Nil

1 Rash and itching; 2 Headache; 3 Nausea and vomiting; 4 Reduced smell and taste

Recently, diltiazem has been found efficacious in the treatment of chronic anal fissure. Studies showed that oral intake and topical applications of diltiazem reduced the anal pressure significantly. As compared with GTN, diltiazem reported minimal side effects, most of the side effects were facial flushing, mild headache because of changes of negligible diastolic pressure and postural changes of blood pressure, which can be avoided by applying topical diltiazem at bedtime [22, 24].

Anal fissures are demonstrated by paucity of arterioles at the anterior and posterior commissures of the distal anal canal sites. Besides this, chronic anal fissure patients usually have high rectal pressure and sphincter hypertonia, which can compromise local blood flow. Treatment with diltiazem relaxes the sphincter and enhances the local blood flow clearly by different pathways [10, 23].

Most of the trials included patients who had failed previous treatment with GTN therapy and in whom efficacy of diltiazem was reported. Therefore, the current practice for management has changed since topical diltiazem was introduced. Most of the investigators believe that it should be preferred as second-line therapy in the treatment of chronic anal fissures [12].

However, medical treatment has two disadvantages: moderate effectiveness (between 30% and 80%) and the need for treatment to be prolonged for more than 8 weeks; lack of response to 2% topical diltiazem gel at the end of the first week reliably predicts failure of the medical treatment of chronic anal fissure, obviating the need to prolong the treatment for 8 weeks. Most of the trials with medical therapy reported early recurrence of fissures, as the resting anal pressures revert to pretreatment level when the treatment is stopped. Only a few trials reported long-term follow-up results, and most of the studies did not report the patients in whom fissures recurred after treatment was stopped. Present analysis showed better efficacy in observational studies compared with controlled clinical trials and none of the patients showed any severe adverse effects with diltiazem topical therapy.

In conclusion, several trials have already been conducted to prove the safety and efficacy of topical diltiazem in chronic anal fissure with only small patient population. Hence, large prospective, placebo-controlled trials should be carried out, as diltiazem may emerge as main therapeutic agent in the management of chronic anal fissures in the near future.

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