CLINICAL INVESTIGATION

Topical diltiazem in management of chronic anal fissure: a review of the literature

Anal fissure is a common painful anorectal condition which affects people of various age groups, and deteriorates their quality of life. Chronic anal fissure requires medical intervention either by pharmacotherapy or by surgery. Various pharmacological agents have been used in the treatment of chronic anal fissure with the aim of relaxation of internal anal-sphincter smooth muscle. Diltiazem is a calcium-channel blocker that has been tried in several clinical studies for management of chronic anal fissure. This review focuses on the available literature data on the use of topical diltiazem (cream, gel, ointment) in the treatment of chronic anal fissure in order to give an overall viewpoint of the work carried on in this field and the results obtained.

Keywords: anal fissure • cream • diltiazem • gel • ointment • topical

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Anal fissure

Definition, symptoms

Anal fissure represents one of the most common anorectal problems encountered in practice. An anal fissure is a linear, longitudinal tear or split in the epithelial lining of the distal anal canal [1–3]. The commonly accepted definition of anal fissure is: 'A linear ulcer of the anoderm, distal to the dentate line, generally located in the posterior midline' [4]. During defecation, the lesion is stretched causing severe sharp pain, often described as 'passing broken glass' and a burning pain which can persist for several hours after defecation and be accompanied by bleeding [3–5]; pruritus, swelling, prolapse and discharge is also present in a minority of patients [6].

Classification

Fissures can be classified as acute or chronic, based on both chronology and morphology. Anal fissures are considered to be acute if they have been present for less than 6 weeks, superficial and have well-demarcated edges. Most of the acute anal fissures heal spontaneously or with conservative medical management. Chronic anal fissures (CAF), on the other hand, persist for more than 6–8 weeks and have different morphological manifestations including ulcer with keratinous edges, presence of a sentinel tag at the external apex, hypertrophied anal papillae and exposed internal anal-sphincter smooth-muscle fibers [1,3–6]. CAF often require medical intervention including surgery or pharmacotherapy.

Etiology

The etiology of anal fissure is not so clear. Previously, anal fissure was thought to be due to severe constipation or straining at defecation. However, current evidence shows that anal fissures are associated with increased tone and spasm of the internal anal sphincter [5–7]. Thus, it is suggested that the primary cause of CAF is increased resting anal pressure, causing a reduction in anodermal blood flow by compressing the blood vessels which pass through the sphincter, which eventually leads to ischemic ulceration of anal mucosa [2,3,6].

Medical therapy

The goal of medical treatment for CAF is to achieve a temporary reduction of pressure of the anal canal to facilitate the healing of the fissure (reversible sphincterotomy), thereby

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reducing muscle tone [4]. This can be achieved by surgical techniques such as anal dilatation, posterior midline sphincterotomy, lateral internal sphincterotomy or by pharmacotherapy. Surgical techniques are generally associated with risk of permanent fecal incontinence. Therefore, since the early 1990s, nonsurgical methods for treatment of CAF emerged, generally referred to as 'chemical sphincterotomy'. Chemical sphincterotomy is mainly based on reducing internal anal-sphincter spasm (resting anal pressure) and/or increasing improving vascularity of internal anal muscle by various mechanisms using pharmacological agents.

The greatest advantage of chemical sphincterotomy over surgical techniques is avoiding the risk of permanent impairment of continence [3,5]. Various pharmacological agents have been used for chemical sphincterotomy including glyceryl trinitrate (GTN), isosorbide dinitrate, botulinum toxin, calcium-channel blockers (CCB) such as nifedipine and diltiazem (DTZ), lidocaine and bethanecol [6].

Contraction of the internal anal-sphincter smooth-muscle depends on increased intracellular calcium concentration, which is mediated either by calcium influx through calcium channels or by stimulation of α1-adrenoceptors. Thus, relaxation of these muscular cells can be achieved by directly decreasing intracellular calcium concentration through blockade of calcium channels, as well as increasing cGMP and cAMP [5]. Therefore, CCB such as nifedipine and DTZ are supposed to be effective in treatment of CAF by decreasing the influx of calcium into the internal anal-sphincter smooth-muscle cell, leading to muscle relaxation and reduction in resting anal pressure.

Diltiazem

Diltiazem is a benzothiazepine CCB. It is a peripheral and coronary vasodilator with limited negative inotropic activity and inhibits cardiac conduction, particularly at the sino-atrial and atrioventricular nodes. DTZ is given orally for the management of angina pectoris and hypertension once, twice or three-times daily. It is also administered by intravenous route in the treatment of various cardiac arrhythmias such as atrial fibrillation, atrial flutter and paroxysmal supraventricular tachycardia [8].

Mechanism of action

CCB cause smooth-muscle relaxation by blocking slow L-type calcium channels, thus preventing the influx of calcium into the smooth-muscle cell, and decreasing intracellular calcium concentration [3,5,8]. This reduces the amount of calcium available to combine with calmodulin and subsequently prevents activation of the myosin light-chain kinase required for smooth muscle cell contraction [5].

Pharmacokinetics

Diltiazem is absorbed almost entirely from the gastrointestinal tract after oral administration. However, due to extensive first-pass hepatic metabolism, primarily by the cytochrome P450 isoenzyme CYP3A4, only about 40% of an oral dose is bioavailable. This also causes considerable interindividual variation in plasma concentrations. Generally peak plasma concentrations are achieved 3–4 h after oral intake. The plasma protein binding of DTZ is approximately 80%. It is distributed into breast milk which limits its use during lactation. The elimination half-life of DTZ is reported to be 3–5 h. It is mainly excreted as metabolites in bile and urine with a small portion (2–4%) being excreted as unchanged drug in urine [8]. However, no information about the pharmacokinetic parameters of topical DTZ could be found in the literature. A registered clinical trial aimed at assessing the single- and multi-dose pharmacokinetics of oral DTZ and topical DTZ is ongoing, but not completed yet [9].

Drug interactions

Concomitant administration of DTZ with amiodarone, β-blockers, digoxin and mefloquine may result in increased depression of cardiac conduction and risk of bradycardia or atroventricular block. Enhanced antihypertensive effect may occur with concomitant use of other antihypertensive drugs and antipsychotics. DTZ may interact with drugs sharing the same metabolic pathway, with enzyme inducers such as carbamazepine, phenobarbital, phenytoin and rifampicin, and with enzyme inhibitors such as cimetidine and HIV-protease inhibitors [8].

Precautions

Diltiazem is contra-indicated in patients with the sick sinus syndrome, pre-existing second or third degree atroventricular block, or marked bradycardia, and should be used with caution in patients with lesser degrees of atroventricular block or bradycardia. DTZ has been associated with the development of heart failure and great care is required in patients with impaired left ventricular function. Treatment with DTZ should commence with reduced doses in elderly patients and in patients with hepatic or renal impairment. Due to teratogenic effects observed in animals, its use should be avoided during pregnancy [8].

Methods

The aim of this review was to summarize and compare the currently available literature data on the use of topical DTZ (ointment, gel, cream), for the treatment of anal fissure, in order to determine the

effectiveness of DTZ as an agent for chemical sphincterotomy, either individually or in comparison with other therapeutic agents or surgical treatments.

All prospective clinical studies including randomized clinical trials (RCTs), pilot studies and nonrandomized interventional studies that evaluated the effectiveness of topical DTZ (in the form of cream, gel or ointment) in the treatment of anal fissure, either individually or in comparison with other therapeutic agents or surgical procedures for any period of time (both short term and long term) were included in this review. No language or date restriction was performed; however, studies were excluded if no translations were available. The retrospective studies, studies with same study population and similar systematic reviews or meta-analyses were excluded.

The keywords used for search were DTZ, topical, cream, gel, ointment, anal fissure and different combinations of them. The following databases were searched for published data using different combinations of the above-mentioned keywords: Medline, Scopus, Science direct, Google scholar, Cochrane library, EBSCO and Clinicatrials.gov. The redundant studies were excluded. The search flow chart is depicted in Figure 1.

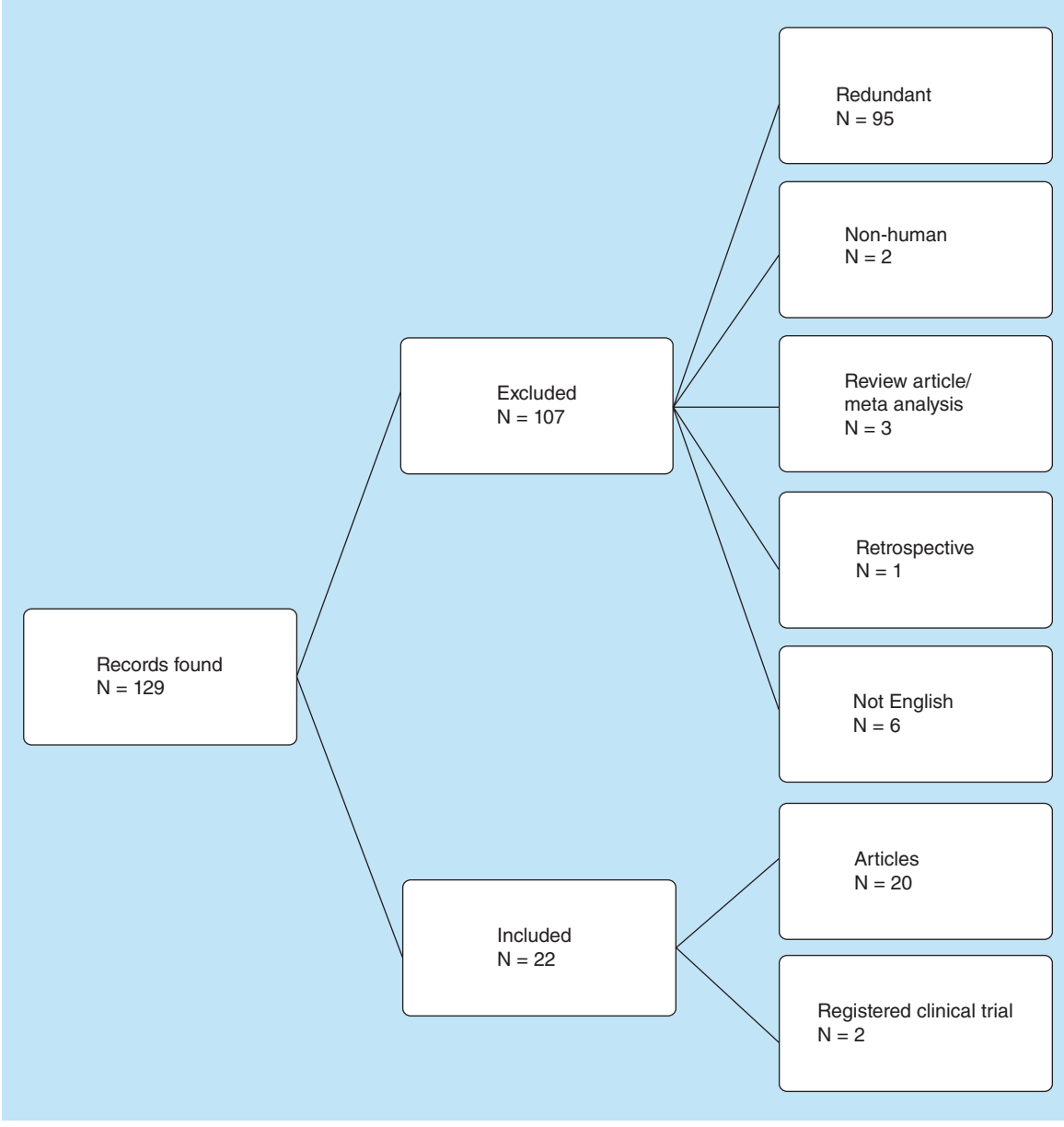

Figure 1. The search flow chart.
N: Number of studies

Table 1. Type and structural features of the included studies (2000–2002).

First author (year)	Type of study	Intervention	Outcomes	Measures	Study duration (weeks)	Follow-up (months)	Ref.
Carapeti (2000)	Pilot study	DTZ gel (2%) 8 mg t.i.d. Bethanechol gel (0.1%) 4 mg t.i.d.	Pain, healing, RAP	VAS, physical examination, manometry	8	-	[10]
Knight (2001)	Interventional	DTZ gel (2%), 2.5 cm (8 mg) b.i.d.	Pain, healing	-	8	14–67 weeks	[11]
Jonas (2001)	RCT	DTZ gel (2%) 14 mg b.i.d. DTZ tablet (60 mg) b.i.d.	Pain, bleeding, MRAP	VAS, physical examination, manometry	8	6	[12]
Jonas (2002)	Interventional	DTZ gel (2%) 14 mg b.i.d.	Pain, bleeding, healing	VAS, physical examination	8	12	[13]
Griffin (2002)	Interventional	DTZ cream (2%) 14 mg b.i.d.	Pain, bleeding, irritation	VAS	8	23–54 weeks	[14]
Das gupta (2002)	Interventional	DTZ gel (2%) 8 mg t.i.d.	healing	-	12	3	[15]
Kocher (2002)	RCT	DTZ cream (2%) b.i.d. GTN ointment (0.2%) b.i.d.	Headache, healing, recurrence	Verbal grading system for side effects, VAS, clinical examination	6–8	1	[16]

b.i.d.: Twice daily; DTZ: Diltiazem; GTN: Glyceril trinitrate; MRAP: Mean resting anal pressure; RAP: Resting anal pressure; RCT: Randomized clinical trial; t.i.d.: Three-times daily; VAS: Visual analogue scale.

Results & discussion

Of the 129 relevant studies which were initially found, 107 were excluded after screening. Of these 95 were redundant, two did not include human subjects, three were review articles and meta-analyses, one was retrospective and six were not in English, and no accurate translation was available. Nevertheless, the mentioned review articles were checked for references but all of the included studies were already obtained from databases and no new studies were found to be added to the records. Finally 20 articles and two registered clinical trials were included in the review and were subjected to data extraction and further analysis. The data extracted from the studies are summarized in Tables 1–5. What comes next is a compilation of the main observations and results of the included studies.

The beneficial effects of topical DTZ in fissure was first reported by Carapeti *et al.* in 2000, who carried out a pilot study consisted of two parallel studies assessing the efficacy of topical DTZ and topical bethanechol in treatment of CAF. Fifteen patients were included in each group receiving either 2% DTZ gel or topical bethanechol three-times daily for 8 weeks, and the outcome was assessed in terms of pain reduction, healing and lowering the mean resting anal pressure (MRAP). This study showed complete healing in 10 out of 15 patients (67%) treated with DTZ gel, and significant reduction in median pain score and MRAP (11 and 4.5 units, $p_1 = 0.0001$, $p_2 = 0.002$ respectively) in all of the 15 patients. Based on the promising results of this study, topical DTZ was suggested as a potential candidate for chemical sphincterotomy of CAF [10].

In 2001, Knight *et al.* carried out a prospective study evaluating the efficacy of 2% DTZ gel in treatment of CAF. Seventy-one patients with CAF were treated with 2% DTZ gel for 8 weeks and the healing of fissure was assessed. However, no information about the methods used to measure the outcomes was provided in the published article. Of 71 patients included in the study, 51 (75%) were healed within 8 weeks of DTZ therapy; 12 patients (16.9%) received a second course of DTZ therapy, 8 of which healed within 16 weeks making a total of 83.09% (59 out of 71 patients) healing rate. The 59 patients who healed were followed up for a median of 32 weeks in order to assess the potential recurrence of fissure. Recurrence was observed in seven patients (11.86%). Seven other patients showed mild recurrent symptoms without recurrence of fissure. The only adverse drug reactions observed were headache in one patient (1.4%) and perianal dermatitis in four patients (5.63%). However, these complications were not severe and did not lead to noncompliance or discontinuation of therapy [11]. This study confirmed the initial

Table 1. Type and structural features of the included studies (2003–2010).

First author (year)	Type of study	Intervention	Outcomes	Measures	Study duration (weeks)	Follow up (months)	Ref.
Bielecki (2003)	RCT	GTN (0.5%) ointment 2.5–4 mg b.i.d. DTZ (2%) ointment 10–14 mg b.i.d.	Pain, healing, side effects	VAS, verbal scale, proctoscopy, anoscopy	8	-	[17]
Shirvastava (2007)	RCT	DTZ (2%) ointment 10 mg b.i.d. GTN (0.2%) ointment 1 mg b.i.d. Placebo	Pain, healing, side effects	VAS, physical examination	6	3	[18]
Dhawan (2009)	RCT	DTZ gel (2%)	Quality of life	GIQLI score	8	-	[19]
Hashmi (2009)	RCT	GTN (0.2%) cream t.i.d. DTZ (2%) cream t.i.d.	Healing, recurrence, side effects	VRS, physical examination	8	12	[20]
Jawaid (2009)	RCT	DTZ (2%) ointment b.i.d. GTN (0.2%) ointment b.i.d.	Pain, healing, side effects	VAS, physical examination	8	-	[21]
Sanei, 2009	RCT	DTZ (2%) ointment 60 mg b.i.d. GTN (0.2%) ointment 6 mg b.i.d.	Pain, healing, side effects	VAS, physical examination	12	-	[22]

b.i.d.: Twice daily; DTZ: Diltiazem; GIQLI: Gastrointestinal quality of life index; GTN: Glyceril trinitrate; RCT: Randomized clinical trial; t.i.d.: Three-times daily; VAS: Visual analogue scale.

Table 1. Type and structural features of the included studies (2011–2013).

First author (year)	Type of study	Intervention	Outcomes	Measures	Study duration (weeks)	Follow-up (months)	Ref.
Ala (2012)	RCT	DTZ (2%) gel 8 mg b.i.d. GTN (0.2%) ointment 6 mg b.i.d.	Pain, healing, side effects	VAS, physical examination	8	-	[23]
Cevik (2012)	RCT	Lidocaine (10%) ointment b.i.d. GTN (0.2%) ointment b.i.d. DTZ (2%) ointment b.i.d.	Healing	Physical examination	8	12	[24]
Hanumanthapa (2012)	RCT	DTZ (2%) ointment b.i.d. Lignocaine (2%) ointment b.i.d.	Pain, healing, bleeding, recurrence	VAS, physical examination	6	12	[25]
Suvarna (2012)	RCT	DTZ (2%) ointment b.i.d. GTN (0.2%) ointment b.i.d.	Pain, healing, recurrence, side effects	VAS, physical examination	6	12	[26]
Tsunoda (2012)	Interventional	DTZ (2%) gel b.i.d.	Healing, quality of life	Physical examination, SF-36	6	6	[27]
Suvarna (2012)	RCT	DTZ (2%) ointment b.i.d. lateral internal sphincterotomy	Pain, healing, recurrence, side effects	VAS, physical examination	6	12	[28]
Bulus (2013)	RCT	ISMN (0.2%) ointment 2 mg b.i.d. DTZ (2%) ointment 20 mg b.i.d. combination (2% DTZ + 0.1% ISMN) b.i.d.	Pain, strain, healing, side effects	VAS, verbal scaling, physical examination	8	-	[29]

b.i.d.: Twice daily; DTZ: Diltiazem; GTN: Glyceril trinitrate; ISMN: Isosorbide mononitrate; RCT: Randomized clinical trial; VAS: Visual analogue scale, SF: short forum health survey.

Table 4. The demographic data of the patients included in the studies (2000–2007).

First author (year)	Number of patients	Age (years)	Female/Male	Duration of symptoms	Drop-outs	Ref.
Carapeti (2000)	15	37 (Med)	8/7	> 3 months	None	[10]
	15	34 (Med)	9/6		None	
Knight (2001)	71	39 (Med)	36/35	4 months (Med)	9	[11]
Jonas (2001)	26	35 (Med)	16/10	7 months (Med)	None	[12]
	24	35 (Med)	17/7	12 months (Med)	7	
Jonas (2002)	39	42 (Med)	26/13	8 months (Med)	1	[13]
Griffin (2002)	47	38 (Med)	23/24	12 months (Med)	1	[14]
Das gupta (2002)	23	45 (Med)	12/13	6 months (Med)	None	[15]
Kocher (2002)	31	45 (Med)	20/11	46 weeks (Med)	3	[16]
	29	39 (Med)	15/14	51 weeks (Med)	9	
Bielecki (2003)	21	54.1 (Mean)	35/8	> 8 weeks	None	[17]
	22	46.6 (Mean)				
Shirvastava (2007)	30	36.8 (Mean)	16/14	14.6 weeks (Mean)	None	[18]
	30	36.7 (Mean)	16/14	17.4 weeks (Mean)	None	
	30	38.3 (Mean)	17/13	16.8 weeks (Mean)	None	

results obtained by Carapeti *et al.* and provided further evidence on effectiveness of topical DTZ in CAF.

On the same year, Jonas *et al.* published an article reporting the results of an RCT comparing the efficacy of oral and topical DTZ in CAF. They studied 50 patients receiving either DTZ tablets or 2% DTZ gel over a period of 8 weeks and found greater reduction in MRAP (23 vs 15%, p = 0.001) and higher healing rate (17 out of 26 or 65.38% vs 9 out of 24 or 37.5%) for topical DTZ. However, the difference in healing rate was not considered significant based on intention to treat, as mentioned by the authors (χ^2, p = 0.09). No side effects were observed in any of the patients treated with topical DTZ, whereas patients treated with oral DTZ developed side effects such as headache, gastrointestinal disturbance and generalized rash, leading to discontinuation of treatment in seven patients (29.16%). Overall, the results from this study demonstrated superiority for topical DTZ over oral DTZ in terms of efficacy and side effect. Nine patients in each study arm were previously treated with topical GTN but had failed to heal, seven of which healed with topical DTZ and one with oral DTZ, suggesting the potential of topical DTZ to treat CAF in patients who failed to heal with GTN [12].

This study was followed by another prospective study evaluating the efficacy of topical DTZ in the management of GTN-resistant CAF. Thirty-nine patients who had failed to heal with topical GTN were treated with 2% DTZ gel for 8 weeks and reduction in MRAP, pain, bleeding and perianal irritation were assessed. The results demonstrated 20% reduction in MRAP (p < 0.0001), as well as considerable reduction in pain, bleeding and perianal irritation. Complete healing was observed in 19 patients (49%) with no recurrence during 1-year follow-up period [13].

In a similar study by Griffin *et al.*, 47 patients with CAF who failed to heal with GTN were treated with 2% DTZ cream for 8 weeks, 22 (46.80%) of which were healed. In addition, significant reduction in average pain score and bleeding was reported. No side effects were observed in any of the patients [14]. Similarly, Das gupta *et al.* evaluated the fissure healing with 2% DTZ gel in 23 patients with CAF, 8 of which had failed to heal with GTN, over a 12-week period and found 47.82% (11 out of 23) healing rate with no side effects and no recurrence within 3-month follow-up period [15]. These studies provided sufficient data to support the claim that DTZ could be regarded as an appropriate candidate for chemical sphincterotomy. Subsequently a number of studies were carried out to compare the efficacy and safety of DTZ with GTN, in order to suggest DTZ as a substitute for GTN whose indication was limited by the incidence of side effects, most notably headache.

In a RCT performed by Kocher *et al.*, the incidence of headache as well as the healing rate, symptomatic improvement and recurrence rate of fissure in patients treated with 2% GTN ointment and patients treated with 2% DTZ cream in a period of 6–8 weeks were compared. The incidence of headache and other side effects was significantly higher in patients treated with GTN (21/29 or 72.41% vs 13/31 or 41.93%, p = 0.01).

Table 5. The demographic data of the patients included in the studies (2008–2013).

First author (year)	Number of patients	Age (years)	Female/ Male	Duration of symptoms	Drop-outs	Ref.
Dhawan (2009)	24	-	8/16	-	None	[19]
Hashmi (2009)	50	30 (Mean)	27/23			[20]
	47		26/21	>3 months	None	
Jawaid (2009)	40	37.3 (Mean)	14/26	24 weeks (Med)	2	[21]
	40	40.1 (Mean)	17/23	20 weeks (Med)	5	
Sanei (2009)	51	28.29 (Mean)	24/27	> 6 weeks	None	[22]
	51	27.90 (Mean)	23/28	> 6 weeks		
Ala (2012)	36	16–81 (Range)	51/10	>2 months	None	[23]
	25				10	
Cevik (2012)	93	32.1 months (Mean)	49/44	> 15 days	11	[24]
Hanumanthapa (2012)	100	38.97 (Mean)	53/47	6–9 months (Range)	None	[25]
	100	40.17 (Mean)	49/51	6–8 months (Range)	None	
Suvarna (2012)	100	18–65 (Range)	56/44	8–9 months (Range)	4	[26]
	100	18–64 (Range)	52/48	8–9 months (Range)	15	
Tsunoda (2012)	30	54 (Med)	17/13	4.5 months (Med)	1	[27]
Suvarna (2012)	100	40.19 (Mean)	56/44	8.17 months (Mean)	9	[28]
	100	39.58 (Mean)	47/53	8.38 months (Mean)	3	
Bulus (2013)	20	37.94 (Mean)		>2 months		[29]
	20	42.83 (Mean)	-	>2 months	5	
	20	40 (Mean)		>2 months	(total)	

However, nonsignificant difference in pain reduction or healing rate was observed between the two groups (25 out of 29 or 86.2% healing with GTN and 24 out of 31 or 77.4% healing for DTZ) [16].

In a similar RCT by Bielecki *et al.*, 43 patients with CAF were treated either with 0.5% GTN ointment or 2% DTZ ointment for 8 weeks and the pain reduction, healing and incidence of side effects were compared. The results did not show any significant difference in healing rate between the two arms (18/27 or 85.7% in GTN group vs 19/22 or 86.36% in DTZ group). However, remarkable difference in incidence of headache was observed between the two groups, seven patients (33.3%) in GTN group developed headache, whereas none of the patients in DTZ group reported any side effects [17].

The results of this couple of studies demonstrated equal efficacy and lower incidence of headache for topical DTZ compared with topical GTN in treatment of CAF. These findings were further confirmed by a number of subsequent studies carried out afterwards which provided further evidence of efficacy and lower incidence of side effects with higher topical DTZ preparations compared with topical GTN preparation used in patients with CAF.

Shirvastava *et al.* studied 90 patients with CAF over a 6-week period followed by a 3-month follow-up; the patients were randomly divided into three groups receiving 2% DTZ ointment, 0.2% GTN ointment and a local anesthetic preparation (control group). Their study demonstrated greater reduction in average pain score in patients receiving DTZ ointment compared with the other two groups. The healing rate in patients treated with DTZ ointment and patients treated with GTN ointment was significantly higher than the control group (80, 73 and 33%, respectively). However, no marked difference between the two treatment groups were observed ($p = 0.303$). The recurrence rates in DTZ group, GTN group and control group were 12.5, 32 and 50% respectively showing superiority for DTZ and GTN groups over control group ($p = 0.303$). The incidence of side effects, mainly headache, was significantly higher in GTN group (20 out of 30 or 67%) compared with the other two groups which did not have any side effects [18].

Dhawan *et al.* evaluated the efficacy of four different formulations of DTZ gel prepared from different polymers (methyl cellulose [MC], hydroxypropyl methyl cellulose [HPMC] and two different grades of polyethylene oxide (PEO 301 and PEO 303) in 24 patients

with CAF (six patients per formulation) over a period of 8 weeks, and assessed the symptom improvement using gastrointestinal quality of life index (GIQLI) score. They reported improved GIQLI score for all of the patients ($p < 0.001$), without any significant difference in GIQLI score change between different formulations ($p = 0.931$) [19].

In a RCT by Hashmi *et al.*, 2% DTZ cream was compared with 0.2% GTN cream in treatment in CAF during a period of 8 weeks followed by 1-year follow-up. There was no considerable difference in improvement of symptoms between the two groups (37% in DTZ group vs 35% in GTN group, $p = 0.345$), however the healing rate was significantly higher in DTZ group (61 vs 52%, $p = 0.02$). The incidence of headache was markedly lower in DTZ group (2 out of 47 or 4% vs 13 out of 50 or 26%, $p = 0.003$), but the incidence of other side effects was not significantly different. The difference in recurrence rate was also statistically insignificant (5 out of 47 or 10.6% in DTZ group vs 8 out of 50 or 16% in GTN group, $p = 0.291$) [20].

Jawaid *et al.* carried out another RCT including 80 patients randomly divided into two groups (40 each) allocated to either 2% DTZ ointment or 0.2% GTN ointment for 8 weeks and found no significant difference in healing rate between the two groups (32 [78%] vs 33 [82.5%] for DTZ and GTN, respectively, $p = 0.775$). However, the incidence of headache was significantly lower in DTZ group (9 [22.5%] vs 27 [67.5%], $p < 0.001$) [21].

Similarly, Sanei *et al.* assessed pain reduction, healing and incidence of side effects in 102 patients with CAF, treated either with 2% DTZ ointment or 0.2% GTN ointment over a period of 12 weeks. Although higher healing rate was achieved with DTZ (66.7 vs 54.9%, $p > 0.05$), the difference was not statistically significant. However, the proportion of patients who showed pain reduction was considerably higher in DTZ group compared with GTN group (45 [88.2%] vs 36 [70.6%], $p = 0.02$). On the other hand, the average healing time was markedly lower in patients treated with GTN (4.85 vs 7.58 weeks, $p = 0.001$), suggesting earlier initiation of action for GTN. Thirty patients (58.8%) in GTN group reported headache, 14 of which led to discontinuation of treatment, whereas none of the patients in DTZ group experienced headache [22].

More recently, Ala *et al.* conducted a two-center RCT including 61 patients with CAF, divided into two groups; 36 patients were allocated to 2% DTZ gel and 25 patients were allocated to 0.2% GTN ointment for 8 weeks and pain reduction, healing and incidence of side effects were compared. The results showed absolutely higher healing rate for DTZ compared with GTN (33 out of 36 [91.66%] vs 15 out of 25 [60%], $p < 0.001$). Although reduction in average pain score was markedly higher in DTZ group at the second week ($p < 0.001$), the difference was not significant during the rest of the trial period. All of the patients in GTN group experienced varying degrees of headache, which led to discontinuation of treatment in 10 patients (40%), whereas none of the patients in DTZ group experienced headache. By the same way, the incidence of other side effects such as constipation and pruritus per ani was also higher in GTN group ($p < 0.001$) [23].

In a similar but larger RCT performed by Suvarna *et al.*, 200 patients with CAF were randomly divided into two groups of 100 and allocated to either 2% DTZ ointment or 0.2% GTN ointment for 6 weeks followed by 1-year follow-up and the pain relief, healing rate, recurrence rate and side effects were assessed. The healing rate was higher in DTZ group compared with GTN group (71.87 vs 68.23%, $p < 0.081$). However, four patients in DTZ group and 15 patients in GTN group were noncompliant (due to headache and cooperation problems) and discontinued treatment. These patients were excluded from analysis. If the analysis was performed on an intention-to-treat basis including these patients, the healing rates in DTZ and GTN group would be 69 and 58%, respectively ($p < 0.0001$). Seven patients in DTZ and 12 in GTN group were lost to follow up. Excluding these patients, 9.67% (6 out of 62) and 19.56% (9 out of 46) recurrence rate was reported for DTZ and GTN groups, respectively. Although no significant difference in pain reduction was noted at any time points during the trial period, consumption of pain killers was significantly higher in GTN group (28 vs 1). The incidence of headache was also considerably higher in GTN group (57 out of 85 [67%] vs 5 out of 96 [52%], $p < 0.0001$) [26].

Compiling the results from all of these studies provides sufficient evidence for superiority of topical DTZ to topical GTN in treatment of CAF in terms of efficacy and side effects, suggesting topical DTZ as a suitable substitute for topical GTN in treatment of CAF.

Tsunoda *et al.* studied not only the fissure healing but also the quality of life in 30 patients with CAF treated with 2% DTZ gel for 6 weeks. The quality of life was assessed using short forum health survey SF-36. Twenty-one out of 30 (70%) patients healed within 6 weeks of treatment. Of the nine patients who did not heal, six received an additional course of DTZ therapy, three of which healed making a total of 24 out of 30 (80%) healing rate. Furthermore, the results showed improved quality of life in patients who healed compared with patients who did not heal ($p < 0.05$). Of 21 patients who healed initially, four (19%) showed recurrence of fissure within 6 months. The incidence of side effects among the patients was rather low; four

patients (13.33%) experienced perianal itching and only one patient suffered from headache [27].

Following successful treatment of CAF with topical DTZ in adults, an RCT was carried out by Cevik *et al.* to assess the efficacy and safety of topical DTZ in children with anal fissure. Ninety-three children aged between 2 and 144 months were randomly divided into three groups receiving 2% DTZ ointment, 0.2% GTN ointment and 10% lidocaine ointment (control group) for 8 weeks and followed up for 12 months. The initial results showed higher healing rate for DTZ compared with GTN and control groups (23 out of 28 [82.1%] vs 11 out of 28 [39.3%] and 7 out of 28 [25%], $p < 0.0001$, respectively). The patients who failed to heal received a second 8-week treatment course, followed by a shift to topical DTZ for further 8 weeks if required. At the end of the 24 weeks, all of the patients were symptom free. The only side effect which was observed in patients was perianal dermatitis in one patient in DTZ group and one patient in GTN group. The average healing time was shorter for DTZ group compared with GTN and control groups (5.4 vs 8.8 vs 8.9 weeks, respectively). The recurrence rate was lower in DTZ group compared with the other two groups (3 [11%] vs 10 [37%] vs 16 [57.17%], respectively) [24].

In a recent RCT performed by Hanumanthapa *et al.*, the effectiveness of 2% DTZ gel was compared with 2% lignocaine ointment (control) in 200 patients with CAF (100 in each group) and higher healing rate (72 vs 23%, $p < 0.0001$), greater decrease in bleeding (80 vs 42%, $p < 0.001$), greater reduction in discharge (90 vs 50%, $p < 0.0001$) and lower recurrence rate (3 out of 65 [4.61%] vs 8 out of 21 [38%], $p < 0.0001$) was reported for DTZ [25].

Further studies compared the effectiveness of topical DTZ with other pharmacotherapies or surgical procedures. Suvarma *et al.* compared chemical sphincterotomy with 2% DTZ ointment with internal lateral sphincterotomy in terms of healing rate, pain reduction, incidence of side effects and recurrence rate. Although the results showed higher healing rate (93 out of 97 [95.87%] vs 63 out of 91 [69.23%]), faster pain alleviation and lower recurrence rate (0 vs 6, $p < 0.0001$) for internal lateral sphincterotomy, due to the significantly higher incidence of fecal incontinence and flatus incontinence in patients who underwent surgery (9 vs 0, $p < 0.001$, 5 vs 0, $p < 0.002$, respectively), it was concluded that chemical sphincterotomy should be regarded as first-line treatment for CAF, keeping the surgical approach reserved for those patients who fail to respond to chemical sphincterotomy. Twelve patients (three in surgery group and nine in DTZ group) were noncompliant and were therefore excluded from analyses [28].

More recently, Bulus *et al.* evaluated the efficacy of a combinatory preparation of DTZ and isosorbide mono nitrate (ISMN) with simple preparations of each drug (2% DTZ ointment and 0.2% ISMN ointment) in 60 patients with CAF. The results did not show any significant difference in pain reduction between the three groups (4.83 ± 2.95 for ISMN, 4.88 ± 3.19 for DTZ and 5.10 ± 3.03 for combination, $p = 0.957$). By the same way, the difference in healing rates was also insignificant (14 out of 18 [77.8%] for ISMN, 13 out of 18 [72.2%] for DTZ and 14 out of 19 [73.3%] for combination, $p = 0.990$). These findings indicate that combination therapy has no advantages over monotherapy with either agent [29].

Methodologic quality of included studies

By far the most prevalent quality problem encountered in this review was failure to analyze results of the investigations on an 'intention-to-treat' basis. Authors' conclusions were mostly based on per protocol analysis.

In some of the randomized trials, the randomization procedure was not specified [17,25,28,29] and in some the randomization procedure was not efficient [20,26]. By the same way, no information about blinding or allocation concealment was provided in majority of these studies. Nevertheless, blinding was clearly difficult in certain cases such as comparison of topical DTZ with internal lateral sphincterotomy [28]. The method of sample size estimation was not mentioned in majority of the randomized trials [12,15,17,25,26,29], which makes the accuracy of the analyses questionable as a small sample size may result in biased data.

Apart from randomization and analysis issues, a major limitation of all of the RCTs included in this review is that none of these studies were placebo-controlled. Only two studies [18,24] included control groups who were receiving local aneasthetics, but not placebo. This casts shadow on the observed results, because the medications must have their efficacy viewed in the context of placebo effect. Hence, in order to establish the real magnitude of efficacy of DTZ in pain reduction or healing in patients with CAF, its effects should be evaluated in comparison with placebo.

Another limitation of the included studies is that all but two of these studies were single centered, which reduces the generalizability of the findings. Only the studies by Kocher *et al.* and Ala *et al.* [16,23] were performed in two medical centers, with no multicenter or nationwide studies being published.

Although a Phase III, multicentered, randomized, placebo-controlled trial including 465 patients from several European countries has been launched and accomplished by S.L.A. Pharma AG evaluating the efficacy of DTZ hydrochloride cream for anal fissure, the

results are not published yet [30]. Another nationwide Phase III, randomized, placebo-controlled, multicenter study of efficacy and safety of topical DTZ hydrochloride 2% cream in subjects with anal fissure has been carried out by Ventrus Biosciences Inc. in United States, including 434 patients from various states; however, the results of this trial has not been published either [31].

The majority of the studies did not report the mean or median duration of symptoms before commencement of the trial. Furthermore, the exact dose of DTZ is not mentioned in a number of the included studies [20,21,24–26,28], which makes it difficult to interpret and compare the results of these studies with other studies. Similarly, the formulation, type and amount of excipients used in topical preparations of DTZ are not mentioned in all but two studies [19,23], which makes more thorough comparison of the formulations used in different studies impossible.

There is also a lack of studies comparing the effect of different doses of DTZ or different administration time intervals on the therapeutic outcomes. Finally, paucity of long-term data on fissure recurrence after treatment with DTZ makes it difficult to compare it with other medical or surgical therapies in terms of recurrence. Only the studies by Knight *et al.* [11] and Griffin *et al.* [14] followed up the patients for more than 1 year and there are no studies with 2 years or more follow-ups.

Conclusion & future perspective

Although surgical sphincterotomy is still the best option for management of CAF in terms of healing and recurrence rate, due to the patient inconvenience and the risk of temporary or permanent fecal incontinence associated with surgical methods, in the past two decades chemical sphincterotomy has become the first-line treatment for CAF, keeping the surgical procedures reserved for patients who are nonresponsive to chemical sphincterotomy or experience fissure recurrence.

Taking into account the results from all of the above-mentioned clinical studies, it could be concluded that topical DTZ (cream, ointment or gel with 2% w/w concentration) applied twice or three-times per day on the perianal skin with total daily doses between 16 and 28 mg could be an effective therapy for CAF, both in drug-naive patients and patients who have failed to respond to or were unable to comply with other pharmacotherapies such as GTN. Overall, a total of 880 patients were treated with topical DTZ, 597 (67.84%) of which were healed within 6–12 weeks. Of these, 86 were patients who failed to respond to GTN 41 (47.67%) of which were healed. The high healing rate, low incidence of adverse drug reactions and low recurrence rate make DTZ a suitable drug for chemical sphincterotomy.

Nevertheless, there were some technical problems with most of the included studies such as lack of information on the duration of symptoms as well as the exact dose and formulation of DTZ which reduces the quality of the study and makes the analysis and comparison of the results difficult.

Although, to date, several pharmacological agents from various classes have been used for chemical sphincterotomy, some of which have shown promising results, most of these medications are not still commercially available and not generally used mainly due to the lack of multicenter or long-term clinical studies providing sufficient data on their safety. Thus, there is still need for further research to provide sufficient data on the long-term efficacy and safety of the currently recognized pharmacotherapies as well as finding new potential drug candidates for management of chronic fissure with higher efficacy and lower recurrence rate or lower incidence of side effects compared with existing medications.

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Executive summary

- Topical diltiazem lowers resting anal-sphincter pressure in patients with chronic anal fissure.
- Topical diltiazem reduces pain and induces healing in patients with chronic anal fissure.
- Topical diltiazem improves quality of life in patients with chronic anal fissure.
- Topical diltiazem heals chronic anal fissure in patients who failed to heal or were unable to comply with topical glyceril trinitrate.
- Topical diltiazem is better tolerated and associated with lower frequency of headache compared with glyceril trinitrate.
- Chemical sphincterotomy with topical diltiazem is associated with low fissure recurrence rate.
- Chemical sphincterotomy with topical diltiazem is superior to internal lateral sphincterotomy in terms of side effects such as fecal and flatus incontinence.

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