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Review

# Oral versus topical calcium channel blockers for chronic anal fissure-a systematic review and meta-analysis of randomized controlled trials

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## HIGHLIGHTS

- Topical or oral calcium blockers are frequently used as treatment, although the optimal formulation is unknown.
- This study shows the topical route to result in better healing and fewer side effects, but similar recurrence.

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## ABSTRACT

*Background:* Chemical sphincterotomy with pharmacological agents is recommended as first line therapy for chronic anal fissures (CAF). Calcium channel blockers (CCB) are associated with similar efficacy but fewer side effects compared to nitrates. However, the optimal formulation (oral versus topical) is unknown. We aimed to perform a systematic review and meta-analysis to compare the effectiveness of oral and topical CCB in the treatment of CAF.

*Methods:* PubMed and Embase online databases were searched for relevant articles. Two independent reviewers performed methodological assessment and data extraction. Random effects models were used to calculate pooled effect size estimates. A sensitivity analysis was also carried out.

*Results:* Four randomized controlled trials describing 279 patients (138 in oral, 141 in topical group) were examined. There was significant heterogeneity among studies. On random effects analysis, topical CCB were associated with a significantly lower rate of unhealed fissure (21.3% vs. 38.4%; OR = 2.65, 95% CI = 1.50 to 4.69, p = 0.0008) when compared to oral therapy. However, there were no significant differences in fissure recurrence (5.4% vs. 5.5%; OR = 1.01, 95% CI = 0.31 to 3.33, p = 0.98) or side effects (15.6% vs. 39.1%; OR = 4.54, 95% CI = 0.46 to 44.3, p = 0.19) between topical and oral CCB. On sensitivity analysis, having excluded the most heavily biased trial, topical CCB were associated with significantly fewer side effects compared to oral therapy (4.3% vs. 38.0%; OR = 13.16, 95% CI = 5.05 to 34.3, p < 0.00001).

*Conclusions:* Topical CCB are associated with better healing and fewer side effects when compared to oral therapy but there is no difference in recurrence rates.



## 1. Introduction

An anal fissure, also known as fissure-in-ano, is a longitudinal, ulcer-like tear in the anal canal, typically located in the posterior midline although a minority (25%) can be appreciated in the anterior midline [1]. An acute fissure is characterised by a simple tear in the mucosa of the anal canal, where as a chronic fissure (defined by symptoms persisting for > 8–12 weeks) is usually accompanied by chronic inflammatory changes such as fibrosis, hypertrophied anal papillae and a sentinel skin tag [1]. Visible fibres of the internal anal sphincter at the ulcer base may also be apparent in the chronic setting. The overall annual incidence of anal fissure is estimated at 1.1 per 1000 person-years, with a peak incidence in females during adolescence and young adulthood, and during middle age in men [2]. Anal fissures usually manifest with

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proctalgia, as well as bright red rectal bleeding seen on the toilet paper, on a background of passing hard, constipated stool [1]. They are usually associated with spasm of the internal anal sphincter (IAS), which may lead to local ischaemia and impaired healing [3]. Guidelines from the American Society of Colon and Rectal Surgeons (ASCRS) recommend nonoperative management of anal fissures as first line therapy, specifically with pharmacological agents such as nitric oxide donors (e.g. nitroglycerin) and calcium channel blockers (CCB) (e.g. nifedipine, diltiazem) [4]. These may either be prescribed in the oral, or topical formulation. Whilst topical nitrate has been shown to significantly reduce pain during the treatment period [5,6], its principal side effect is headache, reported in 20–30% of patients [1]. This adverse effect is dose-dependent and leads to non-compliance in a significant proportion of patients [7]. CCB are an alternative pharmacotherapy to nitric oxide donors and although they have the potential to cause similar headache, the incidence of this undesirable phenomenon is less [8–10]. An updated Cochrane review published in 2012 and evaluating more than 5000 patients concluded that CCB were equivalent to glyceryltrinitrate (GTN) in terms of fissure healing but were associated with significantly fewer adverse events [11]. Furthermore, the incidence of late fissure recurrence after initial successful GTN treatment approached 50% [11]. This has led to some physicians opting for calcium antagonists over nitrates in an attempt to increase patient compliance and improve outcomes.

However, no clear guidelines exist as to the optimal formulation (oral versus topical) approach for CCB in the management of CAF and the latest ASCRS guidelines suggest that either preparation may be used, albeit with more marked systemic toxicity associated with the oral method. Nonetheless, the impact of these differing formulations on fissure healing and recurrence is not clearly established. We aimed to systematically appraise the literature and conduct a meta-analysis to assess the efficacy of oral and topical CCB in the treatment of CAF.

## 2. Materials and methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [12]. There was no published protocol for this review.

### 2.1. Eligibility criteria

We searched for all randomized studies that directly compared oral versus topical CCB for the treatment of CAF. Unpublished reports were excluded from this review, as were studies that examined acute fissures only or those that examined chronic fissures in children and those that examined anal stenosis/stricture. Studies that evaluated oral (or topical) agents only, without direct comparison to the other formulation method were not eligible for inclusion.

### 2.2. Search strategy

The online literature was searched using the following medical subject heading (MeSH) terms in various combinations to maximize article capture: ‘anal fissure’ or ‘fissure-in-ano’ or ‘chronic anal fissure’ and ‘calcium channel blockers’ and ‘oral’ or ‘topical’. The online databases of Medline, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials as well as Google Scholar were searched for relevant articles from inception to February 2017. No language restrictions were applied. The latest electronic search was performed on February 28th, 2017. Two authors (SMS and KA) independently examined the title and abstract of citations, and full texts of potentially eligible studies were obtained. Only randomized controlled trials (RCT's) that directly compared oral with topical CCB for the management of CAF were included for analysis. Disagreement was resolved by discussion, and if remained unsettled, the opinion of the senior author (MRJ) was sought. The bibliographies of retrieved studies were further screened for potential additional studies for inclusion. The primary end point for this review was rate of unhealed fissure. Secondary end points included fissure recurrence rates and side effects.

### 2.3. Data collection

SMS and KA independently extracted data from the included studies on a Microsoft Excel spreadsheet, using a predefined template. The following information regarding each eligible study was recorded: authors' names, journal, year of publication, gender, mean age, sample size, type of study, fissure location, unhealed fissure rates, fissure recurrence rates, side effects and length of follow up.

### 2.4. Data analysis

All pooled outcome measures were determined using the random effects model as described by DerSimonian and Laird [13] and the Odds Ratio (OR) was estimated with its variance and 95% confidence interval (CI). The random effects analysis weighted the natural logarithm of each study's odds ratio by the inverse of its variance plus an estimate of the between-study variance in the presence of between-study heterogeneity. The existing heterogeneity between OR's for the same outcome between different studies was assessed by the $I$ [2] inconsistency test. The $I$ [2] inconsistency test describes the percentage of total variation across studies, which is due to heterogeneity rather than chance. A value of 0% indicates no observed statistical heterogeneity, while larger values signify increasing heterogeneity. The quality of the included studies was assessed using the Cochrane Collaboration tool of bias [14]. A sensitivity analysis was also performed after excluding the most heavily flawed trial. Analyses were conducted using Review Manager software (RevMan, version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

## 3. Results

### 3.1. Study selection and characteristics

Four published RCT's comprising 279 patients met our inclusion criteria. There were 138 patients in the oral group, and 141 in the topical group. A flow diagram of the selection process is shown in Fig. 1. The study characteristics are summarised in Table 1. The risk of bias in each study is shown in Table 2.

### 3.2. Definition of CAF

CAF was clearly defined in Jonas et al. [15] as persistent symptoms for > 6 weeks despite increased fluid intake, dietary fibre and laxatives, while it was defined as a midline anterior or posterior fibrotic ulcer with hypertrophied anal papillae and sentinel pile in Golfam et al. [16]. Ahmed HM [17] defined CAF as persistent symptoms for > 8 weeks associated with classical triad of chronicity. No formal definition was provided in Agrawal et al. [18].

### 3.3. Choice of CCB

Diltiazem was the CCB of choice in Jonas et al. [15], while

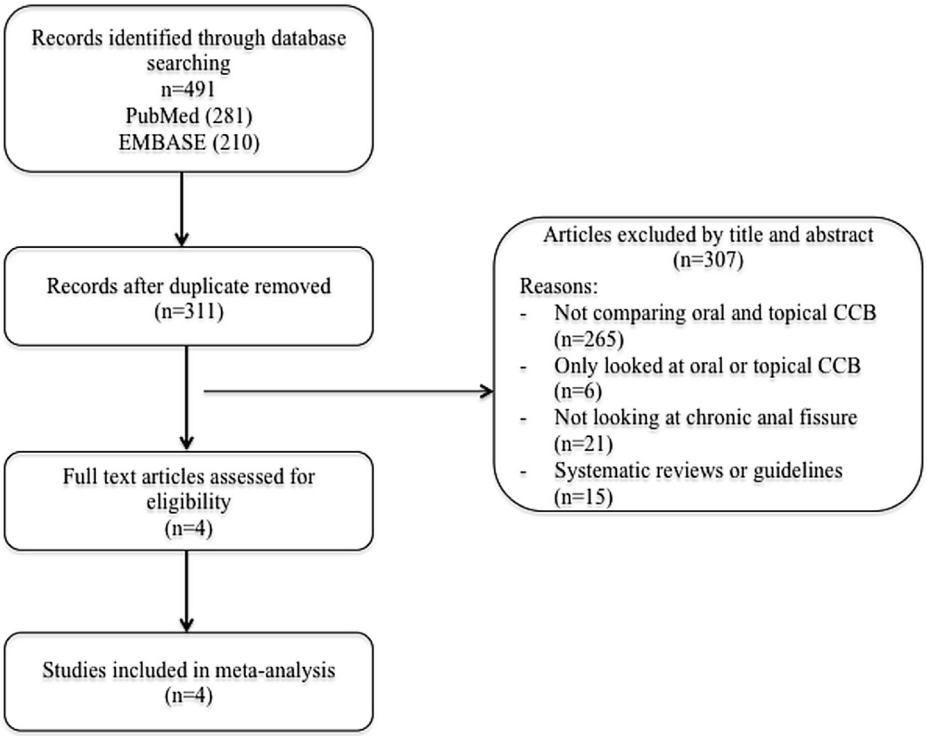


**Fig. 1.** PRISMA diagram of studies included in meta-analysis.

**Table 1**
Characteristics of included randomized controlled trials.

| Author, setting | No of patients in oral/topical groups | Mean (SD) or median (range) age of patients, years | Formulations employed/treatment duration | Relevant outcomes measured | Maximum length of follow up (months) | Comments |
|---|---|---|---|---|---|---|
| Jonas et al. [15], UK, 2001 | 24 oral/26 topical | 35 (18–80) | 60 mg diltiazem PO BD, or 2% top BD/8 weeks | MARP<br>Fissure healing<br>Fissure recurrence<br>Perianal irritation | 6 | Intention-to-treat analysis.<br>No power calculation. |
| Ahmed [17], Soudan, 2010 | 25 oral/25 topical | 25.07 (17–45) | 20 mg nifedipine PO BD x 6–8 weeks, or 0.2% top BD x 2–3 weeks | Fissure healing<br>Fissure recurrence<br>Side effects | 3 | No power calculation.<br>17 patients altogether (5 in oral and 12 in topical) underwent sphincterotomy for failure of medical management; however unclear whether intention-to-treat or per protocol analysis performed. |
| Agrawal et al. [18], India, 2013 | 30 oral/30 topical | 32.4 (9.3) | 20 mg nifedipine PO BD, or 0.2% top BD<br>Treatment duration not specified | Fissure healing<br>Pain scores | 2 | All patients received additional measures (sitz baths, lidocaine ointment, stool softeners and oral antibiotics).<br>No power calculation. |
| Golfam et al. [16], Iran, 2014 | 59 oral/60 topical | 33.2 (6.2) | 10 mg nifedipine PO (frequency not specified), or 0.5% top (frequency not specified)/4 weeks | Fissure healing<br>Pain scores<br>Side effects<br>Fissure recurrence | 6 | Unclear whether intention-to-treat, or per protocol analysis performed.<br>All patients were advised to take dietary fibre and sitz baths. |

MARP: Maximum Anal Resting Pressure.

nifedipine was used in the remaining 3 studies [16,18], albeit with varying doses. Diltiazem was prescribed as 60 mg orally, or 2% topically twice daily for a period of 8 weeks in Jonas et al. [15]. Agrawal et al. [18] evaluated nifedipine 20 mg orally, or 0.2% topically twice daily but the treatment duration was not stated. The same formulation and dosing were employed by Ahmed HM [17], with a treatment duration of 6–8 weeks for oral nifedipine or 2–3 weeks for topical nifedipine. Finally in Golfam et al. [16], the oral dose of nifedipine was 10 mg, and the topical concentration 0.5% but the frequency of the prescription was not specified even though treatment lasted for 4 weeks.

### 3.4. Inclusion and exclusion criteria

Inclusion and exclusion criteria were clearly described in all studies. In Jonas et al. [15], all patients already taking CCB or beta antagonists for other clinical indications were excluded, as were pregnant or breast-feeding females, females not using appropriate contraception and subjects with previously documented allergic reactions to diltiazem. In Agrawal et al. [18], patients with

**Table 2**
Assessment of risk of bias in included studies.

| | Random sequence allocation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data addressed (attrition bias) | Selective reporting (reporting bias) |
|---|---|---|---|---|---|---|
| Jonas [15] (2001) | Low | Unclear | High | Low | Low | Low |
| Ahmed [17] (2010) | High | High | High | High | High | Unclear |
| Agrawal [18] (2013) | Low | Unclear | High | High | Low | Low |
| Golfam [16] (2014) | Unclear | Unclear | Unclear | Unclear | High | Low |

complicated fissures (defined as those with atypical locations or associated with tuberculosis or Crohn's disease), or fissures accompanied by systemic illnesses (such as diabetes mellitus, human immunodeficiency virus infection), patients with an allergy to CCB as well as pregnant and lactating women were excluded. Ahmed HM [17] excluded all pregnant patients, lactating women or patients with cardiovascular diseases. However, patients with prior treatment with topical therapy were eligible for inclusion. Finally in Golfam et al. [16], subjects with a history of anorectal surgery, sexually transmitted diseases, inflammatory bowel disease, migraine, cardiovascular disease and pregnant females were excluded from the study.

### 3.5. Definition of study end points

Fissure healing was categorised as none, partial or complete in Jonas et al. [15] although no formal definition was provided. In Golfam et al. [16] complete fissure healing was defined as complete epithelialisation of the ulcer bed on inspection and absence of pain. Similarly, Agrawal et al. [18] defined ulcer healing as complete epithelialisation on clinical examination. No formal definition was provided by Ahmed HM [17].

No formal definition for fissure recurrence was provided in any of the trials.

### 3.6. Primary outcome

#### 3.6.1. Unhealed fissures

All 4 studies reported healing failure rates (n = 279). This was 38.4% in the oral group, compared to 21.3% in the topical group. On random effects analysis, the difference was statistically significant (OR = 2.65, 95% CI = 1.50 to 4.69, p = 0.0008; Chi [2] = 0.54 (df = 3), p = 0.91; $I^2$ = 0%) (Fig. 2).

### 3.7. Secondary outcomes

#### 3.7.1. Side effects

All 4 studies reported CCB side effects (n = 279). This was 39.1% in the oral group, compared to 15.6% in the topical group. Although notably higher for oral CCB therapy, on random effects analysis, the difference failed to reach statistical significance (OR = 4.54, 95% CI = 0.46 to 44.3, p = 0.19; Chi [2] = 23.2 (df = 3), p < 0.0001; $I^2$ = 87%) (Fig. 3). There was also significant statistical heterogeneity among the studies.

#### 3.7.2. Fissure recurrence

Only 3 studies [15–17] reported fissure recurrence (n = 219). This was 5.5% in the oral group, compared to 5.4% in the topical group. On random effects analysis, the difference was not statistically significant (OR = 1.01, 95% CI = 0.31 to 3.33, p = 0.98; Chi

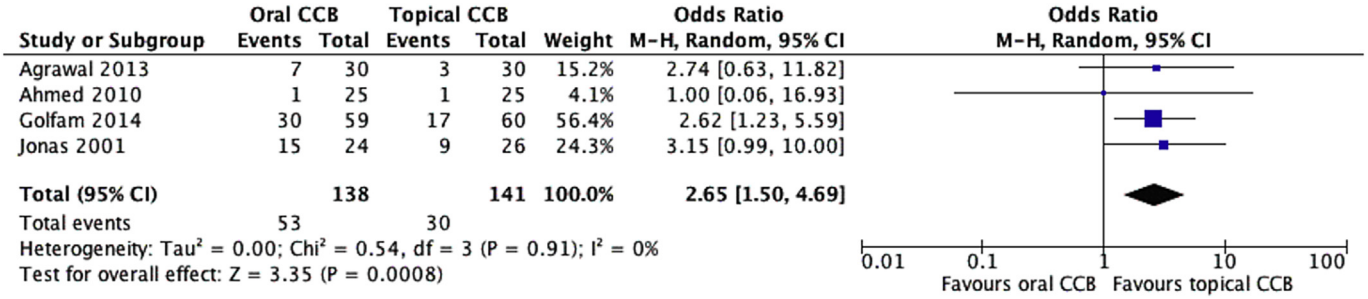


**Fig. 2.** Meta-analysis of unhealed fissure rates of topical and oral CCB.

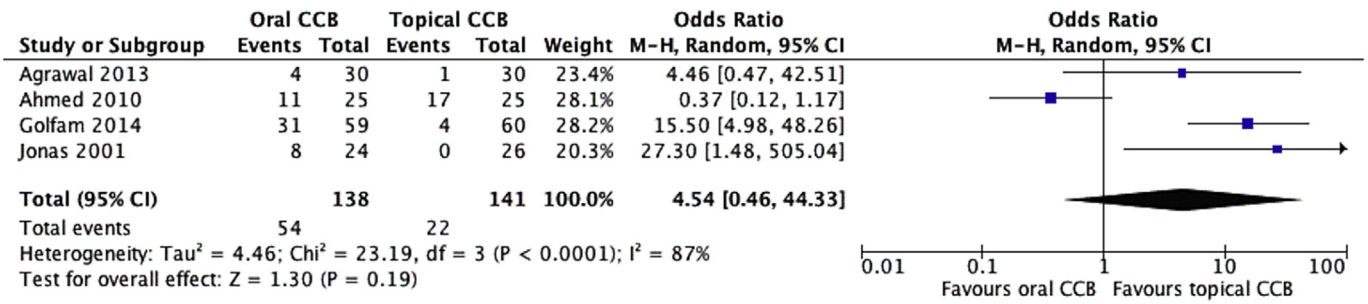


**Fig. 3.** Meta-analysis of side effects of topical and oral CCB.

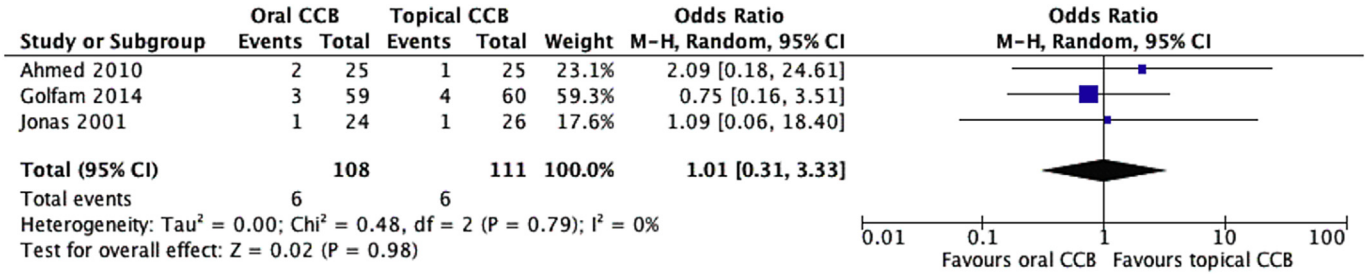


**Fig. 4.** Meta-analysis of fissure recurrence rates of topical and oral CCB.

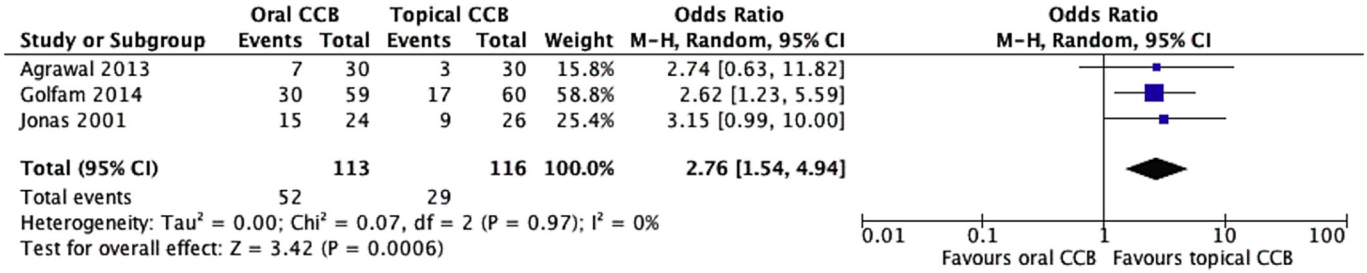


**Fig. 5.** Sensitivity analysis of unhealed fissure rates of topical and oral CCB.

[2] = 0.48 (df = 2), p = 0.79; $I^2$ = 0%) (Fig. 4).

### 3.8. Sensitivity analysis

A sensitivity analysis was carried out excluding the study that scored the highest in the risk of bias assessment (see Table 2) [17]. The latter study had significant drawbacks and data were missing regarding specific outcomes. Therefore, we analysed the data without that study to determine if the results would be different.

#### 3.8.1. Unhealed fissures

On sensitivity analysis, this was 46.1% in the oral group, compared to 25% in the topical group. On random effects analysis, the difference remained statistically significant (OR = 2.76, 95% CI = 1.54 to 4.94, p = 0.0006; Chi [2] = 0.07 (df = 2), p = 0.97; $I^2$ = 0%) (Fig. 5).

#### 3.8.2. Side effects

On sensitivity analysis, this was 38.0% in the oral group, compared to 4.3% in the topical group. On random effects analysis, the difference was statistically significant (OR = 13.16, 95% CI = 5.05 to 34.3, p < 0.00001; Chi [2] = 1.21 (df = 2), p = 0.55; $I^2$ = 0%) (Fig. 6).

#### 3.8.3. Fissure recurrence

On sensitivity analysis, fissure recurrence was reported by only 2 trials [15,16]. Hence it was inappropriate to generate summative outcome from the available data.

## 4. Discussion

Combined data from the current meta-analysis demonstrate that topical CCB are associated with significantly better fissure healing compared to oral CCB but that there is no difference in side effects or fissure recurrence between the 2 formulations. On sensitivity analysis, having excluded the most heavily flawed trial, the results showed further superiority of topical therapy, with significantly better healing rates as well as fewer side effects compared to oral treatment. However, these results have to be interpreted with caution given that the included studies in this systematic review suffer from significant clinical heterogeneity, with non-uniformity of study compound, duration of prescribed medication in addition to short follow ups. Nifedipine was the drug of choice in 3 studies [16–18] while diltiazem was used in Jonas et al. [15]. With respect to nifedipine, the prescribed doses and strengths of the formulations differed across 2 of the 3 studies and either the treatment duration or the frequency of the prescription was not specified in either one trial. In Agrawal et al. [18], all subjects were prescribed additional measures (such as stool softeners,

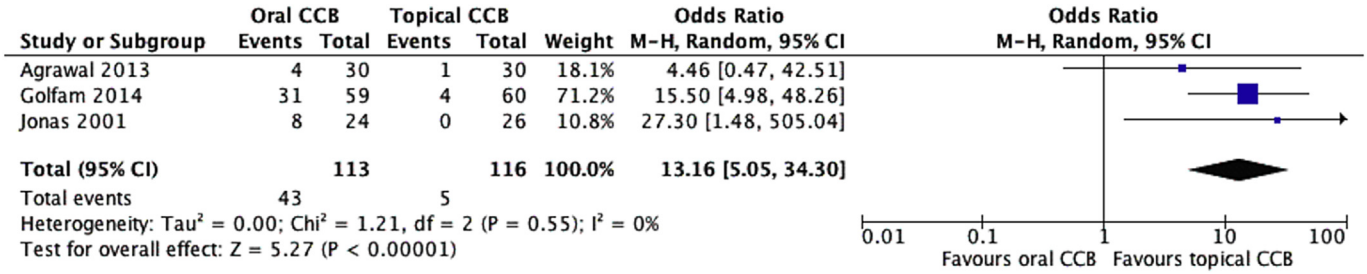


**Fig. 6.** Sensitivity analysis of side effects of topical and oral CCB.

oral antibiotics and lidocaine ointment) while in Golfam et al. [16], patients were advised to increase dietary fibre and use frequent sitz baths. These confounding interventions make it difficult to attribute the observed findings solely to the effectiveness of the CCB being evaluated. The longest follow up was 6 months but had that been lengthier, the resultant recurrence rates might have been different. Furthermore the trials were designed with substantial methodological flaws as evidenced by the high risk of bias inherent to most of them. Meticulous randomization and allocation concealment are of paramount importance to reduce the risk of bias in RCT's; yet in the study by Ahmed HM [17], patients were randomized using simple sequential order with no stringent allocation concealment. Furthermore, in the same study, 34% of patients failed medical management and were offered surgical sphincterotomy but no information was provided as to whether the data were analysed in an intention-to-treat or per-protocol manner. Moreover, all trials were single centre studies except one [16] and only one trial was single-blinded [15]. As such, it would be unwise to generalise the results indiscriminately.

It is postulated that hypertonia of the IAS and resultant local ischaemia underpin the pathogenesis of CAF [1]. Therefore, treatment is aimed at reducing the resting sphincter pressure in an attempt to ameliorate perfusion [11]. While the gold standard therapy is surgery, specifically in the form of lateral internal sphincterotomy, this may result in debilitating anal incontinence, seen in up to 14% of patients [19]. Alternative, more conservative treatment modalities include pharmacotherapy with agents such as nitrates, CCB or botulinum toxin injection into the sphincter. The latter is expensive (costing €271 per treatment preparation) [20] and may require multiple attempts but more importantly is associated with a risk of impaired continence also [21]. A meta-analysis consisting of 7 RCT's and 481 patients that compared topical diltiazem to GTN for CAF reported that diltiazem was associated with a significantly lower incidence of headache as well as fissure recurrence but similar efficacy to GTN [22]. Calcium ions have an important role in the maintenance of normal IAS tone [23]. CCB inhibit calcium influx through voltage-gated L-type calcium channels in smooth muscle, thereby causing smooth muscle relaxation and resultant enhanced blood flow. This in turn translates into fissure healing. Diltiazem has been investigated in randomized studies and shown to be superior to placebo in the treatment of CAF. One study showed that patients receiving topical 2% diltiazem experienced significantly better fissure healing and fewer recurrences compared to controls [24]. On the other hand, Cook et al. [25] showed that oral nifedipine 20 mg twice daily for eight weeks significantly reduced resting anal pressure, thus promoting fissure healing. Both diltiazem and nifedipine are effective in the treatment of CAF but there are no data to illustrate superiority of one agent over the other.

Unlike diltiazem, oral nifedipine has little action on either cardiac or skeletal muscle and thus causes less postural hypotension [25]. Commonly observed adverse events with oral nifedipine include facial flushing and headaches [25]. Side effects are experienced more frequently with oral than with topical therapy [26]. However, topical treatment (specifically diltiazem) may cause perianal itching [27] and contact allergy [28], although uncommon. The superiority of topical CCB therapy observed in the current study may reflect the targeted application of the agent to the diseased anatomical area, thereby limiting systemic dissemination and potentiating local effect. However, patients may find the daily application of an ointment inside the anus troubling or may be unclear about the volume of the paste that needs to be applied. Hence some individuals may prefer a more conventional approach as with a tablet. Furthermore, the unavailability of a practical intra-anal applicator may cause some patients to apply the paste around the perineum rather than inside the anal canal, in turn resulting in decreased effectiveness. Indeed, patients need to be given clear, detailed instructions regarding the application of topical CCB and need to be warned against the potential adverse events associated with oral therapy.

Our study has several limitations. Firstly there were only four trials identified with a relatively small number of patients even when pooled altogether. Secondly, the overall quality of the included studies was low; no power calculation was performed in any of them and most of them had inherent biases. Thirdly, differing CCB agents and strengths were employed across studies, which impairs the generalisability of the observations.

In conclusion, despite the aforementioned weaknesses, and the dearth of well-executed RCT's on this topic, the current meta-analysis provides a systematic assessment of the efficacy of oral versus topical CCB in the management of CAF. Combined, these data demonstrate that topical CCB is associated with improved healing and a superior side effect profile, but similar recurrence rates compared to oral CCB. Further trials evaluating head-to-head comparisons of oral and topical nifedipine as well as diltiazem with adequate sample sizes and follow up are needed to definitively answer this important clinical question.

## Conflicts of interests

None to declare.

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This research received no specific funding.

## Author contributions

Conceived and designed experiments: SMS, KA, SRW, RC, AI, MRJ.
Performed the experiments: SMS, KA, RC, SRW, AI.
Analysed the data: SMS, KA, RC, SRW.
Wrote the manuscript: SMS, KA, SRW, RC, AI, MRJ.

## Category

Systematic review and meta-analysis.

## Ethical approval

N/A.

## Research registration unique identifying number (UIN)

Research Registry UIN 262.

## Guarantor

Shaheel M Sahebally.
Stewart Walsh.
Myles Joyce.

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