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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