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Topical corticosteroids for treating phimosis in boys (Review)

Moreno G, Corbalán J, Peñaloza B, Pantoja T

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[Intervention Review]

Topical corticosteroids for treating phimosis in boys

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ABSTRACT

Background

Until recently, phimosis has been treated surgically by circumcision or prepuceplasty; however, recent reports of non-invasive treatment using topical corticosteroids applied for four to eight weeks have been favourable. The efficacy and safety of topical corticosteroids for treating phimosis in boys has not been previously systematically reviewed.

Objectives

We aimed to 1) compare the effectiveness of the use of topical corticosteroid ointment applied to the distal stenotic portion of the prepuce in the resolution of phimosis in boys compared with the use of placebo or no treatment, and 2) determine the rate of partial resolution (improvement) of phimosis, rate of re-stenosis after initial resolution or improvement of phimosis, and the rate of adverse events of topical corticosteroid treatment in boys with phimosis.

Search methods

We searched the Cochrane Renal Group's Specialised Register through contact with the Trials' Search Co-ordinator using search terms relevant to this review. Date of last search: 16 June 2014.

Selection criteria

We included all randomised controlled trials (RCTs) that compared use of any topical corticosteroid ointment with placebo ointment or no treatment for boys with phimosis.

Data collection and analysis

Two authors independently assessed titles, abstracts and the full-text of eligible studies, extracted data relating to the review's primary and secondary outcomes, and assessed studies' risk of bias. Statistical analyses were performed using the random-effects model and results were expressed as risk ratios (RR) for dichotomous outcomes with 95% confidence intervals (CI). We contacted authors of primary articles asking for details of study design and specific outcome data.

Main results

We included 12 studies that enrolled 1395 boys in this review. We found that both types of corticosteroids investigated and treatment duration varied among studies.

Compared with placebo, corticosteroids significantly increased complete or partial clinical resolution of phimosis (12 studies, 1395 participants: RR 2.45, 95% CI 1.84 to 3.26). Our analysis of studies that compared different types of corticosteroids found that these therapies also significantly increased complete clinical resolution of phimosis (8 studies, 858 participants: RR 3.42, 95% CI 2.08 to 5.62). Although nine studies (978 participants) reported that assessment of adverse effects were planned in the study design, these outcomes were not reported.

Overall, we found that inadequate reporting made assessing risk of bias challenging in many of the included studies.Selection bias, performance and detection bias was unclear in the majority of the included studies: two studies had adequate sequence generation, none reported allocation concealment; two studies had adequate blinding of participants and personnel and one had high risk of bias; one study blinded outcome assessors. Attrition bias was low in 8/12 studies and reporting bias was unclear in 11 studies and high in one study.

Authors' conclusions

Topical corticosteroids offer an effective alternative for treating phimosis in boys. Although sub optimal reporting among the included studies meant that the size of the effect remains uncertain, corticosteroids appear to be a safe, less invasive first-line treatment option before undertaking surgery to correct phimosis in boys.

PLAIN LANGUAGE SUMMARY

Topical corticosteroids for treating phimosis in boys

Phimosis is a condition where the foreskin cannot be fully drawn back (retracted) over the penis. Phimosis is normal at birth and often self-corrects without needing treatment during the first three to four years of life; only 10% of three year old boys have phimosis. This is known as congenital phimosis. Phimosis can also be caused by scarring of the skin protecting the head of the penis that is caused when the foreskin cannot be retracted. Phimosis caused by scarring is estimated to occur among 0.6% to 1.5% of boys less than 18 years of age, but this type of phimosis seldom occurs among boys under five years of age. Making a distinction between types of phimosis can sometimes be difficult.

Treatment for boys with phimosis has become controversial. Operations to remove or widen the foreskin (circumcision and prepuce plasty) have been widely used in the past to treat phimosis. More recently, creams and ointments containing corticosteroids (drugs that reduce inflammation limit or stop immune system activity) that are applied for four to eight weeks have shown promising results. The aim of topical corticosteroid treatment is to reduce skin tightening around the tip of the penis. This offers a much less invasive form of treatment and may limit the need for surgery among some boys.

We assessed the effects of topical corticosteroids to treat phimosis in boys aged up to 18 years compared with non-active treatment (placebo) or no treatment at all. We analysed 12 studies that included 1395 boys aged between 18 days and 17 years, and although we found that topical corticosteroids may increase the likelihood of full or partial resolution of phimosis without significant adverse effects, many studies did not report adverse events.

Topical corticosteroids may be a safe alternative to treat phimosis in boys before undergoing surgical treatment.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Topical corticosteroids compared with placebo for phimosis in children

Patient or population: children 0 to 18 years with phimosis
Settings: ambulatory care
Intervention: topical corticosteroids (creams/ointments)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Steroids				
Resolution of phimosis (complete or partial) 4 to 8 weeks	**343 per 1000**	**840 per 1000** (631 to 1000)	**RR 2.45** (1.84 to 3.26)	1395 (12)	⊕⊕◯◯ **low**	Quality of evidence limited by serious study limitations and inconsistency
Complete resolution of phimosis 4 to 8 weeks	**183 per 1000**	**626 per 1000** (381 to 1000)	**RR 3.42** (2.08 to 5.62)	858 (8)	⊕⊕◯◯ **low**	Quality of evidence limited by serious study limitations and inconsistency
Adverse effects (any) 4 to 8 weeks	**0 per 1000**	**0 per 1000** (0 to 0)	**RR 0.0** (0.0 to 0.0)	978 (9)	⊕⊕◯◯ **low**	Quality of evidence limited by serious study limitations and imprecision
Re-stenosis 6 months	**133 per 1000**	**199 per 1000** (38 to 1000)	**RR 1.50** (0.29 to 7.73)	30 (1)	⊕◯◯◯ **very low**	Quality of evidence limited by serious study limitations, imprecision and possible publication bias

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Assumed risks were computed as the median control group risk across studies

BACKGROUND

Description of the condition

Phimosis is defined as a tight distal preputial ring that makes manual retraction of the prepuce behind the balano-preputial sulcus to expose the glans difficult or impossible. Phimosis creates major concerns for parents and is responsible for significant numbers of consultations, referrals to paediatric surgeons, and circumcisions (Huntley 2003; Rickwood 2000; Spilsbury 2003).

Phimosis in boys is a physiological condition frequently present at birth but which often resolves during the first three to four years of life. It has been estimated that 96% of all newborns have phimosis, but this estimate falls to 50% by babies' first birthday. By three years of age, It is further estimated that 10% of three year old boys have phimosis; falling to 6% to 8% among seven year olds; and 1% among 16 year olds (Gairdner 1949; Oster 1968). These data indicate that in most cases the natural history of physiological phimosis trends towards spontaneous resolution and only a small number of boys will continue into adulthood with phimosis.

The diagnosis of physiological phimosis can be made when phimosis is present from birth (congenital phimosis) and there is a normal appearance of preputial skin. Pathological phimosis has been defined as failure to retract the foreskin due to distal scarring of the prepuce (McGregor 2007; Rickwood 1999; Shankar 1999). At physical examination scarring can be seen as a contracted white, indurated, fibrous ring around the preputial orifice. Scarring of the prepuce can be secondary to balanitis xerotica obliterans, a chronic, progressive inflammatory disease of the skin of unknown aetiology, recurrent episodes of balanoposthitis, or forceful retraction of the prepuce. The cumulative incidence of pathological phimosis in boys aged up to 18 years has been estimated to be 0.6% to 1.5%, and rarely occurs under the age of five (Rickwood 1999). Studies reporting histological diagnosis of circumcised prepuces in boys (Jasaitiene 2008; Kiss 2005; Yardley 2007) have reported an incidence of 34% to 40% of balanitis xerotica obliterans. The incidence of balanitis xerotica obliterans was higher in older children (over 9 years) and in acquired phimosis (phimosis developed after a period of normal retraction of foreskin). In boys with suspected balanitis xerotica obliterans on clinical examination 89% had histological confirmation of the diagnosis and of those with histological diagnosis of balanitis xerotica obliterans 47% had non pathological phimosis on clinical examination (Yardley 2007). However, balanitis xerotica obliterans still represents a highly selected and infrequent group among children with phimosis seen in ambulatory/primary care settings.

Phimosis must also be differentiated from balano-preputial adhesions. In phimosis unretractability of the prepuce over the glans is due to a stenotic distal portion of the prepuce. In small children, the foreskin may not be fully retractable because of inner preputial adhesions to the glans. Balano-preputial adhesions correspond to persistent areas of embryologic fusion of the glans, with the inner preputial epithelium that are still normally seen in most boys at the age of six and in 3% of children at 15 years, but none at 18 years of age (Oster 1968). As a normal condition not associated to complications, it requires no treatment.

Despite of the theoretical distinction between physiological and pathological phimosis, sometimes it is difficult to make this distinction in clinical practice and some of the boys labelled clinically as with physiological phimosis could have balanitis xerotica obliterans when they are circumcised and their prepuces are histologically examined.

Additionally, indications for treating phimosis are controversial. Most authors would agree that asymptomatic physiological phimosis should be left untreated waiting for its spontaneous resolution until puberty, and only true pathological phimosis should be treated. However, recurrent episodes of balanoposthitis, paraphimosis, and urinary tract infections (UTIs) are considered by many as indications for treatment of physiological phimosis at an earlier age.

In the past the only alternative for treating phimosis was surgical resolution by circumcision, and more recently, by prepuce plasty. In the last two decades conservative treatments for phimosis with topical corticosteroids applied to the stenotic distal portion of the prepuce for four to eight weeks have been published with high rates of resolution. Three cost-effectiveness studies based on randomised and non-randomised studies have recommended the initial treatment of phimosis with topical corticosteroids before any surgical intervention (Berdeu 2001; Nobre 2010; Van Howe 1998).

Description of the intervention

Topical corticosteroids of different potency and at different concentrations have been used in the treatment of physiological and pathological phimosis. Corticosteroids are applied as an ointment to the stenotic distal portion of the prepuce, sometimes associated with gentle manual retraction of the foreskin. Most studies use corticoids for four to eight weeks and encourage patients to continue retracting their foreskin and to maintain an adequate hygiene after completing treatment.

How the intervention might work

Corticosteroids may act by two mechanisms in the resolution of phimosis 1) anti-inflammatory action, and 2) immunosuppressive effects (Kikiros 1993; Marques 2005; Shankar 1999; Zampieri 2007).

1. Through the stimulation of lipocortin production it inhibits phospholipase A2, thus reducing the production of arachidonic acid, precursor of prostaglandins and leukotrienes, mediators of skin inflammation. Corticosteroids are known to reduce early manifestations of inflammation (oedema, fibrin deposition,

capillary dilatation, migration of leucocytes and phagocyte activity), and late manifestations (proliferation of capillaries and fibroblasts, depletion of collagen and cicatrisation).

2. By inhibiting collagen synthesis by fibroblasts and its antiproliferative effects on the epidermis, corticosteroids produce skin thinning and increase skin elasticity.

Histologic studies have shown that most prepuces circumcised in boys with phimosis have balanitis xerotica obliterans or nonspecific chronic inflammation (Jasaitiene 2008; Kiss 2005; Shankar 1999; Yardley 2007). In the younger age groups chronic inflammation was the predominant finding, and balanitis xerotica obliterans was most common in boys older than 16 years (Yardley 2007). In a randomised controlled trial (RCT), Kiss 2001 studied the response of balanitis xerotica obliterans to the local application of 0.05% mometasone ointment, all children were circumcised at the end of the study. Only those with early or intermediate forms of balanitis xerotica obliterans responded to corticosteroid treatment and none in the late form, suggesting that local steroids are effective when inflammation mechanisms are active and no irreversible tissue damage has occurred.

Why it is important to do this review

Despite the controversy about the appropriate medical indications for the treatment of phimosis in boys (Farshi 2000; McGregor 2007; Rickwood 1999) a large number of boys are still being circumcised for phimosis (Cathcart 2006; Rickwood 2000; Spilsbury 2003). Education of physicians and parents about the natural history of physiological phimosis and the recognition of pathological phimosis is mandatory in order to reduce unnecessary interventions in boys with the condition.

If we consider the only absolute indication of circumcision (pathological phimosis affecting up to 1.5% of boys), and one of the most common relative indications (recurrent balanoposthitis that affects up to 1% of boys), a number as high as 2.5% of boys less than 18 years could require circumcision (Rickwood 1999). This poses an important burden to any health system (Berdeu 2001; Nobre 2010; Van Howe 1998).

Surgery for phimosis has associated risks. Studies report between 0.1% to 3.5% rate of complications that include haemorrhage, stenotic meatitis, meatitis, meatal ulceration, postoperative local infections, anaesthesia-related adverse events as well as the psychological stress for children and their parents (Cathcart 2006).

In this scenario a conservative treatment with different types of topical corticosteroids for the initial treatment of phimosis in boys appears as an interesting alternative. Despite a growing number of publications about the use of topical corticosteroids for phimosis and some cost-effectiveness studies, there are no systematic reviews of RCTs that evaluate the effectiveness of topical corticosteroids in its treatment in children.

OBJECTIVES

1. To compare the effectiveness of the use of topical corticosteroid ointment applied to the distal stenotic portion of the prepuce in the resolution of phimosis in boys compared with the use of placebo or no treatment.

2. To determine the rate of partial resolution (improvement) of phimosis, rate of re-stenosis after initial resolution or improvement of phimosis, and the rate of adverse events of topical corticosteroid treatment in boys with phimosis.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) comparing the use of any topical corticosteroid ointment with placebo ointment or no treatment in boys with phimosis were included.

Types of participants

Children from birth to 18 years, with any degree of physician diagnosed phimosis (physiological or pathological) in which active treatment of their phimosis is being considered. Phimosis may or may not be described in terms of degree of retractability, as pathological or physiological, as acquired or congenital.

Studies that include boys with non-retractable prepuce due to balano-preputial adhesions without a phimotic ring or boys with previous treatments for phimosis, such as, circumcision, prepuce plasty, topical corticosteroids or other topical medication, will be excluded.

Types of interventions

The use of any type or concentration of a topical corticosteroid ointment applied to the stenotic distal portion of the prepuce, used for varying periods of time compared to placebo, with or without gentle manual retraction of the foreskin. Manual retraction of the foreskin was considered as an active treatment and will be treated as a co-intervention that should be applied to both intervention and control groups in a similar way.

Types of outcome measures

Primary outcomes

The primary outcome sought was resolution of phimosis following treatment. Resolution was defined as a retractable prepuce with exposure of the glans without any visible narrowing. Unretractability of the prepuce due only to balano-preputial adhesions in the absence of a phimotic ring was not considered to be failure.

Secondary outcomes

- Partial resolution or improvement in preputial retractability scores
- Re-stenosis of the prepuce after an initial resolution or improvement of phimosis, and
- Local or systemic adverse effects (irritation, local infection, skin damage, Cushing Syndrome) associated with the use of topical corticosteroids in the prepuce.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group's specialised register to 12 June 2014 through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the specialised register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the specialised register section of information about the Cochrane Renal Group. See Appendix 1 for search terms used in strategies for this review.

Searching other resources

We also searched reference lists of review articles, relevant studies and clinical practice guidelines. Study authors known to be involved in previous studies were contacted to seek information about unpublished or incomplete studies. There were no language restrictions.

Data collection and analysis

Selection of studies

Titles and abstracts of retrieved articles were screened independently by two authors, and full-text copies of the potentially eligible articles were assessed against our predefined inclusion and exclusion criteria by two authors. Discrepancies were resolved by consensus between the two authors involved and if no consensus is reached a third author (arbitrator) was contacted.

The search strategy described was used to obtain titles and abstracts of studies relevant to the review. Titles and abstracts were screened independently by two authors. Two authors independently assessed retrieved abstracts, and where necessary the full text of studies, to identify those that met our inclusion criteria.

Data extraction and management

Data extraction was conducted independently by two authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, reports were grouped together, and the publication with the most complete data was analysed.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
    - Participants and personnel
    - Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (such as complete or partial remission) results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (such as preputial retractability

scores), the mean difference (MD) was used, or the standardised mean difference (SMD) where different scales were used.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I² test (Higgins 2003). I² values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

Although we had planned to construct funnel plots to assess potential for small study effects, such as publication bias, there were insufficient studies included to enable assessment.

Data synthesis

A pooled effect measure for each outcome in the main (and only) comparison was obtained using a random-effects model. We used this model because of the expected clinical heterogeneity regarding population (e.g. age range), interventions (type of corticosteroid and duration of treatment) and outcomes (different measurement scales).

Subgroup analysis and investigation of heterogeneity

Plausible explanations for variations in treatment effects (heterogeneity) were explored using subgroup analysis based on the risk of bias criteria, study population (age, severity of phimosis, physiological versus pathological phimosis) and intervention (type of corticosteroids, use of manual retraction of the prepuce, duration of treatment).

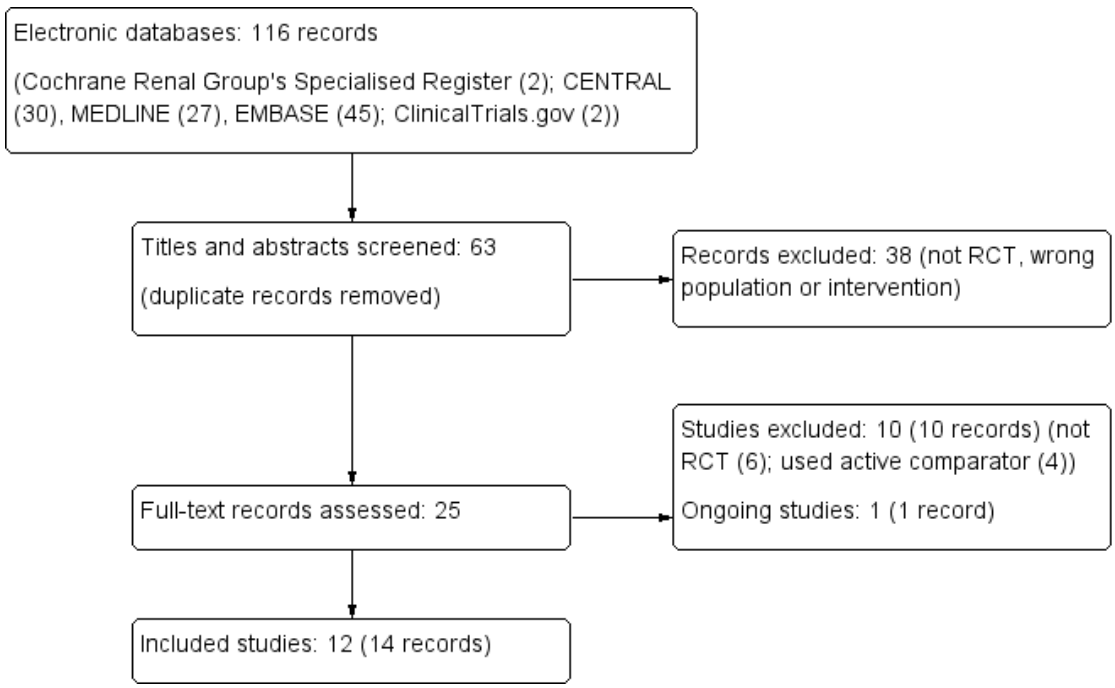
RESULTS

Description of studies

Results of the search

The literature search identified 116 articles and after initial duplicate removal (53), 38 were excluded after assessment of the title and abstract. The major reasons for exclusion at this stage were a non-related intervention, non-randomised design, and duplicate records. Full-text assessment of the 24 potentially eligible reports identified 12 eligible studies (14 reports) enrolling 1395 patients (Figure 1).

Figure 1. Study flow diagram



Included studies

The characteristics of the populations and interventions of the 12 studies included in this systematic review are detailed in Characteristics of included studies.

The studies were carried out in nine countries (Turkey (2), Hong Kong (2), Brazil (2), Italy (1), Yugoslavia (1), Hungary (1), South Korea (1), Canada (1), Sweden (1)) and included children aged from 18 days to 17 years.

The corticosteroids used in the intervention groups were betamethasone (Chao 2006; Golubovic 1996; Lund 2005; Nascimento 2011; Yilmaz 2003a), mometasone furoate (Esposito 20083; Kiss 2001; Pileggi 2007), beclomethasone dipropionate (Balamtekin 2006), hydrocortisone butyrate (Lee 2006a), triamcinolone (Letendre 2009), and clobetasol propionate (Lindhagen 1996). The duration of treatment was variable. The duration of treatment was four weeks on six studies (Esposito 2008; Golubovic 1996; Lee 2006a; Lindhagen 1996; Lund 2005; Yilmaz 2003a), five weeks in one study (Kiss 2001), six weeks in one study (Balamtekin 2006), and eight weeks in four studies (Chao 2006; Letendre 2009; Nascimento 2011; Pileggi 2007). Most of the studies used an aqueous cream (Chao 2006; Esposito 2008; Kiss 2001; Letendre 2009; Lindhagen 1996; Lund 2005; Nascimento 2011; Pileggi 2007) or vaseline (Golubovic 1996; Lee 2006a; Yilmaz 2003a) as the control group; one study used manual retraction (Balamtekin 2006). Most studies used manual retraction of the foreskin as a co-intervention in both the intervention and the control groups (Chao 2006; Golubovic 1996; Kiss 2001; Lee 2006a, Letendre 2009, Lindhagen 1996, Lund 2005, Nascimento 2011; Pileggi 2007, Yilmaz 2003a). One study did not use manual retraction at all (Esposito 2008).

Four studies (Lee 2006a; Lindhagen 1996; Lund 2005; Yilmaz 2003a) measured their primary outcome at four weeks, one at five weeks (Kiss 2001), one at six weeks (Balamtekin 2006), three at eight weeks (Letendre 2009; Nascimento 2011; Pileggi 2007), and one at nine weeks (Chao 2006). Two studies (Esposito 2008, Golubovic 1996) measured their outcomes on a longer timescale (average of 20 and 10.5 months respectively).

Excluded studies

Ten studies (10 reports) were excluded from this review because they were either not a RCT or they used an active comparison group. The specific reasons for exclusion are detailed in Characteristics of excluded studies.

Ongoing studies

We identified one potentially eligible study currently recruiting patients (see Characteristics of ongoing studies).

Risk of bias in included studies

In most of the studies it was difficult to make an informed judgement about the risk of bias because of a lack of information in their reports (Figure 2; Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias (methodological quality) item presented as percentages across all included studies

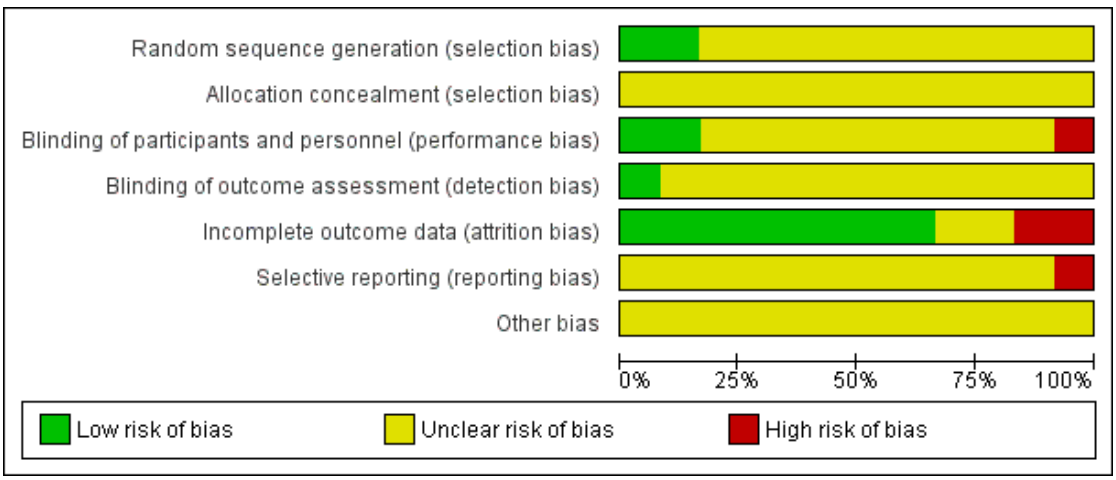
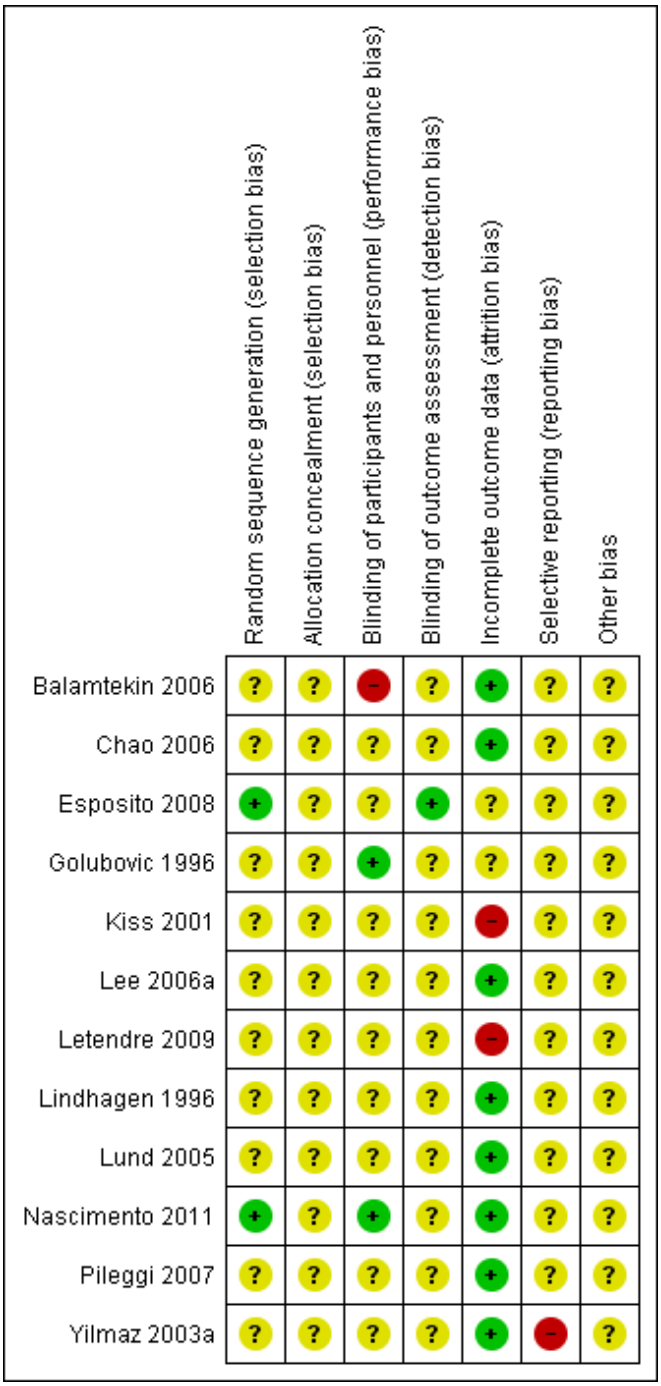


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Sequence generation

A random sequence generation was clearly reported in only two studies (Esposito 2008; Nascimento 2011) and unclear in the remaining studies.

Allocation concealment

Allocation concealment was unclear in all the included studies.

Blinding

Blinding of participants and personnel

The blinding of these groups was assessed as inadequate in one study (Balamtekin 2006) because of the lack of placebo use in the control group, and as adequate in two studies (Golubovic 1996; Nascimento 2011). It was unclear in the remaining studies.

Blinding of outcome assessment

The blinding of outcome assessment was adequate in only one study (Esposito 2008) and unclear in the remaining studies.

Incomplete outcome data

There was a low risk of bias in eight studies (Balamtekin 2006; Chao 2006; Lee 2006a; Lindhagen 1996; Lund 2005; Nascimento 2011; Pileggi 2007; Yilmaz 2003a), because there were minimal losses to follow-up or they were clearly explained. In two studies (Kiss 2001; Letendre 2009) we assessed the risk of bias as high because there was not a clear explanation of the patients lost to follow-up and how they could potentially affect the effects of the intervention. In the other two studies (Esposito 2008; Golubovic 1996) there was not enough information to make a definitive assessment.

Selective reporting

With the exception of Yilmaz 2003a, the risk of selective reporting was unclear because of a lack of detailed information. Yilmaz 2003a planned to measure outcomes at three different timelines and reported only two without a clear justification.

Other potential sources of bias

The visual examination of the funnel plot corresponding to the meta-analysis of the primary outcome (Analysis 1.1) showed some asymmetry with small studies showing no beneficial effects "missed". A statistical test for funnel plot asymmetry was not carried out because of the limited number of studies and the similarities among standard errors of the intervention effect estimates in the studies (Sterne 2011). Even when this could suggest publication bias, heterogeneity (probable), poor methodological design or both of the included studies could also explain that asymmetry.

Effects of interventions

See: **Summary of findings for the main comparison**

Corticosteroids versus placebo

Compared with placebo corticosteroids significantly increased complete or partial clinical resolution of phimosis (Analysis 1.1 (12 studies, 1395 patients): RR 2.45, 95% CI 1.84 to 3.26). Likewise, corticosteroids significantly increased complete clinical resolution of phimosis (Analysis 1.2 (8 studies, 858 patients): RR 3.42, 95% CI 2.08 to 5.62). As expected, both analyses presented significant heterogeneity (79% and 78% respectively).

We were only able to undertake subgroup analyses for two of the 'a priori' specified variables (type of corticosteroid used in the intervention group, and duration of treatment) because they were clearly reported in the studies. For the other variables (age, severity of phimosis, physiological versus pathological phimosis) it was not possible to extract reliable information at the study level or there was not possible to establish subgroups because they were absent in most of the studies (use of manual retraction of the prepuce as a co-intervention, and risk of bias). Additionally, we use study size (above or below the median study size) as a proxy of risk of bias in a post-hoc subgroup analysis. We used the outcome 'clinical resolution of phimosis' as the primary outcome in those subgroups analyses because there was a sufficient number of studies available for each category. The subgroups of studies using corticosteroids of high potency - such as clobetasol (Lindhagen 1996) and betamethasone (Chao 2006; Golubovic 1996; Lund 2005; Nascimento 2011; Yilmaz 2003a) - did not show significant differences in the magnitude of effect compared with those studies using corticosteroids of low-medium potency (RR 2.27 and 2.66 respectively, Test for subgroup differences: $Chi^2 = 0.28$, df = 1, P = 0.60, $I^2 = 0\%$). The subgroup of studies where the duration of treatment was four or five weeks (Chao 2006; Esposito 2008; Golubovic 1996; Kiss 2001; Lee 2006a; Lindhagen 1996; Lund 2005; Yilmaz 2003a) showed a bigger magnitude of effect than that in the subgroup of studies where the duration of treatment

was six or eight weeks (RR 3.14 and 1.82 respectively; test for subgroup differences: Chi² = 4.13, df = 1, P = 0.04, I² = 76%). Finally, there was no significant differences in the effect sizes of studies with a number of participants below or above the median of study size (RR 2.26 and 2.76 respectively; test for subgroup differences: Chi² = 0.46, df = 1, P = 0.50, I² = 0%).

Lindhagen 1996 reported no statistically significant difference in the risk of re-stenosis (Analysis 1.3 (1 study, 30 participants): RR 1.5, 95% CI 0.29 to 7.73), however this study was underpowered to detect any difference in this outcome.

Nine studies (978 patients) reported the assessment of adverse effects but none reported any patient experiencing any event (Analysis 1.4) (Balamtekin 2006, Chao 2006, Esposito 2008, Golubovic 1996, Kiss 2001, Lee 2006a; Letendre 2009; Lindhagen 1996; Lund 2005). In Nascimento 2011 it was not clear which group the three patients reporting minor complications were in.

DISCUSSION

Summary of main results

Topical corticosteroids compared with placebo significantly increased complete or partial clinical resolution of phimosis in boys. Despite the magnitude of the effect - both in absolute and relative terms - it should be viewed with caution because of the high heterogeneity and a number of limitations in the available studies (Summary of findings for the main comparison).

Overall completeness and applicability of evidence

Even when the included studies were carried out in children at different ages (infants, toddlers and adolescents), with different types and degrees of phimosis, and using corticosteroids of different potencies, adverse effects such as re-stenosis were reported in only one study and other adverse outcomes did not occur at all. This makes any judgment difficult about the potential negative effects of the intervention. Taking into account that the studies assessed included a range of relevant types of participants and a range of interventions, the evidence summarised in this review is broadly applicable to different settings both in high- and low-middle income countries.

However, the available evidence did not allow us to explore in a comprehensive way the heterogeneity found in the effect estimates. We were only able to run some of the planned subgroup analyses due to limitations in the reporting and the number of available studies. It was not possible to assess definitively if specific subgroups of participants (e.g. physiological versus pathological phimosis) could obtain benefits beyond the average across studies.

Quality of the evidence

Assessment of risk of bias was uncertain for most of the included studies because of a lack of relevant information in their reports. Even though the included studies were reported to be randomised, in most cases it was not possible to clearly ascertain that an appropriate randomised sequence had been generated and none reported explicitly an allocation concealment procedure. Likewise, blinding of participants, personnel and outcomes assessors were not clearly reported in most of the studies (Figure 2). Secondly, there was important heterogeneity across effect estimators for the primary outcomes in the included studies that could not be clearly explained by the subgroup analyses performed. One of these analyses was counterintuitive, showing that those studies with longer duration of treatment (six to eight weeks) had a smaller effect size than those of shorter duration (four to five weeks). However, this finding could be confounded by the potency of the corticosteroid used in the longer duration studies (Balamtekin 2006; Letendre 2009; Pileggi 2007). Additionally, any of these analyses should be viewed with caution because there were an insufficient number of studies to achieve reliable conclusions about the effects of corticosteroids in the subgroups analysed (Sun 2010). Furthermore, it was not possible to carry out other predefined subgroup analyses because of the paucity of data for the independent variables at study level. Thirdly, publication bias could not be excluded given funnel plot asymmetry in the analysis of the primary outcome (Analysis 1.1). However, such asymmetry could be explained by a number of other factors (Sterne 2011), considering only 12 studies were available and the heterogeneity observed for this outcome. This warrants the need for further exploration of this issue once more and better reported studies become available. Finally, it was not possible to make any judgment about adverse effects because there was none, even when nine of the studies reported their measurement. Therefore any risk related to the intervention is extremely imprecise.

The findings of this review should be interpreted with caution because of the limitations related to the quality of reporting of primary studies (and their uncertain risk of bias); the unexplained heterogeneity of the effect estimators for both main outcomes; the lack of data to produce an estimator of the risks (adverse events) associated with the intervention; and the potential risk of publication bias in the body of evidence found in the review. Therefore the quality of the evidence for the outcomes reported in this review was low, meaning that our confidence in the summary estimates is limited (Summary of findings for the main comparison).

Potential biases in the review process

There were two main limitations in the conduct of this review that could affect its findings: doubts about the comprehensiveness of our search strategy and limitations in the risk of bias assessment of the included studies. Although the search strategy tried to be comprehensive including published and unpublished studies, and without language restrictions, there was some evidence of publication bias (funnel plot asymmetry) that should be further explored. Even when we tried to contact some authors in order to obtain more details about their studies and their knowledge of additional studies, the response rate was limited (only one author answered and his studies were excluded) (Zampieri 2005; Zampieri 2007). Regarding the risk of bias assessments, they were particularly difficult in this case because of the low quality reporting of the included studies. This gives less weight to the judgments concerning the various criteria and makes their assessment less reliable.

Agreements and disagreements with other studies or reviews

The evidence summarised here agrees with a number of reviews carried out during the last decade. The conclusion from this literature using both narrative (Bréaud 2005; Miguelez 2006) and more systematic methods (Vorilhon 2011) and including different study designs or only RCTs is overwhelmingly in favour of the use of topical corticosteroids as the first-line of treatment in both physiological and pathological persistent phimosis. Most of the studies included in those reviews were also included in our review. Likewise, economic analyses have shown that topical corticosteroids are the primary alternative compared with surgery for the treatment of most cases of phimosis in children (Berdeu 2001; Nobre 2010; Van Howe 1998).

AUTHORS' CONCLUSIONS

Implications for practice

Topical corticosteroids are a feasible and effective alternative for the treatment of phimosis in children. Even when we had some uncertainties about the confidence we could place on the size of the effect, they seem to be a safe alternative that could be used previous to the surgical treatment of phimosis.

Implications for research

Taking into account the risk of publication bias, a more comprehensive search could be done focusing on the grey literature and the contact with the studies' authors and other key informants in the specialty. If new studies are planned to be conducted in this area, they should follow sound reporting standards such as those promoted by CONSORT (Schulz 2010). In order to explore in a more comprehensive way different effect modifiers more methodologically sound studies should be carried out. This could potentially allow for the use of meta-regression to better investigate and explain the heterogeneity in the summary estimates found in our review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Balamtekin 2006

Methods	• Study design: parallel RCT • Study duration: 21 months (January 2003 to September 2004) • Study follow-up: 6 weeks
Participants	• Country: Turkey • Setting: Urology clinic • Severity of phimosis: Kikiro's grade 3 • Number: treatment group (36); control group (17) • Age range: 2 to 8 years • Exclusion criteria: not reported

Interventions	Treatment group
	• Beclomethasone dipropionate 0.05%
	  ○ Frequency: twice daily
	  ○ Duration: 6 weeks
	Control group
	• Manual retraction
	Co-interventions
	• Not stated

Outcomes	• Complete or partial resolution of phimosis (6 weeks) • Partial resolution of phimosis (6 weeks)
Notes	• Funding source: not reported • Contact with study authors for additional information: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomised allocation' mentioned but sequence generation methodology was not explicit
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo in the comparison group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Balamtekin 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Chao 2006

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: to 25 weeks
Participants	• Country: Hong Kong • Setting: single centre • Severity of phimosis: > Kikiro's grade 2 • Number: treatment group (149); control group (151) • Mean age (range): 6.88 years (3 to 17) • Exclusion criteria: not reported

Interventions	Treatment group
	• Betamethasone 0.1%
	  ○ Frequency: twice daily
	  ○ Duration: at least 8 weeks
	Control group
	• Aqueous cream
	  ○ Frequency: twice daily
	  ○ Duration: 4 weeks
	• Betamethasone 0.1%
	  ○ Frequency: twice daily
	  ○ Duration: from week 5 for 4 weeks
	Co-interventions
	• Retraction of the prepuce (both treatment and control groups)

Outcomes	• Partial resolution of phimosis (9 weeks)
Notes	• Conference abstract only • Funding source: not reported • Contact with study authors for additional information: no

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Chao 2006 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	The method used to generate the sequence is not clear. Authors mentioned that 'patients underwent double-blind randomization'
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported as 'double-blind' only
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Reported as 'double-blind' only
Incomplete outcome data (attrition bias) All outcomes	Low risk	129/149 (86.5%) treatment group participants completed treatment. 128/151 (84.7%) control group participants completed treatment. Losses to follow-up not reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Esposito 2008

Methods	• Study design: parallel block RCT (30 patients/block) • Study duration: 24 months (June 2003 to May 2005) • Study follow-up: 6 to 30 months
Participants	• Country: Italy • Setting: outpatient centre • Severity of phimosis: grades III to V (scale from I to V) • Number: treatment group (120); control group (120) • Age range: 3 to 13 years • Exclusion criteria: partial exposure of the glans; previous operation of the penis; prior use of steroid treatment for the same pathology; recurrent episodes of balanoposthitis

Interventions	Treatment group
	• Mometasone furoate 0.1%
	  ○ Frequency: twice daily
	  ○ Duration: 4 weeks
	Control group
	• Placebo cream
	  ○ Frequency: twice daily

Esposito 2008 (*Continued*)

	○ Duration: 4 weeks Co-interventions • None
Outcomes	• Complete resolution of phimosis (6 to 30 months, mean 20 months)
Notes	• Funding source: not reported • Contact with study authors for additional information: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A total of 240 patients with phimosis, divided into 8 groups of 30 patients each using a computer randomised choice"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'The results were evaluated by two paediatric surgeons unaware of the type of treatment the patients had undergone'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Time of follow-up and losses are not clear, but "All the patients in our series completed the two treatment periods without interruption"
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Golubovic 1996

Methods	• Study design: parallel RCT • Study duration: 13 months (October 1994 to October 1995) • Study follow-up: 6 to 18 months
Participants	• Country: Yugoslavia • Setting: single centre • Severity of phimosis: not reported • Number: treatment group (20); control group (20)

Golubovic 1996 (*Continued*)

	• Age: 3 to 6 years • Exclusion criteria: not reported

Interventions	Treatment group
	• Betamethasone 0.05%
	  ○ Frequency: twice daily
	  ○ Duration: 4 weeks
	Control group
	• Vaseline
	  ○ Frequency: twice daily
	  ○ Duration: 4 weeks
	Co-interventions
	• Retraction of the prepuce (both treatment and control groups)

Outcomes	• Complete resolution of phimosis (mean follow-up 10.5 months)
Notes	• Funding source: not reported • Contact with study authors for additional information: no

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Two groups of 20 boys each were prospectively assessed in a double-blind, randomised trial'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Kiss 2001

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 5 weeks
Participants	• Country: Hungary • Setting: single centre • Severity of phimosis: balanitis xerotica obliterans • Number: 40 • Mean age (range): 8.9 years (3 to 15) • Exclusion criteria: not reported

Interventions	Treatment group
	• Mometasone furoate 0.05%
	  ○ Frequency: once daily
	  ○ Duration: 5 weeks
	Control group
	• Mometasone furoate vehicle
	  ○ Frequency: once daily
	  ○ Duration: 5 weeks
	Co-interventions
	• Retraction of the prepuce (both treatment and control groups)

Outcomes	• Partial retraction of the prepuce (Meuli scale) (5 weeks) • Improve score (Meuli scale) (5 weeks)
Notes	• Funding source: not reported • Contact with study authors for additional information: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	'In the steroid and placebo group 3 and 4 boys were withdrawn from the study, including 4 lost to follow-up and 3 in whom clinically suspected balanitis xerotica oblit-

Kiss 2001 (*Continued*)

		erans was not confirmed by histological evaluations'
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Lee 2006a

Methods	• Study design: parallel RCT • Study duration: 12 months (August 2002 to July 2003) • Study follow-up: 4 weeks
Participants	• Country: South Korea • Setting: Single centre • Severity of phimosis: not reported • Number: treatment group (39); control group (39) • Mean age ± SD (months): treatment group (5.2 ± 3.24); control group (6.1 ± 3.55) • Exclusion criteria: not reported

Interventions	Treatment group
	• Hydrocortisone butyrate 0.1%
	  ○ Frequency: twice daily
	  ○ Duration: 4 weeks
	Control group
	• Vaseline
	  ○ Frequency: twice daily
	  ○ Duration: 4 weeks
	Co-interventions
	• Retraction of the prepuce (both treatment and control groups)

Outcomes	• Complete resolution of phimosis (4 weeks) • Partial retraction of the prepuce (4 weeks) • Local and systemic adverse effects (4 weeks)
Notes	• Funding source: not reported • Contact with study authors for additional information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The study was presented as 'prospectively randomised' but there was no description of the randomisation procedure

Lee 2006a (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not explicitly mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not explicitly mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant lost to follow-up per group
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Letendre 2009

Methods	• Study design: parallel RCT • Study duration: 31 months (June 2005 to January 2008) • Study follow-up: 12 months
Participants	• Country: Canada • Setting: single centre • Severity of phimosis: grades III to VI (in a scale from I to VI) • Number: treatment group (29); control group (31) • Median age (range): 62 months (20 to 184) • Exclusion criteria: active balanitis, balanitis xerotica obliterans; previous topical steroid treatment; paraphimosis; lichen sclerosus; hypospadias

Interventions	Treatment group
	• Triamcinolone 0.1%
	  ○ Frequency: twice daily
	  ○ Duration: 8 weeks
	Control group
	• Emollient cream Aquatain
	  ○ Frequency: twice daily
	  ○ Duration: 8 weeks
	Co-interventions
	• Retraction of the prepuce (both treatment and control group)

Outcomes	• Complete or partial resolution of phimosis (8 weeks)
Notes	• Funding source: not reported • Contact with study authors for additional information: no

Letendre 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors reported that '59 patients were randomly assigned'. No details about randomisation procedure provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as 'double-blind'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as 'double-blind'
Incomplete outcome data (attrition bias) All outcomes	High risk	Authors reported 8/29 losses to follow-up from the treatment group and 6/31 in the control group
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Lindhagen 1996

Methods	• Study design: parallel RCT • Study duration: 13 months (April 1993 to April 1994) • Study follow-up: 6 months
Participants	• Country: Sweden • Setting: single centre • Severity of phimosis: not reported • Number: treatment group (15); control group (15) • Mean age (range): 7.5 years (5 to 12) • Exclusion criteria: not reported

Interventions	Treatment group
	• Clobetasol propionate 0.05%
	  ○ Frequency: once daily
	  ○ Duration: 4 weeks
	Control group
	• Placebo
	  ○ Frequency: once daily

Lindhagen 1996 (*Continued*)

	○ Duration: 4 weeks Co-interventions • Retraction of prepuce (both treatment and control group)
Outcomes	• Complete resolution of phimosis (4 weeks) • Re-stenosis (6 months) • Adverse effects (6 months)
Notes	• Funding source: not reported • Contact with study authors for additional information: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were randomised to receive a tube of ointment with or without clobetasol propionate 0.05%". There were no details about the randomisation procedure
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described only as 'double-blind'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described only as 'double-blind'
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant lost to follow-up per group for 'factors unrelated to the disorder or treatment'
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Lund 2005

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 8 weeks
Participants	• Country: Hong Kong • Setting: single centre • Severity of phimosis: grades 4 to 6 (in a scale from 1 to 6)

	• Number: treatment group (66); control group (71) • Mean age (range): 6.7 years (3 to 15) • Exclusion criteria: not reported
Interventions	Treatment group • Betamethasone 0.1% ○ Frequency: twice a day ○ Duration: 4 weeks Control group • Aqueous cream ○ Frequency: twice a day ○ Duration: 4 weeks Co-interventions • Retraction of the prepuce (both treatment and control groups)
Outcomes	• Complete resolution of phimosis (4 weeks) • Adverse effects (4 and 8 weeks)
Notes	• Funding source: not reported • Contact with study authors for additional information: no

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	There was no detailed information about the randomisation procedure 'the boys were randomised...'
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There was no detailed information. The study is described as 'double-blind'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was no detailed information. The study is described as 'double-blind'
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no losses to follow up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Nascimento 2011

Methods	• Study design: parallel RCT • Study duration: 15 months (August 2006 to November 2007) • Study follow-up: 60 to 180 days
Participants	• Country: Brazil • Setting: single centre • Severity of phimosis: types I to IV (on a scale from I (no retraction of prepuce) to V (easy exposure of whole glans)) • Number: treatment group 1 (54); treatment group 2 (51); treatment group 3 (52) ; control group (38) • Mean age (range): 5.1 years (3 to 10) • Exclusion criteria: not reported

Interventions	Treatment group 1
	• Betamethasone valerate 0.2% + hyaluronidase
	  ○ Frequency: twice daily
	  ○ Duration: 60 days (8 weeks)
	Treatment group 2
	• Betamethasone valerate 0.2%
	  ○ Frequency: twice daily
	  ○ Duration: 60 days (8 weeks)
	Treatment group 3
	• Betamethasone valerate 0.1%
	  ○ Frequency: twice daily
	  ○ Duration: 60 days (8 weeks)
	Control group
	• Placebo cream
	  ○ Frequency: twice daily
	  ○ Duration: 60 days (8 weeks)
	Co-intervention
	• Retraction of the prepuce (both treatment and control groups)

Outcomes	• Complete and partial resolution of phimosis (8 weeks) • Adverse effects (8 weeks) • Recurrence (8 weeks)
Notes	• Funding source: not reported • Contact with study authors for additional information: no

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were randomised to one of the four groups of intervention according to a computer-generated random choice determined by a research assistant..."
Allocation concealment (selection bias)	Unclear risk	Not reported

Nascimento 2011 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not explicit, but "The formulations were specifically designed for the study by the same pharmacy"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Data collection was performed by a third person based on patients' files" (where some information about treatment could be recorded)
Incomplete outcome data (attrition bias) All outcomes	Low risk	25 (11.4%) patients were not considered in the analysis, but reasons were explicit and distribution across treatment and control groups was similar
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Pileggi 2007

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up: 8 weeks
Participants	• Country: Brazil • Setting: single centre • Severity of phimosis: grade 5 according to Kikiros classification (absolutely no retraction possible) • Number: treatment group (63); control group (61) • Mean age (range): 4.6 years (2 to 13) • Exclusion criteria: not reported
Interventions	Treatment group • Mometasone furoate 0.1% ○ Frequency: twice daily ○ Duration: 8 weeks Control group • Moisturizing cream ○ Frequency: twice daily ○ Duration: 8 weeks Co-interventions • Retraction of the prepuce (both treatment and control groups)
Outcomes	• Complete resolution of phimosis (8 weeks) • Improved score

Pileggi 2007 (*Continued*)

Notes	• Funding source: not reported • Contact with study authors for additional information: no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No detailed description of blinding procedures. Described only as 'double blind'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed description of the blinding procedures. Described only as 'double blind'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up: 88.8% (56/63) in the treatment group and 88.5% (54/61) in the control group
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Yilmaz 2003a

Methods	• Study design: parallel RCT • Study duration: 31 months (December 1999 to June 2002) • Study follow-up: 2 months
Participants	• Country: Turkey • Setting: single centre • Severity of phimosis: patients classified into three groups that included the spectrum of severity • Number: treatment group 1 (51); treatment group 2 (50); control group (48) • Mean age (range): 4.47 years (3 to 6) • Exclusion criteria: not reported
Interventions	Treatment group 1 • Circumcision Treatment group 2 • Betamethasone 0.05%

Yilmaz 2003a (*Continued*)

	○ Frequency: twice daily ○ Duration: 1 month Control group • Vaseline ○ Frequency: twice daily ○ Duration: 1 month Co-interventions • Retraction of the prepuce (both treatment group 2 and control group)
Outcomes	• Complete resolution of phimosis (1 month)
Notes	• Treatment group 1 (circumcision) was not included in our meta-analyses • Funding source: not reported • Contact with study authors for additional information: no

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	High risk	Outcomes were measured at three time points; only two were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ceballos-Gonzalez 2006	Used an active (non-placebo) comparison
Chu 1999	Not RCT
Garcia de Freitas 2006	Used an active (non-placebo) comparison
Jung 2008	Not RCT
Kikiros 1993	Not RCT; compared corticosteroids with a non-placebo control
Nobre 2010	Compared corticosteroids with surgery (circumcision)
Sookpotarom 2013	Compared 2 formulations of betamethasone
Yang 2005	Used an active (non-placebo) comparison
Zampieri 2005	Not RCT
Zampieri 2007	Not RCT

Characteristics of ongoing studies *[ordered by study ID]*

NCT01108198

Trial name or title	Treatment of phimosis with topical steroid cream: double-blind, randomised, placebo-controlled study
Methods	Study design: parallel RCT Study duration: recruitment commenced October 2006; recruitment up to April 2010
Participants	Children aged 6 to 16 years Consecutive patients referred to paediatric surgery outpatient clinic for surgical treatment of non-retractable foreskin
Interventions	Mometasone furoate cream applied once daily for 4 to 8 weeks
Outcomes	Retractability of foreskin
Starting date	October 2006
Contact information	Johanna Rättyä Oulu University Hospital, Department of Children and Adolescents Oulu, Finland, 90029

NCT01108198 (*Continued*)

Notes	Information ClinicalTrials.gov has not been verified by the study investigators since April 2010; record in EU Clinical Trials database does not provide any further information

DATA AND ANALYSES

Comparison 1. Topical corticosteroids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution of phimosis (complete or partial)	12	1395	Risk Ratio (M-H, Random, 95% CI)	2.45 [1.84, 3.26]
2 Complete resolution of phimosis	8	858	Risk Ratio (M-H, Random, 95% CI)	3.42 [2.08, 5.62]
3 Re-stenosis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Adverse effects (any)	9	978	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Topical corticosteroids versus placebo, Outcome 1 Resolution of phimosis (complete or partial).

Review: Topical corticosteroids for treating phimosis in boys

Comparison: 1 Topical corticosteroids versus placebo

Outcome: 1 Resolution of phimosis (complete or partial)

Study or subgroup	Steroids n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Balamtekin 2006	30/36	6/17		7.7 %	2.36 [1.22, 4.57]
Chao 2006	114/149	76/151		12.4 %	1.52 [1.27, 1.82]
Esposito 2008	79/120	20/120		10.2 %	3.95 [2.59, 6.01]
Golubovic 1996	19/20	4/20		5.8 %	4.75 [1.97, 11.48]
Kiss 2001	7/20	0/20		1.0 %	15.00 [0.91, 246.20]
Lee 2006a	35/39	8/39		8.0 %	4.38 [2.34, 8.19]
Letendre 2009	19/29	12/31		9.2 %	1.69 [1.01, 2.83]
Lindhagen 1996	9/15	5/15		6.3 %	1.80 [0.79, 4.11]
Lund 2005	49/66	31/71		11.4 %	1.70 [1.26, 2.30]
Nascimento 2011	149/157	19/38		11.2 %	1.90 [1.38, 2.61]
Pileggi 2007	49/63	28/61		11.4 %	1.69 [1.25, 2.29]
Yilmaz 2003a	42/50	4/48		5.4 %	10.08 [3.91, 25.96]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Steroids n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total (95% CI)	**764**	**631**	◆	**100.0 %**	**2.45 [1.84, 3.26]**
Total events: 601 (Steroids), 213 (Control)					
Heterogeneity: Tau^2 = 0.16; Chi^2 = 51.27, df = 11 (P<0.00001); I^2 =79%					
Test for overall effect: Z = 6.13 (P < 0.00001)					
Test for subgroup differences: Not applicable					

0.002 0.1 1 10 500

Favours control Favours steroids

Analysis 1.2. Comparison 1 Topical corticosteroids versus placebo, Outcome 2 Complete resolution of phimosis.

Review: Topical corticosteroids for treating phimosis in boys

Comparison: 1 Topical corticosteroids versus placebo

Outcome: 2 Complete resolution of phimosis

Study or subgroup	Steroids n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Balamtekin 2006	21/36	1/17		4.9 %	9.92 [1.45, 67.73]
Esposito 2008	79/120	20/120		16.4 %	3.95 [2.59, 6.01]
Golubovic 1996	19/20	4/20		11.7 %	4.75 [1.97, 11.48]
Lee 2006a	23/39	4/39		10.9 %	5.75 [2.19, 15.09]
Lindhagen 1996	9/15	5/15		12.3 %	1.80 [0.79, 4.11]
Nascimento 2011	86/157	11/38		15.4 %	1.89 [1.13, 3.18]
Pileggi 2007	49/63	28/61		17.3 %	1.69 [1.25, 2.29]
Yilmaz 2003a	42/50	4/48		11.1 %	10.08 [3.91, 25.96]
Total (95% CI)	**500**	**358**	◆	**100.0 %**	**3.42 [2.08, 5.62]**
Total events: 328 (Steroids), 77 (Control)					
Heterogeneity: Tau^2 = 0.35; Chi^2 = 32.19, df = 7 (P = 0.00004); I^2 =78%					
Test for overall effect: Z = 4.84 (P < 0.00001)					
Test for subgroup differences: Not applicable					

0.01 0.1 1 10 100

Favours control Favours steroids

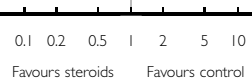
Analysis 1.3. Comparison 1 Topical corticosteroids versus placebo, Outcome 3 Re-stenosis.

Review: Topical corticosteroids for treating phimosis in boys

Comparison: 1 Topical corticosteroids versus placebo

Outcome: 3 Re-stenosis

Study or subgroup	Steroids n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Lindhagen 1996	3/15	2/15		1.50 [0.29, 7.73]



Analysis 1.4. Comparison 1 Topical corticosteroids versus placebo, Outcome 4 Adverse effects (any).

Review: Topical corticosteroids for treating phimosis in boys

Comparison: 1 Topical corticosteroids versus placebo

Outcome: 4 Adverse effects (any)

Study or subgroup	Steroids n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Balamtekin 2006	0/36	0/17			Not estimable
Chao 2006	0/149	0/151			Not estimable
Esposito 2008	0/120	0/120			Not estimable
Golubovic 1996	0/20	0/20			Not estimable
Kiss 2001	0/20	0/20			Not estimable
Lee 2006a	0/39	0/39			Not estimable
Letendre 2009	0/29	0/31			Not estimable
Lindhagen 1996	0/15	0/15			Not estimable
Lund 2005	0/66	0/71			Not estimable
Total (95% CI)	**494**	**484**			**Not estimable**
Total events: 0 (Steroids), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

APPENDICES

Appendix 1. Electronic search strategies

Database	Search strategy
CENTRAL	1. circumcision:ti,ab,kw 2. ph*mosis:ti,ab,kw 3. paraph*mosis:ti,ab,kw 4. penis:ti,ab,kw

(*Continued*)

	5. prepuce:ti,ab,kw 6. foreskin:ti,ab,kw 7. (#1 OR #2 OR #3 OR #4 OR #5 OR #6) 8. MeSH descriptor Glucocorticoids explode all trees 9. MeSH descriptor Adrenal Cortex Hormones, this term only 10. MeSH descriptor Steroids, this term only 11. corticoid*:ti,ab,kw 12. steroid*:ti,ab,kw 13. corticosteroid*:ti,ab,kw 14. glucocorticoid*:ti,ab,kw 15. betamethasone:ti,ab,kw 16. clobetasol:ti,ab,kw 17. triamcinolone:ti,ab,kw 18. mometasone:ti,ab,kw 19. (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18) 20. (#7 AND #19)
MEDLINE	1. exp Phimosis/ 2. Penis/ 3. Foreskin/ 4. Circumcision, Male/ 5. ph#mosis.tw. 6. paraph#mosis.tw. 7. penis.tw. 8. foreskin.tw. 9. prepuce.tw. 10. circumcision.tw. 11. or/1-10 12. exp Glucocorticoids/ 13. Adrenal Cortex Hormones/ 14. Steroids/ 15. steroid$.tw. 16. corticoid$.tw. 17. corticosteroid$.tw. 18. glucocorticoid$.tw. 19. betamethasone.tw. 20. clobetasol.tw. 21. triamcinolone.tw. 22. mometasone.tw. 23. or/12-22 24. and/11,23
EMBASE	1. Phimosis/ 2. Penis/ 3. Prepuce/ 4. Circumcision/ 5. ph#mosis.tw. 6. paraph#mosis.tw. 7. penis.tw.

(*Continued*)

	8. foreskin.tw. 9. prepuce.tw. 10. circumcision.tw. 11. or/1-10 12. exp Glucocorticoid/ 13. Corticosteroid/ 14. Steroid/ 15. steroid.tw. 16. corticoid.tw. 17. corticosteroid.tw. 18. glucocorticoid.tw. 19. betamethasone.tw. 20. clobetasol.tw. 21. triamcinolone.tw. 22. mometasone.tw. 23. or/12-22 24. and/11,23

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)

(*Continued*)

	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been

(*Continued*)

	imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem

(*Continued*)

	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

CONTRIBUTIONS OF AUTHORS

- Gladys Moreno: background, search strategy, selection of studies, statistical analysis, manuscript redaction.
- Javiera Corbalán: search strategy, selection of studies, quality assessment, data extraction.
- Blanca Peñaloza: quality assessment, data extraction.
- Tomas Pantoja: statistical analysis, discrepancies resolution, manuscript redaction.

DECLARATIONS OF INTEREST

- Gladys Moreno: none known
- Javiera Corbalán: none known
- Blanca Peñaloza: "I have received financing support from FONIS, a Chilean government grant, to develop my contribution to this review"
- Tomas Pantoja: none known

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INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Topical; Adrenal Cortex Hormones [administration & dosage]; Beclomethasone [administration & dosage]; Betamethasone [administration & dosage]; Clobetasol [administration & dosage]; Glucocorticoids [*administration & dosage]; Hydrocortisone [administration & dosage]; Mometasone Furoate; Ointments; Phimosis [*drug therapy]; Pregnadienediols [administration & dosage]; Randomized Controlled Trials as Topic; Triamcinolone [administration & dosage]

MeSH check words

Humans; Male