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UROLOGY - REVIEW

Is steroids therapy effective in treating phimosis? A meta-analysis

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Abstract
Purpose We evaluated a systematic review on the therapeutic efficacy of topical steroids in children with phimosis to provide data for the clinical options of pediatric phimosis.
Methods We searched the related original studies on topical steroid therapy in pediatric phimosis before August 2014. Two reviewers independently performed the study selection, data extraction, risk of bias and reporting quality assessment with confirmation by cross-checking. The quality of eligible studies was appraised with the 'Cochrane handbook.' The meta-analysis was performed by REVMAN 5.2 software.
Results Eleven studies were included with 1669 patients among which 1093 received topical steroids and 576 cases treated with placebo or only manual reduction. Significant difference of the treatment efficacy was detected among the three methods [OR 7.46, 95 % CI (4.42, 12.58), $p < 0.00001$]. In subgroup analysis, significant difference of the treatment efficacy was also detected whether with placebo or manual reduction only [respectively, OR 5.04, 95 % CI (3.19, 7.95), $p < 0.00001$; OR 16.28, 95 % CI (6.06, 43.69), $p < 0.00001$].
Conclusions Compared to the placebo or manual reduction method, the topical steroid therapy is more effective in the treatment of phimosis in children. Although there is still controversy in the different type and dosage of steroid, this could be used against phimosis before circumcision.

Keywords Topical steroids · Phimosis · Pediatric phimosis · Meta-analysis

Introduction

Phimosis is defined as a condition with a complete or partial failure to retract the foreskin which may due to either a narrowness of the opening of the prepuce, or congenital adhesion between the glans and prepuce, or both [1]. By 3 years of age, 90 % of foreskins can be retracted, less than 1 % of males have phimosis by 17 years of age [2]. The persistent unretractable prepuce could limit penis' development, cause metal stenosis and dysuresia. Phimosis also predisposes to inflammatory and melanodermia; in most penis carcinoma patients, phimosis or redundant prepuce was found.

Traditionally, the most common treatment of nonretractable foreskin has been circumcisied. The procedure although fundamentally cure phimosis, but as an invasive surgical treatment, there is a certain risk of complications, such as bleeding, infection, preputial edema and pain.

Although many recent studies tend to recommend topical steroid treatment of phimosis as first-line therapy, it is just at the very beginning stage with controversial. The effectiveness remains unproven. The present study evaluates the therapeutic efficacy of topical steroids in children with phimosis using a meta-analysis in order to provide reference evidence for clinical decision making.

Jiaming Liu, Jin Yang and Yuntian Chen have contributed equally to the work.

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Materials and methods

Study selection

A systematic literature research was performed using EMBASE (1974–August 2014), PubMed (1966–August 2014), Cochrane Controlled Trials Register databases, MEDLINE, Pascal, Blackwell Science, Google, Google scholar, SUDOC, international register of trials and congress abstract databases which studies on topical steroid therapy in pediatric phimosis. The following Mesh search headings were used: 'topical steroid,' 'stretching method,' 'unretractable foreskin,' 'case–control study' and 'Pediatric phimosis.' Searches were also performed using the terms 'children phimosis' and 'phimosis in childhood,' and citations scanned were reviewed.

Inclusion criteria

- RCT literature or well-designed nonrandomized comparative study literatures;
- The research cases should under adolescent and meet the diagnostic criteria of phimosis;
- Intervention measure: the experimental group using topical steroids with or without joint reduction, the control group using a placebo and (or) joint manual reduction;
- Primary outcome: all documents required to provide statistical results of clinical efficacy.

Exclusion criteria

- Duplicate publication or data unavailable literature;
- Experimental studies, case reports, lessons learned, discuss theory, review, summary and other types of research literature;
- Noncontemporary comparison study of literature with larger time span.

Data extraction

The following information was extracted from each trial: date, design of study, average age, intervention, drugs and dosage, treatment time, follow-up period, assessment of therapeutic effects. Two independent researchers are responsible for the data extraction.

Quality evaluation

The meta-analysis was performed based on the recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-Analyses (QUORUM) guidelines. Jadad scale was performed to evaluate the quality of evidence of included studies [3]. Studies achieved a score of 3B or higher levels indicated to be a higher quality. The quality evaluation was conducted independently by two investigators under the criterion. Disagreements were resolved by a consensus; when this failed, a third author adjudicated.

Statistical analysis

Statistical analyses were performed with REVMAN 5.2.

A fixed effect model was adopted unless there was evidence of unexplained heterogeneity ($I^2 \geq 25$ %) [4], in which case, a random effects model was used. Heterogeneity was assessed as the proportion of variation, and heterogeneity was assessed by the statistic, with values up to 25, 50 % and above 50 % indicating low, moderate and high levels of heterogeneity, respectively. Odds ratio (OR) was calculated for each study, both with 95 % confidence interval (CI). The p values for overall effect were calculated with the Z test, and significance was set at $p < 0.05$. Publication bias was assessed by funnel plot.

Results

Characteristics of the individual study

Primary searches retrieved 75 relevant literatures in English. After screening titles and abstracts, 61 articles were excluded for not met the inclusion criteria. Then, we found three articles were not RCT or well-designed comparative articles and were excluded after reading full text. Finally, we retrieved 11 [1, 5–14] comparative studies about topical steroid therapy in pediatric phimosis (Fig. 1).

These 11 studies enrolled 1671 patients, 8 of them are placebo controlled and 3 of them are manual reduction controlled. The characteristics of individual studies are shown (Table 1).

Quality of the individual study

Among the 11 studies, no high risk of bias was found. Quality of the individual study is shown (Table 2). However, heterogeneity was found in one study after assessing qualitative estimation of publication bias of the studies from the funnel plot.

Efficacy outcomes

The 11 studies represented 1669 participants (1093 in the steroid therapy group and 576 in the control group). We found significant heterogeneity in our primary analysis ($I^2 = 61$ %). A random model was selected. Besides, a

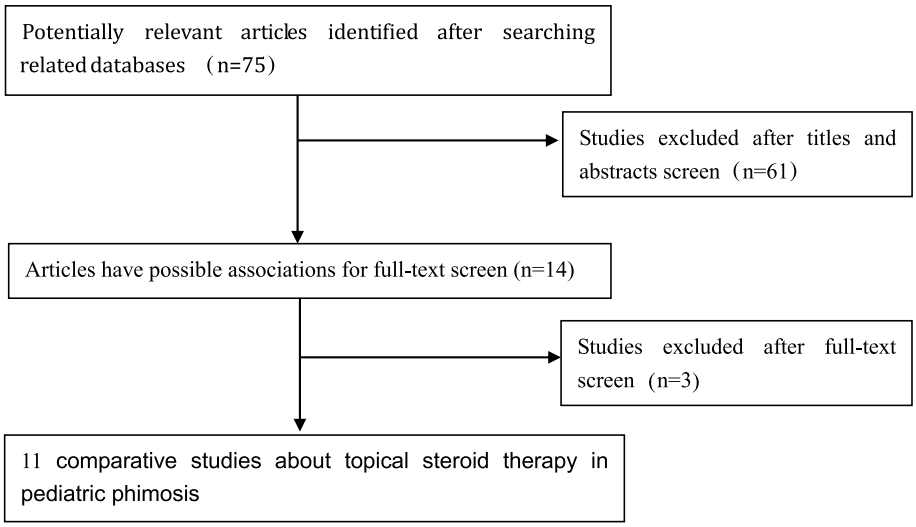

Fig. 1 Flow diagram of the study selection process

subgroup analysis was carried out to detect the heterogeneity more detailedly.

The result showed a significantly statistical difference between the treatment group and the control group (random model), [OR 7.46, 95 % CI (4.42, 12.58), $p < 0.00001$] (Fig. 2). In subgroup analysis, we evaluated the clinical efficacy of steroid therapy compared to placebo and manual reduction, respectively (random model). We also chose the fix model to analysis a subgroup in which all Asian studies were excluded. All of the results showed statistical difference between the treatment group and the control group [respectively, OR 5.04, 95 % CI (3.19, 7.95), $p < 0.00001$ (Fig. 3); OR 16.28, 95 % CI (6.06, 43.69), $p < 0.00001$ (Fig. 4); OR 5.44, 95 % CI (3.69, 8.01), $p < 0.00001$ (Fig. 5)]. The subgroup analysis that only studies using betamethasone were included did not change the significant efficacy [OR 6.96, 95 % CI (4.91, 9.87), $p < 0.00001$ (Fig. 6)].

Discussion

Our study showed that topical steroid treatment of phimosis had advantages in clinical efficacy to other noninvasive treatment, regardless of whether compared to placebo or to manual reduction.

Heterogeneity was detected in our study ($I^2 = 61$ %). According to the subgroup analysis, it came from two factors mainly: patients' race involved in the study and treatment duration of the study. After we excluded all Asian articles and articles in which the drug was not given twice a day for 4 weeks, the heterogeneity decreased to a fine level ($I^2 = 18$ %). But we do not have enough data for more detailed subgroup analysis, for example the race and treatment duration. We must point out that the different treatment duration that caused heterogeneity occurred mainly in the articles that were manual controlled. Therefore, the heterogeneity was extremely in a high level in the manual group ($I^2 = 73$ %).

Traditionally, circumcision is the most common treatment in many areas for pediatric phimosis. But it has been pointed out that between the age of 3 and 6 years—the 'phallic period' of childhood development—circumcision may affect the psychological status of the child and eventually cause psychological and behavioral disturbance. Castration anxiety, despite its controversial nature, may develop during the phallic period. Yilmaz et al. [15] evaluated patients using the Diagnostic and Statistical Manual-III-Revised (DSMIII-R) test with the aim of eliminating castration anxiety of circumcision in the phallic period. One hundred and forty-nine children with phimosis who required circumcision were included in the study. The average age of the children was 4.47 years. DSM-III-R test results showed a significant shift to anxiety in the circumcision group. Therefore, elective circumcision was generally avoided during this period. The conclusion showed necessity of topical steroid therapy before circumcision in children.

The total cure response rate (moderate to no phimosis in last follow-up) in patients involved in our study was 84.26 %. Zavras et al. [16] studied the treatment of phimosis with fluticasone used in 1185 boys, which showed a cure rate in 88.3 %. Reddy [17] has evaluated a long-term prospective study and reached a cure rate in 76.9 %. Both of these studies are used as evidences for EUA guideline on steroids therapy. Their results support our conclusion that topical steroid is an effective method for treating primary pediatric phimosis. We must point out that all of the studies showed a high response rate in the first month of treatment (90 %). So the difference of total cure rate, though it is unobvious, may be related to the difference of the

Table 1 Characteristics of individual studies

Study	Year	Age	Country	Type of study	Sample sizes		Exploring		Treatment duration	Follow-up time	Event/Total	
					Experiment	Control	Experiment	Control			Experiment	Control
Golubovic	1996	4.1 (3–6)	Yugoslavia	Randomized	20	20	0.05 % betamethasone	Vaseline	4 weeks	NR	263/276	19/42
Lindhagen	1996	7.5 (5–12)	Sweden	Randomized, double blind	13	14	Clobetasol propionate 0.05 %	Placebo cream	4 weeks + 4 weeks	6 months	10/13	7/14
Lund	2005	6.7 (3–15)	Hong Kong China	Randomized, double blind	66	71	Betamethasone	Aqueous cream	4 weeks + 4 weeks	18 months	49/66	31/71
Lee	2006	5.6 (3–9)	Korea	Randomized	13	12	0.1 % hydrocortisone	Vaseline	4 weeks	NR	10/13	0/12
Pileggi	2007	4.6 (2–13)	Brazil	Nonrandomized, double blind	56	44	0.1 % mometasone furoate	Placebo cream	8 weeks + 8 weeks	16 weeks	49/56	28/44
Esposito	2008	4.7 (3–13)	Italy	Prospective, nonrandomized	120	120	0.1 % mononmetasone furoate	Placebo cream	4 weeks	24 months	79/120	20/120
Zampieri	2007	7 (4–14)	Italy	Retrospective, randomized	104	100	Betamethasone 0.05 %	Stretching only	15d bid + 15d qd	6 months	93/104	56/100
Letendre	2009	5.1 (1.7–15.3)	Canada	Randomized, double blind	21	25	Betamethasone 0.05 %	Emollient cream (Aristocort)	8 weeks + 8 weeks	12 months	16/21	9/25
Nascimento	2011	5.1 (3–10)	Brazil	Randomized	157	38	Betamethasone 0.05 %	Placebo cream	4 weeks + 4 weeks	8 months	86/157	11/38
Zampieri	2005	7.6 (4–14)	Italy	Retrospective, randomized	247	90	Betamethasone 0.05 %	Stretching only	15d bid + 15d qd	6 months	243/247	60/90
Chin-chun	1999	6.7 (3–15)	China	Prospective, nonrandomized	276	42	Betamethasone 0.06 %	Stretching only	2 weeks + 4 weeks	NR	263/276	19/42

Table 2 The assessment of quality of included studies

Study	Allocation sequence generation	Allocation concealment	Blind	Loss to follow-up	Calculation of sample size	Selective report	Level of quality
Golubovic	B	B	B	0	B	B	B
Lindhagen	B	A	A	3	B	A	B
Lund	B	B	B	26	B	A	B
Lee	A	A	B	2	A	A	B
Pileggi	B	B	A	20	A	A	B
Esposito	B	A	A	0	B	A	B
Zampieri et al. [11]	C	C	C	0	C	B	C
Letendre	B	B	B	7	A	A	B
Nascimento	A	B	B	25	B	A	B
Zampieri et al. [14]	B	B	B	0	B	A	B
Chin-chun	B	B	B	0	B	A	B

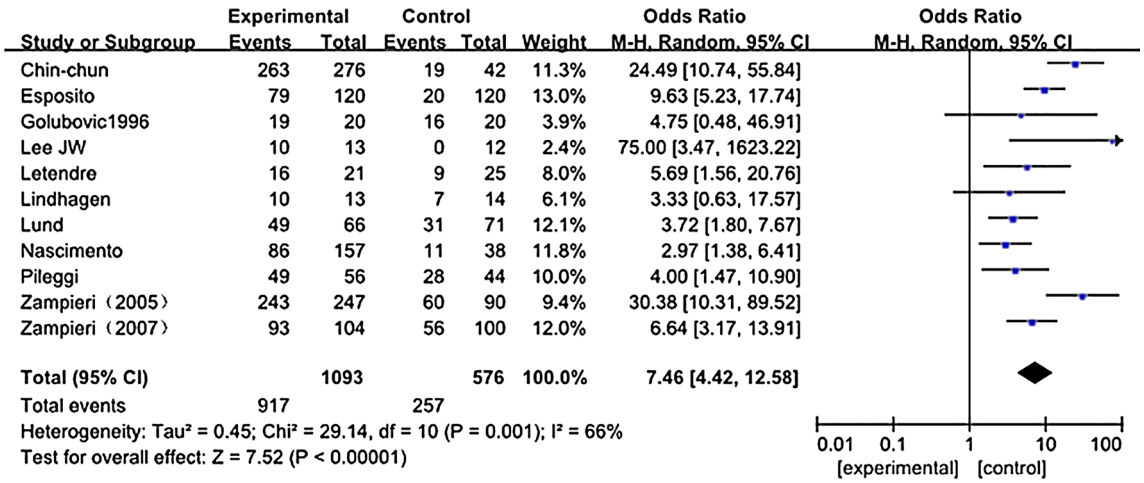

Fig. 2 Results of meta-analysis on clinical efficacy of steroid therapy

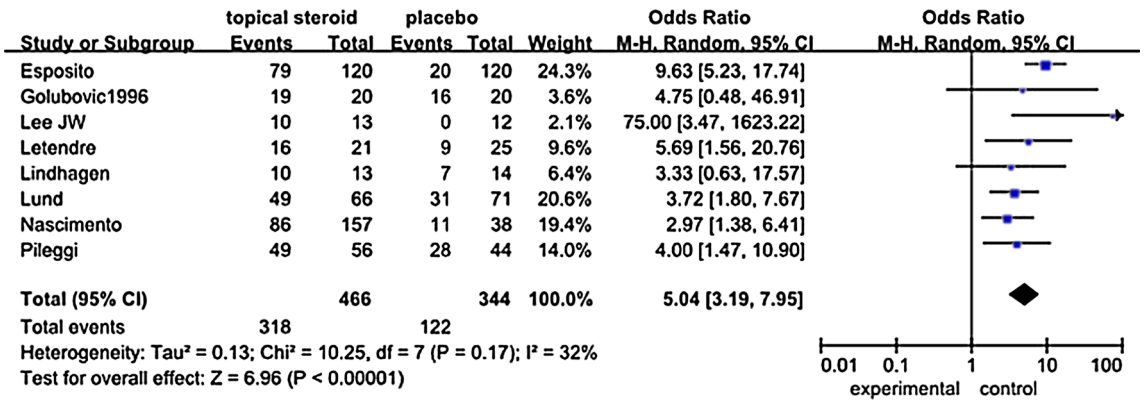

Fig. 3 Results of meta-analysis in clinical efficacy of steroid therapy (placebo controlled)

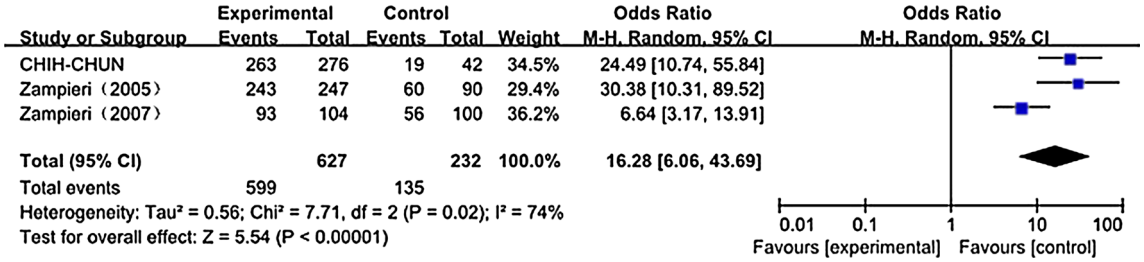

Fig. 4 Results of meta-analysis in clinical efficacy of steroid therapy (manual reduction controlled)

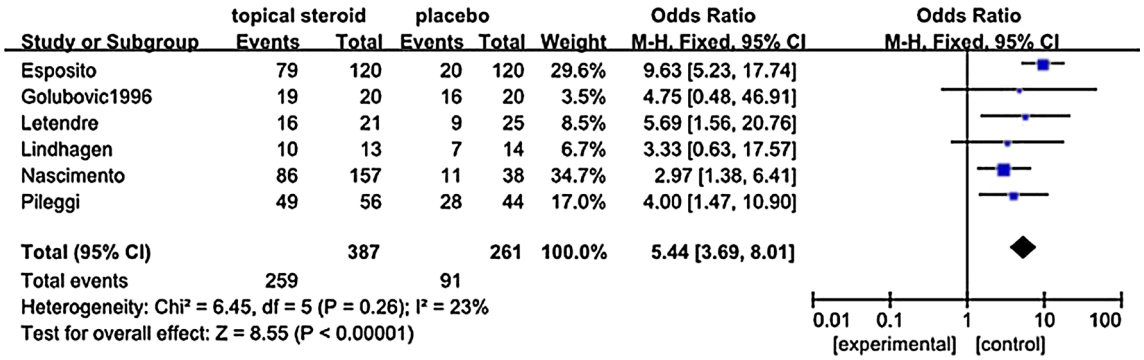

Fig. 5 Results of meta-analysis in clinical efficacy of steroid therapy (placebo controlled, Asian studies excluded)

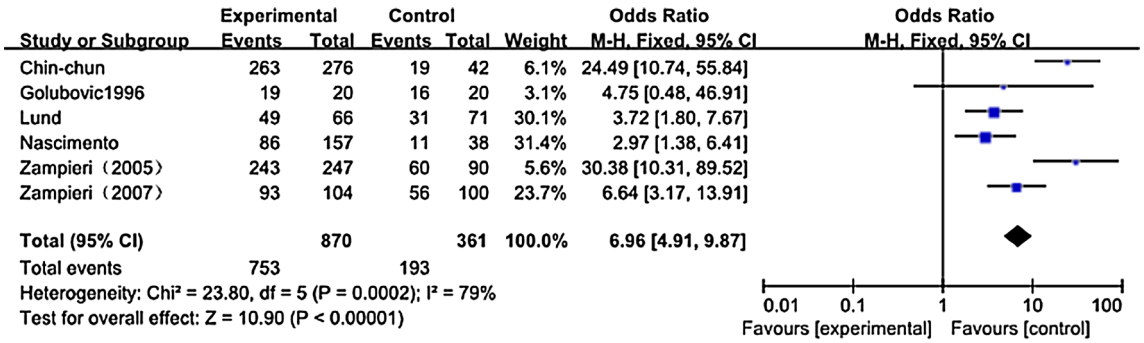

Fig. 6 Results of meta-analysis in clinical efficacy of steroid therapy (only studies using betamethasone were included)

management in the follow-up time. Zampieri et al. [11] studied about the efficacy (response rate) of topical steroids in treating phimosis at different age stages and found that most successful treatment was in patients aged between 4 and 8 years, suggesting the efficacy of an early beginning treatment.

Our study also showed significant difference between topical steroid and placebo or manual reduction. The advantages mainly come from the anti-inflammatory and immuno-suppressive effect of topical steroid. Topical steroids can make some interactions with some specific receptors, producing anti-inflammatory substance, and inhibit pro-inflammatory substance, including the reduction in type I and type III collagen synthesis in many cell types [18, 19]. Besides, Chu and Monsour found that steroids could cause thinning of the skin and improve the elasticity of the foreskin by decreasing the synthesis of hyaluronic acid, which had an anti-proliferative effect on the epidermis [13, 20] which might be the mechanism of topical steroid treatment in phimosis. However, some histological studies showed opponent results. Borges et al. collected the foreskin of 40 patients for 2 years, and these samples were divided into groups with or without previous topical corticosteroid. They carried out histochemical hematoxylin

and eosin and Picrosirius analyses of the foreskin and found that fibrosis was higher in patients who used topical corticosteroid [21]. And Favorito et al. [22] observed an increase in the collagen type III of the patients submitted to topical treatment. In other words, the mechanism still remains unclear.

Yang et al. [23] studied the effects of highly potent and moderately potent topical steroids in treating pediatric phimosis. Both steroids were effective in all age groups. Although there was plenty of evidence regarding the effectiveness of topical steroid therapy, most studies focused on comparison between steroid therapy and placebo rather than on different steroid therapies. Thus, based on current data, what we could conclude was that steroid therapies were effective over placebo in the treatment of phimosis. However, more prospective studies that directly compared the efficacy among different steroid therapies are needed to draw a firm conclusion.

It is also important to compare steroid therapy with other noninvasive or minimally invasive alternatives in a systematic review. Unfortunately, although there are huge amount of articles on the steroid therapy of phimosis, only limited controlled studies are available, especially for the comparison between steroid therapy and other noninvasive or minimally invasive alternatives. We have compared steroid therapy with placebo and manual stretching in our study. Although limited controlled articles were available in minimally invasive alternatives, we could also make a description on such procedures. For example, a French group indicated preputioplasty with circumcision was very effective (0 % recurrence rate) in treatment of 90 children with a phimosis [24]. A similar study was also conducted by a British group which indicated 70 % patient results were good or very good [25]. To directly compare steroid therapy with preputioplasty with circumcision, more prospective case-controlled studies were needed.

Last but not least, the cost-effective analysis is important but difficult to conduct because the medical cost ranges a lot in different countries. Thus, only qualitative conclusion can be drawn in current database. After searching all the articles on steroid therapy again, we found that there were limited articles on cost-effective analysis. All of them concluded that steroid therapy was the most cost-effective strategy. For example, a cost-effective analysis conducted by a French group indicated that steroid therapy only cost 360 French francs ($352.38) per patient, while circumcisions costs 3330 ($3233.01) per patient. [26] Another cost analysis in USA drew the same conclusion: steroid therapy was the most cost-effective strategy which only cost between $758 and $800 per patient [27].

The major limitations were: there were not enough articles met the inclusion criteria so that we could not evaluate the efficacy of different steroids in pediatric phimosis or the different efficacy of the same steroid in different races to reduce the heterogeneity in our study. The ideal model for this study is to include articles with the same steroids, dosage, patient race and control group in one subgroup, which needs a huge amount of articles with high quality in the future.

Besides, we did not get enough data of cure rate in each month in treatment duration. In other words, this study could not show the efficacy of steroids in treating phimosis in each point-in-time during the whole treatment duration.

In summary, current evidence suggests that the topical steroid therapy is more effective in the treatment of phimosis in children compared to the placebo or manual reduction method. Compared with surgical treatment, topical steroid treatment has advantages of noninvasive, fewer complications, significant reduction in health spending and less impact in children's psychological development. Although there is still controversy in the different type and dosage of steroid, topical steroid therapy can be used as conventional treatment methods before circumcision. And it is a more powerful evidence for the EUA guideline recommendation that steroids can be used as a first-line therapy for primary phimosis.

Author contributions JML, JY and YTC drafted the manuscript. YTC, SHC, CX and TD performed the study selection, data extraction, risk of bias and reporting quality assessment. YTC performed the statistical work. All authors have read and approved the final manuscript.

Conflict of interest The authors declare that they have no conflict of interest.

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