Comparison of the Effect of Steroids on the Treatment of Phimosis according to the Steroid Potencies

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Purpose: This study aimed to evaluate the outcomes of topical steroid therapy according to potency as the first-line treatment for boys with symptomatic phimosis.

Materials and Methods: From April 2017 to March 2019, we retrospectively reviewed 45 boys with severe phimosis (Kikiros retractability grade 4 or 5) who presented with phimosis-related complications. During the first year of the study period, methylprednisolone aceponate (MPA, Advantan®, potent topical steroid) was administered in 24 boys. Hydrocortisone butyrate (HCB, Bandel®, moderately potent topical steroid) was administered in 21 boys in the subsequent period. Topical steroids were administered for 4–8 weeks in all patients. Success of the therapy was determined by two conditions at 3 months after therapy: achieving Kikiros grade 3 and less with disappearance of symptoms.

Results: Of 45 boys, 35 (77.8%) achieved success of the therapy. Mean age was 46.64±22.42 months. Recurrence of phimosis with clinical complications was confirmed in three of 35 patients with initial success (8.6%) during the follow-up period. All boys with recurrence showed remission after additional topical steroid therapy. Success rate of the MPA group was higher than that of the HCB group (91.7% and 61.9% respectively, P = .029). Side effects associated with the topical steroid application were not observed in all children.

Conclusion: Topical steroid application is an effective and safe procedure as first-line treatment in symptomatic boys with severe phimosis. Moreover, the potency of topical steroids for the treatment of phimosis is considered a factor affecting the success rate.

Keywords: phimosis; steroid; potency

INTRODUCTION

Phimosis is a common disease in the field of pediatric urology.[1] Phimosis is a condition in which the prepuce cannot be retracted over the glans penis, owing to narrowing of the preputial orifice or adhesions between the glans and prepuce. Of newborn boys, 96% have nonretractable foreskin,[2] which is considered to be physiological phimosis. Generally, adhesions between the prepuce and glans separate gradually with growth. Ballooning of the prepuce on urination can contribute to resolution of physiological phimosis. It resolves in 50% of boys by one year of life but may persist in 6–10% of boys aged 3–9 years.[3]

Although most phimosis cases resolve over time without any symptoms or sequelae, severe phimosis may lead to inflammation of the foreskin and underlying glans (balanoposthitis), urinary retention, and urinary tract infection (UTI), thus requiring treatment.[4] Historically, circumcision has been the first treatment of phimosis. However, recently, topical corticosteroid application has become an efficient, safe, and less invasive alternative treatment.[5]

Numerous topical steroid therapies have been successfully performed in the treatment of phimosis. Several randomized placebo controlled trials have shown that various corticosteroids had 68–96% of efficacy.[6] Furthermore, many clinical trials concerning phimosis therapy have demonstrated that treatment outcomes were most successful when the topical steroid is applied with gentle stretching or traction of the foreskin.[7,8] However, there are few studies comparing phimosis treatment according to topical steroid potency. Therefore, we evaluated the outcomes of topical steroid therapy according to potency as the first-line treatment for boys with symptomatic phimosis.

MATERIALS AND METHODS

This is a retrospective observational study of a single pediatric urology center. The present study was approved by the Ethics Committee (IRB Number: KHUN 2020-03-026). This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

From April 2017 to March 2019, we retrospectively analyzed the data of 45 consecutive pediatric patients with a nonretractile severe phimosis (Kikiros retracta-

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Table 1. Clinical characteristic of the two treatment groups

Variables[a]	All N=45	HCB N=21	MPA N=24	*P*-Value
Age (months), continuous	46.64 ± 22.42	51.05 ± 26.04	42.79±18.40	0.222
Age (months), categorical				0.322
< 36 months	14 (31.1%)	5 (23.8%)	9 (37.5%)	
≥ 36 months	31 (68.9%)	16 (76.2%)	15 (62.5%)	
Phimosis-related symptoms before steroid treatment				
Balanoposthitis	19 (42.2%)	11 (52.4%)	8 (33.3%)	0.197
Ballooning of the prepuce	21 (46.7%)	12 (57.1%)	9 (37.5%)	0.188
UTI	4 (8.9%)	1 (4.8%)	3 (12.5%)	0.611
Voiding dysfunction	14 (31.1%)	5 (23. %)	9 (37.5%)	0.322
Kikiros grade at presentation		0.443		
IV	37 (82.2%)	16 (76.2%)	21 (87.5%)	
V	8 (17.8%)	5 (23.8%)	3 (12.5%)	
Steroid treatment duration (weeks)	5.93 ± 1.70	5.90 ± 1.76	5.96 ± 1.68	0.917
Follow-up period (months)	14.62 ± 6.92	10.14 ± 6.37	18.54 ± 4.69	< 0.001

[a]Data are presented as mean±SD or number (percent)
Abbreviations: HCB, Hydrocortisone butyrate; MPA, methylprednisolone aceponate; UTI, urinary tract infection.

bility grade 4 or 5) who presented with phimosis-related complications, such as balanoposthitis, ballooning of the prepuce, UTI, and voiding dysfunction. Study population and patients' enrollment are shown in **Figure 1**. Patients who had previously underwent phimosis treatment or had recurrent balanoposthitis or recurrent UTI were excluded from this study. If the patients shows signs of secondary (pathological) phimosis which is typically caused by balanitis xerotica obliterans (BXO) such as cicatrizing prepuce scarring, pallor of the preputial opening or contracted white fibrous ring around the preputial orifice, circumcision was performed. There were 2 cases of BXO and we excluded these patients. Patients with unavailable medical records or poor compliance to steroid treatment or without agreement for informed consent were excluded.

Phimosis grade was evaluated according to the classification of Kikiros and Woodward.[5,9,10] Grade classifications are as follows; 1) Grade 0, full retraction, not tight behind the glans, or easy retraction limited only by congenital adhesions to the glans; 2) Grade 1, full retraction of foreskin, tight behind the glans; 3) Grade 2, partial exposure of the glans, prepuce (no congenital adhesions) limiting factor; 3) Grade 3, partial retraction, meatus just visible; 4) Grade 4, slight retraction but some distance between the tip and glans, i.e., neither the meatus nor glans can be exposed; and 5) Grade 5, absolutely no retraction (**Figure 2**).

Topical steroids were used for 4–8 weeks in all patients. Initial success of therapy was determined by two condi-

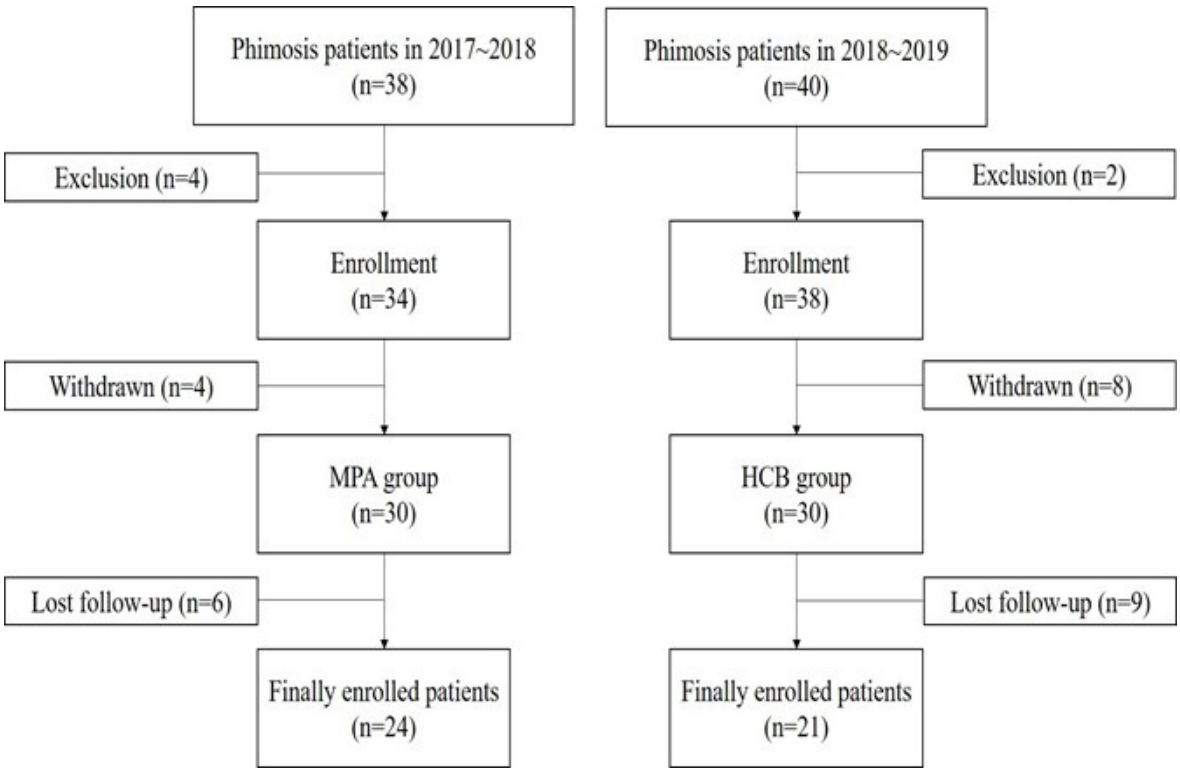

Figure 1. Study population and patients' enrollment.

Table 2. Comparison of the scores of the patients and the control group.

Variables	All N=45	HCB N=21	MPA N=24	*P*-Value
Success	35 (77.8%)	13 (61.9%)	22 (91.7%)	0.029
Kikiros grade after steroid treatment				NA
0	5 (11.1%)	1 (4.8%)	4 (16.7%)	
1	5 (11.1%)	2 (9.5%)	3 (12.5%)	
2	7 (15.6%)	2 (9.5%)	5 (20.8%)	
3	18 (40.0%)	8 (38.1%)	10 (41.7%)	
4	8 (17.8%)	7 (33.3%)	1 (4.2%)	
5	2 (4.4%)	1 (4.8%)	1 (4.2%)	
Kikiros grade ≥ 4 after steroid treatment	10 (22.2%)	8 (38.1%)	2 (8.3%)	0.029
Phimosis-related symptoms after steroid treatment	6 (13.3%)	4 (19.0%)	2 (8.3%)	0.396
Balanoposthitis	1 (2.2%)	1 (4.8%)	0 (0.0%)	
Ballooning of the prepuce	3 (6.7%)	1 (4.8%)	2 (8.3%)	
UTI	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Voiding dysfunction	2 (4.4%)	2 (9.5%)	0 (0.0%)	
Circumcision after steroid treatment	6 (13.3%)	4 (19.0%)	2 (8.3%)	0.396
Recurrence in the success group	3/35 (8.6%)	1/13 (7.7%)	2/22 (9.1%)	0.999

Abbreviations: HCB, Hydrocortisone butyrate; MPA, methylprednisolone aceponate; NA, nonavailable; UTI, urinary tract infection.

tions at 3 months after therapy: achieving Kikiros grade 3 and less with disappearance of symptom. Recurrence was defined as the reappearance of grade IV or V phimosis or related symptoms during the follow-up period after the evaluation of the initial success.

At the first visit and during the follow-up period, the assessment including physical examination of phimosis was performed by a single pediatric urologist with more than 10 years of experience (J.N. Lee). During the first year of the study period (April 2017 to March 2018), methylprednisolone aceponate (MPA, 1mg/g, Advantan®, potent topical steroid) was administered in 24 boys (53.3%). Hydrocortisone butyrate (HCB, 1mg/g, Bandel®, moderately potent topical steroid) was administered in 21 boys (46.7%) in the subsequent year (April 2018 to March 2019). The use of topical steroid ointment was explained to the parents and the steroid was applied to the patients by parents. The parents were educated about the possible adverse effect of the topical steroid. The application of topical steroid with gentle retraction of the prepuce was performed after washing and cleansing the penis. This regimen was repeated twice daily during the whole treatment period. Age, phimosis-related complications before and after steroid treatment, Kikiros grade before and after steroid treatment, combined comorbidities, periods of steroid

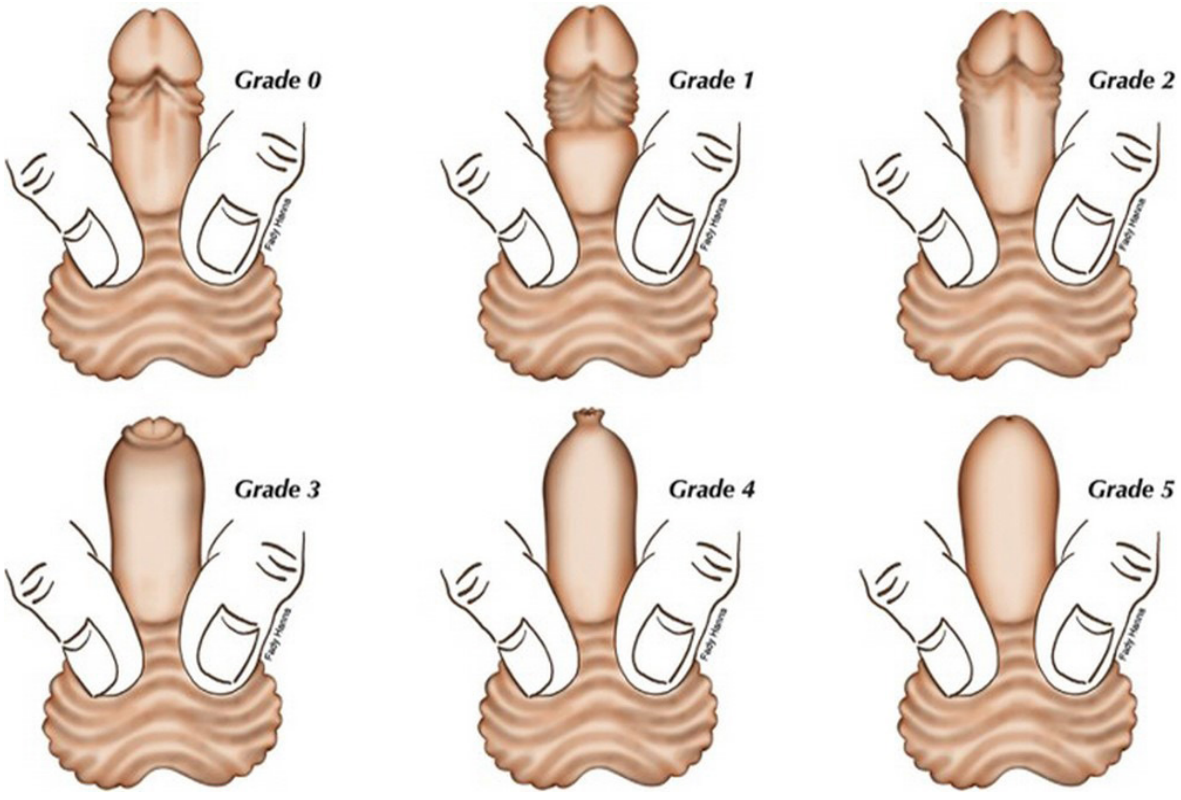

Figure 2. Phimosis grading system according to the classification of Kikiros and Woodward.

Table 3. Univariate and multivariate analyses predicting success.

Variables	Phimosis, n		*P*-value		
	Persistence n = 10	Improvement n = 35	univariate	multivariate	OR (95% CI)
Age (months), continuous	54.10 ± 30.01	44.51 ± 19.77	0.237	-	
Age (months), categorical			0.999*	-	
Age < 36	3	11			
Age ≥ 36	7	24			
Balanoposthitis before treatment	3	16	0.481*	-	
Ballooning before treatment	5	16	0.999*	-	
UTI before treatment	0	4	0.561*	-	
Voiding dysfunction before treatment	4	10	0.700*	-	
Kikiros grade			0.059*	-	
IV	6	31			
V	4	4			
Steroid type			0.029*	0.020	17.705 (1.566-200.219)
HCB	8	13			
MPA	2	22			
Periods of steroid treatment (months)	8.00 ± 3.27	6.23 ± 2.62	0.082	-	

*Fisher's exact test
Abbreviations: OR, odds ratio; UTI, urinary tract infection; HCB, Hydrocortisone butyrate; MPA, methylprednisolone aceponate.

treatment, follow-up periods, circumcision after steroid treatment, success rate, and recurrence rate were analyzed between the two groups.

We used Student's t-test for continuous variables and chi-square test or Fisher's exact test for noncontinuous variables. Multivariate logistic regression model was used to analyze the variables such as age (continuous or categorical), phimosis-related complications and Kikiros grade before treatment, steroid type, and treatment duration which can affect treatment outcome. Statistical analyses were performed using SPSS for Windows version 23 (IBM Corp., Armonk, NY, USA), and statistical significance was established with a $P < .05$.

RESULTS

Patient's demographic features and clinical characteristics before steroid treatment are shown in **Table 1**. The mean age was 46.64 ± 22.42 months. 19 (42.2%) patients showed balanoposthitis, 21 (46.7%) ballooning of the prepuce, 4 (8.9%) UTI, and 14 (31.1%) voiding dysfunction. Kikiros grade IV at presentation was noted in 37 patients (82.2%) and V in 8 patients (17.8%). The mean duration of steroid treatment was 5.93 ± 1.70 weeks. The mean follow-up period was 14.62 ± 6.92 months, and the MPA group were followed longer (10.14 ± 6.37 versus 18.54 ± 4.69, $P = .001$) than the HCB group.

Table 2 shows outcomes of steroid treatment. Overall success rate was 35/45 (77.8%), and there was a significant difference in success rate between the two groups (13/21 [61.9%] versus 22/24 [91.7%], $P = .029$). Persistence of severe phimosis after steroid treatment was shown in 10 patients (22.2%). Eight patients (38.1%) and 2 patients (8.3%) in the HCB and MPA groups, respectively, showed persistent severe phimosis (P = .029). Phimosis-related symptoms after steroid treatment were observed in 4 patients in the HCB group and 2 patients in the MPA group ($P = .396$). Circumcision was recommended in children with persistent symptoms concurrent of phimosis. Furthermore, circumcision was recommended in symptomatic patients with severe phimosis, and 6 patients (13.3%) underwent the procedure (4 in the HCB group and 2 in the MPA group). During the follow-up period of 14.6 months, recurrence of severe phimosis with clinical complications was observed in 3 of 35 patients (8.6%) with initial success. All boys with recurrence showed remission after additional topical steroid therapy using MPA. Side effects associated with topical steroid application were not observed in all children.

Multivariate logistic regression model analyses for predicting success showed that steroid type according to potency was the only independent factor for predicting success (HCB versus MPA, odds ratio [OR] = 17.705 [1.566-200.219], $P = .020$) (**Table 3**).

DISCUSSION

This study evaluated the outcomes of topical steroid therapy according to potency as the first-line treatment for boys with symptomatic phimosis. Before the 1990–2000s, circumcision was the only treatment available for children with phimosis. However, with the introduction of topical steroids and its popularization, surgery has become controversial among pediatric surgeons in the treatment of phimosis.[11] Corticosteroids can be classified according to their potency although the standards of classification vary slightly from each country. Among the topical steroids that we used in this study, HCB can be classified in the moderately potent group (category II/IV) and MPA in the potent group (category III/IV).[13,14] Recently, topical steroid application is thought to be an effective and safe first-line medical therapy for the treatment of symptomatic phimosis in boys.[5] Steroid promotes the resolution of phimosis through anti-inflammatory and immunosuppressive mechanisms, thus inhibiting local edema, fibrin deposition, and collagen synthesis.[14]

Several randomized placebo controlled trials have demonstrated that topical steroids had significant impact on partial or complete clinical resolution of phimosis.[11,15,16] In 2006, Lee et al. evaluated 78 male infants with febrile UTI and nonretractile phimosis who were prospectively randomized into the hydrocortisone (n = 39) and control (n = 39) groups.[17] They demonstrated that the response rate in the hydrocortisone group was 89.7% (35/39), which was significantly higher than the rate (20.5%; 8/39) in the control group. In 2009, Letendre et al. performed double-blind, randomized, placebo controlled study to compare 2 months twice daily treatment of emollient cream (placebo group 1, n = 25) and

0.1% triamcinolone (experimental group 2, n = 21).[16] The success rate in group 1 was significantly lower than in group 2 (9 patients [39%] versus 16 [76%]).

Next, if we attend to the long-term results and side effects of topical steroid therapy as the first-line treatment for symptomatic phimosis, there are several studies performed previously. Ku et al. performed prospective study including 108 boys who were treated with 0.05% betamethasone ointment from August 2001 to July 2014.[18] Age ranged from 0.03 to 12.9 years. The success rate of first treatment course was 81.5%, and 60.2% of boys remained free from phimosis upon latest assessment. There were no side effects and follow-up period ranged from 0.4 to 4.4 years (mean follow-up period: 2.45 years). Another study done by Ghysel et al. in 2009 demonstrated long-term efficacy of topical application of a potent corticoid cream and skin stretching in the treatment of phimosis.[7] 462 prepubertal boys were included and 400/462 boys (86%) had a retractable prepuce after 6 weeks of treatment. After a median follow-up of 22 months, the treatment continued to be successful in 383/462 boys (83%). No local or systemic side effects were noted throughout the entire observation period. Furthermore, there was a study which demonstrated that topical clobetasol propionate used twice daily for clinical treatment of phimosis did not affect the hypothalamus-pituitary-adrenal axis in most patients.[19]

Although there are many trials on topical steroid application as first-line medical treatment for phimosis, there are few trials comparing these various topical steroids according to potency. Interestingly, the high-potency steroids, such as clobetasol and betamethasone, did not show superiority compared with low-to medium-potency steroids, such as hydrocortisone.[6] Similarly, there is a more recent randomized open-label trial that compared topical prescription triamcinolone and over-the-counter hydrocortisone for the treatment of phimosis. In 2019, Chamberlin et al. compared over-the-counter hydrocortisone 1% cream (very mild potency) and prescription triamcinolone 0.1% cream (median potency) for the medical management of symptomatic phimosis.[5] With a total of 32 boys completing the 12-week trial, the success rates were 61.5 % in the hydrocortisone arm and 68.4% in the triamcinolone arm. They revealed that there was no statistical difference between the two arms.

On the contrary, in 2013, Sookpotarom et al. evaluated whether the half-strength formula (0.02%) of betamethasone is as effective as 0.05 % betamethasone.[10] Two strengths, 0.05% (n = 23) and 0.02% (n = 24), were randomly applied to 47 patients twice daily for 2 months. Phimosis grade in the half-strength group was significantly lower than that in the 0.05% betamethasone group. Similarly, in this study, we demonstrated that the success rate of the MPA group (potent topical steroid, category III/IV) was significantly higher than that of the HCB group (moderately potent topical steroid, category II/IV) (91.7% and 61.9%, respectively), and there were no serious side effects of topical steroid in the two groups. The real mechanism of action of the steroid is still unclear although it has been suggested that steroid acts through either a local anti-inflammatory process[20] or improvement of elasticity of the skin through the synthesis of elastic or collagen fibers.[21] Nevertheless, we can provide assurances to parents that the topical steroid is safe and produces nearly no local side effects in the treatment of phimosis. Our trial to verify the effect of potency of topical steroid in the treatment of phimosis would be beneficial in counseling patients with respect to no established topical steroid regimen currently available.

The limitations of the current study include a single-center study design, relatively small cohort size, short follow-up period, heterogeneous groups of patients, absences of control group and randomization, and retrospective nature of data collection. A retrospective study may always lead to a sampling bias. First of all, potential bias can exist due to the fact that two different topical steroid were applied in two different consecutive years leading to a difference in follow-up period between the groups. In addition, higher portion of patients under 36 months in the MPA group, although it is not statistically significant, could have functioned as crucial bias in determining the observed results of present study. Finally, we believe that a strict adherence to the treatment regimen does not always occur when it comes to any treatment of children. In the near future, further large-scale population-based prospective studies of multi-institutional research involving whole factors concerning phimosis management should be performed.

CONCLUSIONS

Topical steroid application is an effective and safe procedure as first-line treatment in symptomatic boys with severe phimosis. In addition, the potency of topical steroids for the treatment of phimosis is considered a factor affecting the success rate.

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CONFLICT OF INTEREST

None of the authors has any personal or financial con¬flict of interest.

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