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Journal of Clinical Nephrology

Research Article

Effectiveness of dexamethasone and hyaluronidase + valerate of bethasone associated with prepucial massage in the treatment of child phimosis

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More Information

Submitted: 21 June 2019
Approved: 08 July 2019
Published: 09 July 2019

How to cite this article: da Rocha AK, Meyer KF. Effectiveness of dexamethasone and hyaluronidase + valerate of bethasone associated with prepucial massage in the treatment of child phimosis. J Clini Nephrol. 2019; 3: 111-115.

DOI: 10.29328/journal.jcn.1001035

ISSN: 2576-9529

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Abstract

Introduction: The phimosis condition is characterized by the inability to retract the foreskin on the glans, making it impossible to expose them. Surgical treatment, although effective, has been questioned by the risk to which the patient is exposed. Therefore, we have opted for the use of topical corticosteroids to resolve this pathology.

Goals: To compare the effectiveness of Dexamethasone and Hyaluronidase + Betamethasone Valerate associated with preputial massage in the treatment of infantile phimosis, the degree of regression of phimosis, the time needed to achieve complete efficacy, possible adverse reactions, long-term outcome and parental adherence to treatment in children attending a specialized service in Blumenau, Santa Catarina.

Materials and methods: Controlled clinical trial, quantitative, non-blind, prospective and randomized sample analysis through the analysis of 523 patients.

Results: After 1 month of treatment, 435 patients presented some degree of regression and 63 children were referred to surgery. The success rate in this period was 45.8% in boys who were taking Hyaluronidase + Betamethasone Valerate and 49.8% in those who used Dexamethasone. In the late evaluation, 398 children reached grade 0, and 213 used Hyaluronidase + Betamethasone Valerate and 185, Dexamethasone; 39 patients were referred to the postectomy. Adherence to treatment was similar in both groups. The average time for degree 0 to be reached similar in both.

Conclusion: Both topical corticosteroids were effective in the resolution of phimosis. However, in the evaluation after the first month and in the regression, Dexamethasone proved to be more effective. The time to resolution of the condition was similar for both. The surgical procedure was taken when there was no clinical improvement. No adverse effects were reported in both groups.

Introduction

The term phimosis has a Greek origin - phimosis - and is defined as the inability to retract the foreskin on the glans, making it impossible to expose them either by preputial meatus stenosis or by bucklings-preputial adhesions [1]. The foreskin formation occurs in the third week of life of the embryo, a period in which there is the development of a skin fold from the base of the glans. As a result of the growth in the distal direction, the dorsal cover is initially formed and after the formation of the glandular urethra, the lateral leaflets fuse in the ventral face, giving rise to the brake [2].

In neonates and during the first years of life, the glans and foreskin are not completely separated [3]. This natural adhesion characterizes physiological phimosis, which in most cases does not require treatment, since the epithelial layers of the foreskin and glans spontaneously disintegrate after the formation of keratinized pearls [4]. At 3 years of age, 90% of foreskins can be withdrawn and less than 1% of men persist with phimosis at 17 years [4]. Pathological or true phimosis occurs when there is persistence of the buckano-preputial adhesions and it is possible to observe a fibrous ring around the preputial orifice - due to a cicatricial process - that prevents retraction [3].

Although circumcision is very effective, its preference as the first line of treatment has been questioned after the results

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of topical corticosteroid treatment. The surgical procedure, besides costing more than double the topical treatment, poses considerable risks to the patient, since general anesthesia is necessary and complications reach 34%, being the most frequent: hemorrhage, pain, infection, urinary obstruction, bad esthetic results and other rarer ones: urethral meatitis and preputial ring stenosis, and even amputation of the glans [5,6].

Clinical treatment, based on the use of topical corticosteroids for phimosis, poses no risk to patients and there is no significant side-effect or systemic effect. However, it is extremely important to perform the preputial massage, since there is no efficacy in the treatment without it [4,7]. After the period of drug therapy, the need to continue the massage and maintain good local hygiene is stressed, in order to avoid relapses [5]. Low cost and promising results, with success rates of up to 95%, make the choice by this plausible therapeutic method before the immediate surgical indication [4].

In the public service of our county, the ointment with topical corticosteroid supplied free of charge is Dexamethasone acetate 0.1% cream. While the cost of the combination of Betamethasone 2.5 mg / g and Hyaluronidase 150 utr / g for specific use in the treatment of phimosis ranges from R$ 75.65 to R$ 102.90. Based on the fact that the patients treated at the outpatient clinics of the public service did not adhere to the proposed treatment, this study was suggested comparing the effectiveness of Dexamethasone (available free of charge in the primary care service) and Hyaluronidase + Valerate, both associated with massage preputial in the treatment of phimosis. The degree of regression of phimosis, the time required to achieve complete efficacy, possible adverse reactions, the long-term outcome, and parental adherence to treatment were evaluated.

Materials and Methods

This controlled clinical trial was approved by the ethics committee of the Regional University of Blumenau (FURB), under the opinion of number 2,190,170 and has the consent of those responsible for the clinic where the study was conducted. A randomized sample of 523 patients, aged 1 to 13 years (mean age of 5.1 years) selected between June and December 2017, with a diagnosis of phimosis of the pediatric urology outpatient clinic in the city of Blumenau , Santa Catarina Brazil.

At the first visit, a clinical examination was performed to confirm the diagnosis of phimosis by a pediatric urologist, who categorized the phimosis according to the classification of Kikiros and Woodward, graduated in: degree 0 - total retraction; grade 1- refers to total retraction of the foreskin, but the ring is tight behind the glans; degree 2 - partial exposure of the glans and the foreskin is the limiting factor; degree 3- partial retraction and only the visible meatus; degree 4- slight retraction but the glans and meatus are not visible; degree 5- no retraction occurs.

Patients were randomly divided into two groups:

- **Group 1**: use of Betamethasone cream 2.5 mg / g and Hyaluronidase 150 utr / g associated with preputial massage.
- **Group 2**: use of Dexamethasone acetate 0.1% cream associated with preputial massage.

The application of the creams and the realization of the preputial massage were explained and demonstrated to the parents, and both creams were provided free of charge to all. An explanatory leaflet[3] was given directing the application of ointment and massage to all patients

Parents were informed of possible and rare side effects caused by topical steroids such as stretch marks, hypertrichosis, burning, itching, irritations, dryness, folliculitis and allergic contact dermatitis.

Twenty-three patients were excluded from the evaluation, being: 4 for recurrent urinary tract infection and 19 for balanoposthitis. Patients with repetitive balanoposthitis, presence of preputial scar, phimosis that shows no resolution signal after 10 years of age and presence of balanitis obliterans were referred for surgery and were not included in this study (8).

The initial treatment lasted 1 month and the creams were applied 2 times a day, associated with the preputial massage, being one of the times after the bath and the second time at any time of day.

After 1 month the patients returned to the clinic and were reassessed using the Kikiros and Woodward classification by the same pediatric urologist of the first consultation. The response to treatment was defined by the degree of preputial retratillation.

Patients who did not reach grade 0, were submitted to more cycles, ranging from 1 to 2 months, according to the initial response. All patients who showed partial or total improvement were instructed to maintain massage and hygiene, as well as to return to the clinic for a third visit after the 6-month to 1-year interval from the start of treatment to evaluate the long-term response. term.

Those who did not obtain any response to the clinical treatment were referred for surgery - postectomy. In this consultation it was also questioned if there was any adverse reaction to the creams during the period.

In the third evaluation, it was verified if the patients maintained the preputial aperture. Those who remained at grade 0 were instructed to maintain hygiene and massage. Those who relapsed, were referred to surgery - postectomy.

Adherence to treatment by the parents was analyzed through the report of the discontinuity of the massage, in the first month and in the third medical evaluation.

The data were organized into descriptive tables containing absolute, relative frequencies and proportion estimates in the form of 95% confidence intervals. The association between qualitative variables was performed through the Qui-square test of independence. In the comparison between the means of the time the Student's Test was used for independent samples. In the comparison of independent proportions, the Independent Proportions Test was used. In all cases, the statistical significance was considered if the P value <0.05. Data analysis was performed using Microsoft Excel 2016 software.

Results

A total of 500 children, of whom 275 were on Hyaluronidase + Betamethasone Valerate and 225 on Dexamethasone (Table 1), were evaluated.

Regarding the phimosis classification, before the start of treatment: 93 boys had grade 1; 123, grade 2; 94, grade 3; 142, grade 4 and 48, grade 5.

Regarding the division of groups by grade, there were no significant differences in percentage of characteristics and type of ointment prescribed (Table 2).

After 1 month of treatment, there was some degree of regression in 435 patients. On average, half of the patients in each group reached grade 0 (Table 3). The regression to grade 0 after 1 month of initiation of treatment was better when the type of ointment was Dexamethasone, since it presented higher frequencies close to grade 0. Likewise, the improvement was greater when the ointment was Dexamethasone, since presented more individuals who regressed.

Sixty-three patients were referred to surgery, mainly due the discontinuity of the preputial massage (Table 4).

At the third medical evaluation, after 6 months to 1 year of initiation of treatment, a total of 398 children with grade 0 (Table 5) were obtained.

There was recurrence of phimosis in 39 cases and as a cause the discontinuity of opening the prepuce daily in the bath as directed was observed. Therefore, the surgery for these patients was surgery (Table 6).

Regarding adherence to treatment, it was concluded that in 62 cases there was no expected collaboration in the first month of treatment. On the other hand, in the long term, 39 patients did not perform the treatment in the proposed way (Table 7).

It was found that the mean time to efficacy of both creams was very similar, approximately 6 weeks (Table 8).

No adverse reactions were reported by any patient and / or responsible due to the use of any of the creams during the study period.

Discussion

Clinical treatment, based on the use of topical corticosteroids for phimosis, was first introduced in the 1990s by Kikiros and Woodward [9]. As a consequence of its simplicity, of not having significant side effects and having a high success rate, it has become the first choice for the treatment of this pathology.

Table 1: Distribution of ointment doses for patients in clinical treatment of phimosis.

Features	Number of patients (%) (n = 500)	IC (95%)
Ointment type		
Group 1- ASSOCIATION	275 (55%)	(50,64 - 59,36)
Group 2-DEXAMETHASONE	225 (45%)	(40,64 - 49,36)

P: P-value of the Qui-square test of independence. If P <0.05 then significant association.

Table 2: Association between the classification of infantile phimosis before treatment and the type of ointment prescribed to patients.

Features	Ointment type		P
	Group 1 (n = 275) B + H	Group 2 (n = 225) DEXAMETHASONE	
Phimosis grade (Kikiros)			
1	42 (15,3%)	51 (22,7%)	0,2206
2	71 (25,8%)	52 (23,1%)	
3	58 (21,1%)	36 (16%)	
4	78 (28,4%)	64 (28,4%)	
5	26 (9,5%)	22 (9,8%)	

P: P-value of the Qui-square test of independence. If P <0.05 then significant association.

Table 3: Association between regression of infantile phimosis and ointment type of patients.

Features	Ointment type		P
	Group 1 (n = 275) B + H	Group 2 (n = 225) DEXAMETHASONE	
Evaluation after 1 month			
0	126 (45,8%)	112 (49,8%)	0,0428
1	66 (24%)	43 (19,1%)	
2	14 (5,1%	22 (9,8%)	
3	28 (10,2%)	22 (9,8%)	
4	26 (9,5%)	23 (10,2%)	
5	15 (5,5%)	3 (1,3%)	
If regressed			
Yes	232 (84,4%)	203 (90,2%)	0,0500
No	40 (14,5%)	22 (9,8%)	

P: P- value of the Qui-square test of independence. If P <0.05 then significant association.

Table 4: Association between surgical management in the infantile phimosis treatment and type of ointment in patients.

Features	Ointment type		P
	Group 1 (n = 275) B + H	Group 2 (n = 225) DEXAMETHASONE	
Conduct Surgery	40 (14,5%)	23 (10,2%)	
Reason for Surgical Treatment At the parents' request	0 (0%)	1 (0,4%)	-
Discontinuation of massage	34 (12,4%)	19 (8,4%)	
Discontinuity of massage and balanoposthitis	3 (1,1%)	3 (1,3%)	
Discontinuation of massage and fibrosis	2 (0,8%)	0 (0%)	
Bleeding the retraction attempt and stenotic ring	1 (0,4%)	0 (0%)	

P: P-value of the Qui-square test of independence. If P <0.05 then significant association.

Table 5: Association between the long-term results of infantile phimosis treatment and the ointment type of the patients.

Features	Ointment type		P
	Gruoup 1 (n =275) B + H	Group 2 (n = 225) DEXAMETHASONE	
Evaluation after 6 months to 1 year			
0	213 (77,5%)	185 (82,2%)	0,1881 (b)
1	0 (0%)	0 (0%)	
2	2 (0,8%)	0 (0%)	
3	4 (1,5%)	0 (0%)	
4	8 (2,9%)	7 (3,1%)	
5	10 (3,6%)	8 (3,6%)	

(b) P: P-value of the Test of independent proportions. If P <0.05 then there were significant differences between proportions.

Table 6: Association between recurrence cases and long-term surgical management of infantile phimosis treatment with patients' ointment type.

Features	Ointment type		P
	Group 1 (n = 275) B + H	Group 2 (n = 225) DEXAMETHASONE	
Recurrence			
Yes	24 (8,7%)	15 (6,7%)	0,3271
No	213 (77,5%)	186 (82,7%)	
Recurrence motives			
Discontinuation of massage	17 (6,2%)	15 (6,7%)	0,2593
Discontinuity of Massage and Balanoposthitis	4 (1,5%)	1 (0,4%)	
Discontinuation of massage and dermatitis on the penis	1 (0,4%)	0 (0%)	
Discontinuation of massage and excess skin	1 (0,4%)	0 (0%)	
Final conduct			
Surgery	24 (8,7%)	15 (6,7%)	0,3496
Dexamethasone for 3 months	0 (0%)	1 (0,4%)	
Maintaining massage and hygiene	213 (77,5%)	185 (82,2%)	

P: P-value of the Qui-square test of independence. If P <0.05 then significant association.

Table 7: Association between lack of parental adherence in the treatment of childhood phimosis and type of ointment in patients.

Features	Ointment type		
	Group 1 (n = 75) B + H	Group 2 (n = 225) DEXAMETHASONE	Total (n= 500)
Evaluation after 1 month			
Discontinuation of massage	39 (13,4%)	23 (9,8%)	62 (12,4%)
Evaluation after 6 months to 1 year			
Discontinuation of massage	23 (8,3%)	16 (7,1%)	39 (7,8%)
TOTAL			101 (20,2%)

Table 8: Association between the time needed to reach grade 0 in the infantile phimosis treatment and the type of ointment of the patients.

Features	Ointment type		P
	Group 1 (n = 275) B + H	Group 2 (n = 225) DEXAMETHASONE	
Time (months) to reach degree 0			
1	128 (46,5%)	111 (49,3%)	0,2511
2	66 (24%)	42 (18,7%)	
3	17 (6,2%)	25 (11,1%)	
4	6 (2,2%)	5 (2,2%)	
5	3 (1,1%)	2 (0,9%)	
6	1 (0,4%)	1 (0,4%)	
Mean Time (Mean ± SD)	(1,61 ± 0,9)	(1,65 ± 0,95)	0,7090 (a)

P: P-value of the Qui-square test of independence. If P <0.05 then significant association. (a) P: P-value of Student's t-Test for independent samples. If P <0.05, then groups present significant differences; SD: standard deviation.

The postectomy surgery triggers stress and anxiety in patients, and these experiences are threat to their physical integrity [10,11]. Although it is very effective, it poses considerable risks, since general anesthesia is necessary and complications reach 34%, being the most recurrent ones: hemorrhage, urethral meatitis and preputial ring stenosis, and even amputation of the glans [5]. Some authors propose that circumcision, without therapeutic purposes, is an unethical act, since the procedure constitutes mutilation of part of the body without the consent of the child [12]. It is suggested that the patient should be considered the most appropriate person to decide whether or not to undergo surgery, analyzing whether the risks of remaining with the foreskin are greater than the risks of operative complications [13]. As a result, the dissemination of results with the proposed clinical treatment is justified.

The present study was the first to compare the efficacy of two corticosteroids associated with preputial massage and the first to evaluate the use of Dexamethasone. In Brazil, patients in the public health service has free charge Dexamethasone.

In a systematic review of the efficacy of clinical steroid treatment by Liu et al. [14], 1669 participants were evaluated, of whom 1093 were on steroid therapy and 576 were control subjects. It was observed that 84.26% of the cases under analysis reached the degree 0 or 1 of phimosis, which supports the fact that the drug is an effective and safe method to treat infantile phimosis. The study also showed that topical steroid use is advantageous when compared to placebo because of its anti-inflammatory and immunosuppressive action [14]. The medication interacts with specific receptors and produces anti-inflammatory substances, in addition to inhibiting pro-inflammatory drugs, such as collagen I and III synthesis. Chu (1999) and Munsour (1999) found that steroids can cause thinning of the skin and improve preputial elasticity, reducing the production of hyaluronic acid, which had an anti-proliferative effect on the epidermis [15,16]. In China [17] and Italy [18], it was found that 74% and 72%, respectively, of children receiving betamethasone had a complete response at the end of the first month of treatment. In Italy, about 65% of patients achieved the same result. It was observed in this study that at the end of the first month of treatment 47.6% reached grade 0, 45.8% were using Hyaluronidase + Betamethasone Valerate and 49.8%, Dexamethasone. In the late regression, 79.6% of the patients were classified as grade 0. Among them, 185 belonged to group 1 and 213 to group 2. A similar analysis was performed by Lund et al. After 18 months, it was found that 86% of the boys who used topical corticosteroids were cured [17].

As to the time required to reach grade 0, on average 47% of patients in both groups required 1 month. A study by Lee and Lee found that 68.2% of the boys achieved success in the same time period [7].

In relation to long-term recurrences, 8.7% of the children in the first group and 6.7% of the second group were diagnosed

with some degree of phimosis. However, a total of 39 people reported that this fact was related to the discontinuity of the preputial massage, and the initial orientation given to the parents and the children was to open the foreskin and wash in the bath once a day. Preputial massage and daily glans hygiene are therefore mandatory for resolution and non-recurrence of the condition [5].

It was also found that regression occurs for all degrees of phimosis. That is, if there is no presence of factors that contraindicate topical treatment, such as local fibrosis, balanitis obliterans, recurrent UTI and recurrent balanoposthitis, surgery is not justified without first attempting the noninvasive method.

Conclusion

In both groups there was improvement in the resolution of phimosis with topical treatment, regardless of the degree to which the patient was initially classified.

It was only possible to observe statistically significant differences between the ointments in the "Evaluation after 1 month" and "If regressed or not", where Dexamethasone proved to be more effective for presenting more patients with degree 0.

At one month, almost 50% of patients in each group had complete response (grade 0).

In the late assessment, from 6 months to 1 year of treatment initiation, 77.5% of the patients in group 1 and 82.2% of the group 2 were classified as grade 0.

The time required to achieve the expected outcome was similar in both groups.

No adverse reactions or complications were reported by any parent or child who was taking topical corticosteroids in this study.

The boys who maintained the daily preputial retraction, as well as the hygiene of the glans, managed to keep the phimosis open.

Surgical management was indicated for patients who did not adhere to the proposed topical treatment - ointment associated with preputial massage - at the end of the first month and those who did not maintain local care after the time of follow-up.

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