EFFICACY OF PREOPERATIVE INTRAMUSCULAR VERSUS TOPICAL TESTOSTERONE THERAPY FOR MICROPHALLIC HYPOSPADIAS

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ABSTRACT

Surgical correction of genital defect was formally proposed when the size of the penis was sufficient to permit easy surgical repair. Testosterone can be used for enlargement of penile size either topical or parenteral route. In this study comparison of the efficacy of topical and parenteral testosterone to enlarge the preoperative size of microphallic hypospadias was done. Boys (n=70) aged 6 months to 5 years mean age 34.19 months having microphallic hypospadias with penile length < 3.5 cm and glans width < 1.4 cm with no previous intervention were included (January 2014 to December 2015) in this study. They were randomly assigned to intramuscular testosterone group (Group A) and topical testosterone group (Group B). The comparative parameters between two groups were alteration of penile length and glans width and the adverse effects of testosterone therapy. In each follow up visit, penile length, glans width were measured and adverse effects were noted. Mean penile length was 2.61 cm in group A and 2.71 cm in group B. Mean glans width was 1.09 cm in group A and 1.13 cm in group B. In both groups, the penile length and glans width increased significantly ($p<0.05$). There was no statistical significant difference in increase in penile length and glans width between the two groups ($p>0.05$). There was statistical significant difference in developing dermatitis and genital pigmentation between the two groups ($p<0.05$). Significant penile growth was observed in both groups but there was less adverse effects in parenteral group.

KEYWORDS

Hypospadias, microphallus, testosterone

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INTRODUCTION

Hypospadias is one of the most common congenital anomalies, occurring in approximately 1 in 125 live male births.[1] According to available data, a small penis in hypospadias is a result of fetal testosterone insufficiency or lack of scrotal fold receptivity during fetal life.[2] A subgroup of boys with hypospadias, especially proximal cases, has been described as having a "significantly smaller than usual" penis in the context of selecting patients for preoperative androgen therapy. Others characterized boys with hypospadias as microphallic based on penile length <2 standard deviations (SD) from normal (3.5cm).[3,4] Accurately determining stretched penile length can be difficult in those proximal cases with ventral curvature and abnormal skin attachments from penoscrotal transposition. Glans size potentially is more readily measured, with several studies reporting circumferences in children with hypospadias selected for androgen stimulation.[3]

The lack of hard scientific data, results in the use of empirical judgment when the surgeon confronts with a hypospadiac microphallic case. Delaying surgical repair until the phallus is of suitable size or pretreatment with hormones and proceeding with early repair is the matter of concern. Surgeons who delay surgery usually do so based on the lack of compelling evidence that endocrine therapy is truly beneficial. It is a matter of concern that prepubertal androgens may be detrimental. In contrast, surgeons who proceed with hormonal treatment and early surgery argue that delaying the operative procedure results in undue and avoidable psychological stress to the infant and parents.[5] This study was done to compare the efficacy of preoperative intramuscular and topical testosterone therapy for microphallic hypospadias.

MATERIALS AND METHODS

A randomized controlled trial was done on boys aged 6 months to 5 years having significantly small phallus with hypospadias in a period of two years (January 2014 to December 2015) at Bangladesh Institute of Child Health, Dhaka. Hypospadiac boys with penile length less than 3.5 cm and glans width less than 1.4 cm were included and were divided into two groups by lottery method. Ethical permission was taken from Institutional Review Board of Bangladesh Institute of Child Heath, Dhaka, Bangladesh, prior to the study. After taking written informed consent from the parents of each patients, boys in "Group A" were given Injection Testosterone (25µg/kg) single dose every 4 weeks for 3 times or until the penile length was 3.5cm or more and glans width 1.5 cm or more. In "Group B", boys were given testosterone cream 3 times daily for 3 weeks. Penile length and glans width were measured before, during and after therapy. Adverse effects such as pigmentation, development of pubic hair and dermatitis were noted. Statistical analysis of findings was done with SPSS version 20. 'Student t' test and 'paired t' test for quantitative data and 'Chi square' test and 'Fisher exact' test for categorical data were performed. P value < 0.05 was considered significant.

RESULTS

Of the total 70 boys; mean age 34.2 ± 17.1 months with microphallic hypospadias randomized into Group A (intramuscular testosterone group) and Group B (topical testosterone group), 35 in each group. Nine had anterior variety, 33 had middle variety and 28 had posterior variety.

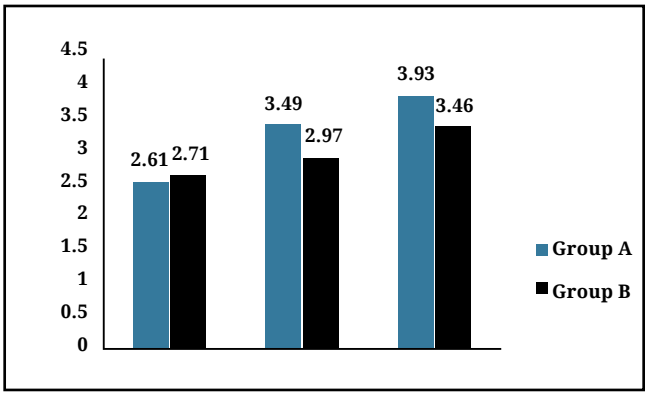

Fig. 1:
Mean penile length before, during and after therapy in two groups.

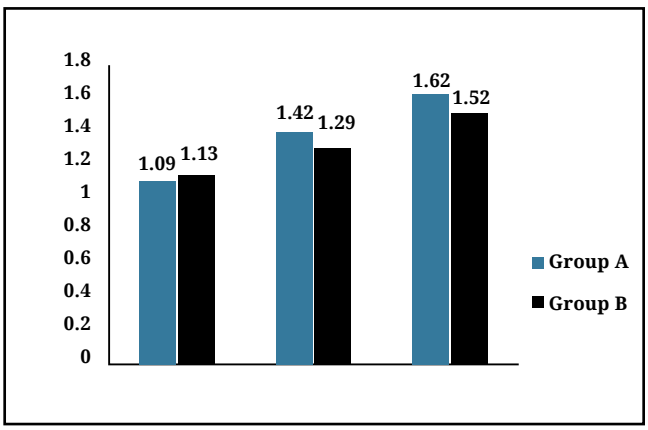

Fig. 2:
Mean glans width before, during and after therapy in two groups.

Mean penile length before starting the treatment in Group A was 2.61 ± 0.57 cm and Group B was 2.71 ± 0.49 cm. Mean penile length before, during and after therapy are shown in Fig. 1. Mean glans width before starting the treatment in Group A was 1.09 ± 0.18 cm and Group B was 1.13 ± 0.18 cm. Mean glans width before, during and after therapy are shown in Fig. 2. There was significant increase in penile length and glans width in both the groups (P<0.05) after completion of the therapy. The difference in increase in penile length and glans width was not significant between 2 groups (P>0.05), Table 1.

Table 1: Mean age, Mean increase in penile length and glans width.			
Mean and SD	**Group A (n=35)**	**Group B (n=35)**	**P value**
Age (months)	34.86±15.04	33.51±19.09	0.745
Increase in Penile length (cm)	0.88±0.41	0.76±0.34	0.2
Increase in Glans width (cm)	0.33±0.17	0.39±0.13	0.107
P <0.05 (significant)			

Table 2: The adverse effects in two groups			
Adverse effects	**Group A (n=35)**	**Group B (n=35)**	**P value**
Pubic Hair	5 (14.3%)	13 (37%)	0.054
Genital Pigmentation	0 (0%)	35 (100%)	0.0001
Dermatitis	1 (29%)	10 (28.6%)	0.006
P <0.05 (significant)			

The adverse effects like pigmentation of genitalia, development of pubic hair and dermatitis were seen, which has been depicted in Table-II. All patients in group B developed pigmentation of genitalia. The difference in development of dermatitis and pigmentation in between two groups were statistically significant. One patient developed sexual precocity.

DISCUSSION

Repair of the microphallic hypospadiac penis can be technically challenging.[5] In boys with various genitourinary anomalies, including micropenis, hypospadias and epispadias, it has been standard practice to administer exogenous testosterone.[6] Malik and Liu conducted a survey on pediatric urologists and found that, a large proportion of providers use intramuscular testosterone. However, topical testosterone continues to be used by a minority.[4]

The optimal age for repair of hypospadias is 6 months to 15 months.[7] Growth in the penile length takes place up to 5 years followed by little change until the onset of puberty.[2] We also included the patients of same age range in this study.

Microphallic hypospadias seem to be commonly associated with severe hypospadias.[8] In the study done by Chalapathi *et al* 34% patients had penoscrotal hypospadias and 19% had proximal penile hypospadias. Study by Luo *et al* found 56% patients with penoscrotal hypospadias. In this study, maximum of cases were posterior (40%) and middle (47%) type. In general, severe hypospadias such as penoscrotal hypospadias and proximal hypospadias have been reported to be associated with microphallus.[8]

It is preferable to increase the penile size before surgery for appropriate preoperative surgical condition and to minimize post-operative complications.[8] The study done by Nerli *et al*.[10] showed that the growth in penile length was significantly increased in both parenteral and tropical testosterone application groups. In our study, penile length increased significantly in both groups. However, there was no significant difference in increase in penile length between two groups.

It is difficult to measure stretched penile length in boys with microphallic hypospadias, especially in proximal cases with ventral curvature and abnormal skin attachment.[3] However, glans size is easy to measure in these cases. Therefore, in this study, the maximum glans width was measured before, during and after the therapy. In both groups, glans width increased significantly. There was no significant difference in increase in glans width between two groups. No study has yet been done comparing the glans width. Glans circumference has been used in some studies.[9,10]

The use of testosterone is limited due to its various adverse effects, such as development of pubic hair, facial hair, acne, bone growth, genital pigmentation and skin reactions.[11] In this study appearance of pubic hair, genital pigmentation and dermatitis were noticed as adverse effects. The bone growth was not evaluated in this study. Chalapathi *et al* reported that all patients, who were treated with topical testosterone, had pigmentation of genitalia. In our study, none of the patients developed genital pigmentation in group A, whereas every patient developed genital pigmentation on applying testosterone topically. This showed a strong association of genital pigmentation with topical testosterone. The incidence of adverse effects such as genital pigmentation and dermatitis in topical testosterone group may relate to unpredictable absorption and uncontrolled application of testosterone by parents.[2] Netto *et al*. showed greater occurrence of adverse effects associated with topical use of testosterone, such as pigmentation of genitals (69%), appearance of pubic hair (35.2%) and skin irritation at the site of application (3.8%).[12]

Appearance of pubic hair was common adverse effect in both our study groups, as it is due to systemic effect of testosterone, which is one of the secondary sexual characteristics in male. These side effects regressed after around 3 months of the cessation of testosterone therapy.[2] Besides, parents were more compliant to

intramuscular testosterone therapy than topical administration of testosterone, considering single dose administration. The limitations of this study were short time period, small sample size and consideration of only few adverse effects due to time constrain.

In conclusion, the desired penile growth can be achieved by administration of testosterone in both intramascular and tropical route in microphallic hypospadias patients without any significant difference. Development of genital pigmentation and dermatitis was significantly less in intramuscular testosterone application and thus it results patient's compliance.

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