

Pre-Operative Testosterone Stimulation Does Not Improve Outcome in Distal and Mid Shaft Hypospadias Repair: A Prospective Study from A Tertiary Hospital in Bangladesh

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Abstract

Background: There are controversies about the use of pre-operative hormonal stimulation for hypospadias repair. This study aims at assessing complications following use of pre-operative testosterone injection for distal and mid shaft hypospadias. **Subjects and Methods:** In this prospective comparative study 51 patients were divided into group A: received pre-operative testosterone and group B: did not receive preoperative testosterone. All underwent tubularized incised plate urethroplasty and were followed up for 6 months after operation to observe for the development of complications. The groups were compared with T test, Man Whitney U test, Chi square test or Fisher exact test where appropriate. **Results:** There were 15 patients in group A and 36 patients in group B. Mean age was 6.59 ± 3.96 years in group A and 6.86 ± 3.32 years in group B ($P=0.81$). Eleven patients (73.3%) received single dose of testosterone while 3 (20%) and 1 (6.7%) patients received 2 and 3 doses respectively. Sub-coronal hypospadias, 21 (41.18%) was the most common variety followed by distal penile, 18 (35.29%) and mid penile, 12 (23.53%) hypospadias. Patients who received testosterone developed more complications (7 patients, 46.67%) than patients who did not receive testosterone (12 patients, 33.33%). However, this difference was not statistically significant ($P=0.48$). Urethro-cutaneous fistula was the most common complications in both groups. **Conclusion:** Preoperative testosterone injection does not improve outcome in distal and mid shaft hypospadias repair.

Keywords: Hypospadias, Testosterone, Tubularized incised plate urethroplasty, UC fistula.

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Introduction

Hypospadias is one of the most common urological anomalies in children and the incidence is 1 in every 250 children. The repair of hypospadias is always challenging specially in small looking penis. To increase the size of the penis use of hormonal stimulation has been a common practice.^[1] Studies have shown that there is temporary increases in penile length, glans circumference, and tissue vascularity with the use of pre-operative hormonal stimulation.^[2,3] However, there are controversial reports in the literature about the effectiveness of preoperative hormone stimulation. There are also differences

in the type of hormone used, timing, dose and routes of use. Most studies suggested that it improves outcome in proximal hypospadias; but its effectiveness in distal and midshaft hypospadias has not been widely studied. This study aims to find whether preoperative testosterone stimulation has any impact on the complications following urethroplasty for distal and mid shaft hypospadias.

Subjects and Methods

Type of study: Hospital based prospective, comparative, observational study

Study period: December, 2017 to March, 2019

Place of study: Department of Pediatric Surgery, Chittagong Medical College Hospital

Study population: All patients of distal and mid penile hypospadias below 12 years of age.

Sampling technique: Consecutive sampling

Group allocation:

Group A: Received pre-operative testosterone

Group B: Did not receive pre-operative testosterone

Study procedure: The study was performed according to the Declaration of Helsinki, and was approved by the ethical review committee of Chattogram Medical College. Patients admitted in the inpatient department with hypospadias were assessed for eligibility in the study. Informed written consent was obtained after explaining the details of the procedures with their advantages and disadvantages and it was ensured to them that there was no potential risk of this study. Patient's particulars, other parameters, and variables were recorded according to the pre-designed case record form. Preoperative testosterone was given fixed dose of half ampoule of 250 mg of Sustanon (testosterone esters of propionate, phenylpropionate, isocaproate and decanoate) once every month and repeated for maximum 3 doses depending on the response assessed subjectively. Surgeries were performed at least 3 months after receiving last dose of testosterone injection. Per-operatively penile characteristics were recorded. All patients underwent tubularized incised plate urethroplasty. Post-operatively patients were followed up for a period of 6 months for the development of urethra-cutaneous (UC) fistula, meatal stenosis and wound dehiscence.

Data analysis: Data were collected using a predetermined approved case record form. Statistical analysis of the results will be obtained by using windows-based software (SPSS-22). The numerical data were expressed as mean with standard deviation (\pm SD) and were compared by the use of the Mann-Whitney U test. The categorical data were expressed as number and percentage and were compared by the use of the Chi-square test or Fisher's exact test. The level of significance was set at 5% ($P < 0.05$).

Results

During the study period a total of 51 patients underwent hypospadias repair for distal and midshaft hypospadias. Among them 15 (29.41%) received pre-operative testosterone and 36 (70.59%) did not receive any testosterone. Mean age was 6.59 ± 3.96 years in group A and 6.86 ± 3.32 years in group B ($P=0.81$). Eleven patients (73.3%) received single dose of testosterone while 3 (20%) and 1 (6.7%) patients received 2 and 3 doses respectively. Sub-coronal hypospadias,

21 (41.18%) was the most common variety followed by distal penile, 18 (35.29%) and mid penile, 12 (23.53%) hypospadias. [Figure 1] shows distribution of types of hypospadias between groups.

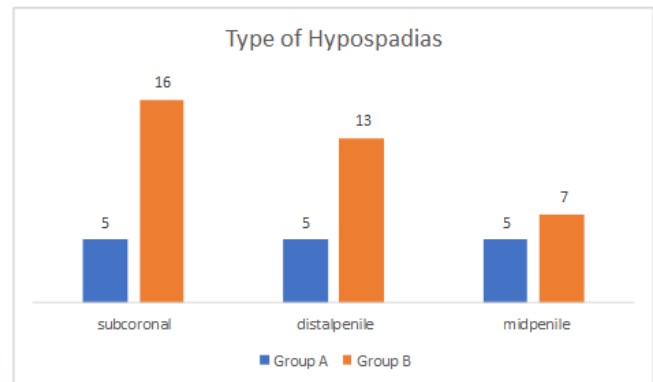


Figure 1: Types of hypospadias between groups.

There was no significant difference between the groups with regards to, glans width, glans UP width, shaft UP width and penile length before and after degloving of penis [Table 1].

There was also no significant difference between the groups with regards to penile characteristics such as, glans score, glans configuration and chordee [Table 2].

Patients who received testosterone developed more complications (7 patients, 46.67%) than patients who did not receive testosterone (12 patients, 33.33%). However, this difference was not statistically significant ($P=0.48$). Urethro-cutaneous fistula was the most common complications in both groups [Table 3].

Discussion

This study did not prove any benefit of pre-operative testosterone stimulation in distal and mid shaft hypospadias. Rather, patients who received pre-operative testosterone had more complications than their counterpart; although the difference was not significant. A systematic review done by Murillo et al also could not show any added benefit of using pre-operative testosterone.^[4] However, several prospective comparative studies showed that pre-operative testosterone use has lower complication rates.^[5,6] On the other hand, Menon et al and Gorduz et al found higher complications with testosterone in distal hypospadias.^[7,8] The benefits of use of testosterone has been suggested to be the increased size of the penis, increased vascularity to aid in healing, softening of tissue to dissect. Bastos et al reported an increased number of preputial blood vessels ($P<0.001$) and blood vessel volume density ($P<0.001$) following use of topical 1% testosterone

Table 1: Penile measurements between the groups

	Group A		Group B		P value
	Mean (mm)	SD	Mean (mm)	SD	
Glans width	18.40	4.85	17.78	4.00	0.64
Glans UP width	7.80	1.01	7.56	1.21	0.49
Shaft UP width	7.33	0.82	7.22	1.27	0.76
Penile length					
Before degloving	39.80	10.97	40.86	9.32	0.73
After degloving	41.47	10.75	41.86	9.45	0.90

Table 2: Penile characteristics between the groups

	Group A		Group B		P value
	No	%	No	%	
Glans score					
Good	6	40.00%	15	41.67%	0.93
Adequate	7	46.67%	15	41.67%	
Small	2	13.33%	6	16.67%	
Glans configuration					
Deep	6	40.00%	14	38.89%	0.98
Moderate	8	53.33%	19	52.78%	
Flat	1	6.67%	3	8.33%	
Chordee					
Absent	7	46.67%	29	80.56%	0.61
Mild	7	46.67%	5	13.89%	
Moderate	1	6.67%	1	2.78%	
Severe	0	0.00%	1	2.78%	

Table 3: Type of complications between group A and group B

	Group A		Group B	
	No	%	No	%
No complications	8	53.33%	24	66.67%
UC fistula	6	40.00%	8	22.22%
Meatal stenosis	0	0.00%	3	8.33%
Both UC fistula and Meatal stenosis	1	6.67%	1	2.78%

propionate compared with normal controls.^[9] There is also suggestions that it moves the urethral orifice towards the tip of the penis and reduces chordee.^[10] On the other hand, the problems with testosterone use has been reported to be inhibition of re-epithelialization by an enhanced inflammatory response by upregulation of tumor necrosis factor α , difficulty in hemostasis and more wound edema, wound dehiscence and other wound related problems. It is commented that the proliferating blood vessels after testosterone injection are still

immature and may not be able to support healing. There was also increased lymphocytic infiltrates.^[8,11,12]

Although hormonal therapy is used more in proximal hypospadias, its use in distal hypospadias is also well documented, especially with small penis, narrow glans circumference or urethral plate.^[8] Testosterone is the most commonly practiced hormone in this purpose. But dihydrotestosterone (DHT) and human chorionic gonadotrophin (hCG) has also been used. In an RCT Kaya et al,^[5] (2008) reported improved local condi-

tions of the skin and less postoperative complications after topical application of DHT.^[5] Koff and Jayanthi (1999) used hCG and detected statistically significant penile growth, especially in the proximal portion of the penis, moving the ectopic urethral meatus toward the tip of the glans.^[13] In a survey of pediatric urologist, 78% reported that they have used preoperative testosterone. However, some discontinued it due to difficulty of access to the medicine and increased per-operative bleeding.^[14,15]

Studies also compared topical, oral and parenteral application of testosterone and did not find any significant benefit of one over another. However, Intramuscular injection has been shown to have lesser side effects than topical use.^[8] Topical use had side effects like skin depigmentation, dermatitis, growth of pubic hair and increased number of erections; although the side effects were temporary and disappeared 3 months after stopping therapy.^[16] In a randomized study of 26 children, significant penile growth was noticed in both topical and parenteral applications. Maximum response was observed during the third week of therapy, the basal serum testosterone was within the normal range and linear growth did not alter significantly for the chronological age.^[17] Monfort and Lucas used topical DHT cream daily for 4 weeks, and reported a mean increase in penile circumference and length by 50% without any lasting side effects or gonadotropin level changes or effects in the pubertal or post-pubertal period.^[17]

There is also no consensus about the dose and timing of application. Use of both fixed dose (25 mg/kg/month) and weight adjusted dose (2 mg/kg/week) of testosterone enanthate showed significant effects on length.^[18,19] Commonly, the intramuscular treatment lasts for 3 months, consisting of a monthly application of testosterone, while the topical treatment lasts on average 3-4 weeks, with 2 daily applications.^[10,17] Most surgeons stop the application 2 weeks before surgery and assessed adequacy of treatment by subjective assessment of increase in size.^[10]

The relationship of glans width with postoperative complications was also controversial. A glans width of 14 mm or less has been found to have a 2.7- fold increased risk of UC fistula with each 1 mm change in size. Glans dehiscence has been noted in 10% patients with glans width less than 14 mm in comparison to 4% in those with width 14 mm or more. On the other hand, Faasse et al. did not find any difference in complications in those with glans width <14 mm (16%) and those with a larger glans (15%).^[20]

The descriptions of intra-operative problems after pre-operative use of testosterone are not homogeneous. The main reports were related to excessive bleeding during surgery. Studies that reported absence of intraoperative complications mainly referred to absence of important bleeding during surgical time, which was an empirical evaluation with no

measurement of the amount of blood with comparison to a control group.^[10,16] Koff and Jayanthi (1999) reported fewer fistulas and a change in the type of surgery required, avoiding use of pedicle flaps and tube repairs in 25% of the boys.^[13] However, their report on changing surgical technique was empirical without any objective data. More often, surgical technique for hypospadias repair is chosen after the child is under anesthesia when the surgeon can evaluate the penis better. Kaya et al. (2008) reported a significant reduction in fistulas, glanular dehiscence, meatal stenosis and a decreased need for re-operation.^[5]

Another aspect is that in many studies, preoperative hormones were used in most severe cases. So, comparing them with less severe types are not free of bias. In this study also, the 2 groups might not be equal since there is no measurement of penile characteristics before application of testosterone. Other limitations of the study are that it was not randomized, sample size was small and follow up period was not long enough.

Conclusion

The benefits of using testosterone preceding hypospadias correction have not been proven in this study. Further randomized controlled trial is necessary for final comment in this subject.

Ethical Considerations

Informed written consent was obtained from parent of the patient. This study was approved by the ethical review board of Chittagong Medical College (ERB memo no-CMC/PG/2017/355). This study is a part of thesis of the principal author under Bangabandhu Sheikh Mujib Medical University, Bangladesh.

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