

# Role of parenteral testosterone in hypospadias: A study from a teaching hospital in India

Reyaz Ahmad, Rajendra Singh Chana<sup>2</sup>, Syed Manazir Ali<sup>3</sup>, Shehtaj Khan<sup>1</sup>

Departments of Pediatric Surgery, and <sup>1</sup>Surgery, Sawai Man Singh Medical College, Jaipur, Departments of <sup>2</sup>Surgery, and <sup>3</sup>Pediatrics, Jawaharlal Nehru Medical College, A.M.U., Aligarh, India

## Abstract

**Objectives:** To evaluate the effect of parenteral testosterone on penile length, preputial skin and side effects in patients with hypospadias.

**Materials and Methods:** 23 patients with hypospadias were included in this study. An oily solution, each ml of which contained testosterone propionate 25 mg, and testosterone enanthate 110 mg, equivalent to 100 mg of testosterone was given deep intramuscularly 4, 3 and 2 weeks before reconstructive surgery at the dose of 2 mg/kg body weight. Increase in penile length, transverse preputial diameter, and diameter at the base of penis were noted. Basal testosterone levels were obtained before the institution of therapy and on the day of operation. In addition, side effect such as development of pubic hair and delay in bone age was noted.

**Results:** Following parenteral testosterone administration, the mean increase in penile length, transverse preputial diameter and diameter at the base of penis was  $1.35 \pm 0.40$  cm ( $P < 0.001$ ),  $1.40 \pm 0.47$  cm ( $P < 0.001$ ), and  $0.72 \pm 0.47$  cm ( $P < 0.001$ ), respectively. Serum testosterone level after injection was well within normal range for that age. Minimal side effects were noted in form of development of fine pubic hair.

**Conclusion:** We conclude that parenteral testosterone can be safely used to improve the surgical outcome of hypospadias repair.

**Key Words:** Hypospadias, microphallus, parenteral testosterone

## Address for correspondence:

Dr. Reyaz Ahmad, 15- Brij Colony, Inside Chambal Power House, Hawa Sadak, Jaipur - 302 019, Rajasthan, India. E-mail: reyazdr@yahoo.co.in

Received: 20.11.2010, Accepted: 17.01.2011

## INTRODUCTION

The child with a hypospadias presents a difficult surgical challenge. Despite being one of the most common congenital defects in boys, the etiology of hypospadias remains largely unknown, although epidemiological studies indicate an etiological heterogeneity.<sup>[1]</sup> Surgical correction of genital defects was formerly proposed when the size of the penis was sufficient

to permit easy surgical repair. Coincidentally, many children with hypospadias also have a small phallus. According to available data, a small phallus in hypospadias is a result of fetal testosterone insufficiency.<sup>[2]</sup> To enlarge penile size, temporary stimulation with testosterone or dihydrotestosterone cream has been used; however, the results were not only inconsistent, but absorption was also variable.<sup>[3]</sup>

With genital repairs being accomplished in younger patients, the use of pre-operative parenteral testosterone for temporary penile stimulation allows the surgeon to operate on a larger and more vascularised organ. This is especially useful in those with a paucity of penile skin, and those who have undergone penile repair unsuccessfully.<sup>[4]</sup> In the present study, we intended to analyze the effect of parenteral testosterone in cases of hypospadias.

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/0974-7796.84966

## MATERIALS AND METHODS

This was a prospective trial conducted as an outpatient study over a period of 18 months. Twenty-three patients with hypospadias aged between 6 months to 10 years, comprising of 9 cases of anterior (3 glanular, 2 subcoronal, and 4 distal penile), 5 middle (3 midshaft and 2 proximal penile) and 9 cases of posterior (8 penoscrotal and 1 perineal) hypospadias were included in this study before the repair of their hypospadias deformity. After obtaining the permission from the research review board, an informed consent was taken from the parents/guardian. Injection Testoviron (oily solution each ml containing testosterone propionate 25 mg, and testosterone enanthate 110 mg, equivalent to 100 mg of testosterone) was given deep intramuscularly at 4, 3 and 2 weeks before reconstructive surgery at the dose of 2 mg/kg body weight.

Penile length, i.e., stretched penile length from pubic bone to the tip of the glans in centimeters using Vernier's caliper, transverse preputial diameter and diameter at the base of penis were measured before the therapy and the surgery. Serum testosterone level was measured using Radioimmunoassay (RIA) technique before the therapy and surgery. Side effects such as development of fine pubic hair and acne were evaluated. Bone age was also checked 1 year after the therapy, by evaluating the ossification centers of the hands and wrists. Pre-versus post-treatment groups ( $P \leq 0.05$ ) were subjected to paired *t* test using Statistical Package for the Social Sciences (SPSS statistical package).

## RESULTS

Twenty-three patients with hypospadias including 9 cases of anterior, 5 middle and 9 posterior hypospadias received injection Testoviron each ml containing testosterone propionate 25 mg, and testosterone enanthate 110 mg, equivalent to 100 mg of testosterone deep intramuscularly at 4, 3 and 2 weeks before reconstructive surgery at the dose of 2 mg/kg body weight.<sup>[4,6]</sup> The mean age of presentation was 4.6 years (range, 6 months to 10 years). Thirteen patients were between 2 and 6 years of age. There were 5 patients less than 2 years of age and 5 patients more than 6 years of age. Mother of three children gave history of receiving steroid hormonal therapy during first trimester of pregnancy, mainly for the treatment of threatened abortion. None of the children were evaluated for endocrinopathies. Familial incidence was seen in three patients. Out of these, one patient had his father, and two children had their brothers suffering from hypospadias. Bilateral undescended testis and inguinal hernia was found in three and two children respectively. No chromosomal analysis was done in these patients. Bilateral congenital talipes equinovarus (CTEV) deformity was seen in one patient. Intravenous urography was done in three patients due to associated anomaly; however, none showed any upper urinary tract anomaly.

The mean penile length of  $3.01 \pm 1.39$  cm increased to  $4.36 \pm 1.38$  cm. The mean increase in penile length was  $1.35 \pm 0.40$  cm ( $P < 0.001$ ). The mean increase in transverse preputial diameter and diameter at the base of penis was  $1.40 \pm 0.47$  cm and  $0.72 \pm 0.47$  cm, respectively ( $P < 0.001$ ). The mean increase in serum testosterone level was  $4.02 \pm 0.76$  ng/ml ( $P < 0.001$ ) [Table 1]. Two patients in the study group developed mild pubic hair, after 2 weeks of first injection. There was no untoward bleeding noted during surgery in any of the children. Only 3 patients could be evaluated for bone age as majority of the patients were lost to follow up. There was no delay in bone age in the children evaluated. Post operative length of penis/circumference of glans was not assessed during the follow-up period.

## DISCUSSION

The role of supplemental preoperative endocrine therapy is not clear. Koff and Jayanthi in a study of 12 patients with proximal hypospadias and severe chordee, administered a 5 week course of human chorionic gonadotropin (hCG) at the dose of 250 IU and 500 IU injected twice weekly in boys younger than 1 year, and 1 to 5 years old respectively, immediately preceding hypospadias repair. They concluded that hCG pretreatment in infancy produces disproportional penile enlargement, which advances the meatus distally to decrease the severity of hypospadias and chordee.<sup>[7]</sup> However, preoperative treatment with gonadotropin has not been well supported because of lack of treatment protocols. Further problems were the wide variations in response to treatment with hCG, failure to assess androgen receptor status or 5- $\alpha$  reductase status and lack of measurement of testosterone before and after treatment.<sup>[8]</sup>

The use of testosterone compounds in patients with a genital defect is not a new concept. Testosterone and dihydrotestosterone

**Table 1: Effect of parenteral testosterone on penile dimensions and serum testosterone**

Variables	Mean	S.D	Paired <i>t</i> -test		
			Paired difference		
			Mean difference	S.D	P value
Penile length (cm)					
Pre-injection	3.01	1.38			
Post-injection	4.36	1.37	-1.35	0.40	0.00
Transverse preputial diameter (cm)					
Pre-injection	2.99	0.81			
Post-injection	4.38	1.04	-1.40	0.41	0.00
Diameter at the base of penis (cm)					
Pre-injection	1.31	0.31			
Post-injection	2.03	0.51	-0.72	0.47	0.00
Serum testosterone (ng/ml)					
Pre-injection	0.31	0.33			
Post-injection	4.34	1.03	-4.02	0.76	0.00

cream have been used previously.<sup>[9,10]</sup> Monfort and Lucas used a 4-week period of local penile stimulation with daily application of 5% dihydrotestosterone cream before hypospadias repair. The author reported a mean increase in penile length and circumference by 50% of pretreatment measurements, without any lasting side effects or gonadotropin level perturbation or effect in the pubertal or post pubertal period.<sup>[9]</sup> Local testosterone stimulation of a poly operated case of hypospadias with consequent penile enlargement and surgical success has been reported.<sup>[11]</sup> Gearhart and Jeffs reported that the result of local application of testosterone cream for temporary penile enhancement were inconsistent because of variable absorption. They used testosterone enanthate injection at the dose of 2mg/kg intramuscularly 5 weeks and 2 weeks before surgery. In patients with hypospadias, epispadias and urethral fistula testosterone caused a mean increase in penile length of 2.7 cm, in circumference of 2.3 cm and transverse preputial diameter by 2.0 cm, as well as increase in local vascularity, with negligible side effects.<sup>[4]</sup> This led us to attempt using parenteral slowly released testosterone for preoperative penile stimulation.

In our study, the effect of parenterally administered testosterone on penile growth upto the day of operation was statistically significant ( $P<0.001$ ). The mean increase in penile length was  $1.35\pm 0.40$  cm. There was an increase in transverse preputial diameter of  $1.40\pm 0.47$  cm [Table 1]. The increase in penile skin availability was in proportion to the increase in penile size. The texture, vascularity and pliability of penile skin improved markedly. This increased transverse length is helpful in proximal and perineal hypospadias, where a pedicled transverse island flap may be used. Negligible side effects were noted in form of development of pubic hair in few patients. The basal testosterone level was well within normal range and there was no delay in bone age in patients evaluated.

Chalapathi *et al.* in a randomized study of 26 patients with microphallic hypospadias, undertaken to compare the efficacy of parenteral versus topical testosterone application on penile length, concluded that significant penile growth ( $P<0.01$ ) was noted in both groups when compared with pre-therapy, with maximum response observed during the third week of therapy. The basal serum testosterone was within the normal range in both the groups. Linear growth did not alter significantly for chronological age, but the authors observed that there was evidence of unpredictable absorption of testosterone in topical group. Although the study was done on small number of children, it does appear that intramuscular administration of testosterone is preferable.<sup>[5]</sup> Similar results were reported by Nerli *et al.* in a randomized study of 21 patients with microphallic hypospadias.<sup>[6]</sup> Luo *et al.* in a study of 25 patients with hypospadias aged 9-12 months, administered testosterone 25mg deep intramuscularly once per month for 3 months. There was an impressive increase in penile length and glans

circumference noted in almost all patients ( $P<0.01$ ). Secondary effects were minimal, there was no untoward bleeding problem at operation, and no delay in bone age was noted.<sup>[3]</sup> In our study too, there was significant increase in penile length, transverse preputial diameter and diameter at the base of penis without any significant side effect. The optimal amount of testosterone to stimulate penile growth significantly is not known with certainty. Rosenfeld *et al.* and Rosenfield have shown that depot form of testosterone in a dosage of 200mg/m<sup>2</sup> per months for 3 months and 44mg/m<sup>2</sup> per months for 6 months can initiate frank virilization. In both these studies, testosterone dosages were significantly higher than that used in our study without an inordinate advancement of bone age.<sup>[12,13]</sup>

## CONCLUSION

Penile augmentation with parenteral testosterone is beneficial in terms of increasing the size of the phallus and penile skin in hypospadias. It improves the texture, vascularity, and pliability of penile skin and its use is associated with negligible side effects. We conclude that parenteral testosterone can be safely used to improve the results of reconstructive surgery on hypospadias.

## REFERENCES

1. Brouwers MM, van der Zanden LF, de Gier RP, Barten EJ, Zielhuis GA, Feitz WF, *et al.* Hypospadias: Risk factor patterns and different phenotypes. *BJU Int* 2010;105:254-62.
2. Feldman KW, Smith DW. Fetal phallic growth and penile standards for newborn male infants. *J Pediatr* 1975;86:395-8.
3. Luo CC, Lin JN, Chiu CH, Lo FS. Use of parenteral testosterone prior to hypospadias surgery. *Pediatr Surg Int* 2003;19:82-4.
4. Gearhart JP, Jeffs RD. The use of parenteral testosterone therapy in genital reconstructive surgery. *J Urol* 1987;138:1077-8.
5. Chalapathi G, Rao KL, Chowdhary SK, Narasimhan KL, Samujh R, Mahajan JK. Testosterone therapy in microphallic hypospadias: Topical or Parenteral?. *J Pediatr Surg* 2003;38:221-3.
6. Nerli RB, Koura A, Prabha V, Reddy M. Comparison of topical versus parenteral testosterone in children with microphallic hypospadias. *Pediatr Surg Int* 2009;25:57-9.
7. Koff SA, Jayanthi VR. Preoperative treatment with human chorionic gonadotropin in infancy decreases the severity of proximal hypospadias and chordee. *J Urol* 1999;162:1435-9.
8. Husmann DA. Editorial: Microphallic hypospadias- the use of human chorionic gonadotropin and testosterone before surgical repair. *J Urol* 1999;162:1440-1.
9. Monfort G, Lucas C. Dihydrotestosterone penile stimulation in hypospadias surgery. *Eur Urol* 1982;8:201-3.
10. Jacobs SC, Kaplan GW, Gittes RF. Topical testosterone therapy for penile growth. *Urology* 1975;6:708-10.
11. Guthrie RD, Smith DW, Graham CB. Testosterone treatment for micropenis during early childhood. *J Pediatr* 1973;83:247-52.
12. Rosenfeld RG, Northcraft GB, Hintz RL. A prospective randomized study of testosterone treatment of constitutional delay of growth and development in male adolescents. *Pediatrics* 1982;69:681-7.
13. Rosenfield RL. Low-dose effect on somatic growth. *Pediatrics* 1986;77:853-7.

**How to cite this article:** Ahmad R, Chana RS, Ali SM, Khan S. Role of parenteral testosterone in hypospadias: A study from a teaching hospital in India. *Urol Ann* 2011;3:138-40.

**Source of Support:** Nil, **Conflict of Interest:** None.