Original Article

Effect of Pre-operative Parenteral Testosterone on Penile Dimensions and Vascularity in Proximal Hypospadias: A Prospective Observational Study

Md Mokarram Ali
Department of Pediatric Surgery, Pt BDS PGIMS, Rohtak, Haryana, India

Abstract

Introduction: Severe or proximal hypospadias is associated with inadequate local tissue and small phallus size. Pre-operative androgens have been used to increase phallus size, but there are very few studies on its role in proximal hypospadias. This study aimed to assess the effects of pre-operative intramuscular (IM) testosterone on proximal penile hypospadias in terms of penile morphology and tissue characteristics of penile skin. **Materials and Methods:** This prospective observational study was conducted on 27 patients of proximal hypospadias over a period from June 2017 to July 2018. The patients were sequentially enrolled into two groups: Group A and Group B. Group A patients received IM testosterone before surgery, whereas Group B patients were operated without pre-operative testosterone. Outcomes were analysed in terms of change in penile dimensions and effect on vascularity of penile skin. **Results:** Pre-operative IM testosterone in Group A caused a significant increase in stretched penile length from a mean of 3.058 cm (±0.691) to 3.9 cm (±0.875) (P = 0.002), penile circumference from a mean of 4.142 cm (±0.772) to 4.667 cm (±1.174) (P = 0.029) and glans width from a mean of 1.225 cm (±0.245) to 1.750 cm (±0.571) (P = 0.002). There was higher microvessel density in the preputial skin of Group A (mean: 12.212 [±4.745] blood vessels/high-power field [HPF]) compared to Group B (8.867 [±3.258] blood vessels/HPF) (P = 0.043). **Conclusion:** Pre-operative testosterone in proximal hypospadias causes significant changes in penile dimensions and tissue characteristics. Improvement in penile dimensions leads to ease in operability and better tissue handling. However, more studies with large sample size are required to establish the beneficial effects of pre-operative hormone stimulation on urethroplasty.

Keywords: Hypospadias, parenteral, testosterone, vascularity

Introduction

Small size of the phallus in proximal hypospadias and paucity of tissue in that area are limiting factors for urethroplasty. Testosterone and dihydrotestosterone (DHT) are the peripherally acting androgens which act on androgen receptors of genitalia causing its growth and development. The effect is more pronounced on the genitals as a result of higher expression of androgen receptors.[1] This is the basis of using pre-operative androgen stimulation in hypospadias surgery. Pre-operative testosterone treatment is known to increase penile length, decreased early fibrosis along with an increased absolute number of blood vessels and blood vessel density.[2] Despite the widespread prescription of pre-operative testosterone in boys with hypospadias, there are growing concerns regarding the side effects such as increased pubic hair growth, aggressive behaviour, accelerated linear height and bone age, though they have been shown to be insignificant.[3] In addition, an exaggerated inflammatory response in the supportive stroma has also been noted.[4] Due to this, androgens may slow down healing and affect the repair.[5]

Data regarding the pre-operative use of testosterone are mostly from non-randomised studies with small sample size. Till date, very few prospective studies exist that have studied the complication rates associated with pre-operative hormonal stimulation (PHS). Kaya *et al*. determined in their

Received: 26-11-2022 **Revised:** 22-01-2023 **Accepted:** 03-04-2023 **Available Online:** 14-03-2024

Access this article online

Quick Response Code:

Website: https://journals.lww.com/AJPS

DOI: 10.4103/ajps.ajps_160_22

Address for correspondence: Dr. Md Mokarram Ali, Department of Pediatric Surgery, Pt BDS PGIMS, Rohtak, Haryana, India. E-mail: mohdmokarramali1990@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Ali MM. Effect of pre-operative parenteral testosterone on penile dimensions and vascularity in proximal hypospadias: A prospective observational study. Afr J Paediatr Surg 2024;21:228-31.

study that complication rates in patients who were treated preoperatively with DHT therapy were significantly lower, but the effects of testosterone therapy were not determined in this study and the study population was heterogeneous.[6] In a randomised controlled study by Asgari *et al*., in which parenteral testosterone was used, the overall complication rate in terms of urethrocutaneous fistula and meatal stenosis was significantly higher in the control group than in the testosterone group, although they were very selective in their choice of patients.[7] The effect of pre-operative hormone stimulation on both short-term and long-term outcomes has not been studied adequately in the literature with no uniform guidelines regarding its use. In proximal hypospadias, the effect of testosterone is not likely to be seen uniformly in all patients unlike distal hypospadias due to variations in androgen receptors.[8] There are very few randomised studies on post-operative results after androgen use, especially in proximal hypospadias. According to a systematic review by Wright *et al*., the effect of PHS on operative outcomes after proximal hypospadias repair remains unclear which requires further investigation.[9] In this prospective study, the effect of pre-operative parenteral testosterone in proximal penile hypospadias was studied by assessing the pre-operative changes induced by testosterone on penile dimensions and penile vascularity.

Materials and Methods

This was a prospective observational study, carried out in a tertiary care referral centre, on patients with proximal hypospadias. Requisite approval from the institute ethics committee was taken. Proximal hypospadias was defined as urethral opening located at or proximal to the penoscrotal junction. All patients with proximal hypospadias with or without chordee and those who had already undergone chordee correction and were awaiting urethroplasty were prospectively enrolled between June 2017 and July 2018. Patients who had previously undergone urethroplasty which had failed, previous testosterone use by either local application or intramuscular (IM) injection and those with distal and mid-penile hypospadias were excluded from the study.

The selected patients were sequentially enrolled into two groups (A and B) using a computer-generated table created by the investigator. Group A patients received pre-operative IM testosterone in three doses (2 mg/kg/dose [maximum up to 25 mg]) at 1-month interval for 3 months followed by urethroplasty 1–3 months after the last injection. Group B patients did not receive testosterone.

Penile dimensions such as stretched penile length (SPL), glans width (GW) and penile circumference (PC) in centimetres (cm) were noted before the start of therapy in the outpatient department at the time of inclusion in the study and 2 weeks after the third dose of testosterone in Group A. In Group B, it was measured in the outpatients at the time of inclusion in the study. During surgery (chordee correction or urethroplasty), preputial/penile skin was taken for histopathological examination to assess the vascularity using monoclonal mouse anti-human CD31 antigen acting on paraffin sections as a marker. The microvessel density (MVD) was estimated by immunohistochemical staining of the preputial or penile skin. Three ×40 microscopic fields were randomly chosen and photographed. Cycloid points were superimposed on these images, and only those vessels that touch these points were counted. The absolute number of blood vessels per field was counted, and the mean number of blood vessels per field was determined. The pathologist was kept blinded regarding the group allocation.

Statistical analysis

Data were analysed using the software, Statistical Package for the Social Sciences (SPSS®) for Windows 11.5 (IBM, Chicago, USA). The comparison of pre-operative penile dimensions between the two groups was performed using one-way ANOVA and *post hoc* Bonferroni tests. Data were expressed as mean ± standard error, with statistical significance considered at $P < 0.05$. Pre- and post-testosterone results in Group A were analysed using paired *t*-test.

Results

A total of 27 patients were included in the study, of which 12 were in the study group (A) and 15 were in the control group (B).

Table 1a: Baseline serum testosterone level in Group A (*n*=12) and B (*n*=15)

	Group	Mean (range)	SD	*P*
Serum testosterone level (nmol/L)	A	0.201 (0.087–0.926)	0.274	0.793
	B	0.232 (0.087–1.14)	0.321	

SD: Standard deviation

Table 1b: Comparison of serum testosterone level pre- and post-intramuscular testosterone therapy in Group A (*n*=12)

Serum testosterone level (nmol/L)	Mean (range)	SD	*P*
Pre	0.201 (0.087–0.926)	0.274	0.001
Post	15.844 (0.087–33.07)	12.429	

SD: Standard deviation

Table 2a: Baseline penile dimensions in Group A (*n*=12) and B (*n*=15)

Penile dimensions (cm)	Group	Mean (range)	SD	*P*
SPL	A	3.058 (2–4.5)	0.691	0.409
	B	3.313 (2–4.5)	0.850	
PC	A	4.142 (3–5.5)	0.772	0.724
	B	4.033 (3–5.5)	0.790	
GW	A	1.225 (1–1.8)	0.245	0.965
	B	1.220 (0.7–1.9)	0.326	

SPL: Stretched penile length, PC: Penile circumference at base, GW: Glans width, SD: Standard deviation

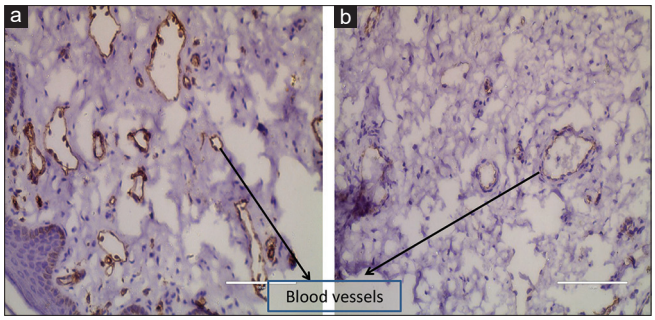


Figure 1: (a) CD31-stained slide (×40) of preputial skin of Group A patients showing increased blood vessel count. (b) CD31-stained slide (×40) of preputial skin of Group B patients showing less blood vessel count

Table 2b: Comparison of penile dimensions in Group A (*n*=12) pre- and post-intramuscular testosterone therapy

Penile dimensions (cm)	Mean (range)	SD	*P*
SPL			
Pre	3.058 (2–4.5)	0.691	0.002
Post	3.900 (2.5–5.5)	0.875	
PC			
Pre	4.142 (3–5.5)	0.772	0.029
Post	4.667 (4–8)	1.174	
GW			
Pre	1.225 (1–1.8)	0.245	0.002
Post	1.750 (1.2–3)	0.571	

SPL: Stretched penile length, PC: Penile circumference at base, GW: Glans width, SD: Standard deviation

Table 3: Comparison of micro vessel density in Group A and B on the basis of CD 31 staining

	Group	*n*	Mean (range)	SD	*P*
MVD	A	12	12.212 (6.667–23)	4.745	0.043
	B	15	8.867 (4.667–16)	3.258	

MVD: Micro vessel density, SD: Standard deviation

The mean age in Group A was 3.237 years (range: 1–7 years), whereas the mean age in Group B was 3.666 years (range: 1–12 years). The mean baseline serum testosterone level was 0.201 nmol/l (0.087–0.926) in Group A and 0.232 nmol/l (0.087–1.14) in Group B, which was comparable with no significant difference. However, the mean serum testosterone level increased to 15.844 nmol/l (0.087–33.07) after the administration of three doses of IM testosterone with significant $P = 0.001$ [Table 1a and b].

The baseline penile dimensions (SPL, GW and PC) were comparable in both the groups. However, after IM testosterone therapy, there were significant changes in these dimensions [Table 2a and b]. SPL increased from a mean value of 3.058 to 3.9 cm with $P = 0.002$. Similarly, GW increased from a mean value of 1.225 to 1.750 cm ($P = 0.002$). PC increased from a mean value of 4.142 to 4.667 cm with $P = 0.029$.

The MVD was found to be significantly higher in Group A as compared to Group B with $P = 0.043$ [Table 3 and Figure 1].

Discussion

Correction of hypospadias is usually recommended at an early age, but size of penis and paucity of tissue in that area may discourage surgeons from undertaking the corrective operations. The issue of small-sized penis and small GW is more pronounced in proximal hypospadias. It is speculated to be due to foetal testosterone therapy.[10] PHS in the form of topical or IM therapy has been used to improve the availability of tissues for good surgical correction.[6] Testosterone is the most commonly recommended hormone therapy before hypospadias correction and has been found to be beneficial in various studies.[11,12] According to Krishnan *et al*., the pre-operative testosterone therapy is effective in achieving the primary goal of increasing penile dimensions. However, there is no consensus regarding the route of administration. According to Ishii *et al*., the IM testosterone significantly increases penile length for hypospadias in prepubertal boys. Surgery for proximal hypospadias is associated with high rate of complications, urethrocutaneous fistula, glans dehiscence and meatal stenosis being the most common complications each occurring in variable range.[13] There are many factors responsible for high rate of complications in proximal hypospadias surgery. The corpus cavernosum and the erectile bodies of the penis are smaller, and the elasticity of the corporal tissues is compromised adding anatomical complexity to repair.[14] A small glans size, particularly when the width is 14 mm or less, increases the risk of complication.[15] Supplemental testosterone increases GW before surgery, thereby potentially reducing this risk.[16]

Ahmad *et al*. in their study in 23 hypospadias cases concluded that parenteral administration of testosterone had a statistically significant effect on penile growth. They reported a significant improvement in pliability and vascularity of the penile skin intraoperatively in the treatment group. The mean increase in penile length, transverse diameter at the base of penis and preputial diameter was 1.35 ± 0.40 cm ($P < 0.001$), 0.72 ± 0.47 cm ($P < 0.001$) and 1.40 ± 0.47 cm ($P < 0.001$), respectively, in the parenteral testosterone-treated group.[17] In our study, in Group A, after three doses of IM testosterone enanthate given at monthly intervals, we found an increase in mean SPL from 3.058 cm (±0.691) to 3.9 cm (±0.875) with $P = 0.002$. There was also significant increase in GW from 1.225 cm (±0.245) to 1.750 cm (±0.571) with $P = 0.002$. PC also increased from a mean value of 4.142 cm (±0.772) to 4.667 cm (±1.174) with $P = 0.029$ which is significant.

Bastos *et al*. demonstrated that the application of 1% testosterone propionate ointment before hypospadias surgery induced neovascularisation, increasing the absolute number of vessels and blood volume density.[2] Testosterone-treated prepuces showed an increased absolute number of blood vessels (mean ± standard deviation: 8.5 ± 1.3 vs. 4.8 ± 1.8

vessels per field, $P < 0.001$). Testosterone induced significantly increased blood vessel volume density (mean: 50.5% ±7.8% vs. 24.8% ±8.6% vessels per point, $P < 0.001$) compared to those in the control group. Stern *et al*. also demonstrated that with the treatment of human foreskin with testosterone, increased vascularity and decreased early fibrosis in an experimental transplant model were noted. The tissue of the testosterone-treated group demonstrated increased factor VIII staining (31.14 ± 1.53 vessels per high-power field [HPF]) compared to the control samples (18.25 ± 2.3 vessels per HPF; $P < 0.005$).[18] In our study, we found a significantly high MVD ($P = 0.043$) in preputial skin of patients in Group A who received IM testosterone before surgery, with a mean value of 12.212 (±4.745) blood vessels per HPF as compared to only 8.867 (±3.258) blood vessels per HPF in control Group B.

Thus, in our study, we found that after the administration of 3 monthly doses of IM testosterone, there was a significant increase in SPL, PC at base and GW which led to an ease in operability. There was also significant high MVD in Group A as compared to Group B.

Conclusion

Pre-operative IM testosterone therapy causes a significant increase in penile dimensions as well as MVD. Improvement in penile dimensions leads to ease in operability and better tissue handling. However, more studies with large sample size are required to establish the beneficial effects of pre-operative hormone stimulation on urethroplasty.

Limitations

The overall sample size was small to compare various outcomes in Groups A and B.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Baskin L, Cao M, Sinclair A, Li Y, Overland M, Isaacson D, *et al.* Androgen and estrogen receptor expression in the developing human penis and clitoris. Differentiation 2020;111:41-59.
2. Bastos AN, Oliveira LR, Ferrarez CE, de Figueiredo AA, Favorito LA, Bastos Netto JM. Structural study of prepuce in hypospadias – Does topical treatment with testosterone produce alterations in prepuce vascularization? J Urol 2011;185:2474-8.
3. Netto JM, Ferrarez CE, Schindler Leal AA, Tucci S Jr., Gomes CA, Barroso U Jr. Hormone therapy in hypospadias surgery: A systematic review. J Pediatr Urol 2013;9:971-9.
4. Hassan JM, Pope JC 4th, Revelo P, Adams MC, Brock JW 3rd, DeMarco RT. The role of postoperative testosterone in repair of iatrogenic hypospadias in rabbits. J Pediatr Urol 2006;2:329-32.
5. Ashcroft GS, Mills SJ. Androgen receptor-mediated inhibition of cutaneous wound healing. J Clin Invest 2002;110:615-24.
6. Kaya C, Bektic J, Radmayr C, Schwentner C, Bartsch G, Oswald J. The efficacy of dihydrotestosterone transdermal gel before primary hypospadias surgery: A prospective, controlled, randomized study. J Urol 2008;179:684-8.
7. Asgari SA, Safarinejad MR, Poorreza F, Asl AS, Ghanaie MM, Shahab E. The effect of parenteral testosterone administration prior to hypospadias surgery: A prospective, randomized and controlled study. J Pediatr Urol 2015;11:6.e1-6.
8. Zhao W, Yin J, Yang Z, Xie J, Zhang Y, Xu W, *et al.* Meta-analysis of androgen insensitivity in preoperative hormone therapy in hypospadias. Urology 2015;85:1166-72.
9. Wright I, Cole E, Farrokhyar F, Pemberton J, Lorenzo AJ, Braga LH. Effect of preoperative hormonal stimulation on postoperative complication rates after proximal hypospadias repair: A systematic review. J Urol 2013;190:652-59.
10. Feldman KW, Smith DW. Fetal phallic growth and penile standards for newborn male infants. J Pediatr 1975;86:395-8.
11. Krishnan A, Chagani S, Rohl AJ. Preoperative testosterone therapy prior to surgical correction of hypospadias: A review of the literature. Cureus 2016;8:e677.
12. Ishii T, Hayashi M, Suwanai A, Amano N, Hasegawa T. The effect of intramuscular testosterone enanthate treatment on stretched penile length in prepubertal boys with hypospadias. Urology 2010;76:97-100.
13. Cousin I, Basmaison C, Cousin E, Lebonvallet N, Germouty I, Leven C, *et al.* Complication rates of proximal hypospadias: Meta-analyses of four surgical repairs. J Pediatr Urol 2022;18:587-97.
14. Camoglio FS, Bruno C, Zambaldo S, Zampieri N. Hypospadias anatomy: Elastosonographic evaluation of the normal and hypospadic penis. J Pediatr Urol 2016;12:5.e1-5.
15. Bush NC, Villanueva C, Snodgrass W. Glans size is an independent risk factor for urethroplasty complications after hypospadias repair. J Pediatr Urol 2015;11:5.e1-5.
16. Paiva KC, Bastos AN, Miana LP, Barros Ede S, Ramos PS, Miranda LM, *et al.* Biometry of the hypospadic penis after hormone therapy (testosterone and estrogen): A randomized, double-blind controlled trial. J Pediatr Urol 2016;12:6.e1-6.
17. 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.
18. Stern JM, Chen J, Peters SB, Stahl PJ, El-Chaar M, Felsen D, *et al.* Testosterone treatment of human foreskin in a novel transplant model. Urology 2004;63:999-1003.