



EFFECT AND SAFETY OF PARENTERAL TESTOSTERONE ENANTHATE IN MICROPHALLIC HYPOSPADIAS - AN AMBISPECTIVE STUDY.

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Abstract

Background and objective: Microphallic hypospadias is challenge to surgical repair. There is deficiency of the tissues. But, with parenteral use of testosterone there is increase in dimensions and neovascularisation in all penile tissues. Surgery performed on augmented penile tissue has better blood supply and outcome. This study focuses to estimate the size of microphallic hypospadias after administration of parenteral testosterone in pre-operative period. To determine the adverse effects of parenteral testosterone given to children pre operatively. To determine the complications in intraoperative and postoperative period.

Methods: Penile dimensions are measured pre and post testosterone therapy in preoperative period. Testosterone enanthate in a dose of 2mg/kg/dose deep intra muscular given at 0,3 and 6 weeks. Adverse effects of testosterone therapy and complications of the surgery noted.

Results: There is increased mean penile length from penoscrotal junction (37.4%), transverse preputial diameter (38.7%), glans width (76%), and width of the urethral plate (58%). Injection site redness is the only adverse effect seen in 13.6% of children in preoperative period. Intraoperative bleeding (18.1%), urethrocutaneous fistula (9%), postoperative haematoma (9%), wound infection (4.5%) and wound dehiscence (4.5%) were the commonest side effect observed.

Conclusions: Use of testosterone is safe and effective in children with microphallic hypospadias. The complications rate of surgery in microphallic hypospadias with preoperative testosterone parenteral therapy is similar as with normal hypospadias without use of preoperative parenteral testosterone therapy.

Key words: Microphallic hypospadias, Parenteral testosterone therapy

Introduction

Abnormal ventral opening of urethra proximally is defined as Hypospadias. The prevalence in Asia is 0.6 per thousand of live male births^[1]. It is associated with various penile abnormalities. They are a micropenis, meatal stenosis, torsion, chordee, narrow urethral plate and deficient dorsal prepuce.

Of all of them, micropenis is challenge to surgical repair of hypospadias. Micropenis in children is defined as size of the penis less than two standard deviation (<2 SD) below the mean for the age^[2]. There is deficiency of the tissues. Urethra is narrow (<7 mm) so TIP (Tubularised incised plate) urethroplasty is not possible. It is so deficient that even onlay or transverse preputial island flap urethroplasty is not a viable option. The penile dartos is also deficient, thus lacking adequate cover on urethroplasty. The structures are so miniaturized that even with gentle and meticulous handling of tissue the blood supply gets damaged leading to probable necrosis. Further, simultaneous presence of undescended testis and high riding scrotum warrants further investigation to rule out disorders of sexual differentiation. Such children need multidisciplinary team approach for management. Team includes Paediatricians, Paediatric Endocrinologist and Paediatric Surgeons. The goal of treatment is to achieve penile length and girth within the SD of the mean for the age. Generally speaking, short term use of intramuscular testosterone esters has been prescribed. Immediate adverse effects associated with it are local redness at the site of injection and an allergic reaction. However, with the use of oil-based esters these are very uncommon. Use of dihydro testosterone in gel form is also used. But its availability is difficult. Pubic hair and darkening of scrotal skin is the most common side effect observed in literature with topical use of testosterone. Effects observed with parenteral or topical use of testosterone are increase in penile length, increase in width of the glans, increased transverse preputial skin and neovascularisation in all penile tissues. There was no statistically significant increase in width of urethral plate^[3].

Effect of testosterone on outcome of hypospadias has also been described in literature. The results are mixed. Some studies show less complications like reoperation: glandular dehiscence, meatal stenosis, urethrocutaneous fistula. While others have high rates of wound dehiscence, surgical site inflammation and oedema with parenteral use of testosterone prior to surgery^[4]. So, to overcome the doubt about outcome of surgery in hypospadias we want to initiate a study. It will also cover the effect of testosterone on the size of penis and the adverse effects of the therapy.

Aims

The aim of the study was to estimate the size of microphallic hypospadias after administration of parenteral testosterone in pre-operative period. To determine the adverse effects of parenteral testosterone given to children pre operatively. To determine the complications in intraoperative and postoperative period.

Methodology

An ambispective study in the General Surgery department of a tertiary care hospital was carried out. After ethics approval, retrospective data of last one year was taken and the study was carried prospectively for eighteen months. Children (< 18 years) with distal penile, mid penile and proximal penile hypospadias were included in the study. Children with penile length within 2 SD of the mean for the age, dense chordee (>30°), hypospadias cripple and disorders of sexual differentiation were excluded from the study. With the use of Vernier calliper scale, the penile length from penoscrotal junction, transverse preputial diameter, glans width, and width of the urethral plate was taken before receiving the injection. Testosterone enanthate in a dose of 2mg/kg/dose deep intra muscular (upper outer quadrant of gluteal muscle) was given to children after the test dose^[5]. Children with allergic reaction to the drug was excluded from the study. The dose of testosterone enanthate was repeated after every 21 days. Maximum of three doses were given at 0,3 and 6 weeks. Penile length from penoscrotal junction, transverse preputial diameter, glans width, and width of the urethral plate was taken again after 21 days of receiving the injection. Any adverse effects of testosterone therapy were also noted simultaneously. Surgery was planned in 9th week. All patients under went Snodgraft urethroplasty^[6]. Urethroplasty was given cover of dorsal Byars flap by ventral rotation^[7]. In children

undergoing surgery for the second time tunica vaginalis flap was used [8]. Intraoperative and postoperative complications were recorded.

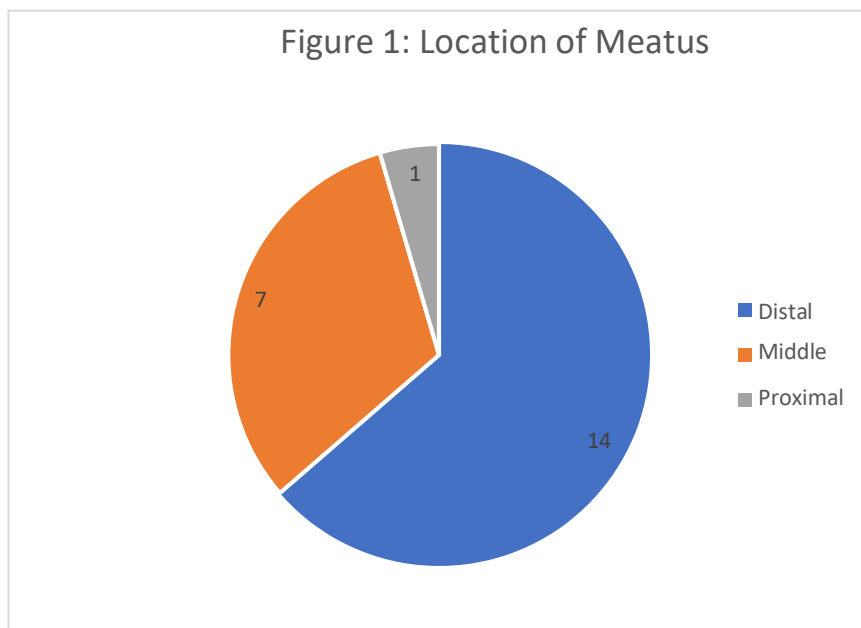
Analysis

Results were tabulated, mean, standard deviation (SD) and increase of penile dimensions in percent (%) was calculated. Statistical significance ($P \leq 0.05$) was done using paired t – test.

Results

After applying the inclusion criteria data of 49 children with hypospadias was collected. There were 20 children taken retrospectively and 29 taken prospectively. Then exclusion criteria were applied and 27 children were excluded. The sample is size $n = 22$.

In our sample 14 children had distal penile microphallic hypospadias, 7 had mid penile microphallic hypospadias and 1 had distal penile microphallic hypospadias. Undescended testis and inguinal hernia are the most common associated anomalies seen in 3 and 2 boys respectively.



Only 3 children developed local redness after the injection. In 7 children intraoperative bleeding was more. The table 1 below shows the postoperative complications in the surgery of microphallic hypospadias.

S. no.	Complication	No. of children
1.	Bleeding	4
2.	Haematoma	2
3.	Wound infection	1
4.	Wound dehiscence	1
5.	Urethrocutaneous fistula	2

Table 2: The table below shows the increase in dimensions of microphallic hypospadias following parenteral testosterone therapy

S. no.	Variables	Pre testosterone dimensions (cm)		Post testosterone dimensions (cm)		Percentage increased (%)	P value significant (<0.05)
		Mean	SD	Mean	SD		
1.	Penile length	3.07	0.09	4.22	0.12	37.4%	Yes
2.	Transverse preputial diameter	2.99	0.18	4.15	0.09	38.7%	Yes
3.	Glans width	1.26	0.18	2.23	0.017	76%	Yes
4.	Urethral plate width	0.24	0.05	0.38	0.04	58%	Yes

Discussion

Hypospadias is a very rare congenital anomaly. The prevalence is 0.6 children per 1000 male live births. Whereas the incidence of micropenis is 0.15 neonates per 1000 male live births^[9]. It is associated with hypospadias, undescended testis and genital abnormalities. Micropenis is defined as penile length less than 2 SD below the mean for the age. However, some studies defined it as less than 2.5 SD below the mean for the age^[10]. Distal penile microphallic hypospadias was the most common in our study as shown in figure 1. 14 (63.6%) children had distal penile microphallic hypospadias, 7 (31.8 %) had mid penile and 1 (4.6%) had proximal penile microphallic hypospadias. This was consistent with literature as distal penile hypospadias is most common type accounting for 60% – 70 % of the cases^[11]. In our study most common genitourinary anomalies associated with microphallic hypospadias are undescended testis (13.6%) and inguinal hernia (9%). Rodríguez Fernandez et al observed that undescended testis and inguinal hernia were the most common genitourinary abnormalities seen^[12]. Side effects of testosterone therapy in children described in literature were local redness, allergic reaction, acne, early growth of pubic hair, short stature and erythrocytosis^[5, 13]. In our study local redness was seen in 3 (13.6%) patients after 48 hours of administration. It was managed conservatively by oral antibiotics. In our study intra operative bleeding and postoperative haematoma formation was the most common complication. This clearly shows that there is increased vascularity following testosterone therapy. Local increase in vascularity has also been observed in various historical studies in literature^[14,15]. In our study, the urethrocutaneous fistula was seen in 2 (9%) children. Urethrocutaneous fistula without preoperative testosterone therapy were 8% seen in study by Malhotra et al^[16]. Some studies suggest increased rate of postoperative complications due to oedema and inflammation, whereas others show lower rates^[17,18]. There is no case of meatal stenosis and acceptable rate of wound dehiscence with infection in our study. This finding is consistent with studies in literature^[19]. In our study there is significant increase penile length from penoscrotal junction, transverse preputial diameter, glans width and width of the urethral plate following doses schedule of testosterone enanthate as shown in table 2. Literature has also shown significant increase in penile length from penoscrotal junction, transverse preputial diameter, glans width and diameter at the base of penis^[3,5,20]. In our study we have observed significant increase in width of the urethral plate. In the literature similar findings were seen by Khokar D Set al^[21].

Conclusions Use of testosterone is safe and effective in children with microphallic hypospadias. There is significant increase of penile length from penoscrotal junction, transverse preputial diameter, glans width and width of the urethral plate preoperatively. Increased dimensions of the penis with precise, meticulous and gentle technique brings good surgical outcome.

Conflict of interest: Nil

References

1. M. Van den Heijkant, S. Baumann, Worldwide prevalence of hypospadias, journal of paediatric urology. A. Springer, [VOLUME 12, ISSUE 3, P152.E1-152.E7, JUNE 2016.
2. Bhakhri BK, Meena SS, Rawat M, Datta V. Neonatal stretched penile length: relationship with gestational maturity and anthropometric parameters at birth. Paediatr Int Child Health. 2015 Feb; 35(1):53-5. doi: 10.1179/2046905514Y.0000000114. Epub 2014 Jan 26. PMID: 24621243.
3. Taghavi K, O'Hagan LA, Hewitt JK, Mouriquand P. Defining the role of pre-operative hormonal therapy in hypospadias. J Paediatr Child Health. 2022 Sep; 58(9):1508-1519. doi: 10.1111/jpc.16087. Epub 2022 Jul 6. PMID: 35791898; PMCID: PMC9545156.
4. Menon P, Rao K, Handu A, Balan L, Kakkar N. Outcome of urethroplasty after parenteral testosterone in children with distal hypospadias. *J. Pediatr. Urol.* 2017; 13: 292.
5. 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 Sep; 3(3):138-40. doi: 10.4103/0974-7796.84966. PMID: 21976926; PMCID: PMC3183705.
6. Peyvasteh M, Askarpour S, Mohamadi A, Ilkhani Pak H. Evaluation of Complications and Effectiveness of Snodgraft Method on the Treatment of Distal Hypospadias or Midshaft. *World J*

- Plast Surg. 2022 Mar; 11(1):38-43. doi: 10.52547/wjps.11.1.38. PMID: 35592229; PMCID: PMC9018042.
7. Li J, Li S, Yang Z, Ke Z, Zhang T, Yin J. A simple technique to repair distal and mid-shaft hypospadias using a de-epithelialized Byars' flap. *Journal of International Medical Research*. 2022; 50(8). Doi: 10.1177/03000605221115150.
 8. Pierre Pescheloche, Benoit Parmentier, Thevy Hor, Olivier Chamond, Maud Chabaud, Sabine Irtan, Georges Audry, Tunica vaginalis flap for urethrocutaneous fistula repair after proximal and mid-shaft hypospadias surgery: A 12-year experience, *Journal of Pediatric Urology*, Volume 14, Issue 5, 2018, Pages 421.e1-421.e6, ISSN 1477-5131, <https://doi.org/10.1016/j.jpuro.2018.03.026>.
 9. Nelson CP, Park JM, Wan J, Bloom DA, Dunn RL, Wei JT. The increasing incidence of congenital penile anomalies in the United States. *J Urol*. 2005 Oct; 174(4 Pt 2):1573-6.
 10. Nihal Hatipoglu, Selim Kurtoglu, *J Clin Res Pediatr Endocrinol*. 2013 Dec; 5(4): 217–223.
 11. Halaseh SA, Halaseh S, Ashour M. Hypospadias: A Comprehensive Review Including Its Embryology, Etiology and Surgical Techniques. *Cureus*. 2022 Jul 31; 14(7): e27544. doi: 10.7759/cureus.27544. PMID: 36060359; PMCID: PMC9428502.
 12. Rodríguez Fernández V, López Ramón Y Cajal C, Marín Ortiz E, Sarmiento Carrera N. Accurate Diagnosis of Severe Hypospadias Using 2D and 3D Ultrasounds. *Case Rep Obstet Gynecol*. 2016; 2016:2450341.
 13. Grech A, Breck J, Heidelbaugh J. Adverse effects of testosterone replacement therapy: an update on the evidence and controversy. *Ther Adv Drug Saf*. 2014 Oct; 5(5):190-200. doi: 10.1177/2042098614548680. PMID: 25360240; PMCID: PMC4212439.
 14. Sakakibara N, Nonomura K, Koyanagi T, Imanaka K. Use of testosterone ointment before hypospadias repair. *Urol. Int*. 1991; 47: 40–3
 15. Gearhart JP, Jeffs RD. The use of parenteral testosterone therapy in genital reconstructive surgery. *J. Urol*. 1987; 138: 1077–8.
 16. Malhotra NR, Schaeffer AJ, Slade AD, Cartwright PC, Lau GA. Post-hypospadias urethrocutaneous fistulae: no difference in repair success between proximal and distal fistulae. *Can J Urol*. 2020 Dec; 27(6):10466-10470. PMID: 33325350; PMCID: PMC9831685.
 17. Bush N, Keays M, Villanueva C, Snodgrass W. Preoperative testosterone injection does not decrease hypospadias urethroplasty complications. *Congress of the European Society for Paediatric Urology*. 2014: 198
 18. Babu R, Chakravarthi S. The role of preoperative intra muscular testosterone in improving functional and cosmetic outcomes following hypospadias repair: A prospective randomized study. *J. Pediatr. Urol*. 2018; 14: 29.e1–6
 19. 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.
 20. Krishnan A, Chagani S, Rohl AJ. Preoperative Testosterone Therapy Prior to Surgical Correction of Hypospadias: A Review of the Literature. *Cureus*. 2016 Jul 8; 8(7):e677. doi: 10.7759/cureus.677. PMID: 27551655; PMCID: PMC4977217
 21. Khokar DS, Patel RV. Can Testosterone Alter the Degree of Hypospadias? A Comprehensive Study. *J Indian Assoc Pediatr Surg*. 2021 Jan-Feb; 26(1):38-43. doi: 10.4103/jiaps.JIAPS_214_19. Epub 2021 Jan 11. PMID: 33953511; PMCID: PMC8074826.