
The Efficacy of Dihydrotestosterone Transdermal Gel Before Primary Hypospadias Surgery: A Prospective, Controlled, Randomized Study

Cevdet Kaya, J. Bektic, C. Radmayr, C. Schwentner, G. Bartsch and J. Oswald

From the Department of Urology, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey (KC), and Department of Pediatric Urology, Medical University of Innsbruck, Innsbruck, Austria

Purpose: We sought to evaluate the efficacy of transdermal dihydrotestosterone treatment based on the results of hypospadias repair in children with primary hypospadias.

Materials and Methods: A total of 75 randomized consecutive children who were a mean of 33.4 ± 3.7 months old and had primary hypospadias were included in the study between September 2004 and April 2006. While 37 children were treated with 2.5% transdermal gel daily, applied directly onto the penile shaft and glans for 3 months (group 1), 38 children did not receive any treatment preoperatively (group 2). All children underwent hypospadias repair using tubularized incised plate urethroplasty. Postoperative complications were analyzed using the Mann-Whitney U test with respect to fistulas, urethral strictures, diverticula, meatal stenosis, glanular dehiscence and scar formation according to the results at 1-year followup.

Results: Mean ages of the children in groups 1 and 2 were similar (30.8 ± 5.4 months and 35.1 ± 5.1 months, respectively). The urethral meatus was coronal in 70%, penile in 24% and penoscrotal in 5% of the patients in group 1, while it was coronal in 84% and penile in 16% of the patients in group 2. Postoperative complications included urethrocutaneous fistula in 4 patients (11%) in group 2, compared to 1 patient (3%) in group 1 ($p > 0.05$). While 3 patients (8%) in group 2 had glanular dehiscence, no patient in the dihydrotestosterone group had this complication ($p < 0.05$). There were 2 patients with meatal stenosis in group 2 (5%), and no patient with meatal stenosis in group 1 ($p > 0.05$). In addition, there were 16 patients (42%) with moderate to severe postoperative scar formation in group 2, compared to only 2 patients (5%) in the dihydrotestosterone group ($p < 0.05$). Finally, there was a significant difference between the overall reoperation rates of group 2 (9 patients, 24%) and group 1 (1 patient, 3%, $p < 0.05$). None of our patients had signs or symptoms of urethral stricture or urethral diverticulum.

Conclusions: Pretreatment with dihydrotestosterone transdermal gel was effective in decreasing the complications and improving the cosmetic results after hypospadias repair.

Key Words: hypospadias; urethra; testosterone; urologic surgical procedures, male

Hypospadias is one of the most common congenital anomalies in male children, with a prevalence that has nearly doubled in the last 30 years.¹ Since the significance of this disease pattern relates to its frequency and the functional and cosmetic impairment, the aim of hypospadias surgery is to reconstruct the urethra to the tip of the glans, and to achieve an excellent cosmetic result.²

However, even in the most experienced hands hypospadias repair is associated with a number of complications, including urethrocutaneous fistula, stenosis and scar formation. Although many articles on the results of hypospadias surgery have been published, only a few have discussed cosmetic results after the repair. In a study investigating the effects of hypospadias surgery on psychosexual adjustment approximately one fourth of patients were dissatisfied with penile appearance and consequently desired cosmetic improvement.³ The reasons for dissatisfaction especially relate to penile scars such as skin tags, skin bridges and keloid scar formation; persistent chordee; meatal configuration and

glanular shape, with the consequence that up to 40% of adolescents want to correct the surgical results. Even if the penis is flaccid, the incidence of persistent chordee ranges up to 22%.

To improve the surgical results, androgen stimulation with testosterone, DHT or human chorionic gonadotropin has been recommended because it temporarily promotes phallic growth, which makes correction easier and results in fewer complications.^{4,5} The desired therapeutic effect of testosterone has been achieved with local and systemic administration in a few studies.⁶ It has been suggested that since externally administered DHT does not require 5α -reductase, it could be more effective than testosterone in enlarging the external genitalia.⁷ After binding to specific receptor proteins and translocation into the nucleus DHT initiates protein synthesis and stimulates the anabolic effects, ie increased mitotic activity, cell turnover time and thickness of the epidermis.⁸ To our knowledge our prospective, controlled, randomized study is the first to evaluate the efficacy of dihydrotestosterone transdermal gel on the complications and cosmetic results of hypospadias surgery in children with primary hypospadias.

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MATERIALS AND METHODS

A total of 75 consecutive children with primary hypospadias and a mean age of 33.4 ± 3.7 months (range 10.6 to 159.1) were enrolled in the study between September 2004 and April 2006. After informed parental consent was obtained the children were randomized into 2 groups based on whether they would (group 1) or would not (group 2) be treated with topical DHT preoperatively. Children with any endocrinological or clinical evidence of hypopituitarism and children with a history of hypospadias surgery were excluded from the study (table 1).

Dihydrotestosterone Treatment Protocol

A total of 37 children with primary hypospadias were treated with topical DHT, consisting of application of 2.5% DHT transdermal gel directly onto the penile shaft and glans once daily before bedtime for 3 months (group 1).⁹ The DHT gel was provided in a dispenser delivering a dose of 0.2 to 0.3 mg/kg body weight. At 5 weeks preoperatively testosterone pretreatment was terminated, preventing profuse bleeding due to the angiogenic effects of DHT. Parents had been advised to wear rubber gloves when they applied the testosterone gel to the penis. A total of 38 children did not receive any treatment preoperatively (group 2).

Surgical Technique

All the patients from both groups underwent hypospadias repair using TIP urethroplasty with or without chordee correction. The procedure was performed using micro-instruments with 2.5 to 4 times optical magnification in a standardized manner, as described previously.¹⁰

After degloving the penis an artificial erection was achieved to assess any deviation. If there was still a significant deviation after excising ventral tethering tissues lateral to the urethral plate and corpus spongiosum, it was corrected by dorsal plication using 6-zero polydioxanone monofilament absorbable sutures.¹¹ The glans wings were created with lateral mobilization after performing parallel longitudinal incisions to define the urethral plate. Following the midline incision of the urethral plate from meatus to the glans tip the plate was tubularized with a 7-zero polyglactin running suture. A dorsal vascularized pedicle of subcutaneous tissue dissected from the dorsal hooded prepuce was brought in ventrally via a buttonhole technique to cover the neourethra. Finally, the glanular wings were symmetrically closed over the neourethra with 6-zero poliglecaprone sutures in 2 layers. The neourethra was stented for 7 days with an 8Fr silicone stent.

Followup Evaluation

Followup visits with photographs of the operated penis were taken according to Baskin,¹² assessing the cosmetic outcome



FIG. 1. Hypertrophic and scarred mucosal collar after hypospadias repair.

impartially. Further postoperative assessments were documented, including urinary stream, straightness of erection and valuation of the penile tissue, every 3 months until 1 year postoperatively. Postoperative complications were analyzed with respect to fistulas, glanular dehiscence, urethral strictures, diverticula and meatal stenosis according to the results of the 1-year followup. Meatal stenosis was determined based on the combination of symptoms, appearance of the meatus and results of uroflowmetry. Patients were also evaluated for the appearance of the mucosal collar. A normal mucosal collar was defined as 5 mm smooth skin around the base of the glans without abundant inner preputial tissue or scarred areas.¹³ In addition, the reoperation rates due to fistula, diverticulum, stenosis, glanular dehiscence, residual chordee and scar formation were also assessed.

Statistical Analysis

Differences between the groups were analyzed using the Mann-Whitney U test. Data are expressed as mean \pm standard error, with statistical significance considered at $p < 0.05$. SPSS® for Windows 11.5 software was used for all analyses.

RESULTS

Mean age in patients receiving DHT treatment before hypospadias correction (30.8 ± 5.4 months, range 11.3 to 152.1) was similar to that in patients not receiving DHT (35.1 ± 5.1 , 10.6 to 159.1, $p > 0.05$). Patient characteristics for the 2 groups are summarized in table 1.

In group 1 (pretreatment with DHT) the urethral meatus was coronal in 26 patients (70%), penile in 9 (24%) and penoscrotal in 2 (5%). A total of 32 children (84%) in group 2 (no DHT) had coronal hypospadias, while the remaining patients presented with penile hypospadias. In addition, 31 patients (84%) in group 1 and 32 patients (84%) in group 2 underwent concomitant chordee correction. Finally, 3 patients in group 1 and 2 patients in group 2 underwent an additional orchiopexy operation together with the hypospadias repair.

At 1-year followup 1 patient (3%) in group 1 and 4 patients (11%) in group 2 had urethrocutaneous fistulas ($p > 0.05$, fig. 1). No patient in group 1 and 3 patients (8%) in group 2 had glanular dehiscence ($p < 0.05$). The patients with glanular dehiscence underwent a second TIP urethroplasty, which was successful in all instances. No patient had

TABLE 1. Patient characteristics

Variables	No. DHT Group (%)	No. Control Group (%)
Total pts	37	38
Meatus location:		
Coronal	26 (70)	32 (84)
Penile	9 (24)	6 (16)
Penoscrotal	2 (5)	0
Chordee corrections	31 (84)	32 (84)
Additional orchiopexy	3	2



FIG. 2. Results after hypospadias repair without scarring

meatal stenosis in group 1, compared to 2 patients (5%) in group 2 ($p > 0.05$). These 2 cases of meatal stenosis required simple meatotomy. Analysis of the overall complications revealed that fistula, glanular dehiscence and meatal stenosis were found in 7%, 4% and 3% of the patients, respectively.

There was a statistically significant difference between children from group 1 and group 2 concerning scar formation. There were 16 cases (42%) with moderate to severe scar formation postoperatively in group 2, compared to 2 (5%) in group 1 ($p < 0.05$, *figs. 1 to 3*). There was also a significant difference between the overall reoperation rates of group 2 (9 patients, 24%) and group 1 (1 patient, 3%, $p < 0.05$, *table 2*). The causes of reoperation in group 2 were fistula and/or dehiscence in 7 patients and severe scarring in 2, compared to fistula in 1 patient in group 1 (*fig. 4*).

None of our patients had signs or symptoms of urethral stricture or urethral diverticulum. The secondary effects of transdermal dihydrotestosterone gel were minimal, and there were no therapy associated bleeding problems perioperatively. At the beginning of DHT treatment 13 parents (18%) complained of irritating symptoms on the penile skin, such as itching and redness, which disappeared after 2 weeks of ongoing therapy. Parents also had noticed that the penile skin became darker during treatment but it normalized after cessation of treatment.



FIG. 3. Results after hypospadias repair with straight urinary stream.

TABLE 2. *Complications of hypospadias surgery*

Variables	No. DHT Group (%)	No. Control Group (%)	Total No.	p Value
Total pts	37	38	75	—
Meatal stenosis	0	2 (5)	2 (3)	> 0.05
Fistula	1 (3)	4 (11)	5 (7)	> 0.05
Glanular dehiscence	0	3 (8)	3 (4)	< 0.05
Scarring	2 (5)	16 (42)	18 (24)	< 0.05
Reoperation rate	1 (3)	9 (24)	10 (13)	< 0.05

No patient in either group had a diverticulum or urethral stricture.

DISCUSSION

Although the etiology of hypospadias is still unclear, defects anywhere along the pathway of androgen production could potentially be responsible for the occurrence of hypospadias.¹⁴ Hypoplastic development of the phallus is thought to render repair of hypospadias more difficult, and often limits functional and cosmetic results. Even in cases of careful preoperative evaluation, precise surgical technique and appropriate postoperative care the repair of hypospadias is associated with a number of complications, including urethrocutaneous fistula, stricture and scar formation.³ Therefore, preoperative androgen therapy seems to be useful to enlarge the penis, make the repair less difficult and decrease the possibility of complications.

The use of testosterone in male children with a genital defect is not a new concept. Many studies have demonstrated that the effect of parenteral testosterone on penile growth and the prepuce up to the day of surgery is significant in the correction of severe cases of hypospadias, with mild side effects. Particularly in boys with micropenis parenteral testosterone therapy has been applied to enlarge the glans, facilitating glanuloplasty.¹⁵ Koff and Jayanthi found that in contrast to somatic growth, human chorionic gonadotropin caused the disproportional growth of the hypospadiac phallus, turning the meatus distally, as well as decreasing the severity of chordee in all cases.¹⁶

Although variable results have been reported with the use of intramuscular and topical testosterone to stimulate penile growth in patients with microphallic hypospadias, no significant difference has been shown between the 2 routes of administration.⁷ Nevertheless, transdermal creams and gels can be formulated to provide high local concentrations at the site of application. Medication administered transder-

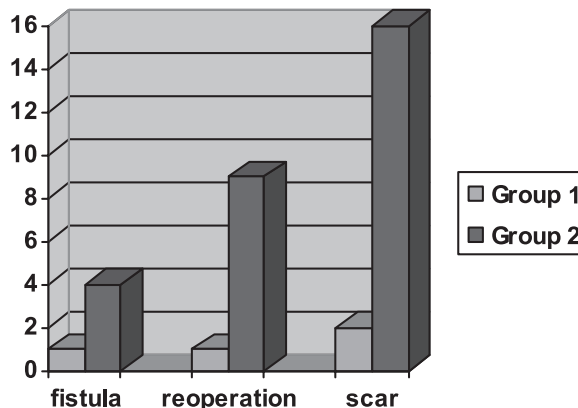


FIG. 4. Comparison of complications between groups

mally is not absorbed through the gastrointestinal system, does not undergo first pass hepatic metabolism and is associated with no side effects. The unpleasant effect of intramuscular injection might limit parental compliance compared to nonparenteral hormone therapy, particularly when injection of the hormone is not mandatory. Fowler-Kerry and Lander reported that a bad early experience with injections may generate anxiety in children, which can make the next injection experience worse, resulting in pain.¹⁷

Since hypospadias repair is complex and involves several variables, such as anatomical variations, surgical technique, tissue handling, suture material and stenting, it is difficult to compare complication rates. Since it was first described in 1994, TIP urethroplasty has become increasingly popular, and is believed to have the most cosmetically appealing result.¹⁸ The Snodgrass technique, with the advantage of using native urethral mucosa to reconstruct the urethra, a single urethral suture line and vascularized subcutaneous flap to cover of the neourethra, has become the preferred technique at many pediatric urology centers worldwide.

We performed TIP urethroplasty in all cases to compare the complication rates and cosmetic results of both groups. In the cases of meatal location the presence of chordee and mean patient ages were similar in both groups. Although not statistically significant, the rates of meatal stenosis and fistula were higher in the first year of followup in children not receiving DHT. The number of patients with glanular dehiscence and, consequently, the reoperation rates were significantly higher in group 2 compared to group 1. Despite the presence of penoscrotal hypospadias and the higher rate of penile meatus location, the complication rate was lower in children who received DHT preoperatively. With respect to complications from all of these consecutive patients, our results are consistent compared to other studies in the literature.

Since an objective assessment of the cosmetic appearance following hypospadias is difficult, and surgeons have mostly been interested in functional results, there is a lack of information about scar formation after hypospadias repair in the literature.¹⁹ The mucosal collar is a well established standard in hypospadias surgery, with the goal to recreate the appearance of a circumcised penis. It has been reported that the healing of the coronal sulcus is difficult after reconstructive surgery, due to its poor vascularization. Additionally, dissection of the penile skin and the urethral plate in the coronal sulcus may completely impede coronal vascularization.²⁰

Up to now, corticosteroids have been used to increase scar elasticity and retractability of the foreskin. In the present study scar formation after hypospadias repair was significantly lower in children receiving DHT treatment. This benefit might be explained by the angiogenesis effects of dihydrotestosterone. Stern et al observed in a human skin transplant model that the treatment of human foreskin with testosterone increased vascularity, and, hence, possibly increased intraoperative bleeding.²¹ Therefore, we terminated testosterone treatment at least 1 month preoperatively.

The safety experience with 3 months of DHT treatment in this controlled clinical trial proved satisfactory. Likewise, the secondary effects of transdermal DHT gel were minimal, and only complaints of irritating symptoms on the penile skin were reported in some children.

CONCLUSIONS

Based on our preliminary experience, we suggest that pre-treatment with DHT transdermal gel is beneficial in decreasing complication and reoperation rates after hypospadias repair, as well as improving cosmetic results. Scar formation after hypospadias repair is an important parameter for cosmetic assessment, and it was found to be significantly lower in children receiving DHT treatment. Due to the proved importance of psychosocial satisfaction and the development of self-esteem in later periods of life, the prevention of scar formation with DHT is thought to be an important parameter for the cosmetic outcome after hypospadias repair.

Abbreviations and Acronyms

DHT	=	dihydrotestosterone
TIP	=	tubularized incised plate

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