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Objective use of testosterone reveals androgen insensitivity in patients with proximal hypospadias

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Abstract *Objective:* We report preoperative testosterone stimulation based on glans width measurements in patients with midshaft and proximal hypospadias, revealing androgen resistance in those with proximal hypospadias.
Methods: Patients had maximum glans width measured preoperatively. Those <14 mm initially received 2 mg/kg testosterone cypionate intramuscularly for two to three doses, with the aim of increasing glans width ≥15 mm. Not all patients achieved targeted growth, and some were subsequently treated with escalating doses of testosterone.
Results: 5/15 midshaft patients had two to three doses of 2 mg/kg testosterone, with all increasing glans width to ≥15 mm. 29/47 proximal patients had testosterone, with 13 (57%) not reaching desired glans width. Six of these and another six patients had escalating doses from 4 to 32 mg/kg testosterone, with 11 then achieving targeted glans width. Relative androgen resistance was found in 19/29 (66%) proximal cases, including all treated patients with perineal hypospadias.
Conclusions: 39/62 (63%) patients met objective criteria for preoperative testosterone stimulation based on glans width <14 mm, which is less than the average normal newborn glans diameter. Evidence of relative androgen resistance was found in 19 (49%), all with proximal hypospadias.
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Introduction

Preoperative androgen stimulation has been reported to increase glans circumference, penile length, and/or improve prepucial vascularization before hypospadias surgery. To our knowledge, dosing recommendations are empiric, with various regimens of intramuscular or topical androgens administered to patients with a subjectively small-appearing penis before repair. Neither objective size indications for preoperative stimulation nor endpoints to stop treatment have been reported. The aim of our study is to report preoperative testosterone treatment based specifically on glans diameter measurements in patients with primary midshaft and proximal hypospadias.

Patients and methods

Patients

Consecutive patients with midshaft and proximal hypospadias (proximal shaft to perineal) with operations from June 2009 to October 2012 were included. Pubertal patients (Tanner 2 and above) were excluded. Standard preoperative assessment of these patients included measurement of widest transverse glans width using a ruler in the outpatient clinic (Fig. 1), as previously described [1]. Glans width in these patients was compared with measurements we made in both normal neonates undergoing elective circumcision and infants with distal hypospadias. At median ages 5 weeks and 9 months, mean glans widths were 14 mm and 15 mm, respectively.

Preoperative testosterone stimulation was used in patients with midshaft and more proximal hypospadias for glans width $<$14 mm, with the goal of enlargement to $\geq$15 mm. Initially, the preoperative regimen was 2—3 monthly injections of 2 mg/kg testosterone cypionate intramuscularly (IM), with surgery scheduled within 6 weeks after the final dose. Intraoperative measurement of glans width was repeated. When failure to reach the target size was noted in some cases following this protocol, treatment changed to initial injection with 2 mg/kg followed by repeat measurement performed in the outpatient clinic in 3—4 weeks. Those with glans size $\geq$ 15 mm had no further stimulation, whereas patients without growth to this extent next received 4 mg/kg injection and repeat measurement in 3—4 weeks, progressing as needed to 8 mg/kg, 16 mg/kg, etc. Surgery was then scheduled within 6 weeks after the final injection. All injections were testosterone cypionate.

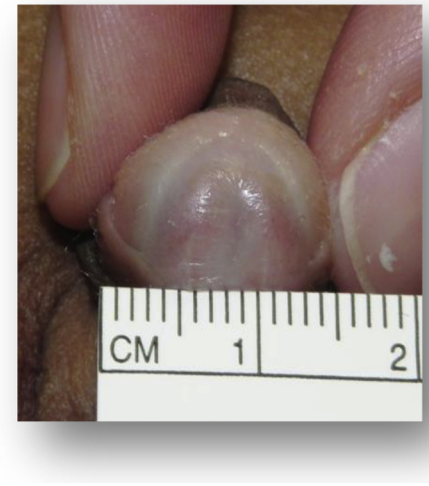

Figure 1 Sample glans size measurement with a ruler in the clinic. The ruler measures the widest point, irrespective of prepuce. Maximum glans diameter in this patient was 14 mm.

Newborns and neonates with hypospadias and glans width $<$14 mm who were initially evaluated in the outpatient clinic at ages $<$6 months had re-examination at 6 months of age to allow for spontaneous growth from postnatal endogenous androgen secretion.

Karyotyping was only done for patients having both hypospadias and undescended testis. Hormonal assays were not performed either before or during testosterone therapy. Syndromic hypospadias was defined as occurring in patients with syndromes known to be associated with hypospadias.

Statistical analysis was performed using Mann Whitney U for between group comparisons. All analyses were performed using Prism 6 for Windows statistical software.

Results

During the study period 62 consecutive patients with primary midshaft (n = 15) and proximal (n = 47) hypospadias were evaluated by WS and NB (Fig. 2). Of these, 28 boys (45%) did not receive preoperative testosterone stimulation. There was no difference in the median age and intraquartile range (IQR) in boys who did versus those who did not receive testosterone, 11 (IQR 8.3—14.5) and 10 (IQR 6—22.2) months, respectively, p = 0.57.

Midshaft patients

Five out of 15 (33%) boys with midshaft hypospadias received preoperative testosterone. Mean glans width in these five patients was 11.6 mm (SD 1.1), versus 15.1 mm (SD 1.4) in the 10 not treated. Two of these 10 boys had outpatient clinic glans measurement $\geq$14 mm, which was found intraoperatively to be $<$ 14 mm when the prepucial hood was retracted, and so by our protocol should have received preoperative testosterone. All five midshaft cases treated with 2 mg/kg testosterone for two to three doses increased their glans width to $\geq$15 mm, to a mean of 16.0 mm (SD 0.8).

Proximal patients

Twenty-nine out of 47 boys (60%) with proximal hypospadias had preoperative testosterone for mean glans width of 11.1 mm (SD 1.7), versus 15.1 mm (SD 1.7) in the 18 not treated. Three of these 18 boys had intraoperative measurements $<$14 mm when the prepucial hood was retracted, and so by the protocol should have received preoperative testosterone.

In the 29 patients with proximal hypospadias who had testosterone stimulation, 23 initially received 2 mg/kg for