



Echocardiographic evaluation of left ventricular mass index in children with hypospadias after hormonal stimulation with topical testosterone: A randomized controlled trial

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Summary

Introduction

Testosterone is often used in the preoperative period of hypospadias surgery. Previous studies have demonstrated the presence of androgen receptors in cardiac myocytes that can modulate the phenotype. The use of supraphysiological doses of androgens can lead to toxicity on the heart muscle and, in some cases, to left ventricular hypertrophy. This randomized double blind controlled clinical trial aims to evaluate the effect of topical testosterone on left ventricular mass index in boys with hypospadias.

Materials and methods

Boys with hypospadias aged 6 months to 9 years were included. Children were divided into two groups: G1 - boys who received testosterone propionate 1% ointment twice a day for 30 days, and G2 - boys receiving placebo ointment in the same regimen. All children were submitted to bi-dimensional echocardiographic evaluation to compare the left ventricular mass index, blood pressure, and body mass index before and after treatment (30 and 90 days). Levels of serum testosterone, LH, and FSH were measured.

Results

Thirty-five children were analyzed: 17 in G1 and 18 in G2. No differences were found in left ventricular mass index (left ventricular mass indexed by body surface area) prior to treatment. Left ventricular mass index was 59.21 ± 11.91 g/m² in G1 and 55.12 ± 8.29 g/m² in G2 ($p = 0.244$) after 30 days of treatment, and 61.13 ± 11.69 g/m² in G1 and 62.84 ± 35.99 g/m² in G2 ($p = 0.852$) after 90 days. Serum testosterone levels were 12 (7–80) ng/dL in G1 and 5 (5–7) ng/dL in G2 ($p = 0.018$) after 30 days of treatment, and 10 (5–11) ng/dL in G1 and 5 (4–5) ng/dL in G2 ($p = 0.155$), after 90 days (Figure). There was a small increase in systolic blood pressure (SBP) after 30 days (83.82 ± 7.18 mmHg) in the group who receive testosterone (G1) compared with controls (77.5 ± 6.69 mmHg) ($p = 0.010$). After 90 days, SBP levels returned to basal levels in G1 (82.35 ± 5.62 mmHg) and in G2 (81.38 ± 4.79 mmHg) ($p = 0.588$).

Conclusion

Topical testosterone can be considered safe in the preoperative period of children with hypospadias with no risk of left ventricular hypertrophy. An increase in systolic blood pressure occurs while using testosterone but it is transitory, returning to normal levels after 90 days.

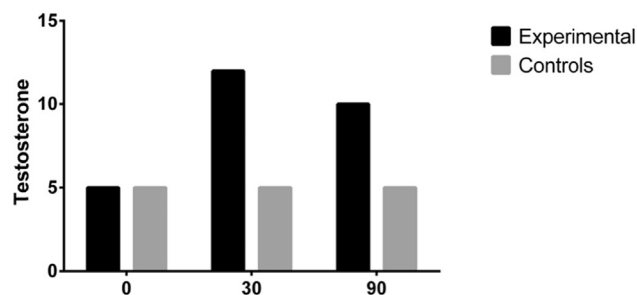


Figure Testosterone levels prior to, 30, and 90 days after use of 1% testosterone propionate ointment treatment.

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Introduction

Hypospadias is one of the most common congenital anomalies [1,2], and surgery is the treatment of choice in most cases. Testosterone has been used preoperatively to increase penile length and glans circumference [3], providing better surgical conditions and, consequently, decreasing complications and improving results [4], especially in the case of small penis, reduced glans, or proximal hypospadias.

In the 1970s, androgen receptors were observed in rat myocytes [5]. Later, in the 1980s, they were found in myocytes of various species, including humans (children and adults of both sexes). Testosterone and dihydrotestosterone (DHT) act on these receptors producing a hypertrophic response [6]. A compromise in cardiac remodeling has been observed in rats with acute myocardial infarction following the use of supraphysiological doses of testosterone, with the onset of hypertrophic cardiomyopathy, left ventricular dilatation and increased blood pressure [7].

Chorionic gonadotrophin (hCG) has been used in treatment of cryptorchidism. Pirgon et al. evaluating children treated with hCG observed an increase in left ventricular mass and also in serum levels of total and free testosterone [8].

Testosterone is the major androgen that binds to myocardial receptors and is capable of altering the adaptive cardiac function to exercise [9].

The present authors are not aware of any previous study evaluating the effect of topical testosterone on ventricular mass in boys using androgen stimulation before hypospadias surgery. Thus, this clinical trial aimed at evaluating the effect of topical testosterone on left ventricular mass index in boys with hypospadias.

Material and methods

This experimental, double-blind, randomized, controlled clinical trial was designed to assess the risk of left ventricular hypertrophy in male children using topical testosterone in the preoperative period of hypospadias surgery.

Forty-one boys with ages ranging from 6 months to 9 years, with distal, mid-penile and proximal hypospadias attending the pediatric urology outpatient clinics of our university hospital were followed during the study period.

The study was approved by the institutional ethics committee and those responsible for all children who agreed to participate signed an informed consent form.

Children were randomly divided into two groups using the Research Randomizer Form 4.0 program (<http://www.randomizer.org/form.htm>).

- **Group 1:** Boys who used 1% topical testosterone propionate on the entire penis twice a day for 30 days before surgical correction.
- **Group 2:** Boys who used topical placebo cream, twice a day for 30 days before surgical correction.

The decision to use ointment as the route of administration was made according to results from other studies, and the experience of our service, to have the same route of administration in both groups, reducing application bias. All parents were advised to use gloves when applying the

ointments. After randomization, parents were given the appropriate ointment and instructed to apply it over the dorsal and ventral surface of the penis and glans twice a day for 30 days before surgery.

Patients were excluded from the study if they were using testosterone or chorionic gonadotropin or had a history of treatment with one of these drugs within 6 months, if they had a history of previous cardiovascular disease or obesity, if they were participating in competitive sports activities, using medications that may affect the cardiovascular system, if they had secondary sexual characteristics suggestive of puberty, if they had endocrine diseases, or if they had made inadequate use of the prescribed medication or abandoned the protocol.

It was established that a sample of 18 subjects in each group would be adequate to detect a difference of 20% in left ventricular mass index, indexed by body surface (g/m^2), with the use of topical testosterone in relation to the use of placebo cream, with a power of 80% and level of significance of 0.05.

Retrospective data from children of the same age group demonstrated that a standard deviation of ± 10 (20% increase) in left ventricular mass indexed by body surface area (g/m^2) would be considered a difference of clinical importance. Thus, given the absence of studies for occurrence of left ventricular hypertrophy in children who used topical testosterone, this difference was defined by a group of experts to be significant.

All children underwent a bi-dimensional echocardiographic evaluation to compare left ventricular mass index. The left ventricular mass (g/m^2) was calculated through the transverse parasternal window (short axis) at the level of the papillary muscles and measured in Mode M traced through the anterior and posterior walls and indexed by the body surface [10]. Other determinant parameters in the diagnosis of an increase in ventricular mass, interventricular septum, and posterior wall of the left ventricle were also evaluated. The Vivid-i GE device, 3.5 MHz probe, was used to perform the echocardiograms at our cardiology outpatient clinic (Fig. 1).

All children underwent clinical and anthropometric evaluation, and had measurements taken of body mass index, blood pressure, and serum levels of testosterone, LH, and FSH before starting the medication, and 30 and 90 days after.

The quantitative variables were expressed as means \pm SD or medians and interquartile ranges, while the nominal or qualitative variables were expressed as absolute values, percentages, or proportions. The Student *t* test or Mann–Whitney *U* test was used to compare continuous variables while categorical variables were compared using the chi-square test or Fisher's exact test. All tests were two-sided with $p < 0.05$ considered to be statistically significant, and were performed using GraphPad Prism version 6.03 for Windows.

Results

Of the 47 boys with hypospadias eligible for the study, six were excluded from the protocol, three because of other urological malformations and three because of severe cardiac defects. Forty-one boys were randomized, 20 to

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