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Original Article

Post-operative use of human chorionic gonadotrophin (u-hCG) inpatients treated for intrabdominal unilateral undescended testes

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Abstract: Objective: To report our experience with post-operative use of human chorionic gonadotrophin to achieve higher testicular volume and function, respect to untreated patients. Materials and methods: A prospective study was done using subjects who underwent orchidopexy between Sptember 2010 and September 2016 for unilateral intrabdominal undescended testes. All patients were treated by the same surgeon with laparoscopic one-stage Fowler-Stephens technique. After surgery (2 weeks) those patient parents who accepted to use hormonal therapy, had to follow a 6 weeks scheme. Patients received subcutaneous 500 UI (Gonasi-HP) weekly. A follow-up was performed at the end of therapy and 6 months later. Testicular volume was measured at each visit by ultrasound and by sonoelastography and compared with the untreated ones. Results: Forty-five patients were enrolled and treated with a mean age of 18.0±9.7 months. 32 patients received post-operative hormonal therapy. There were no cases of adverse effects nor droupout. All patients completed follow-up. There were no cases of testicular atrophy in both groups. At 6 months among treated patients 26 (81%) subjects achieved normal testicular size while the other had still smaller volume. Among untreated patients, 6 (46%) subject achieved normal testicular size ($P < 0.05$). Conclusion: Despite the role of hormonal therapy is still under discussion, especially for post-operative treatment, our results suggest that it is safe and useful to improve testicular volume and morphology; treated testes have also a good stiffness respect to untreated testes.

Keywords: Undescended testes, hormone, HCG, treatment

Introduction

Testicular growth depends on many different factors. The normal development and function of the testis is strictly correlated with normal spermatogenesis and subsequent normal fertility. Testicular size is highly correlated with fertility, poor fertility often being associated with small testes. It is, therefore, vital to ensure the regular development of the testes at any stage. The regular development and function of the testis in the fetus can be impaired by various congenital malformations. In such cases, the imbalance in testicular hormonal stimulation caused by many diseases results in damage to the spermatogenesis and subsequent infertility [1].

The testicular volume is strictly correlated to fertility potential and spermatogenesis; undescended testis is the most frequently diagnosed andrological disease before 3 yrs of age; hormonal treatment has been used for years before surgery, but recently this treatment is under discussion [2-5].

The esticular volume and function improvement of intrabdominal testes after orchiopexy is still the main outcome for surgeons. It was reported that testicular volume and hormonal function at 18 years in patients diagnosed and treated for cryptorchidism during childhood are strongly influenced by the age at operation and whether the undescended testis was unilateral or bilateral [1].

The aim of this prospective study is to report the Authors' experience with the post-operative use of human chorionic gonadotrophin to

achieve higher testicular volume and function versus untreated patients.

Materials and methods

A prospective study was carried out on subjects treated with orchiopexy for unilateral intrabdominal undescended testes between September 2010 and September 2016. All patients were treated by the same surgeon using the laparoscopic one-stage Fowler-Stephens technique.

Inclusion criteria for this study were as follows: full term baby; unilateral non-palpable testes; no genetic diseases; no other malformations.

Informed consent was obtained from all the parents and patients' compliance with treatment assessments was 100%. No dropouts were recorded. The internal IRB approved the study.

Patients were divided into two groups: a study group and a control group. After surgery (2 weeks), the patients whose parents had accepted to use the hormonal therapy had to follow a 6-week scheme. Patients received subcutaneous 500 UI (human chorionic gonadotrophin extracted from human urine u-hCG) weekly. Follow-up was performed at the end of the therapy and 6 months hence after.

Patients without hormonal therapy were included in the control group. The testicular volume was measured at each visit by Ultrasound (US) and sonoelastography and then compared with untreated patients (controlateral subjects and study group vs control group).

Sonoelastography is an imaging technique to assess the elasticity of a tissue; results are expressed following a color scale, where red shows well vascularized tissue with good elasticity, blue indicates stiffer tissue and green represents mixed stiffness. The testicular elasticity was expressed as a three-point scale (1: normal; 2: mild to moderate stiffness; 3: severe stiffness) [6].

The advantage of this ultrasound technique lies in its real-time evaluation of the tissue, with any relevant stiff areas, allowing the operator to focus on a specific point.

Ultrasounds were performed using Siemens Sonoline Elegra Ultrasound Imaging System, with 5 to 10 MHz probes. With testicular US, clinicians can assess the patients' testicular volume and parenchymal echostructure.

In this study, US scans were performed by the same radiologist and the testes were scanned with the same instrument described before using a 7.5 MHz probe. Testicular length, width, and height were measured using electronic callipers. The figures obtained were then substituted into the formula of a prolate ellipsoid to estimate the testicular volume [Vol (ml) = .523 × L × W × H] [6].

Statistical analysis was performed using the chi-square test, T-student test and Fischer exact tests. P value < .05 was considered significant for the correlation between the variables.

Results

During the study period, forty-five patients were enrolled and treated, mean age of 18.0±9.7 months. 32 patients received post-operative hormonal therapy. There were no cases of adverse effects including dropout or major surgical complications (I.e. retracted testis or scrotal bleeding). All patients completed follow-up. All data collected were monitored and recorded in an electronic database. Before each visit, the patients were contacted by phone. For this reason, compliance for this study was 100%. There were no cases of testicular atrophy in either group (P>0.05).

The injections were performed by the patients' parents at the samehour each week, with full compliance with the procedure.

At 6-month follow-up, treated patients showed different outcomes: 26 (81%) subjects achieved normal testicular size versus the controlateral testis, while in the remaining subjects the testis was still reduced in volume. In the group of untreated patients, 6 (46%) subjects achieved normal testicular size (P < 0.05).

The mean testicular growth improvement in treated patients was 23% in volume versus untreated patients. Based on the elastosonographic results, treated patients had better vascularizied testes with a soft pattern than untreated patients. The mean score for each testis at sonoelastography was 1.5±0.3 in the treated group and 2.1±0.3 in the untreated group (P < 0.05).

Treated testes were bigger and less stiff than the testes of the control group; considering the controlateral testis per each group, the treated group did not show significant statistical differences, while in the control group the operated testes were stiffer than their controlateral (2.1±0.3 vs 1.4±0.5) ($P < 0.05$).

Discussion

Many testes that are undescended at birth reach the scrotum soon afterwards. It has been found that 2% of full-term and 18% of premature babies have one or two undescended testes at birth and that in 75% of these cases the testes have descended by year 1, at which age the overall incidence of undescended testes is 1% [3].

Unilateral cryptorchidism accounts for about 85% of all recoreded cases [5]. The incidence of this condition decreases to about 1% within 6 months of age because of spontaneous descent. It has been estimated that a normal testis results if descent occurs within 6 weeks from birth in a full-term infant or 3 months in a premature baby. With later descent the testis fails to reach the bottom of the scrotum and remains smaller than the opposite scrotal organ [7].

Evolutionarily speaking, testicular descent is a costly process, and many developmental or physiological difficulties might occur during its course. The descent of the testis is a complex, multistage process requiring the interaction of both anatomical and hormonal factors [4-12].

The most accepted theory describes the descent from an intra-abdominal location into the bottom of the scrotum in two major phases, the transabdominal and the inguinoscrotal descent. This two-stage process is guided by two mesenteric ligaments: the cranial suspensory ligament (CSL) and the caudal genitoinguinal ligament or gubernaculum.

Under the effects of hormones, CSL regresses whereas the gubernaculum develops its caudal segment into the so-called gubernacular bulb, a reaction called the “swelling reaction” or “gubernacular outgrowth”, protruding into the forming scrotal sac. The swelling reaction of the gubernaculum holds the testis very close to the developing internal inguinal ring; this causes the transabdominal migration of the testes into the inguinal region. Therefore, the transabdominal phase of the testicular descent is the result of the vector sum of traction by the CSL and the gubernaculum. During the second inguinoscrotal phase the testes move from the inguinal region to the scrotum. This phase is due to the shortening of the gubernacular cord and the outgrowth of the gubernacular bulb. The transabdominal stage occurs between 10 and 23 weeks of gestation in human embryos, while the inguinoscrotal phase starts at around 26 weeks of gestation to end between 28 weeks of gestation and birth.

Many studies found gonocytes (human testicular tissue) in the testis of 2-year-old boys. At the age of 3 years spermatogonia can be observed on the basal lamina. Spermatocytes appear at 4 years, immature spermatids at 11 years, and mature spermatids at 13 years of age. Leydig cells are not recognized in the testes of 2- to 6-year-olds. Only fibroblast-like cells can be observed in the interstitial tissue. At the age of 7 years, immature Leydig cells are recognized in the interstitial tissue. Mature Leydig cells are also observed in the testes of 13-year-old boys. All these results explain how important the normal descent of the testes is for spermatogenesis and how testicular failure or disease during infancy may severly compromise adult fertility [2].

Many studies in humans and animals reported the role of the gubernaculum: histologically, the gubernaculum is composed of an abundant extracellular matrix that is rich in glycosaminoglycans and mesenchymal cells such as fibroblasts and smooth muscle cells. The connective tissue of the gubernaculum undergoes remodelling so that at the end of migration it has essentially become a fibrous structure, rich in collagen and elastic tissue. But, as reported in animals, during this transformation, if treated with hormone, the gubernaculum becomes rich in vessels under the effect of testosterone, which increases the androgen receptor expression in the fibroblasts, with secondary gubernacular muscle contraction [8-11].

Chedane et al reported a link between low maternal serum hCG level and cryptorchidism; relative hCG insufficiency could contribute to cryptorchidism, as hCG is known to stimulate fetal testicular androgen production with peak

hCG levels at weeks 8-11 of gestation. Starting from week 20 of gestation hCG levels then drop to 10-15% of peak concentrations. For this reason, for many years hormonal therapy was the first-line treatment for undescended testes [15].

If at present the standard goal still remains the surgical procedure, less is known about the role of hormonal therapy associated with orchiopexy. For intraabdominal undescended testes, the first issue is whether or not surgeons should preserve the spermatic vessels. The Fowler-Stephen technique, in which the testicular artery and vein are ligated, allows extensive mobilization of the testis, which then depends on the deferential artery and gubernaculum for blood flow. It was reported that pre-operative human chorionic gonadotropin on intra-abdominal rat testes undergoing orchiopexy doubled the testicular blood flow [13].

This technique can be performed in single or two-staged procedure; at present, there are no consistent data available to support either option. However, all the series reported a success rate between 80 and 85% with 20% of atrophy [14].

The aim of this study was to improve the testicular vascularization; based on the different studies reported in the literature, it was decided to evaluate the role of the hormonal therapy after surgery; it is also clear that the surgeon's experience still plays an important role to avoid gubernacular injuries during the procedure.

At follow-up, the study patients treated with hCG had better vascularization detected on Doppler ultrasound and good stiffness detected on sonoelastography. This means that even when the surgeon or procedure do not change, post-operative gubernacular stimulation can improve the testicular growth by enhancing the vascularization of the testes. It is clear that this finding does not relate to the testicular function.

Also, it is known that hCG stimulates the androgen secretion of Leydig cells, thus allowing the identification of any intra-abdominal testicular tissue in patients with true bilateral cryptorchidism. High level of hCG could bind to FSH receptors to stimulate the hormonal production of Sertoli cells. Thus, hCG implementation after surgery adds both improvement in interstitial tissue and in the stimulation of Sertoli cells.

Conclusions

Despite the role of hormonal therapy being still under discussion, especially as a post-operative treatment, the results collected in this study, and confirmed by other authors [16-18], suggest that this approach is simple (subcutaneous injection), safe and useful to improve testicular volume and morphology. Also, stiffness in treated testes was milder than in untreated testes, due to improved vascularization. Further studies may show that such findings can be associated with enhanced testicular function, thus preserving the patients' fertility potential.

Disclosure of conflict of interest

None.

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References

[1] Varela-Cives R, Mendez-Gallart R, Estevez-Martinez E, Rodriguez-Barca P, Bautista-Casasnovas A, Pombo-Arias M, Tojo-Sierra R. A cross-sectional study of cryptorchidism in children: testicular volume and hormonal function at 18 years of age. Int Braz J Urol 2015; 41: 57-66.

[2] Mandat KM, Wieczorkiewicz B, Gubala-Kacala M, Sypniewski J, Bujok G. Semen analysis of patients who had orchidopexy in childhood. Eur J Pediatr Surg 1994; 4: 94-97.

[3] Toppari J. Physiology and disorder of testicular descent. Endocr Dev 2003; 5: 104-109.

[4] Foresta C, Zuccarello D, Garolla A, Ferlin A. Role of hormones, genes, and environment in human cryptorchidism. Endocr Rev 2008; 29: 560-580.

[5] Tasian GE, Hittelman AB, Kim GE, DiSandro MJ, Baskin LS. Age at orchiopexy and testis palpability predict germ and Leydig cell loss: clinical predictors of adverse histological features of cryptorchidism. J Urol 2009; 182: 704-709.

[6] Camoglio FS, Bruno C, Peretti M, Bianchi F, Bucci A, Scirè G, Patanè S, Zampieri N. The role

of sonoelastography in the evaluation of testes with varicocele. Urology 2017; 100: 203-206.
[7] Kojima Y, Mizuno K, Nakane A, Kato T, Kohri K, Hayashi Y. Long-term physical, hormonal, and sexual outcome of males with disorders of sex development. J Pediatr Surg 2009; 44: 1491-1496.
[8] Vigueras RM, Reyes G, Moreno-Mendoza N, Merchant-Larios H. Gubernacular fibroblasts express the androgen receptor during testis descent in cryptorchid rats treated with human chorionic gonadotrophin. Urol Res 2004; 32: 386-390.
[9] El Zoghbi CS, Favorito LA, Costa WS, Sampaio FJ. Structural analysis of gubernaculum testis in cryptorchid patients submitted to treatment with human chorionic gonadotrophin. Int Braz J Urol 2007; 33: 223-229.
[10] Favorito LA, Costa SF, Julio-Junior HR, Sampaio FJ. The importance of the gubernaculum in testicular migration during the human fetal period. Int Braz J Urol 2014; 40: 722-9.
[11] Costa WS, Sampaio FJ, Favorito LA, Cardoso LE. Testicular migration: remodeling of connective tissue and muscle cells in human gubernaculum testis. J Urol 2002; 167: 2171-2176.
[12] Favorito LA, Hidalgo A Jr, Pazos HM, Costa WS, Sampaio FJ. Stereological and morphometric analysis of collagen and seminiferous tubules in testes of patients with cryptorchidism submitted or not to treatment with human chorionic gonadotrophin. Int Braz J Urol 2005; 31: 562-566.
[13] Matthews LA, Abdul-Karim FW, Elder JS. Effect of preoperative human chorionic gonadotropin on intra-abdominal rat testes undergoing standard and Fowler-Stephens orchiopexy. J Urol 1997; 157: 2315-2317.
[14] Elyas R, Guerra LA, Pike J, DeCarli C, Betolli M, Bass J, Chou S, Sweeney B, Rubin S, Barrowman N, Moher D, Leonard M. Is staging beneficial for Fowler-Stephens orchiopexy? A systematic review. J Urol 2010; 183: 2012-2018.
[15] Chedane C, Puissant H, Weil D, Rouleau S, Coutant R. Association between altered placental human chorionic gonadotrophin (hCG) production and the occurrence of cryptorchidism: a retrospective study. BMC Pediatr 2014; 14: 191-195.
[16] Hjertkvist M, Lackgren G, Ploen L, Bergh A. Does HCG treatment induce inflammation-like changes in undescended testes in boys? J Pediatri Surg 1993; 28: 254-258.
[17] Kaleva M, Arsalo A, Louhimo L, Rapola J, Perheentupa J, Henriksen K, Toppari J. Treatment with human chorionic gonadotrophin for cryptorchidism: clinical and histological effects. Int J Androl 1996; 19: 293-298.
[18] Samir H, Sasaki K, Ahmed E, Karen A, Nagaoka K, El Sayed M, Taya K, Watanabe G. Effect of a single injection of gonadotropin-releasing hormone (GnRH) and human chorionic gonadotropin (hCG) on testicular blood flow measured by color doppler ultrasonography in male shiba goats. J Vet Med Sci 2015; 77: 549-556.