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HUMAN CHORIONIC GONADOTROPHIN FOLLOWING ORCHIDOPEXY FOR UNILATERAL PALPABLE UNDESCENDED TESTIS: EFFECT ON TESTICULAR VOLUME AND VASCULARITY

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ABSTRACT

Background: Cryptorchidism is a common male genital anomaly discovered at birth. Orchiopexy is the sole curative option. However, hormonal treatment has its potential role. The type and regimen of hormonal treatment is widely different.

Objective: To evaluate the effect of the use of human chorionic gonadotrophin (hCG) as an adjunctive therapy after orchiopexy.

Patients and Methods: The study included 60 boys presented with unilateral palpable undescended testis. Their ages at presentation ranged between 10 months and 6 years. All patients were subjected to history taking, clinical and radiological examination and orchiopexy. Patients were randomized into two equal groups. Randomization was done by a closed envelope that opened 2 weeks postoperatively by a nurse not included in the study. Group A received supportive hCG injection, two weeks after operation by single intramuscular injection weekly for 4 consecutive weeks. The dose was adjusted according to patient weight (< 10kg received 500 IU/week; 10-20 kg received 1000 IU/week and above 20 kg received 1500 IU/week). Group B received orchiopexy without postoperative hormonal support.

Results: About 88.4% of studied children were underwent orchiopexy in the first two years of life. Both groups were comparable as regard to pre-intervention hormonal profile, and testicular volume before intervention, while after the intervention, volume significantly increased in group A with good blood supply.

Conclusion: hCG postoperative supplementation for children with unilateral palpable undescended testis appears to be beneficial in subsequent outcome as expressed by increase in the size and vascularity of the testis.

Keywords: Undescended testis; Orchidopexy; Human chorionic gonadotrophin, Testicular volume.

INTRODUCTION

Cryptorchidism is defined as the nonexistence of one or both testes from the scrotum. It affects about 3% and up to 30% of full-term and premature neonates respectively. Thus, it is the most prevalent male genital anomaly recognized at birth **(Miller et al., 2009).** It is essential to treat cryptorchidism to diminish the potential of cancer transformation, prevent atrophy, guard against trauma and torsion and improve fertility **(Mouriquand, 2008 and Miller et al., 2009).**

The therapeutic modalities include medical treatment, which includes hormones potentially promoting testicular descent. Human chorionic gonadotrophin (hCG) and luteinizing hormone-releasing hormone are the most common 2 hormones used for the therapy of cryptorchidism**.** Success rates of hormonal treatment vary from 0–55 % with hCG and from 9–78 % with LHRH **(Bu et al., 2016).**

Undescended testis often comprises distorted tubules, undeveloped Sertoli cells or micro-calcifications, representing testicular dysgenesis. Testicular dysgenesis syndrome may be produced by genetic conditions as well as by ecological reasons **(Guminska et al., 2010).**

On the other hand, it had been proposed that undescended testis (UT) had been showed to have a decreased number of germs cells at birth, and the loss had been documented to be progressive. High temperature destruct germ cells by reactive oxygen species and certain heat shock proteins that damages germ cells as well as sertoli cells **(Hutson et al., 2017).** Orchiopexy even if implemented as early as before one year of age may not inhibit postnatal changes in the testes **(Liu and Li, 2010).**

The rationale for postoperative hCG administration in the current work is based on the fact that, even with orchidopexy, impaired fertility was detected in 33% of unilateral cryptorchidism **(Hutson et al., 2010).**

The aim of the present work was to evaluate the effect of postoperative therapy with hCG in boys with unilateral palpable undescended testis on the testicular volume and vascularity.

PATIENTS AND METHODS

The present study was conducted at Al-Azhar University hospital, Damietta, Egypt (Tertiary healthcare center). The protocol was discussed and approved by the Ethical Research Committee of Al-Azhar University and an informed consent was obtained by guardians. The study was conducted during the period between January 2013 and January 2016. It included 60 boys presented with unilateral palpable undescended testis 38 on right side (63.3%), and 22 on left side (36.7%). Their ages at inclusion were between 10 months and 6 years (mean 38.06 months). Boys with ectopic testis, previous surgery for undescended testis, and previous preoperative hCG therapy were excluded from the study.

All patients were subjected to history taking, clinical and radiological examination and finally surgical orchiopexy was done. The diagnosis of undescended testicle was done clinically and by ultrasound examination. US with a high resolution transducer (> 7.5 MHz) was used as it offered the greatest accuracy in assessment of both testicular position and volume.

The scrotal ultrasound examinations included the scrotum and the inguinal area. Length and thickness of the testis were estimated in maximal longitudinal plane and width in axial plane. Testicular volumes were calculated by prolate ellipsoid formula: V= Length (L; vertical diameter) × Height or depth (thickness; antero-posterior diameter) × Width (W; transverse diameter) x 0.52 (**Hagag et al., 2017).** Patients were randomized into two equal groups. Randomization was done by a closed envelope that opened 2 weeks

postoperatively by a nurse not included in the study. Group A received small supportive dose of hCG injection, two weeks after operation by single intramuscular injection weekly for 4 consecutive weeks. The dose was adjusted according to patient weight (< 10 kg received 500 IU/week, 10-20 kg received 1000 IU/week and above 20 kg received 1500 IU/week). Group B received orchiopexy without postoperative hormonal support. Color doppler ultrasound was repeated at 3, 6 months, 1 and 2 years for all boys, and testicular volumes were re-estimated and compared for both groups. The majority of patients were followed up for 2 years either by physical visit to the outpatient or by home visits to the patients. In addition, the final testicular position at two years postoperatively was documented. Serum levels of FSH, LH and testosterone were determined at baseline (before surgery) in all boys. Then, blood samples were taken 72h after the last hCG injection. Blood was centrifuged and serum was stored at -20^{o}C until analysis.

In patients with severe diminution of testicular size, the testicular atrophy was calculated by the testicular atrophy index (TAI), which was calculated according to the formula: TAI = ((volume of contralateral (healthy) testis– volume of affected testis)/contralateral testis volume (healthy testis) x 100 and expressed as a percentage **(Spinelli et al., 2014).**

Statistical analysis of data: Collected data were analyzed by statistical package for social science (SPSS) version 22 (IBM®SPSS® Inc., USA). Data were represented as mean ± SD (standard deviation) or number and percentage for numerical or categorical data respectively. Student's *t* and Chi square tests were used for comparison between groups for numerical and categorical data respectively. Paired samples *t* test was used to compare the same variable before and at a specific point of time after intervention. For interpretation of results, P value < 0.05 was considered significant.

RESULTS

The study included 60 boys with palpable unilateral undescended testis. There was no significant difference between group A and group B as regards to patient's age (17.96±11.03 vs 20.10±14.68 months respectively). About 88.4% (53/60) of studied boys underwent orchiopexy in the first two years of life. In addition, both groups were comparable as regards to body weight (11.78±4.68 vs 12.72±6.07 kg respectively), and pre-intervention hormonal profile. There was no significant difference between both groups as regards FSH, LH, and testosterone before intervention. However, after intervention, there were significant decreases of FSH and LH after surgical intervention in group A when compared to group B, and significant increase of testosterone in group A when compared to group B (21.33±5.19 vs 13.52±2.42 nmol/L respectively). Furthermore, in groups A and B, there were significant decreases of LH and FSH, and significant increase of testosterone after intervention when compared to corresponding values before intervention. Finally, testicular volume before intervention revealed non-significant difference between both groups, while after the intervention, volume significantly increased in group A (0.581±0.071 vs 0.390±0.119 respec-

tively) with good vascularity as shown by follow up duplex study (Table 1).

As regard to postoperative follow up, there were significant increases of hydrocele formation and testicular pain in Group A when compared to group B (16.7%, 16.7% vs 0.0% and 0.0% respectively). On the other hand, suprapubic hair growth was reported in 3 (10.0%) boys of group A compared to none (0.0%) in group B. However, the difference was statistically non-significant. In addition, there was non-significant increase testicular atrophy in group B when compared to group A (6.7% vs 0.0% respectively). On the other hand, there were statistically significant increase of diminished testicular size, and unchanged testicular size in group B when compared to group A (26.7%, 36.7% vs 0.0% and 3.3% respectively). Finally, testicular re-ascent was reported in 5 patients in group B; 3 at scrotal neck and 2 at lower inguinal canal with significant increase when compared to group A (16.7% vs 0.0% respectively). Hydrocele and suprapubic hair growth were relieved completely without medication, while testicular pain needed non-steroidal anti-inflammatory drugs. Testicular ascent needed another surgical intervention (Table 2).

Table (1): Demographic data of both groups.

Variables \ Groups		Group A	Group B	P value
Age (months)		17.96±11.03	20.10±14.68	0.53
Age	First year	7(23.3%)	6(20.0%)	0.94
	Second year	20(66.7%)	20(66.7%)	
	Third year	1(3.3%)	1(3.3%)	
	Fourth year	1(3.3%)	1(3.3%)	
	Fifth or older	1(3.3%)	2(6.7%)	
Weight (kg)		11.78±4.68	12.72±6.07	0.50
FSH before (IU/L)		0.844±0.318	0.803±0.257	0.58
FSH after (IU/L)		0.064±0.012#	0.199±0.092#	***<0.001****
LH before (IU/L)		0.179±0.303	0.224±0.378	0.61
LH after (IU/L)		0.054±0.008#	0.147±0.228#	***0.029****
Testosterone before (nmol/L)		0.289±0.082	0.311±0.063	0.24
Testosterone after (nmol/L)		21.33±5.19$	13.52±2.42$	***<0.001****
Volume before (cm^3)		0.386±0.055	0.382±0.032	0.85
Volume after (cm^3)		0.581±0.071$	0.390±0.119	***<0.001****

#: significant decrease after treatment when compared to corresponding values before treatment.

$: significant increase after treatment when compared to corresponding values before treatment.

* = significant difference between groups.

Table (2): Comparison between groups A and B as regard to postoperative follow up.

Variables \ Groups		Group A	Group B	P value
Hydrocele formation		5 (16.7%)	0(0.0%)	***0.020****
Suprapubic hair growth		3 (10.0%)	0(0.0%)	0.08(ns)
Testicular pain		5 (16.7%)	0(0.0%)	***0.020****
Diminished testicular size		0(0.0%)	8(26.7%)	***0.002****
Testicular atrophy		0(0.0%)	2(6.7%)	0.15(ns)
Unchanged testicular size		1(3.3%)	11(36.7%)	***0.001****
Testicular-ascent	Scrotal neck	0(0.0%)	3 (10.0%)	***0.20****
	Lower inguinal canal	0(0.0%)	2(6.7%)	

Figure (1): Preoperative right palpable undescended testis

Figure (2): complete orchiopexy for right palpable undescended testis, before closure of scrotal skin

Figure (3): Left orchiopexy with hormonal therapy, 8 months postoperative with good testicular size

Figure (4): Left orchiopexy with hormonal therapy, 24 months postoperative with good testicular size

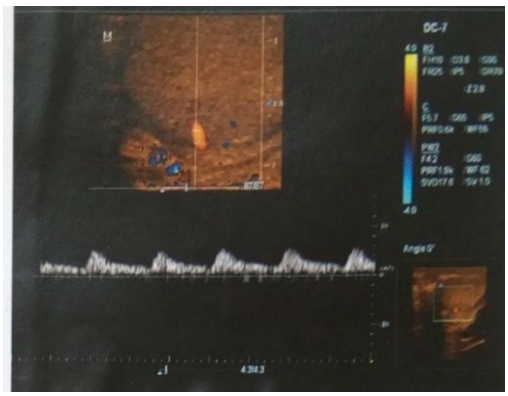

Figure (5): Postoperative Duplex ultrasound of a boy in group A, showing normal scrotal position of right testis which measures about 0.72 CC, had normal echo-pattern and normal tissue differentiation, uniform color saturation, normal biphasic Doppler flow wave of right testicular artery.

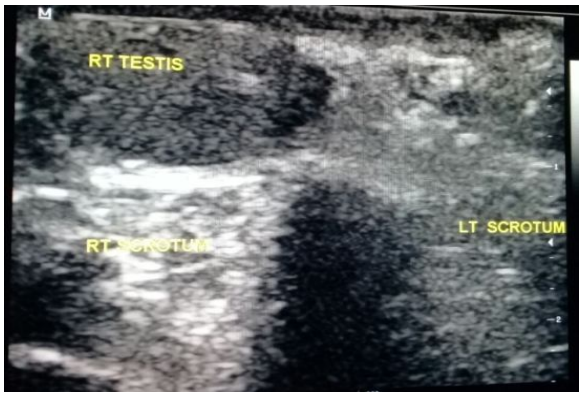

Figure (6): Empty left scrotum post orchiopexy in child with atrophic left testis

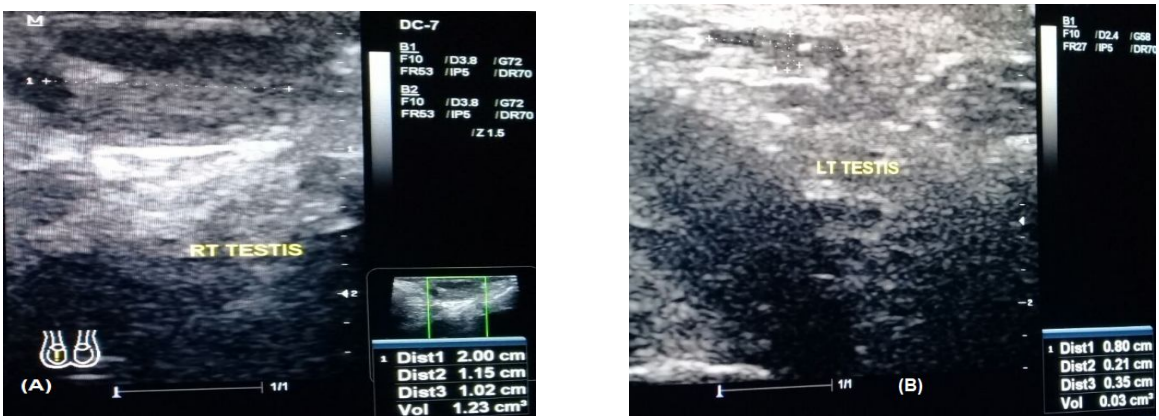

Figure (7): Ultrasound picture showing post-operative left testicular atrophy of a child 5 years old in group B.(testicular volume of Rt testis (A) =1.23 cm^3, Lt (B) = 0.03 cm^3). Testicular atrophy index = 97.5 %.

DISCUSSION

The current trial was designed to assess the effect of hCG administration after orchiopexy of unilateral palpable testicle regarding volume and vasculature. The is unique in the substance used (hCG), its regimen, titration and timing of administration. However, it remains in the field of hormonal therapy with orchiopexy, the filed which is still debated. For example, European Society of Pediatric Urologists' (ESPU) advocated the use of gonadotrophin releasing hormone (GnRH) analogues to improve fertility in boys with bilateral UT **(Biers and Malone, 2010).** In addition, GnRH analogues (used alone or with hCG) do

appear to have a statistically significant beneficial effect on fertility indices both when used before **(Jallouli et al., 2009)** and after early surgery **(Hadziselimovic, 2008).** For example, **Hollowell (2014)** reported that, biopsies at time of orchiopexy revealed that, boys who tried hormonal therapy had greater number of germ cells than boys who had gone straight to surgery. These data led to the proposal that hormonal treatment given during childhood could possibly hasten fertility in adulthood.

On the other hand, **Varela-Cives et al. (2015)** reported that hormone therapy before surgery does not appear to exert any benefit on testicular volume. In addition, there were no significant differences in hormone levels between patients undergoing primary surgery and those who were operated on after hormonal treatment failure. However, they found a marked increase in testicular volume in children whose testes descended with HCG therapy alone. These data in addition to results of the present one signified the postoperative administration of hCG as an adjuvant therapy after orchiopexy.

In the present work, the majority of children (88.4%) were treated in the first two years of life. These results were in accordance with general recommendations for the timing of orchiopexy is within the first 1.5 years of age to avoid primary histologic aberrations **(Kolon et al., 2014).** Otherwise, the percentage of children with UT undergoing surgery before 2 years of age increased slightly from 15.8% to 28.5% between 2001 and 2005 in Great Britain **(McCabe and Kenny, 2008).** Another survey from United States of America showed that 18% of orchiopexy were done by 1 year of age, and 43% by the age of 2 **(Kokorowski et al., 2010).**

Oliveira et al. (2016) reported that, hCG stimulation significantly increased testosterone levels in cryptorchid children. These results are in agreement with the present work. On the other hand, **Varela-Cives et al. (2015)** reported that FSH, LH, and testosterone levels did not show statistically significant differences.

Results of the present study revealed that the most common undesirable sequelae of hCG therapy were hydrocele formation, testicular pain and suprapubic hair growth that relieved spontaneously without medications except non-steroidal anti-inflammatory drugs for testicular pain. These results were in agreement with **Niedzielski et al. (2016)** who reported that momentary side-effects of hCG therapy have been detected including penile growth, pubic hair growth and groin pain.

In the present work, testicular atrophy was reported in 6.7% of boys in group B. These results were going with **Kucharski and Niedzielski (2013)** who reported that the most complication of orchiopexy is testicular atrophy resulting in loss of a testis. The atrophy rate was up to 8% for palpable and of up to 25% for non-palpable testes.

In the present study, ascent of testis was reported in 5 boys (16.7%) in group B. They underwent another surgical intervention, 6 months after the first intervention. **Khirallah et al. (2015)** reported that no cases presented with testicular re-ascend during the follow-up period. However, their follow up period

was extended to 6 months only postoperatively.

In agreement with results of the present study, **Niedzielski et al. (2016)** reported that reoperation for testicular ascent should not be planned earlier than 6 months after the first operation.

CONCLUSION

hCG adjunctive therapy after orchiopexy for unilateral palpable undescended testis increased significantly the testicular volume and vascularity.

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تأثير حقن هرمون الغدد التناسلية المشيمي البشري بعد تثبيت الخصية المعلقة المحسوسة بجهة واحدة على حجم الخصية وأوعيتها الدموية

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خلفية البحث: تمثل الخصية المعلقة واحدة من أكثر الأمراض الخلقية شيوعا فى الجهاز البولى التناسلى لدى الأطفال الذكور ويتم تشخيصها بعد الولادة. ويعتبر التدخل الجراحى لتثبيت الخصية المعلقة داخل كيس الصفن هو الخيار العلاجي الأكيد. والعلاج الهرموني له دور، ولكن نوع ونظام إعطاء العلاج الهرموني يختلف بصورة كبيرة.

الهدف من البحث: تقييم إستخدام هرمون الغدد التناسلية المشيمي البشرى كعلاج مساعد بعد تثبيت الخصية المعلقة.

المرضى وطرق البحث: اشتملت الدراسة على ٦٠ طفلا يعانون من خصية معلقة محسوسة وبجهة واحدة، وقد تراوحت أعمار الأطفال ما بين ١٠ شهور و٦ سنوات. وقد تم أخذ التاريخ المرضي لكل المشاركين في الدراسة وخضع الجميع لفحص إكلينيكي وفحص بالموجات فوق الصوتية، وجراحة تثبيت الخصية. وتم تقسيم المرضي بصورة عشوائية إلي مجموعتين متساويتين: المجموعة الأولى تم حقن الأطفال بالهرمون بعد إجراء عملية تثبيت الخصية بأسبوعين وكانت الجرعات حسب وزن الأطفال كالتالى : ٥٠٠ وحدة دولية حقن عضلى لكل طفل وزنه أقل من ١٠ كيلوجرام جرعة واحدة أسبوعيا ، ١٠٠٠ وحدة دولية جرعة واحدة أسبوعيا للأطفال الذين يتراوح وزنهم ما بين ١٠ -٢٠ كيلوجرام، ١٥٠٠ وحدة دولية جرعة واحدة أسبوعيا لكل طفل وزنة أكثر من ٢٠ كيلوجرام ومدة العلاج ٤ أسابيع متتالية٠و تتضمن المجموعة الثانية الأطفال الذين أجريت لهم الجراحة ولم يتم حقنهم بالهرمون بعد العملية ٠

النتائج: خضع حوالي ٨٨،٤% من الأطفال المشاركين في الدراسة لعملية تثبيت الخصية في أول عامين من أعمارهم. ولم توجد فروق ذات دلالة إحصائية بين مجموعتي الدراسة بالنسبة لقياسات الهرمونات، وحجم الخصية قبل الجراحة. ولكن بعد الجراحة زاد حجم الخصية بصورة يعتد بها إحصائيا في المجموعة الأولي، وكانت الزيادة في الحجم مصحوبة بتغذية دموية جيدة.

الاستنتاج: يبدو العلاج بهرمون الغدد التناسلية المشيمي البشرى بعد تثبيت الخصية المعلقة علي جهة واحدة كعلاج مفيد بالنسبة للنتائج بعد الجراحة، كما ظهر في زيادة حجم الخصية والتدفق الدموي إليها.