

Utilization Of Human Corionic Gonadotropin Hormone In The Treatment Of Undescended Testicle

İnsan Koryonik Gonadotropin Hormonunun İnmemiş Testis Tedavisinde Kullanılması

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Abstract

Introduction: Undescended testis is one of the most common congenital anomalies with an incidence up to 9% in term male babies. Its incidence is closely related to the week of birth and weight.

Objective: In this research we aimed to elucidate the response of undescended testicles to Human Chorionic Gonadotropin treatment and to investigate whether patient age, total hormone dose, hormone administration time and anatomical localization of the testis affected this response.

Method: A total of 45 patients with undescended testicles, whose age range was between 5 months and 11 years and were treated with hCG have been enrolled in this retrospective analysis. Human Chorionic Gonadotropin treatment has been administered to patients who were followed-up by the same pediatric surgeon. Testicular location, testicular volume, penis size, scrotal pigmentation and genital hair growth were evaluated before and after hormone therapy. Patients were divided into five groups according to their age as: Group A (<12 months), Group B (12 to 36 months), Group C (37 to 60 months), Group D (61 to 84 months) and Group E (>84 months).

Results: Following hCG treatment, 23 (46.9%) out of 49 individuals had non-palpable testes and they were located in the inguinal canal and suprascrotal descended into the scrotum. It was found that in 7 subjects testes did not completely descend into the scrotum, although they were displaced from their settlements to the scrotum before hCG treatment. This result was considered as treatment failure. Of the 10 patients that were considered as gliding testicles, all descended into the scrotum.

Conclusion: In conclusion, hormonal therapy appears to be of limited benefit in cases of true undescended testis and is more effective in cases with distal undescended testicles than in other abnormally located cases. However, the growth of the funiculus spermaticus structures as a result of hormone therapy, albeit partially, facilitates future surgical intervention.

Keywords: Undescended Testis, Human Chorionic Gonadotropin, Testicular Location, Testicular Volume.

Özet

Giriş: İnmemiş testis term erkek bebeklerde %9'a varan insidansı ile en sık görülen doğumsal anomalilerden biridir. Görülme sıklığı doğum haftası ve kilosu ile yakından ilişkilidir.

Amaç: Bu çalışmada inmemiş testislerin Human Chorionic Gonadotropin tedavisine verdiği cevabın aydınlatılması ve hasta yaşı, total hormon dozu, hormon uygulama zamanı ve testisin anatomik lokalizasyonunun bu cevabı etkileyip etkilemediğini araştırmayı amaçladık.

Yöntem: Bu retrospektif analize yaşları 5 ay ile 11 yıl arasında değişen ve hCG ile tedavi edilen inmemiş testisli toplam 45 hasta dahil edildi. Aynı çocuk cerrahisi tarafından takip edilen hastalara human koryonik gonadotropin tedavisi uygulandı. Hormon tedavisi öncesi ve sonrası testis yerleşimi, testis hacmi, penis boyutu, skrotal pigmentasyon ve genital kıllanma değerlendirildi. Hastalar yaşlarına göre gruplara ayrıldı: Grup A (<12 ay), Grup B (12 – 36 ay), Grup C (37 – 60 ay), Grup D (61 – 84 ay) ve Grup E (>84 ay).

Bulgular: HCG tedavisi sonrası 49 kişiden 23'ünde (%46,9) non-palpabl testis inguinal kanalda ve skrotuma inen supraskrotal yerleşimliydi. Vakaların 7'sinde testislerin hCG tedavisi öncesi yerleşim yerlerinden skrotuma

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döndüğü halde testislerin tamamen skrotuma inmediği saptandı. Bu sonuç tedavi başarısızlığı olarak kabul edildi. Kayan testis olarak kabul edilen 10 hastanın tamamında skrotuma inme sağlandı.

Sonuç: Sonuç olarak, hormonal tedavinin gerçek inmemiş testis vakalarında sınırlı yararı olduğu ve distal inmemiş testis vakalarında diğer anormal yerleşimli vakalara göre daha etkili olduğu görülmektedir. Ancak hormon tedavisi sonucunda funiculus spermaticus yapılarının kısmen de olsa büyümesi ilerideki cerrahi müdahaleyi kolaylaştırmaktadır.

Anahtar Kelimeler: İnmemiş Testis, Human Koryonik Gonadotropin, Testis Yerleşimi, Testis Hacmi.

INTRODUCTION

Undescended testis is one of the most common congenital anomalies in boys and is seen in 2 – 9% of term male babies. This rate is reported as 0.8 – 1% in children who have completed the age of 1 year and 35 – 43% of congenital cryptorchidism cases can spontaneously descend within the first 3 – 6 months after birth. However, it has been reported that 22% of these cases develop repeated cryptorchidism. Its incidence is closely related to the week of birth and weight. The incidence in boys born under 1500 grams is 60 – 70%, while this rate is 33% in premature babies thus, it decreases to 3% in term babies (1-3).

Undescended testis can be located in the abdominal, inguinal, superficial inguinal, high scrotal pouch and rarely ectopic. The testis can be palpated in 70% of patients with undescended testicles. It has been reported that 30% of non-palpable cases are inguinoscrotal, 55% are intra-abdominal, and 15% are vanishing testis (4, 5). Palpable undescended testis can be seen in true undescended testis, ectopic testis, and retractile testis. In the case of true undescended testis, the testis is trapped at any level of the path before completing the normal descent path. It is most commonly seen in inguinal localization. Non-palpable testis accounts for 30% of undescended testis patients. It is seen in the abdomen in 50%, loss in 10% and inguinal-scrotal localization in 40% (6). The testicles in the abdomen are mostly located close to the internal inguinal ring. Rarely, it can be seen close to the kidney hilum, localized to the anterior abdominal wall or behind the bladder (7).

In cases with bilateral undescended testis, it is not checked whether the testis can be palpated or not. If bilateral non-palpable testis is in question, genitalia ambigua should be kept in mind, and endocrinological and genetic examinations should be performed (8).

The fact that the testis stays on the path it travels during normal embryological development and does not descend to the place where it should normally be located in the scrotum is called true undescended testis. The final descent of the testis may be intra-abdominal, proximal or distal to the inguinal canal, or under the outer ring. To detect this, the testis is rubbed and stretched towards the scrotum. When it is released again, its location is important in determining its location in the scrotum (9).

In more than 70% of the patients, adequate diagnosis can be made by physical examination, and there is no need for additional imaging techniques. Radiological procedures are especially required in non-palpable testicles. Ultrasonography (USG), computerized tomography (CT) or magnetic resonance imaging (MRI) are utilized in the diagnosis. USG is most commonly used test in non-palpable testis, with a sensitivity of 45% and a specificity of 78%. The reliability of USG is low in non-palpable testicles. Although MRI has high sensitivity and specificity, the requirement for anesthesia during imaging are its negative aspects. No radiological test is 100% reliable. Therefore, surgical exploration (open or laparoscopic) is preferred. Diagnostic laparoscopy is considered as the gold standard because of its high sensitivity and specificity (9-11).

Within the scope of this research was to elucidate the response of undescended testicles to Human Chorionic Gonadotropin (hCG) treatment and to investigate whether patient age, total hormone dose, hormone administration time and anatomical localization of the testis affected the response to the treatment.

METHOD

A total of 45 patients with undescended testicles, whose age range was between 5 months and 11 years and were treated with hCG Çukurova University Faculty of Medicine in Department of Pediatric Surgery have been enrolled in this retrospective analysis. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The study has been approved at by the ethics committee of our institution.

Human Chorionic Gonadotropin treatment has been administered to patients who were followed-up by the same pediatric surgeon. Testicular location, testicular volume, penis size, scrotal pigmentation and genital hair growth were evaluated before and after hormone therapy. Testicles were classified as intra-abdominal (non-palpable), inguinal (palpable), supra-scrotal and gliding testis according to anatomical localization. Testicles that were not in the scrotum during the examination, but descended into the scrotum with manipulation and remained in the scrotal location after the manipulation were considered as retractile testicles. Human Chorionic Gonadotropin treatment was given to 39 patients at 100 U/kg/week (2 days a week Monday & Thursday) for a total of 4 weeks. The remaining 6 patients were given daily hCG injection twice a week for a total of 2, 3, 6 and 8 weeks, and 2 patients were administered daily for three days, once a day. The total hCG dose was 4000 units in patients under 1 year of age and 6000 units in patients over 1 year old.

Clinical records including the number and location of undescended testicles were analyzed after hCG treatment. Physical examination has been performed in week 1 and 12 weeks after the completion of hCG therapy.

The treatment was interpreted as successful when the testis or testicles descended into the scrotum. HCG administration was considered unsuccessful in patients if testicles were located in the abdominal or inguinal canal before treatment and descended to the upper scrotal region after treatment, and those whose location did not change after treatment or who underwent surgical intervention. Comparisons were made for patient age, hormone dose, treatment duration and undescended testis location parameters.

Patients were divided into five groups according to their age as: Group A (<12 months), Group B (12 to 36 months), Group C (37 to 60 months), Group D (61 to 84 months) and Group E (>84 months) (Table 1).

The patients were excluded from the analysis if they received hormonal treatment and/or undergone surgical intervention involving the inguino-scrotal region previously. Patients with major anatomical defects (inguinal hernia, hydrocele, hypospadias), malformation syndrome, multisystem anomaly, anorchidism, monorchidism, testicular dysgenesis, hypopituitarism, Prune-Belly Syndrome, myelomeningocele, partial androgen resistance, Klinefelter syndrome and complete gonadotropin syndrome were also non included in the study.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY)

package program. Frequency and percentage were given for categorical data, and median, minimum and maximum descriptive values for continuous data. "Mann Whitney U Test" was used for comparisons between groups, "Friedman Test" for comparison of measurement values, "Fisher's Exact Test" for comparison of categorical variables, and "Sperman Correlation Analysis" for evaluation of the relationship between continuous data. The results were considered statistically significant when the p value was less than 0.05.

RESULTS

In this study, a total of 45 patients have been enrolled in our institution. The segmentation could be elaborated as: 31 patients (68.8%) had unilateral and 14 (31.1%) patients had bilateral undescended testicles. Of the unilateral undescended testicles, 14 (45.1%) were on the right and 17 (54.8%) were on the left. In addition to the pathologies listed above, ectopic and retractile testicles were also excluded from the study. When the testicles were classified according to anatomical location, their distribution was 2 in the intra-abdominal (3.38%), 24 in the inguinal canal (40.67%), 23 suprascrotal (38.98%) and 10 gliding (16.94%) (Table 2).

Table 1. Comparison Of Hormone Therapy By Age Groups

Age	Number of Undescended Testes	Number of Descended Testes	P Value
Group A	4	0 (0%)	<i>p=0.194</i>
Group B	25	14 (56%)	
Group C	19	12 (63.1%)	
Group D	4	3 (75%)	
Group E	7	4 (57.1%)	
All Groups	59	33	

Table 2. Comparison Of Descents Of Gliding And Non-Gliding Testicles

	Non-palpable, Inguinal Canal and Suprascrotal testicles	Gliding testicles
Number of testicles treated	49 (83%)	10 (17%)
Number of testes responding to treatment	23 (46.9%)	10 (100%)

Following hCG treatment, 23 (46.9%) out of 49 individuals had non-palpable testes and they were located in the inguinal canal and suprascrotal descended into the scrotum. It was found that in 7 subjects testes did not completely descend into the scrotum, although they were displaced from their settlements to the scrotum before hCG treatment. This result was considered as treatment failure. Of the 10 patients that were considered as gliding testicles, all descended into the scrotum (Table 3) (Table 4).

Table 3. Hormone Responses Of Undescended Testicles According To Their Right And Left Placement

	Number of Undescended Testes	Number of Descended Testes	P Value
Right	28	16 (57.1%)	<i>p=0.859</i>
Left	31	17 (54.8%)	
Total	59	33 (55.9%)	

After hCG administration, 16 (n=16/28 – 57.1%) individuals with undescended testes on the right and 16 (n=31 – 51.6%) individuals with undescended testes on the left descended into the scrotum. When results were compared with each other, no significant difference was found. When the responses of a total of 59 unilaterally and bilaterally testicles were

examined, it was found that 15 (48.3%) of 31 unilateral testicles and 18 (64.2%) of 28 bilateral testicles descended into the scrotum and no significant difference was found (Table 3) (Table 4).

Table 4. Hormone Responses Of Undescended Testicles According To Bilateral/Unilateral Location

	Number of Undescended Testes	Number of Descended Testes	
Unilateral	31	15 (48.3%)	<i>p=0.219</i>
Bilateral	28	18 (64.2%)	
Total	59	33 (55.9%)	

Hormone therapy allowed 33 of the 59 undescended testes to settle in the scrotum and 10 of them were gliding testicles. There was a complete response in all gliding testes treated with hCG and the rate of descent into the scrotum was 100%. In terms of 23 other descended testicles, the testes were mostly inguinal canal and suprascrotal and not palpable before hormone administration. The descent rate in this group was 46.9%. When this rate was compared with the rate of descent of gliding testicles, a statistically significant difference was found ($p=0.01$).

DISCUSSION

The aim of treatment in patients with undescended testicles is the acquisition of fertile testicles located in the scrotum. The use of hormonal therapy is based on the hypothesis that the hypothalamo-pituitary-testicular axis is inadequate due to low serum testosterone levels compared to the control group detected in the first 1 to 4 months of life in studies of children with undescended testes (11). Peak LH values are also low in children with undescended testes. However, low testosterone and gonadotropin levels were not found in infants with undescended testes in all publications. In one study, the presence of antigonadotropic antibodies in children with undescended testes was shown at a rate of 50%. (12). Karpe et al. elaborated that surgical obstruction was shown in 10% of cases that did not respond to hormone therapy (13). Data on known undescended testis indicate an early partial deficiency of LH secretion, which can be demonstrated within the first post-natal weeks and persist until mid-puberty; may result in subnormal secretion of testiclesterone by prepubertal Leydig cells and failure of the testis to descend normally. The incidence of undescended testes in cases of ongoing hypogonadotropic hypogonadism provides complementary evidence for the role of gonadotropin deficiency in both bilateral and unilateral testicular descent disorder (14).

Success rates ranging from 10% to 65% have been reported with hCG used to achieve testicular descent in children with undescended testicles. It is understood that the inclusion of children of various ages and with retractile testicle in the treatment affects the success rates. In the study of Rajfer et al. (15), the success rate in the treatment of true undescended testes with hCG was only 6%. Hadziselimovic et al. (16) also found that hormonal therapy contributed little to true undescended testicle descent, with less than 20% of testes descending in most series.

Parenterally administered hCG stimulates Leydig cells and increases testosterone synthesis. Thus, the hormone itself or the more active de-hydrotestosterone (DHT) allows the testicles to descend into the scrotum. Administration of exogenous testosterone is not recommended because high local testosterone levels cannot be achieved with exogenous testosterone given to the treatment. In addition, exogenous testosterone may cause precocious puberty (17, 18). However, higher local testosterone levels are obtained in the gubernaculum region with parenterally administered hCG. In a study by Job et al. (19), the success rate was found to be

45%. This rate was found to be 59% by Adamsen et al. (20), 14% by Christiansen et al. (21), and 31% by Cacciari et al. (22).

In the success of hormone therapy, the initial position of the testicles has an important role in the response to the treatment. The success rate is higher in distal localized testicles. For this reason, hormonal therapy should be the first choice, especially in low type undescended testicles. Hormonal therapy may be more successful in low-type undescended testicles that can be palpated at the upper levels of the scrotum, interpreted as gliding. Almost all of the retractile testicles descend into the scrotum with hCG (23). Therefore, hormonal therapy can also be used to differentiate true undescended testis from retractile testis in borderline cases. As a matter of fact, this rate is 99% in suprascrotal patients, while this rate is 0% in non-palpable patients. Since intra-abdominal testicles are especially refractory to hCG treatment, the first testicular location is important for response to treatment. However, the effect of hormonal therapy in higher undescended testes types is quite limited and surgery should be planned without delay. In high type undescended testicles, although hormonal therapy has little effect, it may have positive effects on testicular functions (24).

In our study, we found that all of the abnormally located undescended testes were displaced after hormone therapy, but some of them completely descended into the scrotum. There was no response to hCG hormone in non-palpable undescended testes. Testes that were treated but not completely descended into the scrotum were included in the group that did not respond to treatment. When the testicles were classified according to their pre-treatment location, the descent response to hCG treatment was mostly in the gliding testicles. When we compared the descent rate of gliding testicles to other groups, a statistical significant difference was found ($p=0.01$).

The age to start treatment for undescended testis is still controversial. There is general agreement that the undescended testis should be treated as early as possible to avoid structural changes in the gonadal tissue (25). Over the past years attention has been focused on the degenerative changes that occur in the undescended testes from the second year of age, and many authors have recommended early treatment (26). In some reports, it is recommended that hormonal therapy should be started before the age of two, while others argue that the treatment should be started between the ages of 3 and 4 years (25). It has been stated that optimal success is achieved after the age of five, and treatment administered between 3 and 4 years of age constitutes an acceptable treatment range. hCG therapy is mainly indicated for patients with undescended testicles localized to the inguinal canal and lower levels, but between 3 and 4 years of age, abdominal and internal. Its usefulness is low in children with undescended testicles located in the inguinal ring (25, 26).

Garagorri et al. (27) showed that age is important in success rates. The worst outcomes occur between the ages of one and two, which are the most favorable ages at which descending is desired. The success rate was 9% until the age of 2, 15% between the ages of 2 and 5, and 44% between the ages of 10 and 14. According to Hadziselimovic et al. (28), medical treatment can only be beneficial if it is administered at an appropriate dose, as early as 10 – 18 months.

Despite the recommendations of the World Health Organization, the treatment dose and duration of hCG are still controversial and there is no established consensus. The World Health Organization uses hCG as 250 IU twice a week for five weeks (2500 IU in total) for boys under one year of age, 500 IU for children 1 to 5 years old, twice a week for five weeks (total 5000 IU), in older children, it recommends 1000 IU twice a week for five weeks (10000

IU in total). Good results have been achieved with hCG therapy, without serious side effects (29).

In our study, a total of 6000 IU of hCG hormone therapy was applied to 19 patients, and 4000 IU of hCG hormone therapy was applied to 17 patients. The remaining patients received a total treatment dose between 2000 IU and 12000 IU. Hormone dose was calculated considering the weight of the patients. Of the 39 patients in the study, that is, 50 undescended testicles, were given hormones twice a week for four weeks. Hormone therapy lasted for a minimum of four weeks, and a maximum of 16 weeks for hormone therapy. The highest dose of hormone administered to a patient was 128000 units.

On the other hand, 10 – 20% testicular descent into the scrotum with hormonal treatment saves patients from surgical intervention. Therefore, in cases of undescended testis, as seen in our study, hormone therapy is inevitable in the first place. Surgical intervention should be limited to cases where hormonal therapy has failed, and should also be applied to all patients with major anatomical defects. Surgery should be secondary to failure of hormonal therapy or if there is associated hernia with abdominal or non-palpable undescended testis (because hCG therapy is very dangerous here) (30, 31).

CONCLUSION

In conclusion, hormonal therapy appears to be of limited benefit in cases of true undescended testis and is more effective in cases with distal undescended testicles than in other abnormally located cases. However, the growth of the funiculus spermaticus structures as a result of hormone therapy, albeit partially, facilitates future surgical intervention.

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Ethical Declaration: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. As this was a retrospective analysis informed consent was not mandatory from enrolled patients. The study has been approved by the ethics committee of our institution.

Abbreviations

CT	:Computerized Tomography
DHT	:Dehydro Testosterone
FSH	:Follicle-Stimulating Hormone
GnRH	:Gonadotropin Releasing Hormone
hCG	: Human Chorionic Gonadotropin
HMG	: Human Menopausal Gonadotropin
LH	:Luteinizing Hormone
LHRH	: Luteinizing Hormone-Releasing Hormone
MIS	: Müllerian Inhibiting Substance

MRI	: Magnetic Resonance Imaging
SPSS	: Statistical Package for the Social Sciences
SRY	: Sex Determining Region Y
TDG	: Testis Determining Gene
USG	: Ultrasound Imaging

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