



The Effect of Human Chorionic Gonadotropin Treatment Before Testicular Sperm Extraction in Non-Obstructive Azoospermia

Non-Obstruktif Azoospermide Testiküler Sperm Ekstraksiyonu Öncesi Human Koryonik Gonadotropin Tedavisinin Etkisi

The Effect of hCG Treatment Before TESE

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Özet

Amaç: İdiyopatik non-obstruktif azospermili (NOA) hastalarda, ampirik hCG tedavisi ile ilgili sonuçları araştırmak. **Gereç ve Yöntem:** hCG grubunu normal testis hacimlerine ve normal serum FSH ve LH düzeylerine sahip olan ve ampirik hCG ile tedavi edilen 34 hasta oluşturdu. hCG, testiküler sperm ekstraksiyonundan (TESE) 10-14 hafta önce 2500 IU olarak haftada iki kere deri altına enjeksiyon şeklinde uygulandı. Kontrol grubunu yaş ve eş yaşları hCG grubu ile denk olup aynı dönemde TESE uygulanan 49 hasta oluşturdu. Gruplar arasındaki sperm elde etme oranı (SRR), folikül uyarıcı hormon (FSH), luteinize hormon (LH), testosteron seviyeleri, testis hacimleri, fertilizasyon oranları (FR), implantasyon oranları (IR), gebelik oranları (PR), canlı doğum oranları (LBR), iptal oranları (CR) ve cerrahi tekniği arasındaki ilişki değerlendirildi. **Bulgular:** Konvansiyonel teknik ile başarılı sperm elde edilmesi, hCG grubundaki 17 hasta'nın 14'ünde (% 82,3) olurken kontrol grubundaki 28 hasta'nın 18'inde (% 64,3) sağlandı ($p = 0,170$). SRR açısından gruplar arasında fark yoktu ($p = 0,338$). Hastaların yaşı, ortalama infertilite süresi, serum FSH, LH, testosteron, östradiol düzeyleri ve testis hacimleri açısından iki grup arasında anlamlı farklılık saptanmadı ($p > 0,05$). FR, IR, PR, LBR açısından iki grup arasında istatistiksel olarak anlamlı fark saptanmadı ($p > 0,05$). **Tartışma:** İdiyopatik NOA hastalarda ampirik hCG tedavisi ile SRR iyileşme sağlanamamıştır. hCG tedavisinin ICSI başarısı üzerinde herhangi bir etkisi bulunamamıştır.

Anahtar Kelimeler

Azospermi; Hormon Tedavisi; Sperm Eldesi; Gebelik Oranı

Abstract

Aim: To investigate our experience on empirical hCG treatment of patients with idiopathic non-obstructive azoospermia (NOA). **Material and Method:** hCG group consisted of 34 patients who were empirically treated with hCG despite normal serum FSH and LH levels and normal testicular volumes. hCG was administered as 2500 IU twice weekly subcutaneous injections for 10 to 14 weeks prior to testicular sperm extraction (TESE). Control group consisted of 49 age and spouse age matched patients who underwent TESE in the same time period. Sperm retrieval rate (SRR), and follicle stimulating hormone (FSH), luteinizing hormone (LH) and testosterone levels, volume of testicles, fertilization rate (FR), implantation rate (IR), pregnancy rate (PR), live birth rate (LBR) and cancel rate (CR) and surgical technique were compared between the two groups. **Results:** Conventional technique was used in 14 of the 17 patients (82.3%) with successful sperm retrieval in the hCG group, and 18 of the 28 patients (64.3%) in the control group ($p=0.170$). There were no differences between groups in terms of SRR ($p=0.338$). There were no significant differences in patient age, mean infertility period, mean values of FSH, LH, testosterone, estradiol levels, and testis volume between the two groups ($p>0.05$). There were no statistically significant differences for FR, IR, PR, LBR between the two groups ($p>0.05$). **Discussion:** Empirical hCG treatment in patients with idiopathic NOA did not result in improved SRR. hCG treatment did not have any effect on the success of ICSI.

Keywords

Azoospermia; Hormone Therapy; Sperm Retrieval; Pregnancy Rate

DOI: 10.4328/JCAM.3332

Received: 19.02.2015 Accepted: 24.03.2015 Printed: 01.01.2016 J Clin Anal Med 2016;7(1): 55-9

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Introduction

Azoospermia defined as the absence of spermatozoa in the ejaculate after assessment of centrifuged semen on at least two occasions, is observed in 1% of the general population and in 10–15% of infertile men [1, 2]. Non-obstructive azoospermia (NOA) refers to absence of spermatozoa in semen analysis due to minimal or no production of fully developed spermatozoa in the testicles. NOA results from a testicular failure. This problem affects 10% of infertile men and is diagnosed in 60% of azoospermic men [2, 3]. Hypospermatogenesis, maturation arrest and Sertoli cell-only syndrome (SCOS), with or without focal spermatogenesis are the commonest histological patterns of patients with NOA.

The positive clinical outcome of gonadotrophin treatment for infertile men whose azoospermia is caused by hypogonadotropic hypogonadism has been well documented. However, no established hormonal therapy is available for treatment of men with idiopathic NOA and normal plasma gonadotrophin levels. A recent survey among American Urological Association members showed that two thirds of the respondents used empirical medical therapy for idiopathic male infertility and the most common medications used were clomiphene citrate, human chorionic gonadotropin and anastrozole [4] Overall 60.5% of respondents would treat with empirical therapy for 3 to 6 months and 70% of the fellowship trained urologist counselled patients that empirical medical therapy has unknown effects on pregnancy and sperm count. The authors concluded that there is need for additional studies to establish recommendations on the empirical use of medical therapy in the setting of male infertility.

We aimed to investigate our own experience on empirical hCG treatment of patients with idiopathic NOA and normal plasma gonadotrophin and testosterone levels. We retrospectively examined the effects of empirical hCG treatment on sperm retrieval rate by TESE procedure and the success of intracytoplasmic sperm injection (ICSI) performed with the extracted sperm.

Material and Method

In a retrospective Case – Control study we reviewed the files of 429 consecutive patients with NOA who underwent TESE between March 2004 and November 2010. We identified 34 patients who were empirically treated with hCG despite normal serum FSH (1-12 mIU/ml) and LH(2-10 mIU/ml) levels and normal testicular volumes (≥ 15 cc) (hCG group). The hCG was administered as 2500 IU twice weekly subcutaneous injections for 10 to 14 weeks prior to TESE. TESE was performed by the conventional method initially, and carried on as microdissection TESE in the same session if the conventional technique failed to retrieve sperms. Control group consisted of 49 age and spouse age matched patients who underwent TESE in the same time period, had normal serum FSH and LH levels and normal testicular volumes, and did not receive hormone treatment. None of the couples in the treatment or control groups had any female factors involved.

The presence of azoospermia was confirmed by at least two semen analyses. Serum FSH, LH, testosterone (1.66-8.77 ng/ml) and estradiol (11-44 pg/ml) levels were measured in all patients

in the morning after 8 hours of overnight fasting. Testicular volume was measured in all patients by using an orchidometer. Informed consent was obtained from all patients before the operation.

The study was conducted according to the ethical standards of the Declaration of Helsinki. Since this was a retrospective design no ethical committee approval was sought.

None of the patients in the study had karyotype abnormalities or Y chromosome microdeletion.

The relation between SRR and FSH level, LH level, testosterone level and the volume of testicles were compared between groups. Additionally, FR, IR, PR, LBR and CR were determined. Relation between SRR and surgical technique was also analyzed.

In patients who underwent conventional TESE, microdissection TESE was also performed if the conventional technique failed to retrieve sperms [5]. Conventional and microdissection TESE procedures were performed under spinal anaesthesia. For conventional TESE, the tunica albuginea was incised for approximately 5mm at the upper pole near the head of the epididymis. If no sperms were seen in the initial sample, subsequent samples were taken from the middle part and the lower pole of the testis opposite the rete testis. When there was not a sufficient number of spermatozoa in the tubules obtained from these fields, the procedure was continued (maximum 7 biopsies) until sufficient spermatozoa were collected. The procedure was terminated when sufficient sperm were retrieved. When no sperm could be detected in 3 poles through the conventional technique, microdissection TESE was performed by enlarging the middle incision vertically (Combined technique). For microdissection TESE, the subtunical vessels were identified under the surgical microscope and avoided. Direct examination of the testicular parenchyma was performed at $\times 20$ to $\times 40$ magnification with an operating microscope. Small samples were excised from large, opaque seminiferous tubules. The procedure was terminated when a sufficient volume of spermatozoa had been retrieved for intracytoplasmic sperm injection. When there was no sperm in one testis, these procedures were performed on the contralateral testis. At the same session, a surgically-obtained small tissue specimen was placed in Bouin's solution and sent to the histopathology laboratory [5].

Ovarian stimulation and ICSI procedure [6]:

We used long luteal GnRH agonist protocol, ovarian down-regulation was initiated with daily leuprolide acetate 1 mg (Lucrin, Abbott, France), beginning on day 21 of the preceding menstruation (last 3 tablets of OCP). After ovarian suppression was achieved, the dose was reduced to 0.5 mg until the day of hCG. If there were no cysts ≥ 2 cm and the E2 was < 50 pg/mL, gonadotropin stimulation with 150-300 IU of rFSH was performed, with E2 monitoring commencing on the morning of stimulation day 5. Ultrasound and blood E2 monitoring continued until hCG administration criteria were met with at least three follicles having a maximum diameter of > 17 mm. Transvaginal ultrasound-guided oocyte retrieval was performed 35-36 hours after 10,000 IU hCG injection. An oocyte pick-up was performed with a 17-gauge single lumen needle for oocyte retrieval under sedation with propofol (propofol 1% Fresenius

KabiR, Germany). The oocyte-corona complexes (OOC) were denuded, and ICSI was performed after 2 hours of incubation and embryos were transferred on day 3. Our clinical policy is to use ICSI routinely in all patients. All patients had luteal support with 90 mg of progesterone intravaginally daily after embryo transfer until gestation reaches to 8 weeks.

Statistical analysis:

Statistical analysis was performed using the statistical package SPSS v 17.0 (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago, USA: SPSS Inc.). For each continuous variable, normality was checked by Kolmogorov Smirnov and Shapiro-Wilk tests and by histograms. Comparison between groups was made with Mann Whitney-U test for data not normally distributed and with student's t test for data normally distributed. The categorical variables between the groups were analyzed by the Chi-square test. Values of $p < 0.05$ were considered statistically.

Results

Spermatozoa were retrieved in 195 of 429 (45.5%) patients with NOA in whom TESE was performed. The hCG group consisted of 34 patients who received hCG treatment prior TESE, and the control group consisted of 49 patients who did not receive hCG treatment. There were no significant differences in patient age, mean infertility period, mean values of FSH, LH, testosterone, estradiol levels, and testis volume between the two groups (Table 1).

Table 1. Comparison of clinical and laboratory data for patients

	hCG Group	Control Group	P
Age, (years)	34±5.7	33.1±3.8	0.316*
Infertility time, (years)	7±5	6.6±4.2	0.706**
Age of the spouses, (years)	28±4.2	28±3.9	0.815*
FSH, mIU/ml	7±3.9	8±3.6	0.086**
LH, mIU/ml	4.2±1.5	4.7±1.9	0.298**
Testosteron, ng/ml	5±2	5.1±1.8	0.113**
Estradiol, pg/ml	22±9.1	23.6±9.4	0.381**
Testis volume, ml	20±4	20±3	0.546*

FSH: follicle-stimulating hormone, LH: luteinizing hormone.

Values are presented as mean±SD.

*Student's t test, **Mann Whitney-U test

In the hCG group, TESE was performed by conventional technique in 14 (41.2%), and combined technique in 20 (58.8%) patients. In the control group, TESE was performed by conventional technique in 18 (36.7%), combined technique in 31 (63.3%) patients ($p=0.428$). Sperm retrieval was achieved in 17 patients (50%) in the hCG group and 28 patients (57.1%) in the control group. There were no differences between groups in terms of SRR ($p=0.338$). Conventional technique was used in 14 of the 17 patients (82.3%) with successful sperm retrieval in the hCG group, and 18 of the 28 patients (64.3%) in the control group ($p=0.170$).

None of the patients showed any acute or chronic complications after TESE. No side effects of the treatment were observed. We were not able to perform postoperative serum testosterone level measurements in most of the patients due to low patient

compliance, therefore postoperative testicular failure could not be evaluated.

When the spouses were concerned, there were no differences between the groups for age, basal FSH level, antral follicle count, of the spouses and the number of transferred embryos (Table 2). There were no statistically significant differences for FR, IR, PR, LBR between the two groups (Table 3). In the hCG

Table 2. Clinical characteristics of the spouses and the number of transferred embryos in the hCG and the control groups

	hCG Group	Control Group	p
Female Age	29.8±4.9	28.2±5.3	0.08*
Basal FSH	6.2±1.8	5.6±1.5	0.65*
AFC	6.1±2.7	6.7±2.5	0.14**
Number s of transferred embryos	2.4±1.2	2.9±1	0.55**

AFC: Antral follicle count; FSH: follicle stimulating hormone

Values are presented as mean±SD.

*Student's t test, **Mann Whitney-U test

Table 3. Comparison of fertilization, implantation, pregnancy and birth rates in the hCG and the control groups

	hCG Group	Control Group	p
Fertilization Rate	60.7±25.3	54.4±26.2	0.392*
Implantation Rate	60.1±26.3	53.1±26.1	0.459*
Pregnancy Rate (per started cycle)	57.7(15/26)	64.5(20/31)	0.339**
Live Birth Rate (per started cycle)	38.5(10/26)	54.8(17/31)	0.167**
Live Birth Rate (per patient)	62.5(10/16)	63(17/27)	0.613**
Cancel Rate	6,3	11.1	0.567**

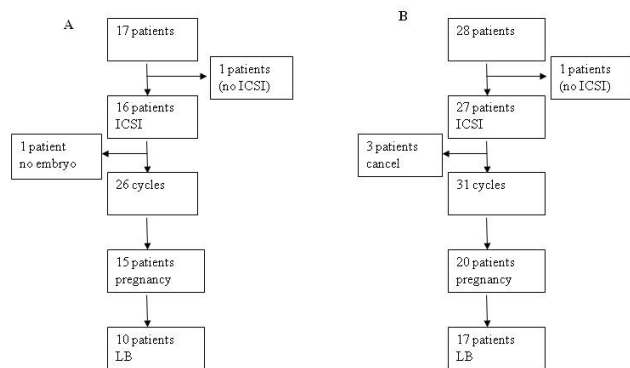
Numbers are given as percentages (%).

*Mann Whitney-U test, **Chi-square test

group sperms were retrieved in 17 patients. At the time of this report sperm was still cryopreserved in one patient. Embryo transfer was cancelled in one patient because of fertilization failure. In the remaining 15 patients 26 cycles of ICSI were performed which yielded 15 pregnancies and 10 live births (Figure 1a). In the control group sperms were retrieved in 28 patients. At the time of this report sperm was still cryopreserved in one patient. Embryo transfer was cancelled in three patients, two due to fertilization failure, and one because no mature oocytes could be found. In the remaining 27 patients 31 cycles of ICSI were performed which yielded 20 pregnancies and 17 live births (Figure 1b).

In the hCG group hypospermatogenesis, maturation arrest, and Sertoli cell only were found in 14.7%, 79.4% and 5.9% of the patients, respectively. In the control group hypospermatogenesis, maturation arrest, and Sertoli cell only were found in 10.2%, 71.4%, and 18.4% of the patients, respectively. There was no difference in the histopathological findings between the hCG and the control groups ($p=0.238$). Spermatozoa were successfully retrieved in all patients with hypospermatogenesis. In patients with maturation arrest spermatozoa were retrieved in 12 (44.4%) and 19 patients (54.3%) in the hCG and control groups, respectively. In Sertoli cell only patients spermatozoa could be retrieved in none of the patients in the hCG group, and in 4 patients (44.4%) in the control group.

Figure 1. (A) Flow chart of ICSI for hCG group patients, (B) Flow chart of ICSI for control group patients.



ICSI: Intracytoplasmic sperm injection, LB: Live birth

Discussion

The role of hormonal treatment is well established for male infertility caused by hypogonadotropic hypogonadism [7-9]. On the other hand the effect of hormonal treatment in patients with idiopathic NOA is not clear.

The actions of FSH and LH on germ cells are indirect and mediated by paracrine signals from Sertoli and Leydig cells, and close cell-cell interactions are required to maintain normal spermatogenesis [10]. hCG has effects similar to LH on the testicles. It was generally believed that gonadotrophin treatment would be ineffective in the presence of high plasma levels of endogenous gonadotrophin. Previous attempts to improve spermatogenesis in men with NOA by treatment with either recombinant human (rh)-FSH alone or in combination with hCG have been partly successful [9, 11]. Shiraishi and coworkers studied the effect of human chorionic gonadotrophin treatment prior to second microdissection testicular sperm extraction after failed previous micro-TESE in men with NOA. Forty-eight men with NOA who had negative sperm retrieval results by the micro-TESE procedure were studied. Twenty patients did not receive any medical treatment and 28 patients received 5000 IU subcutaneous injections of hCG three times a week prior to the second micro-TESE. In the treatment group all of the patients received hCG for 3 months. At the end of this period 15 patients with low serum FSH levels received rec FSH in addition to hCG for 2 months. Thirteen patients with normal FSH levels received hCG only for additional 1 to 2 months. No spermatozoa were retrieved from the 20 patients in the no medical treatment group. In the hCG only group, spermatozoa were retrieved in 2 of 13 patients (15.4%). In the recFSH + hCG group spermatozoa were retrieved in 4 of 15 patients (26.7%). The authors concluded that hCG-based hormonal therapy prior to second micro-TESE attempt is effective in some men with NOA and normal FSH levels, and that increased intratesticular testosterone following hCG treatment promotes spermatogenesis [12].

Efesoy and coworkers treated 16 patients with oligoasthenospermia and 11 patients with maturation arrest with 100-150 IU rhFSH 2-3 times /week. They detected no difference in total motile sperm counts before and after treatment in patients with oligoasthenospermia. On the other hand in the maturation arrest group 2 patients had (18.1%) spermatozoa in the ejaculate, and 2 patients had (18.1%) spermatozoa on TESE after treatment. They concluded that rhFSH may have some positive

effects in patients with maturation arrest by providing sperm in the ejaculate or TESE [9].

Our study group consisted of patients with idiopathic NOA who had not previous TESE procedure. The treatment did not cause any differences on SRR and surgical method. However, even though not statistically significant, sperm retrieval was achieved by conventional technique in more patients in the treatment group (82.3% versus 64.3%). This result may be regarded as a possible positive effect of empirical hCG treatment. TESE procedure can be performed faster when compared to microdissection technique and this may be regarded as clinically significant. None of the patients in our study showed any acute or chronic complications after TESE. In the literature it has been reported that although fewer complications occur after microTESE clinical complication rate between microdissection and conventional technique are similar [13].

Our doses are lower than given by Shiraishi and coworkers who used 5000 IU subcutaneous injections of hCG three times a week for 4 to 5 months. There are no accepted guidelines on the dosage of hCG for the empirical treatment of NOA. All patients in our group had normal serum FSH levels, therefore we did not administer FSH. Considering results from the study of Efesoy and coworkers, administering FSH along with hCG might be useful in an additional percentage of patients.

Similar results after ICSI between the hCG and control groups show that the hCG treatment does not have any negative effect on the fertilization capacity of the retrieved sperms. Fertilization and pregnancy live birth rates were studied in patients with NOA. In NOA, FR, CPR, LBR has been reported as 38.6-64.4% [14, 15], 21-42.9% [14, 16], and 20-42.9% [14, 16], respectively. Our fertilization and pregnancy rates in patients with NOA are similar with the previous reports of patients with NOA. This implies that empirical hCG treatment does not have any effect on fertilization and pregnancy rates.

Aydin and co-workers reported [17] that sperm retrieval rates are higher in hypospermatogenesis than MA and SCOS and fertilisation and pregnancy rates are similar once successful sperm retrieval is achieved. In the present study spermatozoa were successfully retrieved in all patients with hypospermatogenesis. In patients with maturation arrest spermatozoa were retrieved in 12 (44.4%) and 19 patients (54.3%) in the hCG and control groups, respectively. In Sertoli cell only patients spermatozoa could be retrieved in none of the patients in the hCG group, and in 4 patients (44.4%) in the control group.

Testicular sperm extraction (TESE) along with ICSI is a first-line treatment modality for patients with NOA 15 Sperm retrieval rates (SRR) in TESE operations ranges from 41.6% to 89.6% [18, 19]. Microdissection TESE is currently the best method for the definitive identification of spermatozoa, resulting in a high spermatozoa retrieval rate and minimal postoperative complications for patients with NOA [5, 20]. However microdissection technique is lengthier and more costly than the conventional technique. In the present study successful sperm retrieval was achieved by the conventional technique in 14 of the 17 patients (82.3%) in the hCG group, and 18 of the 28 patients (64.3%) in the control group. The dose and time of hCG given to patients with NOA did not prove to be useful in this study. One of the possible causes for this is may be the dose and time of treat-

ment. Reifsnnyder and coworkers evaluated the role of medical therapy in men with NOA before microdissection TESE [21]. They treated men with preoperative testosterone levels less than 300 ng/dl with aromatase inhibitors, clomiphene citrate or hCG. This study showed that such treatment was able to elevate testosterone levels however neither baseline testosterone level nor response to hormonal treatment affected sperm retrieval rate. In another study from the same center, Ramasamy and coworkers reported that men with Klinefelter's syndrome who respond to medical therapy with a resultant testosterone higher than 250 ng/dl, may have a better chance of sperm retrieval [22]. The limitations of this study include retrospective design and low number of patients. Prospective trials in which different doses of hCG administered for various time periods, combinations with other agents, and comparison the results of hormonal manipulations in men with or without established hypogonadism would be the next steps.

Empirical hCG administered as 2500 IU twice weekly subcutaneous injections for 10 to 14 weeks prior to TESE in patients with idiopathic NOA did not result in improved SRR. hCG treatment did not have any effect on the success of micro-injection. Prospective studies may prove useful to define any role of empirical hormonal treatment in patients with idiopathic NOA.

Acknowledgments

The authors thank Cagla Sariturk, Baskent University, Adana Clinic & Research Center, Biostatistics Unit.

Competing interests

The authors declare that they have no competing interests.

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How to cite this article:

Gül Ü, Turunç T. The Effect of Empirical Human Chorionic Gonadotropin Treatment Before Testicular Sperm Extraction in Idiopathic Non-Obstructive Azoospermia. *J Clin Anal Med* 2016;7(1): 55-9.