

Varicocelelectomy in Patients with Non-obstructive Azoospermia

Obstrüktif Olmayan Azospermili Hastalarda Varikoselektomi

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What's known on the subject? and What does the study add?

Varicocele is the most common surgically correctable cause in males evaluated for fertility problems. Approximately 5% of patients with non-obstructive azoospermia (NOA) are accompanied by varicocele. Available data reveal that varicocelelectomy can improve semen parameters in NOA patients with varicocele. Although the primary treatment option for NOA patients with varicocele seems to be testicular sperm extraction and intracytoplasmic sperm injection, varicocelelectomy may reduce the need for this option.

Abstract

Objective: We evaluated the outcomes of varicocelelectomy in men with non-obstructive azoospermia (NOA) and a palpable varicocele.

Materials and Methods: We retrospectively evaluated 25 male patients with NOA having a palpable varicocele, between May 2006 and December 2018. Age, duration of infertility, testicular volume, grade and side of varicocele, varicocelelectomy technique, and serum follicle-stimulating hormone, serum luteinizing hormone and serum testosterone levels were analyzed.

Results: The mean age of the patients was 30.68±3.91 years. Of the 25 patients, 5 (20%) had motile sperm in the ejaculate in the postoperative semen analysis. There were no predictive factors affecting the appearance of the sperm in the ejaculate.

Conclusion: Varicocelelectomy should be considered a treatment option for men with NOA having a palpable varicocele.

Keywords: Varicocele, Azoospermia, Male infertility

Öz

Amaç: Palpe edilebilir varikoseli ve obstrüktif olmayan azospermisi olan erkeklerin tedavisinde varikoselektomi sonucunu değerlendirdik.

Gereç ve Yöntem: Mayıs 2006 ile Aralık 2018 arasında, palpe edilebilir varikoseli olan 25 obstrüktif olmayan azospermik erkeği retrospektif olarak değerlendirdik. Bu hastaların yaşı, infertilite süresi, testis hacmi, varikosel derecesi, varikoselin tarafı, varikoselektomi tekniği, serum folikül uyarıcı hormon, serum lüteinleştirici hormon ve serum testosteron düzeyleri belirlendi.

Bulgular: Hastaların yaş ortalaması 30,68±3,91 yıldır. Yirmi beş hastanın 5'inde (%20) postoperatif semen analizinde ejakülatta hareketli sperm görüldü. Ejakülatta sperm görülmesini etkileyen hiçbir faktör bulunamadı.

Sonuç: Palpe edilebilir varikoseli olan obstrüktif olmayan azospermik erkekler için varikoselektomi bir tedavi seçeneği olarak düşünülmelidir.

Keywords: Varikosel, Azospermi, Erkek infertilitesi

Introduction

Varicocele is the most common abnormality in males evaluated for fertility problems (1). Although the pathogenesis of varicocele remains uncertain, the negative effect of varicocele on spermatogenesis and semen quality, ranging from

oligozoospermia to complete azoospermia, is well documented (1,2).

Varicocele is found in approximately 5% of patients with non-obstructive azoospermia (NOA) (3). Although the contribution of varicocele to the pathophysiology of azoospermia is unclear, it is known that varicocelelectomy may

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cause improvements in semen parameters in some patients with NOA (3,4).

The purpose of this study was to evaluate the outcomes of varicocelectomy in men with NOA having a palpable varicocele and to determine possible predictive factors for postoperative improvement in semen parameters.

Materials and Methods

Patients

We reviewed files of 65 primary infertility patients with NOA who were operated for a palpable varicocele between May 2006 and December 2018. A total of 25 patients were included in the study. Patients whose postoperative semen analysis results could not be reached (31 patients), patients without karyotype and Y chromosome microdeletion analyses (8 patients), and patients with genetic abnormalities (1 patient with Klinefelter syndrome) were excluded from the study. All the patients included in the study had complete azoospermia.

Clinical Evaluation

The baseline clinical evaluation for each patient included a comprehensive history and a complete physical examination. Varicocele identified on scrotal examination performed with the patient in the standing position before and during Valsalva maneuver was classified as grade 1 (palpable only during the Valsalva maneuver), grade 2 (palpable without the Valsalva maneuver), or grade 3 (visible through the scrotal skin without need for palpation) according to the Dubin and Amelar (5) varicocele grading system. The diagnosis of varicocele was confirmed by ultrasound. Testicular volume was measured using a Prader orchidometer. At least two preoperative semen analyses were performed in all patients using semen specimens obtained by masturbation after 2 to 5 days of abstinence. All analyses were performed according to the World Health Organization guidelines (6). The diagnosis of complete azoospermia was confirmed by pellet analysis, as described by Jaffe et al. (7), and only patients with complete azoospermia (pellet-negative) were enrolled in the study. Retrograde ejaculation, obstructive pathologies and other causes of infertility were excluded. Three patients had a history of unsuccessful testicular sperm extraction (TESE) procedure.

Serum follicle-stimulating hormone (FSH), serum luteinizing hormone (LH) and total testosterone levels were evaluated using blood samples collected in the morning.

The G banding karyotype analysis was performed on the peripheral blood lymphocytes according to the general protocols (8). Multiplex polymerase chain reaction-based screening for Y chromosome microdeletions was carried out in all patients

according to the European Academy of Andrology and the European Molecular Genetics Quality Network guidelines (9).

Written informed consent was obtained from all patients. The study was approved by Başkent University Institutional Review Board (project no: KA19/37).

Varicocelectomy was performed using the subinguinal techniques (open non-microsurgical and microsurgical) (10,11,12). All procedures were performed under general anesthesia.

Postoperative follow-up was performed with semen analysis performed at 3-month intervals in the first year and every 6 months thereafter. The staff evaluating the semen analysis had no knowledge of the patient. The most improved postoperative semen analysis was used for data analysis.

Data Interpretation

Age, duration of infertility, testicular volume, grade and side of varicocele, varicocelectomy technique, serum FSH, serum LH and serum testosterone levels were determined. Success was defined as the presence of sperm in the ejaculate during postoperative follow-up.

Statistical Analyses

Statistical analysis was performed using the IBM Statistical Package for the Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA). Continuous variables with normal distribution were presented as mean \pm standard deviation [$p > 0.05$ in Shapiro-Wilk test ($n < 30$)] and non-normal variables were reported as median. The Mann-Whitney U test was used for comparison of differences between the groups. The distribution of categorical variables was compared between the groups using the chi-square test or Fisher's exact test. A p value of less than 0.05 was considered statistically significant.

Results

Patient Characteristics

All patients had no known medical problems. The medical history of the patients revealed inguinal hernia repair in 2 patients. Patient characteristics are presented in Table 1.

Postoperative semen analysis revealed motile sperm in the ejaculate in 5 (20%) of 25 patients. Semen analysis results were consistent with extremely severe oligozoospermia in all cases. All the 5 patients were in the microsurgical group and all, except one (grade 2), had grade 3 varicocele. Of the remaining 12 patients in microsurgical group, 2 had grade 1, 4 had grade 2 and 6 had grade 3 varicocele. In the non-microsurgical group, 2 patients had grade 1 and 6 patients had grade 3 varicocele.

Parameter	Sperm (+)	Sperm (-)	Total	p
Age (years)				
Mean ± SD	29.6±2.19	30.95±4.236	30.68±3.91	0.575
Infertility period (years)				
Median (min-max)	1.5 (1-5)	2.75 (1-13)	2 (1-13)	0.371
Varicocele side (n)				
Left	4	17	21	1.00
Bilateral	1	3	4	
Varicocele grade (n)				
1	0	4	4	0.535
2	1	4	5	
3	4	12	16	
Testis volume (mL)				
Median (min-max)	8 (6-10)	8 (2-18)	8 (2-18)	0.712
FSH level (mIU/mL)				
Median (min-max)	10.95 (6.0-28.33)	19.86 (1.39-45.27)	14.87 (1.39-45.27)	0.446
LH level (mIU/mL)				
Median (min-max)	7.21 (4.81-8.13)	8.96 (2.42-23.80)	7.65 (2.42-23.8)	0.587
Testosterone level (ng/mL)				
Median (min-max)	3.72 (2.53-6.32)	3.96 (1.4-7.16)	3.81 (1.4-7.16)	0.891
Varicocelectomy technique (n)				
Non-microsurgical	0	8	8	0.140
Microsurgical	5	12	17	

SD: Standard deviation, min: Minimum, max: Maximum, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone

The median duration of postoperative follow-up period was 9 months (range=3-25 months). We compared age, infertility duration, testicular volume, varicocele grade, varicocele side, varicocelectomy technique, serum FSH, serum LH and serum testosterone levels in the success group and the failure group. This comparison showed no statistically significant difference between the success group and the failure group (Table 1).

No intraoperative and/or postoperative complications were observed.

After the surgery, none of the patients in the success group achieved spontaneous pregnancy. Intracytoplasmic sperm injection (ICSI) was performed using ejaculated sperm in 2 patients and these 2 patients achieved pregnancy with ICSI during follow-up. One of these pregnancies was lost-to-follow-up and the other resulted in live birth. In the patient group without any change in ejaculate, microdissection TESE was performed in 14 of 20 patients. The overall sperm retrieval rate (SRR) was 28.5% (4/14). SRR was 11.1% (1/9) in microsurgical group and 60.0% (3/5) in non-microsurgical group. ICSI was performed using testicular sperm in 3 patients and 1 patient achieved pregnancy with ICSI during follow-up. The pregnancy resulted in a healthy infant.

Discussion

Varicocele is the most common surgically correctable cause of male infertility and is found in about 15% of adult males, 35-40% of males with fertility problems and 80% of males with secondary infertility (13,14). The etiology and pathophysiology of varicocele is likely multifactorial (15,16). Despite the several mechanisms including testicular blood stasis, testicular underperfusion and hypoxia, testicular venous hypertension, autoimmunity, elevated testicular temperature, reflux and increase of adrenal catecholamines in spermatic veins, and increased oxidative stress that explain the negative impact of varicocele on testicular function, none of these can fully clarify the variable effects of varicocele on spermatogenesis and male fertility (3,17).

Although the contribution of accompanying varicocele to the pathophysiology of azoospermia is unknown, existing data suggest that varicocelectomy may improve seminal parameters in NOA patients with clinical varicocele (3,18). Previously published data in a group of NOA patients with varicocele have shown that the improvement of semen parameters was 20.8-55% after varicocelectomy (2,4,18,19,20,21,22,23,24,25,26,27,28,29,30,31). All of these studies were performed with small patient groups

(number of patients: 6-35). In our study, after varicocelectomy, spermatozoa were seen in the ejaculate of 5 patients (20.0%).

In a recent meta-analysis, the only prognostic factor that seems to consistently predict the chances of finding sperm in the ejaculates of NOA men after varicocele repair is testicular histopathology (3). However, it should be kept in mind that diagnostic testicular biopsy is an invasive option that may be associated with complications similar to the TESE procedure and cannot identify the entire testis pattern in NOA patients (32). No statistical analysis could be performed for this parameter since no simultaneous biopsy was performed with varicocelectomy in any of the patients included in our study.

Although the blood FSH level was lower in the patient group who began to show sperm in the ejaculate after varicocelectomy (median=10.95 mIU/mL, 6.0-28.33) compared to the patient group without any change in ejaculate (median=19.86 mIU/mL, 1.39-45.27), this was not statistically significant ($p=0.446$). Furthermore, we could not find a statistically significant relationship between success and the other parameters analyzed (Table 1).

In the literature, as far as we know, there is no study that evaluated the relationship between varicocelectomy technique and improvement in semen parameters in NOA patients with varicocele. In our study, although all patients who began to show sperm in the ejaculate after varicocelectomy were in the microsurgical group, this finding was not statistically significant ($p=0.140$).

The indications for varicocelectomy in NOA patients with varicocele remain controversial because the primary treatment option for these patients seems to be TESE and ICSI (18). However, varicocelectomy may reduce the need for TESE, which is a more invasive option, in couples who still require ICSI for conception (18). In our study, ICSI procedure was performed with the sperm obtained from ejaculate in 2 patients. Pregnancy was achieved in these two patients. In the literature, it was reported that ICSI was performed in 54 patients using postoperative ejaculate. In 11 of these patients, pregnancy was achieved (19,22,23,29,30). Although spontaneous pregnancy was reported in 12 patients in the literature, no spontaneous pregnancy was observed in any patient in our study (4,19,20,21,22,29,30).

Study Limitations

The prominent limitations of this study are its retrospective nature and its small sample size. Further prospective studies with a larger sample size would provide more reliable results.

Conclusion

Varicocelectomy may cause the appearance of motile sperm in the sperm of infertile men with NOA and clinically palpable varicoceles. Varicocelectomy should be considered a treatment

option for this patient group. However, when this treatment option is recommended to couples, detailed advice should be given on the relative risks and benefits of the procedure.

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Ethics

Ethics Committee Approval: This study was approved by Başkent University Institutional Review Board (project no: KA19/37) and was supported by Başkent University Research Fund.

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.Ö., M.R.G., Ü.G., T.T., S.G., Concept: C.Ö., M.R.G., Design: C.Ö., M.R.G., Data Collection or Processing: C.Ö., Analysis or Interpretation: C.Ö., M.R.G., Literature Search: C.Ö., Writing: C.Ö., M.R.G., T.T.

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