Is Learning Curve Short for MicroTESE Operation in Nonobstructive Azoospermic Patients?

Original Research

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Nonobstrüktif Azospermik Hastalara Yapılan MikroTESE Operasyonunun Öğrenme Eğrisi Kısa Mıdır?

MicroTESE and Learning Curve

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Özet

Amaç: Nonobstrüktif azospermi hastalarında uygulanan mikrodiseksiyon testiküler sperm ekstraksiyonu (mikroTESE) operasyonunundaki öğrenme eğrisini değerlendirmek. Gereç ve Yöntem: Çalışmaya tek ürolog tarafından mikroTESE uygulanan 300 nonobstrüktif azospermi (NOA) hastası alındı. Hastalar 3 gruba ayrıldı (ilk 100 hasta, ikinci 100 hasta, üçüncü 100 hasta) ve bu gruplar sperm elde etme oranı (SRR) ile diğer klinik parametreler açısından karşılaştırıldı. Eğer gruplar arasında SRR açısından fark saptanmazsa ilk 99 hastanın kendi aralarında karşılaştırılması planlandı. Bulgular: Üçyüz hastada toplam SRR %47 idi. Her üç grup arasında SRR açısından anlamlı bir farklılık saptanmadı (sırasıyla %49, %46 ve %46). Bunun üzerine ilk 99 hasta SRR açısından yeniden karşılaştırıldı (ilk 33 hasta, ikinci 33 hasta, üçüncü 33 hasta). Bu gruplar arasında da SRR açısından anlamlı bir farklılık olmadığı görüldü (sırasıyla %54.5, %42.4, %51.5). Ayrıca gruplar arasında hastaların yaşları, testis volümleri, serum folikül stimüle edici hormon ve testosteron düzeyleri açısından da anlamlı bir farklılık yoktu. Operasyon süresinin ise cerrahi sayısının artması ile birlikte tüm gruplarda anlamlı şekilde azaldığı görüldü. Tartışma: MikroTESE operasyonundaki öğrenme eğrisi, diğer ürolojik cerrahilerdeki öğrenme eğrilerine göre daha kısadır.

Anahtar Kelimeler

Öğrenme Eğrisi; MikroTESE Operasyonu; Nonobstrüktif Azospermi; Sperm Elde Etme Oranı

Abstract

Aim: To evaluate learning curve in microdissection testicular sperm extraction (microTESE) surgery performed in non-obstructive azoospermia patients. Material and Method: The study included 300 non-obstructive azoospermic (NOA) patients, who underwent microTESE surgery performed by a single urologist. The patients were divided into three groups (the first 100 patients, the second 100 patients, and the third 100 patients) and these groups were compared in terms of sperm retrieval rate (SRR) and other clinical parameters. It was planned to compare the patients in first 99 patients between themselves in case there is no difference between the groups in terms of SRR. Results: The overall SRR was 47% in 300 NOA patients. No significant difference was determined between the three groups in terms of SRR (49%, 46%, and 46%, respectively). Accordingly, the first 99 patients were re-compared in terms of SRR (the first 33 patients, the second 33 patients, and the third 33 patients). It was observed that there is also no significant difference between these groups in terms of SRR (54.5%, 42.4%, and 51.5%, respectively). Moreover, no significant difference was determined between all of the groups in terms of patient age, testis volume, and serum follicle-stimulating hormone and testosterone levels. It was observed that duration of surgery has been significantly shortened in all groups as the number of surgical procedures increased. Discussion: Learning curve in microTESE surgery is shorter according to learning curves in other urological surgeries.

Keywords

Learning Curve, MicroTESE Operation, Nonobstructive Azoospermia, Sperm Retrieval Rate

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Introduction

Azoospermia means that there is no sperm in the ejaculate, and it is present in averagely 1% of males and in 10% of infertile males [1]. Non-obstructive azoospermia (NOA) refers to the detection of no sperm in semen analysis due to minimal or no production of fully developed sperms in the testicles [2]. Today, the most important advancement in the treatment of infertile male cases is detection of small foci with ongoing spermatogenesis in the testicles of NOA cases and retrieving mature sperm cells from these foci (testicular sperm extraction: TESE). Whilst TESE surgery used to be performed by conventional multiple biopsies in the past, it is performed by microdissection method (microTESE) today. This method is the ideal procedure to obtain high sperm retrieval rate [3]. Direct visualization using surgical microscope in microdissection TESE is of great advantage since larger, more opaque, whitish tubules, presumably containing more intratubular germ cells with active spermatogenesis, can be identified [4].Today, it is known that averagely 50% sperm is retrieved by microTESE surgery [5]. In some studies, however, sperm retrieval rate can be significantly low in microTESE surgeries [6].

Experience of the surgeon in urological surgery depends on many factors. Learning curve of the surgeon as well changes depending on these factors. In a systematic review on learning curve, it has been propounded that learning curve is surgery-related, oncological-related, or related to the quality of life [7]. No doubt, numberof cases is the most important factor in learning curve. Experience of the surgeon is enhanced directly proportional to the increased number of cases. Whilst learning curve is long in some cases, it may be shorter in other cases. Success in microsurgery for male infertility heavily depends on the surgeon's microsurgical skills. MicroTESE learning curve may be shorter if the surgeon has performed microsurgery before. Conventional TESE surgeries, which used to be performed in the form of multiple biopsies, could be learned much more easily since the surgical technique was a simple standard method. However, learning curve may be longer in microTESE surgery since it requires microsurgery experience different from the conventional microTESE surgery.

In the present study, we aimed to evaluate learning curves of the surgeons in microTESE surgery performed in NOA patients, to determine ideal number of cases to gain skill, and to assess whether there is difference between the outcomes of clinical parameters as the number of surgery increases.

Material and Method

The study included 300 NOA patients who underwent microTESE between 2004 and 2014 by single surgeon (T.T.) in our institution. Semen analysis was performed according to World Health Organization guidelines to evaluate sperm parameter and at least 2 analysis confirmed azoospermia in each patient. The patients with normal spermatogenesis, obstructive azoospermia, or hypogonadotrophic hypogonadism were excluded from the study. Patients enrolled in the study were divided into three groups as the first 100 (group A), second 100 (group B) and third 100 (group C) patients. SRR results of these patients were compared. Moreover, patient age, duration of infertility, testis volume, serum follicle-stimulating hormone (FSH) and testosterone levels, and duration of surgery were measured. Testicular volume was measured in all patients by a Prader orchidometer. In addition, karyotype analysis and Y chromosome gene micro-deletion analysis were also performed. All data obtained were compared between three groups. It was planned to compare the patients in Group A between themselves in case no difference was determined between the groups in terms of SRR. The surgeon of the present study has had experience in microsurgery before performing microTESE surgery. In addition, he had assisted another surgeon experienced on this subject in seven cases before he operated his own cases and had watched CDs about microTESE surgery performed previously. MicroTESE procedures were performed under spinal anesthesia. A 4-cm midline incision was made in the scrotum, the tunica vaginalis was opened, and the testis, which is covered with the tunica albuginea, was visualized. The remainder of the procedure was performed under an operative microscope. Tunica albugina was opened with longitudinal incision. The subtunical vessels were identified under the surgical microscope and damaging the vessels was avoided. Direct examination of the testicular parenchyma was performed at ×20 to ×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 were no sperm in one testis, these procedures were performed in the contralateral testis. At the same time as the testicular intervention, a surgically-obtained small tissue specimen was placed in Bouin's solution and sent to the histopathology laboratory.

Descriptive statistics were presented as mean ± SD, as well as frequencies and percentages. The categorical variables between the groups were analyzed by the chi-square test. Values of $p < 0.05$ were consideredas a statistically significant difference. Data that did not show normal distribution were compared by Mann-Whitney U test. This study was approved by Baskent University Institutional Review Board (Project no: KA14/210) and supported by Baskent University Research Fund.

Results

The overall sperm retrieval rate was 47% (141/300). The mean age of the patients was 35.1±6 years (range 19-65 years), the mean duration of infertility was 7.5±5 years, the mean testis size was 12.4±6.5 ml, the mean operation time was 70±16.5 minute, the mean FSH concentration was 17.1±12.2 mIU/ml, and the mean testosterone concentration was 420±187 ng/dl. Sperm retrieval rate by microTESE in the group A, group B and group C were 49%, 46% and 46%, respectively. There was no significant difference between the groups ($p>0.05$) according to SRR. Thus, no significant result was obtained in ROC analysis since the SRR were similar among groups ($p=0.732$). Also, there were no differences in the patient age, testicular volume,FSH and testosterone concentration among the three groups ($p>0.05$). Duration of infertility showed difference between the groups. It was observed that duration of surgery was significantly decreased as the number of surgeries increased ($p<0.05$). Accordingly, whether there is a significant difference in the first 99 patients in terms of SRR was also evaluated. The first 99 patients were divided into three groups (first 33: group

D, second 33: group E, third 33: group F). No difference was observed either between these three groups (54.5%, 42.4% and 51.5% respectively) in terms of SRR. An ideal cut-off value cannot be established in the ROC analysis to define an ideal patient number in the learning curve of the microTESE operation since there wasn't any difference between the groups among SRR (p=0.801).The mean age of the patients in these three groups was 36.1±6.3 years (range 26-65 years), the mean duration of infertility was 8.2±5 years, the mean testis size was 12.5±6.5 ml, the mean duration of surgery was 76.3±17.8 minutes, the mean FSH concentration was 16.3±11.1 mIU/ml, and the mean testosterone concentration was 448±204 ng/dl. There was no significant difference between these three groups in terms of patient age, duration of infertility, testis volume, and serum FSH and testosterone levels. It was observed that duration of surgery was significantly decreased also in these groups as the number of surgeries increased(p<0.05). Clinical characteristics of the patients are demonstrated in Table 1.

those without spermatozoa following TESE are shown in Table 2.None of the patients showed any acute complications after microTESE operations in early period. No side effects of the treatment were observed.

Discussion

MicroTESE in combination with intracytoplasmic sperm injection is the first line treatment for patients with NOA. Sperm retrieval rates in microTESE operations range from 22.2% to 79.6% [6,8]. The fact that there are substantial differences between the studies in the literature in terms of sperm retrieval rates by microTESE method and moreover, high sperm retrieval rates even in chromosomal abnormalities such as Klinefelter syndrome in which lower sperm retrieval rates are expected [9], suggested us that there might be important factors that determine success of microTESE.

Before microTESE surgery has been defined, TESE surgery used to be performed in the form of taking multiple biopsies by

Table 1. The clinical impressions of the NOA patients who underwent microTESE operation

	Group A	Group B	Group C	p value	Group D	Group E	Group F	p value
Age (year)	36.1±6.2	34.9±5.6	34.1±6	,107	36±5.7	35.7±6.1	36.7±7.1	,726
Duration of infertility (year)	8.3±5	7.6±5.1	6.5±4.9	,021	8.6±4.6	7.6±5.9	8.6±4.5	,406
Testis volume (ml)	12.5±6.5	12±6.6	12.5±6.6	,867	12.3±6.4	12.2±6.4	12.9±6.8	,921
FSH (mIU/ml)	16.2±11.1	18.6±12.6	16.5±13	,209	16.3±11.2	16.1±10.8	16.6±11.6	,996
Testosterone (ng/dl)	449±203	427±196	403±157	,350	432±206	445±180	460±229	,980
Operation time (minute)	76.4±17.8	69±15.1	64.4±14.4	,0001	83.9±20	75.4±17.1	69.6±13.1	,015
Patients (n)	100	100	100		33	33	33	
SRR (%)	49	46	46	,887	54.5	42.4	51.5	,591

NOA: Nonobstructive azoospermia; FSH: Follicle stimulating hormone; KS: Klinefelter's syndrome; SRR: Sperm retrieval rate

Table 2. The SRR according to the histopathological findings of the patients who underwent microTESE operation

	Group A		Group B		Group C		Group D		Group E		Group F	
	SRR (+)	SRR (-)	SRR (+)	SRR (-)	SRR (+)	SRR (-)	SRR (+)	SRR (-)	SRR (+)	SRR (-)	SRR (+)	SRR (-)
Patients (n)	49	51	46	54	46	54	18	15	14	19	17	16
Hypospermatogenesis (%)	100	0	100	0	100	0	100	0	100	0	100	0
Maturation arrest (%)	60	40	59.5	40.5	54.5	45.5	64.3	35.7	47.3	52.7	76.4	23.6
SCOS (%)	12.5	87.5	34.1	65.9	27.2	72.8	27.2	72.8	14.3	85.7	0	100
Fibrosis and atrophy (%)	16.6	83.4	9	91	18.7	81.3	0	100	0	100	14.3	85.7
KS (n)	2	8	2	8	5	9	0	0	0	1	2	7

SRR: Sperm retrieval rate; SCOS: Sertoli cell only syndrome; KS: Klinefelter's syndrome

Karyotype analysis and Y chromosome microdeletion analysis were made only in 147 patients. Karyotype analysis showed non-mosaic Klinefelter's syndrome in 34 patients. Out of 34 patients, 9 (26.4%) had spermatozoa. Only six patients were diagnosed as Azfc microdeletion for Y microdeletion. Four of these patients had spermatozoa.

Histopathological examination showed hypospermatogenesis in 26 patients (8.7%), maturation arrest in 148 patients (49.3%), Sertoli cell-only syndrome (SCOS) in 87 patients (29%) and tubular sclerosis and atrophy in 39 patients (13%). The sperm retrieval rate was 100% (26/26) in the patients with hypospermatogenesis, 54% (80/148) in the patients with maturation arrest, 32.1% (28/87) in the patients with SCOS, and 17.9% (7/39) in the patients with tubular sclerosis and atrophy. Histopathological features in patients with spermatozoa and

standard conventional method. In the conventional method, 3-7 biopsies are taken from the testes particularly including upper and lower poles as well. In this procedure, there was nothing to be paid attention except for subtunical vascular injury. Thereby, it could be easily performed by all surgeons since there was no particular issue to pay attention during surgery. Later on, along with microTESE surgery's being put into routine practice in NOA patients, the number of issues that have to be paid attention during surgery was increased. It is known that taking more opaque and dilated seminiphere tubules enhances probability of sperm retriaval. Hence, recognizing such tubules requires surgical experience. Detecting more opaque and dilated seminiferous tubules that contain focal spermatogenesis foci enhances likelihood of success in microTESE surgery particularly in atrophic testicles and if the tissues are fibrotic. Since removal of higher amount of testis tissue during surgery in the patients with atrophic testis might cause decrease in serum testosterone level and trigger hypogonadism, therefore, biopsy from the testis tissue should not be taken arbitrarily [5].Moreover, whilst many studies reported the probability of retrieving sperm to be 50-60% by microTESE method, these rates' decreasing to 22% in some studies suggests that surgical experience is also important in microTESE.

Gaining surgical experience in urological surgeries depends on many factors. The most important of these factors include experience of trainer senior surgeon, surgical technique (open, endoscopic, laparoscopic, microsurgical, etc), degree of difficulty of the technique, surgeon's skill, simulation-based education, technical skills, number of cases, limited number of surgical complications, short duration of surgery, negative surgical margin, experience of auxiliary staff, and patient safety [7]. Laboratory practice as well has an important role in gaining surgical experience in microTESE; because, laboratory-based practice to enhance microsurgical skills improves the surgeon's self-confidence and reduces stress and duration of surgery, and is of benefit both to the patient and the surgeon [10]. However, it is known that the laboratory environment necessary to learn microTESE technique is not available in many urology clinics.

The "learning curve" is defined as a graph that represents the progress in the mastery of a skill against the time required for such mastery.It would be useful to know how many procedures a surgeon may have to carry out before reaching a safe and competent level of performance. It is given that learning curve shortens with increasing experience. No doubt, number of surgical cases is one of the most important factors in gaining surgical experience. A surgeon's case volume equates to better surgical outcomes [7]. Ideal number of cases to perform a successful surgery shows variation according to the type of surgery. For example, 12 cases are necessary to learn high-quality transrectal ultrasound-guided prostate biopsies [11]. Nevertheless, at least 50 adult percutaneous nephrolithotomy (PCNL) surgeries are required to perform PCNL surgery safely [12]. On the other hand, the learning curve ranges from 250 to 1000 cases for open radical prostatectomy and from 200 to 750 cases for laparoscopic radical prostatectomy [7]. As is seen, number of surgeries necessary to gain experience shows great variations among cases.

In the present study, we aimed to determine the number of surgeries necessary to gain experience in microTESE surgery. In the present study, the fact that there is no significant difference between the first 300 patients and then between the first 99 patients in terms of SRR suggested that learning curve for microTESE is short despite the above-mentioned factors. Hence, even 33 patients are adequate to perform microTESE surgery successfully. In another study performed with similar learning curve in microTESE to that in the present study, 150 patients were divided into three groups according to SRR as the first 50, middle 50 and the last 50 patients; whilst SRR was 32% in the first 50, it was 44% in the middle 50 and 48% in the last 50 patients. The authors stated that surgical outcomes and SRR have improved as the number of cases increased. Moreover, authors claimed that more than 50 cases are needed to reach an optimal level in surgical outcomes [13]. Increased case number no doubt enhances surgical success. However, different from the above mentioned study, even 33 cases were adequate to gain surgical experience in the present study. The difference between two studies might have arisen from the skills of surgeons in learning surgical technique and to the adequacy of medical equipment. In addition, the present surgeon's previous experience in microsurgery might have led him to learn microTESE in a short time. Thereby, learning curve may be shorter than expected in those that have been experienced in microsurgery before performing microTESE.

The present study demonstrated that duration of surgery shortened in all groups as the number of surgeries increased. The present review has several limitations. Amount of testis tissue obtained during surgeries, length of hospital stay, bleeding in the surgical area in early postoperative period, infection, and changes in serum testosterone concentration have not been compared between the groups. The reason for this is unavailability of adequate and precise information about complications particularly in the initial cases.

Conclusions

As in all surgical techniques, surgical experience is important also for microTESE. For surgical experience, it is important for a surgeon to learn the technique from an experienced surgeon in a place with adequate technical equipment; moreover, surgical experience directly depends on surgeon's case volume. Different from the other urological surgeries with long learning curves such as laparoscopy, we think that surgical experience in microTESE surgery can be gained with less number of cases and in a short time by decent education.

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Competing interests

The authors declare that they have no competing interests.

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