Analysis of factors affecting repeat microdissection testicular sperm extraction outcomes in infertile men

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ABSTRACT

Objective: There is no clear consensus on which patients and how many of microscopic testicular sperm extraction (mTESE) procedures will be successful. In this study, we aimed to evaluate the sperm retrieval rates and factors affecting these rates in men who underwent repeat mTESEs.

Material and methods: A total of 346 patients who underwent mTESE for sperm retrieval were included in the study. Patients were divided into groups according to the number of mTESE operations. Patients' karyotype, follicle-stimulating hormone (FSH) and testosterone levels, varicocele presence, and testis volumes were recorded from patient files. The sperm retrieval rates were compared between groups, and predicting factors for successful sperm retrieval were evaluated.

Results: Microscopic TESE was applied for the first time in 244 patients, 1-2 times in 73 patients, and 3-4 times in 29 patients. There was a significant difference between groups in preoperative FSH values and postoperative testicular histopathology (p=0.004 and p<0.001). The sperm retrieval rate in the group of patients who had not undergone previous TESE was higher than the group of patients that had undergone TESE for 1-2 times and 3-4 times (p=0.028). In addition, testicular volume, histology, karyotype, and Y-chromosome microdeletion were predicting factors for successful sperm retrieval (p=0.011, p=0.039, p=0.002, and p<0.001, respectively).

Conclusion: Our results confirm the necessity for repeat mTESE operations to be performed by experienced surgeons in reference centers to optimize the chance of reduced sperm retrieval rates with recurrent biopsies.

Keywords: Infertility; microscopic testicular sperm extraction; non-obstructive azoospermia; sperm retrieval.

Introduction

Azoospermia is defined as the absence of any spermatozoa in the ejaculate.[1] It affects about 1% of the male population and is categorized based on the etiology: obstructive azoospermia (OA) characterized by a mechanical obstruction at the seminal tract and non-OA (NOA) caused by intrinsic testicular disorders of sperm production.[2] A 1% incidence of NOA in the population, 10% in individuals subjected to fertility assessment, and 60% in azoospermic men have been reported.[3,4]

In NOA cases, the conventional testicular sperm extraction (TESE) technique allows sperm retrieval of up to 56% of the patients.[5] This ratio can rise up to 63% with microscopic TESE (mTESE), which is first identified by Schlegel in 1998.[6,7] Several factors have been defined for predicting successful sperm retrieval with TESE. Testicular volume, serum follicle-stimulating hormone (FSH) value, serum inhibin B value, and testis histopathology are the factors most focused on.[8] Predictive models were developed to evaluate all these factors and determine successful sperm retrieval with TESE.[9] However, the predictive ability of all these models is limited. In addition to the economic burden, loss of work power, and physiological and emotional effects, the TESE process harbors its risks and complications. Hematomas, inflammation, and persistent devascularization, which may be seen after the procedure and may lead to significant loss of testicular tissue.[10] For this reason, the deter-

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mination of the factors predicting successful sperm retrieval is very important for preventing all negative results. The effect of the number of TESEs on recurrent procedures in patients who had previously undergone a failed TESE procedure is worth investigating and is a factor affecting the success of subsequent biopsies. However, not many studies have evaluated this issue in literature. In this study, we aimed to analyze the effect of the number of previous mTESEs and other demographic-clinical factors on sperm retrieval rates in patients who underwent repeat mTESE in our clinic.

Material and methods

Patient groups

The study included 346 patients who underwent mTESE between January 2016 and June 2018. TESE procedures were performed by different urologists with sufficient experience. All TESE procedures were performed bilaterally. Patients were divided into 3 groups according to the number of previous mTESE operations: those who had never undergone previous TESE (Group I), those who had previously undergone TESE 1-2 times (Group II), and those who had undergone TESE 3-4 times (Group III). Patients were then divided into 3 groups according to their preoperative testis volumes: testis volume 2-5 cc (Group A), 6-10 cc (Group B), and >10 cc (Group C). A prader orchidometer was used to measure the testis volume.

Patients' preoperative karyotype, FSH values, varicocele presence, number of mTESE operations, and testis volumes were recorded. The percentage of patients with spermatozoa after TESE was determined as the sperm retrieval rate. All patients underwent a testis biopsy for a histopathological diagnosis together with the TESE procedure. Patient characteristics and sperm retrieval rates were compared between groups. Informed consent was obtained from the patients, and the study was conducted in compliance with the Helsinki Declaration.

The outcome measures of the study

The comparison of sperm retrieval rates between groups was the primary outcome measure, and the evaluation of the effect of patient characteristics and demographic data on sperm retrieval rates was the secondary outcome measure of the study.

The technique of the testicular sperm extraction

Scrotal layers were incised using a medial scrotal incision with laryngeal mask anesthesia or spinal anesthesia. First, the tunica vaginalis and then the tunica albuginea was incised and the testes were delivered. Expanded seminiferous tubules were identified using 20× magnification of a surgical microscope. The enlarged tubules, which are likely to have spermatozoa, were collected with the help of a micro-forceps and given to the embryologist. Then tunica albuginea and tunica vaginalis were closed using a 3/0 Vicryl Rapide® suture. The same procedure was applied to the other testis. The subcutaneous and skin tissues were closed using 3/0 Vicryl Rapide® suture, and the procedure was terminated.

Statistical analysis

Descriptive statistics were defined as mean ± standard deviation. The Chi-square analytical test was used to compare the sperm retrieval rates between the groups, and the ANOVA analytical tests were used to compare the demographic data and patient characteristics. A multivariate statistical analysis was performed using the logistic regression model to identify independent factors predicting successful sperm retrieval with mTESE. P values less than 0.05 were accepted for statistical significance. All statistical analyzes were performed using the IBM Statistical Package for Social Sciences statistical software version 22.0 (IBM SPSS Statistics Corp.; Armonk, NY, USA).

Results

A total of 346 patients underwent mTESE during the study period. Among them, 244 patients underwent mTESE for the first time (Group I), 73 patients 1-2 times (Group II), and 29 patients 3-4 times (Group III). The testicular volume of 272 patients was 2-5 cc (Group A), 44 patients was 6-10 cc (Group B), and 30 patients was 10 cc (Group C).

There was a significant difference between the groups in preoperative FSH values and postoperative testicular histopathology; other demographic data were similar. The comparison of patient characteristics and demographic data according to the number of mTESE procedures and testis volumes are shown in Table 1.

The sperm retrieval rate in Group I was higher than in Groups II and III (p=0.028). In contrast, the sperm retrieval rate in the group with a large testis volume (>10 cc) was higher than the group with low testis volume (p=0.011). The sperm retrieval rate in the sertoli-cell-only histopathology testis was significantly lower (11.8% vs. 88.2%, p=0.039) compared to the sperm retrieval rate of other histopathologic types according to the number of mTESE. Abnormal karyotypes were detected in 47 patients, and there was a significant correlation between sperm retrieval rates and karyotypes (p=0.002). There were 35 patients with Kleinefelter's syndrome in our patient group. We obtained sperm from 11 (31.4%) of them using mTESE. Sixty-seven patients had Y-chromosome microdeletions, and there was a significant relationship between sperm retrieval rates and microdeletions (p<0.05). The relationship of the number of mTESE operation, testis volume, testis histopathology, karyotype, and Y-chromosome microdeletion with the sperm retrieval rates is summarized in Table 2.

Table 1. Comparison of demographic and clinical data according to the number of mTESE operations and testis volume

Variables	Number of previous mTESE			p	Testis volume (cc)			p
	0	1-2	3-4		2-5	6-10	>10	
Patients (n)	244	73	29	***0.022***	272	44	30	***0.019***
Age (years)	24.4±4.8	27.2±3.9	28.1±3.1	0.721	26.9±4.4	27.2±3.8	28.8±3.3	0.544
BMI (kg/m^2)	24.1±2.2	25.5±2.4	23.9±2.5	0.229	25.8±2.0	24.2±2.3	23.6±2.6	0.482
Preoperative FSH (mIU/mL)	4.8±0.8	7.4±1.2	12.8±2.6	***0.004***	14.9±3.8	8.1±2.8	3.3±1.9	***0.027***
Total testosterone (ng/dL)	688±38.4	422±29.8	302±31.2	***0.018***	276±34.2	392±28.4	510±43.3	***0.034***
Varicocele	34 (13.9)	9 (12.3)	4 (13.8)	0.651	42 (15.4)	6 (13.6)	4 (13.3)	0.081
Histopathology				***<0.001***				***0.031***
Hypospermatogenesis	64 (66.7)	21 (21.9)	11 (11.4)		14 (14.5)	29 (30.2)	53 (55.3)	
Maturation arrest	78 (42.8)	61 (33.5)	43 (23.7)		48 (26.4)	66 (36.3)	68 (37.3)	
Sertoli-cell only	11 (16.2)	22 (32.3)	35 (51.5)		36 (52.9)	23 (33.8)	9 (13.3)	

Values are given as mean ± standard deviation or number (percentage). Statistically significant p values were given in bold and italic. BMI: body mass index; FSH: follicle-stimulating hormone; mTESE: microscopic testicular sperm extraction

Table 2. Relationship of the number of mTESE, testicular volume, testicular histopathology, karyotype, and Y-chromosome microdeletion with sperm retrieval rates

	Sperm retrieval status		
Variables	Sperm positive	Sperm negative	p
Number of mTESE			0.028
0 (n=244)	141 (57.8)	103 (42.2)	
1-2 (n=73)	30 (41.1)	43 (58.9)	
3-4 (n=29)	6 (20.7)	23 (79.3)	
Testis volume (cc)			0.011
2-5 (n=272)	96 (35.3)	176 (64.7)	
6-10 (n=44)	25 (56.8)	19 (43.2)	
>10 (n=30)	19 (63.3)	11 (36.7)	
Histopathology			0.039
Hypospermatogenesis (n=96)	56 (58.3)	40 (41.7)	
Maturation arrest (n=182)	86 (47.2)	96 (52.8)	
Sertoli-cell only (n=68)	8 (11.8)	60 (88.2)	
Karyotype			0.002
47, XXY	11 (31.4)	24 (68.6)	
Isodicentric Y-chromosome	2 (33.3)	4 (66.7)	
Translocation	1 (16.7)	5 (83.3)	
Y-chromosome microdeletion			
AZFa	0 (0)	14 (100)	<0.001
AZFb	0 (0)	13 (100)	
AZFb/c	1 (7.7)	12 (92.3)	
AZFc	19 (70.4)	8 (29.6)	

Values are given as number (percentage). mTESE: microscopic testicular sperm extraction; AZF: azoospermia factor

Table 3. Logistic regression analysis of factors predicting successful sperm retrieval in mTESE

Variables	OR	95% CI	p
Number of mTESE	1.82	1.69-2.11	0.020
Testis volume	1.09	0.81-1.43	0.018
Testis histopathology	2.14	1.98-2.29	<0.001
Karyotype	1.74	1.66-1.91	0.032
Y-chromosome microdeletion	3.24	3.16-3.41	<0.001
Preoperative FSH	0.98	0.76-1.27	0.029
Total testosterone	0.81	0.42-1.95	0.314

CI: confidence interval; OR: odds ratio; mTESE: microscopic testicular sperm extraction; FSH: follicle-stimulating hormone

The multivariate logistic regression model determined the number of mTESEs, testis volume, testis histopathology, karyotype, Y-chromosome microdeletion, and preoperative FSH as independent factors predicting the success of mTESE. Logistic regression analysis of independent factors is summarized in Table 3.

Discussion

In this study, we mainly evaluated the effect of recurrent mTESE procedures on sperm retrieval rates and found that there was a significant correlation of the number of previous mTESEs, testis volume, testis histopathology, karyotype, and Y-chromosome microdeletion with sperm retrieval rates. In recent years, the mTESE procedure conducted with the help of an operation microscope has become an important method for patients with NOA, making it possible to obtain healthy spermatozoa for assisted reproductive techniques. Due to the widespread endocrine

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disruption, there is an increase in the number of patients presenting with NOA, and this process has to be applied to a larger number of men. Although it is a reproducible procedure, it is important to determine the maximum attempts of performing this procedure and the factors that predict the success of the procedure because of the negative effects on the testis tissue with limited volume and reserve besides possible financial and psychological effects.

It has been demonstrated that the sperm extraction process, which was previously performed as random biopsies, resulted in less loss of testis function after the introduction of mTESE, and the outcome was more favorable.[11] The blood flow of the testis may be negatively affected in recurrent biopsies. Reduced vascular support may lead to a reduction in the quality and number of spermatozoa and consequently the chance of obtaining sperms may be reduced in repeat biopsies.[12] In our study, we found that the sperm retrieval rate decreases as the number of mTESEs increases; the sperm count was significantly higher in the patients who underwent a first mTESE compared to those who underwent 1-2 and 3-4 mTESEs. It is likely that the reduction in testis volume and blood supply with recurrent biopsies is the cause for a low rate in the latter groups. Microscope use in previous unsuccessful TESE procedures in patients in our study group may be another reason for the poor success in recurrent biopsies. Ramasamy and Schlegel[13] assessed the spermatozoa retrieval in recurrent biopsies in 311 patients and found that the retrieval rate was lower in patients with 3-4 biopsies than in those with one biopsy and 1-2 biopsies similar to our study. The authors underlined that there is no threshold for the number of negative biopsies that predict successful spermatozoa with repeat mTESE and emphasized that a limited number of testis biopsies has a limited prognostic value for sperm retrieval with mTESE. The results of the present study showed that it is more likely to obtain sperms in the maturation arrest and hypospermatogenesis histology at similar rates than in sertoli-cell-only histology, similar to our study. Unlike our study, there was no significant difference in serum mean FSH values according to the number of TESE operations in this study. In our study, the increase in FSH levels and reduction in the testosterone levels as the number of applications of mTESE increases may be due to poorer testis histopathology, prior to multiple biopsies, and testicular tissue damage caused by repetitive biopsies. These results confirm that repeat biopsies should be performed by experienced surgeons at reference centers for optimizing the diminished chance of obtaining sperms. The sertoli-cell-only histology has been reported to yield lower sperm rates than hypospermatogenesis and maturation arrest.[14] A routine diagnostic testicular biopsy is not recommended before TESE, as the subsequent mTESE procedure may become more complicated. European Urology Guidelines also recommend a testicular biopsy to identify testicular histopathology simultaneously with mTESE. The rate of sperm retrieval from hypospermatogenetic testis in our study is lower than those indicated in literature.[15,16] This is because the other factors (testicular volume, hormone profile, etc.) related to the testes were lower in these patients, and they were subject to recurrent mTESE operations.

In our study, as the number of mTESEs increased, the mean preoperative FSH value increased, and the total testosterone value decreased. Mainly disease- and operation-related factors are also influential for this outcome. Increased FSH levels and decreased testosterone levels in patients with recurrent procedures affect the success of subsequent procedures. For this reason, hormone replacement therapy before the second and subsequent mTESE procedures may be a factor increasing the success. Mehta et al.[17] found that topical testosterone treatment did not suppress spermatogenesis and that successful spermatozoa were obtained in 70% of Klinefelter's syndrome patients with high FSH values and low testosterone values.

Y-chromosome microdeletion is an important factor for predicting successful sperm retrieval in mTESE. In complete azoospermia factor (AZF)a AZFb deletions and absence of AZFa-c, the seminal phenotype of the patient is azoospermia, and the sperm retrieval with TESE is quite low in these patients.[18] In our study, we obtained sperms from 70.4% of the patients with AZFc deletions. In addition, Dabaja and Schlegel also reported this ratio as 72%.[19]

Karyotype analysis has been reported as an important predictor of mTESE success. However, in many studies, abnormal karyotype cases were excluded and only Klinefelter cases were included. Sperm retrieval rates between 41% and 72% were reported in different series.[20-22] In non-mosaic dominant Klinefelter patients with low testicular volume, extensive tubular sclerosis, and high FSH, the rate of sperm retrieval after hormonal manipulation increased.[22] In our study, the rate of sperm retrieval was 31% in cases with Klinefelter's syndrome. Hormonal manipulation in appropriate cases has probably been effective for this outcome.

Xu et al.[23] investigated the factors predicting successful sperm retrieval with TESE after failed TESE in patients with NOA. They performed salvage-mTESE in 52 patients and evaluated age, body mass index, presence of Klinefelter's syndrome, varicocele, cryptorchidism, mean testicular volume, hormone profile, and testicular histology. Multivariate logistic regression analysis revealed that testosterone and testis histopathology were important predictors of sperm retrieval. Unlike this study, although testis volume was found to be a predictor of sperm retrieval in our study, it may not be an important factor predicting successful sperm retrieval for intracytoplasmic sperm injection because of the topographic differences in testis histology.[24] Var-

icocele repair can improve the sperm retrieval in azoospermic men with severe hypospermatogenesis or maturation arrest.[25] However, it is also important to consider that assisted reproductive techniques may even be necessary for pregnancy in these patients. We did not perform varicocelectomy in patients with high FSH value, low testicular volume, and sertoli-cell-only and early stage maturation arrest histology because the benefit of varicocelectomy was negligible in these patients. The benefit of varicocelectomy in patients with NOA is controversial. A meta-analysis of studies on varicocele repair in NOA patients has shown that some absolute pathologic subtypes would benefit from varicocelectomy, and motile sperm could be obtained in 39% of patients who underwent varicocelectomy.[26] In our clinical practice, varicocele repair is preferred in patients who are oligozoopermic and have sufficient time (>6 months) for sperm recovery in the ejaculate after varicocelectomy.

The scenarios in which recurrent biopsies are more successful are the cases of mTESE after the conventional TESE. Fasouliotis et al.[27] found spermatozoa in 2 of 18 patients, Friedler et al.[28] in 1 of 4 patients, and Borges et al.[29] in 3 of 18 patients after salvage-conventional-TESE procedures in the firstbiopsy-failed patients. However, spermatozoa was found in 45% patients in a study by Ramasamy and Schlegel[13], 45.7% in the study by Tsujimura et al.[30], and 46.5% in the study by Kalsi et al.[31] with salvage TESE procedure.

In addition to hematomas, inflammation, fibrosis and permanent devascularization, the mTESE procedure may have potential financial and emotional effects.[32] Microscopic TESE cannot guarantee 100% sperm retrieval, especially for men with a history of unsuccessful TESE. Hence, many factors have been investigated in literature to predict successful sperm retrieval and prevent unnecessary re-biopsies. Tsujimura et al.[24] showed that age, testosterone, and FSH values are important predictors of successful sperm extraction with mTESE. In contrast, Ando et al.[33] reported that the effect of age and hormonal profile was insignificant, but testicular histology and vasa mRNA levels were important predictive factors. Many factors, such as inhibin B and FSH, have been investigated, but no consensus has been established on this topic. Thereupon, predicting models have been developed that evaluated many factors together, and it has been suggested that more accurate estimations are made with these models.[24] For example, Cissen et al.[34] reported that high patient age, high serum testosterone, and low FSH and luteinizing hormone values were predictive of successful sperm retrieval in the model they developed.

The retrospective nature, some previous mTESE procedures in different centers, and patient inhomogenization due to operations performed by the different urologists are the main limitations of our study.

In conclusion, the success rate in recurrent mTESE procedures was lower and testicular volume, histology, karyotype, and Y-chromosome microdeletion were important predictors of success. Data that are more consistent can be obtained regarding factors predicting the success of recurrent mTESE operations, with studies analyzing predictive models in prospective studies with a large sample size and evaluating multiple factors together.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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