International Urology and Nephrology (2023) 55:2177–2182
https://doi.org/10.1007/s11255-023-03668-0

UROLOGY - ORIGINAL PAPER

Comparison of unilateral and bilateral microdissection testicular sperm extraction (MD-TESE) in patients with non-obstructive azoospermia: a prospective study

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Received: 24 April 2023 / Accepted: 5 June 2023 / Published online: 18 June 2023

Abstract

Objective To compare sperm retrieval rates between unilateral and bilateral microdissection testicular sperm extraction (MD-TESE) procedures in patients with non-obstructive azoospermia and to contribute to the literature by comparing them with literature data.

Methods This prospective study included 84 males with primary infertility who had azoospermic NOA, who had been married for at least one year, and whose female partners did not have a history of infertility. The study was conducted between January 2019 and January 2020. MD-TESE was applied bilaterally to 48% (n:41) (Group 1) and unilaterally to 52% (n:43) (Group 2) of the patients, and sperm retrieval rates were compared.

Results There was no statistically significant difference between Group 1 patients and Group 2 patients in terms of sperm availability (61%, 56.5%, p=0.495, respectively). In addition, while no complications were observed in unilateral MD-TESEs, 3 complications were observed in bilateral MD-TESEs.

Conclusions In our study, it was determined that there was no significant difference between the groups in terms of sperm availability in patients with NOA. Considering the operative time and complication rates of bilateral MD-TESE in patients diagnosed with NOA and the possible MD-TESE procedures that may be performed later, we believe that unilateral MD TESE is a more preferable procedure for the patient and surgeon in this patient group.

Keywords Azoospermia · Bilateral · Inhibin B · Microdissection · Unilateral · Testicle

Introduction

Male infertility is defined as the failure of pregnancy within 12 months despite the presence of a fertile female partner and coitus via a normal vaginal route without contraception [1]. The microscopic absence of spermatozoa in the ejaculate in at least two semen analysis samples is defined as azoospermia. Azoospermia plays a role in the etiology of male infertility with a rate of 10–15% and is also observed in 1% of the normal population [2]. Azoospermia is divided into two subgroups: obstructive azoospermia (OA) and non-obstructive azoospermia (NOA). Azoospermia is detected in 10% of males examined for infertility and NOA is detected in 60% of patients with azoospermia [3].

The etiopathogenesis of NOA includes genetic disorders, Y chromosome microdeletions, testicular torsion, cryptorchidism, toxins, radiation, varicocele and idiopathic factors [4, 5]. Although many techniques including Percutaneous Sperm Aspiration (PESA), Testicular Sperm Aspiration (TESA), Conventional Testicular Sperm Extraction (cTESE), Microdissection Testicular Sperm Extraction (MD-TESE) have been used to detect sperm in patients with NOA, MD-TESE is currently accepted as the method with

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the highest sperm retrieval rate and the least complications and tissue loss. The MD-TESE procedure is preferred as the gold standard in terms of sperm retrieval rate in this patient group [6]. However, no standard consensus is available for searching for appropriate tubules during the MD-TESE procedure [7]. A limited number of studies are available in the literature on whether the testicle should be explored transversely or longitudinally, bilaterally or unilaterally, to increase the sperm detection rate in MD-TESE, and there is still no standard systematic procedure for MD-TESE today to minimize the possibility of missing appropriate tubules and obtaining sperm. Furthermore, despite the presence of studies in the literature indicating that parameters such as hormonal values, testicular volume, genetics, age, weight, environmental factors, varicocele and cryptorchidism predict the possibility of finding sperm before the MD-TESE procedure, none of these parameters have a definite predictive value on sperm finding [8–10].

The present study aimed to investigate the effect and reliability of unilateral or bilateral MD-TESE on sperm detection rates in patients with NOA.

Material–method

This is a prospective study and was approved by the Ethics Committee of Atatürk University Faculty of Medicine. A total of 84 azoospermic primary infertile male patients who had presented to the Atatürk University Research Hospital IVF Center for assisted reproductive techniques between January 2019 and January 2020, who had been married for at least one year and had no history of infertility in their female partners, and who had been diagnosed with NOA were included in the study.

A detailed anamnesis was obtained from the patients and a urogenital physical examination was performed. Age, weight, presence of comorbidities, presence of varicocele and hydrocele, history of operation for these diseases, history of previous scrotal operation or TESE and the duration of infertility were questioned. Testicular volumes were measured by Prader orchidometry and recorded. Semen samples were collected from the patients at least two times at 15-day intervals with sexual abstinence of for at least 3 days, and at most, abstinence of 5 days. The samples were analyzed with a Makler® sperm counting camera by the same biologist in the andrology laboratory.

In our study, in patients diagnosed with NOA, fasting blood samples were obtained and placed into biochemistry tubes between 08:00–10:00 am to examine the plasma levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), inhibin B, total testosterone, prolactin, estradiol and photometrically examined in the Beckman Coulter brand DXI 800 autoanalyzer in the biochemistry laboratory: FSH: 1.3–19 mIU/ml, LH: 1.3–8 mIU/ml, inhibin B: 25–225 pg/ml, testosterone: 2–7 ng/ml, prolactin: 2.6–13 pq/L, estradiol: 20–45 pg/ml, were considered as normal range.

All operations were performed by a single surgeon. The patients were randomized into two groups bilateral MD-TESE or unilateral MD-TESE. In all cases, the MD-TESE procedure was performed under general anesthesia by disinfecting the scrotal skin with betadine, passing through the layers with an incision of approximately 5 cm over the raphe, opening the tunica albuginea with a transverse incision, and removing the testicular tissue. An incision was made at 10× optical magnification under a microscope in the non-vascularized area near the middle of the testis. Then, approximately 10 large white and shiny tubules were selected at 25–40× optical magnification under the microscope and collected with a micropen set. The collected tissues were placed into a medium and delivered to the IVF (In Vitro Fertilization) team in the room. The tissues from all patients were examined by the same embryologist. In patients who underwent a bilateral MD-TESE procedure, cases in which sperm was found in either testicle were accepted as "sperm retrieved "and statistical analysis was carried out. In patients with unilateral MD-TESE procedure, if testis volumes and consistencies are the same in both testicles, testicular preference was made randomly, whereas in patients with different testicular volume and consistency, the better testis was preferred.

Statistical analysis

Statistical analyses were performed using the IBM SPSS 20 statistical analysis program. The data were presented as mean, standard deviation, median, minimum, maximum percentage and number. The normal distribution of continuous variables was examined by the Shapiro–Wilk-*W* test and the Kolmogorov–Smirnov test. In comparisons between two independent groups, the Independent Samples *t* test was used if the variables were distributed normally, and the Mann–Whitney *U* test was used for the non-normally distributed variables. For 2×2 comparisons between the categorical variables, the Pearson chi-square test was used if the expected value was (> 5), the chi-square Yates test was used if the expected value was [3–5], and the Fisher's exact test was used if the expected value was (< 3). For comparisons greater than 2×2 between categorical variables, the Pearson chi-square test was used if the expected value was (> 5) and the Fisher–Freeman–Halton test was used if the expected value was (< 5). The statistical significance level was accepted as $p < 0.05$.

Table 1 Group 1 and Group 2 demographic data

	Group 1** $n=41$	Group 2*** $n=43$	p value
Age (average)	37.4	32.2	
FSH	23.9 (0.31–73)	21.7 (0–63)	0.671*
LH	10.1 (0.2–27)	9.1 (0–28)	0.642*
Testosterone	3.1 (0.7–75)	3.2 (1–6.4)	0.724*
Estradiol	38 (7–144)	22.5 (1–54)	**0.009***
Inhibin B	69.5 (11–165)	77.3 (1–205)	0.393*
Right testicular volume (average)	11.5 (4–20)	12.9 (0–22)	0.162*
Left testicular volume (average)	11.6 (4–20)	12.5 (0–22)	0.344*
Operation time (average) (min)	40.1	56.3	**0.004***
Complication	3 2 (wound infection) 1 (fever)	0	

Statistically significant values are in bold ($p < 0.05$)

FSH follicle stimulating hormone, *LH* Luteinizing hormone

*Man–Whitney *U* test

**Group 1: bilateral MD-TESE

***Group 2: unilateral MD-TESE

Table 2 Statistical analysis of sperm presence/absence between groups

	Group 1[a] $n=41$ (%)	Group 2[b] $n=43$ (%)	p value
Presence of sperm	23 (56.1)	26 (60.5)	0.495*
Absence of sperm	18 (43.9)	17 (39.5)	0.310*

[a]Group 1: bilateral MD-TESE

[b]Group 2: unilateral MD-TESE

*Chi-square test

Table 3 The relationship between hormonal values and sperm presence/absence in Group 1 and Group 2

	Presence of sperm	Absence of sperm	p value
Group 1[a]			
FSH (mIU/ml)	23.1 (0.4–73)	24.9 (0.3–61)	0.462*
LH (mIU/ml)	14 (0.2–26)	11 (0.3–27)	0.184*
Testosterone (ng/ml)	3.4 (1.5–7.5)	2.8 (0.7–5.9)	0.222*
Inhibin B (pg/ml)	86 (50–165)	48 (11–110)	0.001*
Group 2[b]			
FSH (mIU/ml)	17.2 (0.08–63)	27.8 (0–50)	0.015*
LH (mIU/ml)	8.1 (0.1–20)	10.7 (0–28)	0.184*
Testosterone (ng/ml)	3.1 (1–6.4)	3.3 (1.4–5.3)	0.567*
Inhibin B (pg/ml)	86 (16–205)	64 (1–138)	0.233*

FSH follicle stimulating hormone, *LH* luteinizing hormone

[a]Group 1: bilateral MD-TESE

[b]Group 2: unilateral MD-TESE

*Mann–Whitney *U* test

Results

Of the 84 patients included in our study, 41 underwent bilateral MD-TESE (Group 1) and 43 underwent unilateral MD-TESE (Group 2). The demographic characteristics, preoperative laboratory results and the testicular volumes of patients in Group 1 and Group 2 have been summarized in Table 1.

Of the 84 patients who underwent MD-TESE, while 49 (58.3%) had spermatozoa, 35 (31.7%) had no spermatozoa. No statistically significant difference was determined in sperm retrieval rates between Group 1 and Group 2 (56.1%, 60.5%, $p=0.495$, respectively) including the 3 patients in Group 1 in whom sperm was found in one testicle but not in the other testicle, and therefore considered as sperm retrieved (Table 2).

In Group 1, no significant difference was determined in the mean serum T levels between patients who had sperm compared to the patients who did not have sperm (3.4 ng/ml, 2.8 ng/ml, respectively, $p=0.222$). The mean Inhibin B level was significantly higher in patients who had sperm compared to the patients who did not have sperm (86 pg/ml, 48 pg/ml, respectively, $p=0.001$). Furthermore, serum T and Inhibin B values were 3.15 ng/ml and 86.19 pg/ml, respectively, in patients with sperm in Group 2 and 3.3 ng/ml and 64 pg/ml, respectively, in patients without sperm. In Group 2, no statistically significant difference was found between the mean serum T and Inhibin B levels of patients with sperm and patients without sperm ($p=0.567$, $p=0.233$, respectively) (Table 3).

Discussion

The number of infertility cases is gradually increasing and if azoospermia is detected in patients with infertility, it is determined whether the azoospermia is obstructive azoospermia or non-obstructive azoospermia. While the treatment of obstructive azoospermia is directed toward the etiology, treatment of non-obstructive azoospermia can be administered using assisted reproductive techniques. In patients with NOA, the MD-TESE technique, which has the least complication and the highest success rate, is the most frequently preferred assisted reproductive technique [6, 11, 12]. With this technique, the sperm detection rate varies between 35 and 75% depending on the experience of the surgeon [13, 14]. Previous studies have investigated many factors in determining the success of MD-TESE including patient's age, body mass index, testicular volume, serum FSH, LH, prolactin, estradiol, testosterone, inhibin B levels, Klinefelter Syndrome, presence of AZF gene deletion, history of previous scrotal surgery and/or TESE and the unilateral or bilateral performance of the MD-TESE procedure, but no significant single factor has been found affecting the success of TESE [15].

Despite the presence of no consensus in the literature on whether MD-TESE should be performed unilaterally or bilaterally, Plaset et al. who investigated males with azoospermia demonstrated that bilateral testicular biopsies had higher sperm detection rates than unilateral biopsies. While 28% of bilateral biopsies showed histopathological differences, 72% displayed similar histopathological findings. When measured using the Prader orchidometry, 54.8% of testes were symmetrical and 45.2% were asymmetrical, and it was reported that focal spermatogenesis in the opposite testis could be missed in 20% of patients when only unilateral testicular biopsy was performed. Different histopathological findings were determined in bilateral testicular biopsies performed in 21.7% of patients with symmetrical testes and 26.3% of patients with asymmetrical testes. In the present study, it was reported that focal spermatogenesis in the contralateral testicle could be missed in 8.6% of patients with symmetrical testicles and 21.1% of patients with asymmetrical testicles when unilateral biopsy was performed [16]. Schulze et al. showed a 32.7% difference in sperm retrieval rates between the two testes in their study [17]. In a study by Moein et al. on 419 infertile males, unilateral TESE was performed in 254 patients and bilateral TESE in 165 patients. In 22 (13.3%) of the patients who had undergone bilateral TESE, it was reported that no sperm was found in one testicle, while sperm was obtained in TESE performed on the opposite testicle [18]. Ramasy et al. reported that only 40 (7.9%) out of 506 patients who underwent bilateral MD-TESE had no unilateral spermatozoa and spermatozoa were found on the contralateral side [19]. In a study by Franco et al. on 64 patients named "staged TESE", it was reported that no sperm was found in MD-TESE performed on the same testicle and contralateral testicle in patients in whom sperm could not be found in conventional TESE, and it was stated that MD-TESE after single TESE biopsy on the same testicle or multiple contralateral TESE did not improve the sperm detection rate [20].

The present study, which investigated the effect of unilateral or bilateral MD-TESE procedure on sperm retrieval in patients with NOA, was conducted with 84 patients. Of these, 43 patients underwent unilateral, and 41 patients underwent bilateral MD-TESE. In our study, we detected no significant difference in sperm retrieval rates in patients who underwent bilateral TESE compared to patients who underwent unilateral TESE. We also found a rate of 7.3% in which sperm was not found in one testicle and sperm was found in the other testicle in patients who underwent bilateral MD TESE.

The results of our study support the results of the studies by Moein et al., Ramasy et al., and Franco et al. However, contrary to the results of the retrospective study by Plaset et al. in which azoospermic patients were not divided into subgroups, we found that bilateral MD-TESE did not increase the sperm detection rate compared to unilateral MD-TESE in our study. We consider that the prospective design of our study and the fact that our study was conducted in the non-azoospermic patient group by categorizing azoospermic patients, makes our study results more significant than the results of the study by Plaset et al. In addition, the mean operating time was 40.1 min for unilateral MD-TESE and 56.3 min for bilateral MD-TESE. Although this difference is statistically significant considering that the procedure is invasive, that it is performed under anesthesia, and, furthermore, considering the complications that may develop due to anesthesia, infection, fever, wound dehiscence, bleeding and hematoma, the short duration of the procedure is an advantage. Although complications such as pain, hematoma and infection are rarely seen after TESE, it should be kept in mind that the risk may increase in bilateral MD-TESEs compared to unilateral procedures [21]. In our study, while no complications were detected in Group 1 cases, complications developed in a total of 3 patients in the Group 2 procedures, including wound infection in 2 patients and fever in one patient. A second surgery is necessary for patients in whom no sperm is found following a unilateral MD-TESE procedure. This might be seen as a disadvantage for the unilateral MD-TESE method. However, we believe that the unilateral MD-TESE may cause less tissue loss

in the testis compared to bilateral MD-TESE performed in the same session, potentially leading to less temporary hypogonadism in patients. Additionally, the possibility of providing hormonal therapy until the second MD-TESE surgery in patients who develop temporary hypogonadism after a unilateral MD-TESE procedure may increase the likelihood of finding sperm, which we believe could make this approach advantageous. Considering the risk of hypogonadism after the MD-TESE procedure and that multiple testicular biopsies and procedures (such as bilateral MD-TESE and repeated MD-TESEs) may cause androgen deficiency by decreasing Leydig cell function and consequently testosterone levels(22), we suggest that the results of our study can be a warning and pioneering for clinicians regarding the preference of the method to be utilized for MD-TESE in non-azoospermic patients.

Although the study has some limitations including the limited number of patients, lack of long-term outcomes of the patients after TESE, failure to obtain spermatozoa in unilateral and bilateral TESE, and the fact that the hormonal manipulations performed prior to the second TESE were not evaluated regarding whether or not they were different between the groups, the prospective design of the study, all procedures being performed by a single surgeon, and thus the elimination of surgeon-related factors affecting the success of intraoperative TESE, constitute the strengths of our study.

Conclusion

Although the MD-TESE procedure is less invasive and has higher sperm retrieval rates compared to the other types of TESE, in our study, there was no difference in sperm retrieval rates between unilateral MD-TESE and bilateral MD-TESE, and it should be kept in mind that these procedures are invasive, postoperative pain, hematoma and infection may develop and the likelihood of these complications may increase as the operating time increases. In addition, if no sperm is obtained after the first MD-TESE, the rate of sperm retrieval decreases gradually as testicular volume loss may occur in subsequent procedures. The first attempt to obtain sperm has the highest chance for that patient. Hence, in case of failure to obtain sperm after unilateral procedures, considering the complications that may develop and the prolonged anesthesia time, we recommend that unilateral TESE be performed first in non-azoospermic patients to increase the success of a second TESE with additional treatments (hormonal treatment, varicocelectomy if a varicocele is present).

Author contributions All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by [AU]. The first draft of the manuscript was written by [AU] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Conceptualization: FO, IO; Methodology: SOD, AEC; Formal analysis and investigation: MSA, SGU; Writing—original draft preparation: AU; Writing—review and editing: AU, AEC; Supervision: IO, IK.

Data availability The datasets analyzed in the current study are not publicly available due to patient privacy concerns but are available from the corresponding author on reasonable request.

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