Psychological and Pain Factors in Microsurgical Testicular Sperm Extraction (Micro-TESE) for Non-Obstructive Azoospermia: A Comparative Study of Successful and Unsuccessful Cases

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Purpose: This study aimed to assess postoperative pain, depression, and anxiety levels in infertile men who underwent microsurgical testicular sperm extraction (micro-TESE) for non-obstructive azoospermia (NOA) and compare results between patients with successful and unsuccessful sperm retrieval.

Material and Methods: A total of 105 NOA patients participated, completing preoperative Beck Depression Inventory (BDI) and Situational and Transient Anxiety Inventory (SAI and TAI) questionnaires. Postoperatively, Visual Analog Scale (VAS) scores were recorded. Patients were categorized into primary and repeated micro-TESE groups, and scale scores, operation duration, and collected tubule count were compared. The relationship between micro-TESE outcomes, VAS scores, and additional analgesia needs was also examined.

Results: Successful sperm retrieval was achieved in 55.9% of patients. While BDI, SAI, and TAI scores showed no significant intergroup differences, micro-TESE (-) patients exhibited significantly higher mean VAS scores ($p < 0.001$). VAS scores positively correlated with BDI score, operation duration, and tubule count, while patient age inversely correlated with micro-TESE results.

Conclusion: Infertility, azoospermia, and unsuccessful sperm retrieval impact psychogenic status and pain levels in male patients. Additionally, a history of micro-TESE procedures and their outcomes elevate depression levels.

Keywords: Anxiety; Depression; Infertility; Micro-TESE; Non-obstructive azoospermia.

INTRODUCTION

Non-obstructive azoospermia (NOA) stands out as a condition characterized by the absence of sperm during ejaculation due to impaired spermatogenesis. NOA results from spermatogenic failure with various congenital and acquired causes. It has been reported in approximately 60% of azoospermic patients and 15% of all infertile men[(1)]. The etiology of NOA can be either intrinsic testicular impairment or insufficient gonadotropin production. In such patients, it's essential to evaluate chromosomal or genetic abnormalities, as they exhibit a higher incidence compared to the normal population. Unfortunately, there is no specific treatment to restore spermatogenesis in most NOA patients, and it is generally considered a non-medically manageable cause of male infertility. NOA can be distinguished from obstructive azoospermia based on patient history, clinical examination findings, and hormone profiles. Unlike obstructive azoospermia, NOA is characterized by high follicle-stimulating hormone (FSH) and low testosterone levels, along with a significant reduction in testicular volume. As a result, the development of more efficient treatment methods for male infertility has become imperative. The use of an ideal surgical technique can achieve efficient sperm retrieval while minimizing testicular trauma[(2)]. To this end, Schlegel introduced microsurgical testicular sperm extraction (micro-TESE) as a sperm retrieval technique in 1999[(3)]. This technique has helped reduce testicular damage, and the reported sperm retrieval rate ranges around 55-60%[(4)]. However, predicting the success of micro-TESE remains challenging. Infertility is already a significant issue leading to anxiety and depression among couples, and the presence of azoospermia and the need for a surgical procedure can exacerbate anxiety levels.

To the best of our knowledge, there is no study examining depression and anxiety levels in patients with NOA who have undergone micro-TESE. Therefore, the objective of our study was to evaluate depression and anxiety in infertile male patients who underwent micro-TESE due to NOA. Additionally, we investigated the association of micro-TESE results with patients' preoperative stress status and postoperative pain.

MATERIAL & METHODS

This prospective study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the local ethics committee of our hospital. Before all patients received detailed information about the study's objectives by the doctor who will perform the surgery and provided informed consent.

A total of 105 patients with NOA, presenting to our fertility clinic with the complaint of absent sperm dur-

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Table 1. Compared parameters according to Mic-TESE result.

	Mic-TESE Results				
	n	Negative	n	Positive	*p*
Age	45	34.82 ± 6.06	60	35,8 ± 7.09	0.459
STAI	45	40 (20:53)	60	41.5 (22:60)	0.396
TAI	45	44 (19:70)	60	45.5 (20:66)	0.203
BDI	45	4 (1:18)	60	3.5 (1:25)	0.607
OPERATION TIME	41	70 (30:100)	52	35 (20:90)	< 0.001
TUBULE COUNTS	41	42 (4:56)	52	15.5 (7:63)	< 0.001
VAS	45	4 (2-8)	60	2 (0:8)	< 0.001

Data are expressed as median (minimum: maximum) and mean±standard deviation.

ing ejaculation and diagnosed with non-obstructive azoospermia, were enrolled in the study. All patients underwent a thorough physical examination, hormonal evaluation, and genetic investigations. The diagnosis of azoospermia was established according to WHO guidelines. After centrifuging the samples at 600 g, two separate semen analyses were performed under 400x magnification using an inverted microscope[5].

Patients with obstructive azoospermia, those who underwent micro-TESE due to cryptozoospermia, those with a history of repeated implantation failures, those with total immotile sperm, and those who did not consent to complete the questionnaire forms were excluded from the study.

Detailed information about the study's objectives by the doctor who will perform the surgery was given to all patients and provided informed consent during the final out-patients evaluation. The questionaries forms including the Beck Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI; SAI and TAI) were filled in the patients' room before going the operation.

Surgical Technique

The operation was conducted under general anesthesia. A midline scrotal incision was made to access the scrotum. The procedure began with the testis with a larger volume. After making a longitudinal incision in the tunica, the seminiferous tubules were meticulously evaluated. Mature spermatozoa-containing seminiferous tubules were identified as they were larger and whiter than atrophic tubules. Tubule pieces were collected from one or both testes until mature spermatozoa were found. This procedure followed established guidelines and techniques[6].

During all procedures, the operation time, and the number of collected tubules were recorded. Intravenous analgesia (Diclofenac sodium 75 mg/3 ml) was administered to all cases at the end of the operation. Additionally, local anesthesia was applied to the spermatic cord and surgical incision with 20 ml Marcaine %0.5 ® (Bupivacaine HCl 5 mg/mL). In the recovery room, patients complete to record the need for additional analgesia and the time to the additional analgesia requirements (Paracetamol fl 10 mg/ml). We also evaluated the relationship between micro-TESE results, VAS scores, and the need for additional analgesia.

The patient's relatives were immediately informed about the results after the first evaluation of Mic Tese samples in the operating room. Once detailed evaluation of the samples in the laboratory, the final result was given to the patients within 60-90 minutes.

The results were compared between the micro-TESE (+) and (-) groups. Additionally, we compared the same parameters between patients with positive or negative results in previous micro-TESE procedures.

Questionnaire Forms

- BDI: A 21-item questionnaire was designed to assess the degree of existing depressive symptoms within the last two weeks. Each item is assessed on a four-point Likert-type scale, with scores ranging from 0 to 3 points. The total score varies from 0 to 63 points, with higher scores indicating more severe depressive symptoms. Originally developed by Beck in 1961[7], it was revised as BDI-II in 1996 to align with changes in the Diagnostic and Statistical Manual-IV criteria for depressive symptoms. The Turkish version of BDI's validity and reliability were established by Hisli et al. in 1988[8].
- STAI: A 40-item self-report evaluation tool that measures state and trait anxiety separately, with 20 items each. Spielberger et al. originally developed the STAI in 1970, and it has since been translated into 30 different languages[9]. Various reliability and validity tests have shown that STAI is appropriate and sufficient for measuring anxiety in research and clinical settings. Oner et al. conducted a reliability and validity study of the Turkish version[10]. STAI consists of 40 items scored from 1 to 4 points. SAI and TAI scores separately evaluate state and trait anxiety. The total score ranges from 20 to 80 points, with higher scores indicating higher anxiety levels.
- VAS: This scale is designed to measure the severity of pain in various medical conditions. Patients are asked to mark their pain severity on a 10-cm ruler, where 0 represents no pain and 10 represents unbearable pain.

Statistical Analysis

Table 2. Postoperative analgesia requirements in the patients.

	ANALGESIA				
	n	YES	n	NO	*p*
STAI	72	41.32 ± 6,85	33	41.21 ± 6,95	0.941
TAI	72	45 (20:70)	33	45 (19:66)	0.587
BDI	72	3(1:24)	33	4 (1:25)	0.268
VAS	72	2(0:6)	33	6(2:8)	< 0.001

Table 3. Compared the parameters according to previous Mic.TESE result.

	Previous Mic. TESE Result				
	n	Negative	n	Positive	*p*
Age	21	36,29 ± 7.00	28	38.61 ± 6.41	0.234
STAI	21	38,81 ± 8.20	28	41.36 ± 7.00	0.248
TAI	21	46 (19:66)	28	44.5 (20:61)	0.430
BDI	21	3 (1:14)	28	5 (1:25)	0.495
OPERATION TIME	21	70 (30:90)	25	55 (20:90)	0.074
TUBULE COUNTS	21	42 (4:56)	25	21 (10:63)	0.085
VAS	21	3 (1:7)	28	3 (0:6)	0.363

All data were analyzed using the Statistical Package for the Social Sciences, v. 22 (SPSS Inc., Chicago, IL, USA). Data normality was assessed using the Shapiro-Wilk test, and the homogeneity of variances for the T-test was tested by the Levene test. If normal distribution was not achieved, the relationships between the variables were examined with the Spearman rank correlation coefficient. In the case of a normal distribution, independent t-tests were used for group comparisons, and descriptive values were presented as mean ± standard deviation. Pearson's chi-square test was employed to compare variables between groups. When the data followed a normal distribution, the Spearman rank correlation coefficient was used to examine the relationships between variables. Statistical significance was defined as $p < 0.05$.

RESULTS

Out of the 105 patients, 45 (42.9%) were in the micro-TESE (-) group, and 60 (57.1%) were in the micro-TESE (+) group. Comparative parameters are detailed in **Table 1**.

There was no statistically significant difference between the micro-TESE (-) and (+) groups in terms of patient age ($p = 0.459$). The two groups also did not show statistically significant differences concerning anxiety and depression scores. However, the micro-TESE (-) cases had significantly higher VAS scores, longer operation times, and a greater number of dissected tubules ($p < 0.001$).

Additional postoperative analgesia requirements were more frequent in patients who underwent bilateral micro-TESE and those with high VAS scores. Out of the 33 cases requiring additional analgesia, 10 (30.3%) were unilateral, and 23 (69.7%) were bilateral micro-TESE ($p = 0.010$). The median VAS scores of patients with and without analgesia requirements were $6^{(2-8)}$ and 2 (0-6), respectively ($p < 0.001$). On the contrary, no difference was observed in terms of anxiety and depression scores (**Table 2**).

The same parameters were compared for the 49 patients who had previously undergone micro-TESE procedures. In these cases, the new micro-TESE achieved successful sperm retrieval in 28 (57.1%) patients and failed in 21 (42.9%). No statistically significant differences were observed in any of the compared parameters (**Table 3**).

A total of 22 (20.9%) cases had additional health problems. When comparing anxiety, depression, and VAS scores between patients with and without comorbidities, it was found that the BDI score was significantly higher [7.5 (1-24) vs. 3 (1-25), $p = 0.048$], and the VAS score was significantly lower [2 (0-7) vs. 3 (0-8), $p = 0.007$] in those with comorbidities. However, no significant differences were observed between these two groups regarding STAI ($p = 0.059$) and TAI scores ($p = 0.460$) (**Table 4**).

DISCUSSION

The results of this study have highlighted a significant association between azoospermia and micro-TESE outcomes in infertile male patients, particularly concerning their depression levels and Visual Analog Scale (VAS) scores. These findings contribute to the growing body of knowledge surrounding male infertility and its psychological implications.

In our study, we evaluated a homogeneous NOA group without considering the etiological factor. In a study evaluating similar parameters in patients with Klinefelter syndrome, it was stated that stress and depression scores and postoperative VAS values were higher in patients with KS compared to the NOA group[11]

Previous research has examined various aspects of male infertility and the efficacy of micro-TESE procedures. Franco et al. conducted a study in 2016 involving 64 azoospermic patients, reporting a mean age of 35.2 years among the participants[12]. Similarly, Hendriks et al., in their evaluation of patients with Non-Obstructive Azoospermia (NOA), found a mean age of 37.0 years [13]. In our current study, the mean age of the patients was 35.3 years, aligning closely with the findings of previous research in the literature. This consistency in patient demographics helps contextualize our results within the broader landscape of male infertility studies.

Regarding the micro-TESE procedure, Ghalayini et al. examined 65 patients and reported a sperm retrieval rate of 56.9%[14]. In a larger-scale study, Ramasamy et al. conducted micro-TESE on 460 azoospermic patients, achieving a sperm retrieval rate of 57%[15]. In our study, we found a sperm retrieval rate of 56.9%, in line with similar rates reported in the literature. Historically, most studies have indicated a sperm retrieval rate around 50% [16,17]. However, recent advances in micro-TESE technology have led to improved rates, as observed in our study. This increase in success rates can be attributed to the evolving capabilities of micro-TESE.

It can be thought that the VAS score was high in this group due to the long duration of micro TESE in negative cases. However, the fact that the same results have been revealed in previous similar studies eliminates this possibility[11]. Our study is the first study to evaluate the relationship between surgery duration and VAS. This issue can be evaluated in more detail with further studies.

While the literature contains numerous studies assessing the outcomes and efficacy of micro-TESE, there is a noticeable gap in research specifically examining depression and anxiety levels in patients with NOA who have undergone this procedure[18,19,20]. Nevertheless,

Table 4. Comparisons of comorbidities.

	COMORDITY				
	n	No	n	Yes	*p*
STAI	83	41(20:60)	22	39(22:48)	0,059
TAI	83	45(19:70)	22	45(32:66)	0,460
BDI	83	3(1:25)	22	7,5(1:24)	0,048
VAS	83	3(0:8)	22	2(0:7)	0,007

Data are expressed as median (minimum: maximum).

few studies have touched upon this issue, with some reporting higher Beck Depression Inventory (BDI) scores in male patients with azoospermia[21]. In a study by Abedi et al., anxiety levels were found to be elevated in patients with NOA[22]. In our study, both depression, as measured by BDI, and anxiety, as assessed by State-Trait Anxiety Inventory (SAI) and Trait Anxiety Inventory (TAI), were notably elevated among patients with NOA. However, we did not observe any statistically significant differences between the micro-TESE (-) and (+) groups concerning mean BDI, SAI, and TAI scores. It's worth noting that various studies in the literature have explored the psychopathological characteristics of patients with sexual dysfunction, infertility, and azoospermia, often employing different questionnaires and methodologies. For example, Lotti et al. found a higher mean Middlesex Hospital Questionnaire score among infertile men in their study. Furthermore, they observed a negative correlation between erectile dysfunction and psychopathological disorders.[23]

In our study, we also evaluated the prevalence of sexual dysfunction in infertile male patients with NOA using the Visual Analog Scale (VAS). The mean VAS score during treatment was 3.55, noticeably lower than scores reported in a study assessing sexual dysfunction in similar patients, where the mean VAS score was 5.2 during treatment and decreased to 4.1[24]. While no specific studies in the literature investigated postoperative VAS scores in NOA patients, we did draw insights from studies on VAS scores in patients undergoing other surgical procedures. For instance, a systematic review encompassing 13 randomized clinical trials involving 1808 adult patients who underwent appendectomy revealed that laparoscopic surgery resulted in superior postoperative VAS scores compared to open surgery[25]. Similarly, Myles et al. observed an increase in VAS scores in more extensive surgical procedures[26]). This supports our finding of a significantly lower operation time in the micro-TESE (-) group.

Strengths of our study include its prospective design, a relatively large patient cohort, and its distinction as the first study in the literature to comprehensively examine depression and anxiety levels based on micro-TESE outcomes in patients with NOA. Moreover, we utilized three distinct scales to measure anxiety and depression levels, enhancing the robustness of our findings. However, certain limitations should be acknowledged. First, the study was designed as a multicenter study, introducing potential variations in data collection and analysis. Second, we were unable to analyze Follicle-Stimulating Hormone (FSH) and testosterone levels or determine the time to initial infertility diagnosis, which could have provided additional context. Another important point is that the anxiety and stress in the patients were measured only before the study; these parameters were not measured following postoperative outcome information. However, it is not difficult to predict that these parameters will be more obvious in negative cases. However, it should be noted that the main purpose of this study is to reveal the pre-operative depression and anxiety levels in patients undergoing micro-TESE, rather than the effect of the operation results.

In conclusion, our study sheds light on the intricate interplay between male infertility, micro-TESE outcomes, and psychological well-being. By emphasizing the associations between azoospermia, micro-TESE, and depression levels, we contribute to the evolving discourse on male infertility management. While challenges persist, the continuous advancement of micro-TESE technology offers promise for improving sperm retrieval rates. Further research is warranted to explore the multifaceted dimensions of male infertility and its psychological ramifications, ultimately leading to more comprehensive patient care and treatment strategies.

CONCLUSIONS

Our study sheds light on various aspects of micro-TESE procedures in infertile male patients, particularly those related to pain, success rates, and psychological factors. These findings underscore the importance of patient counseling and postoperative pain management strategies in the context of micro-TESE. Further research is warranted to better understand the interplay between patient characteristics and micro-TESE outcomes, ultimately leading to improved patient care and outcomes in the field of male infertility. It is important to provide psychological support to couples who undergo to assisted reproductive techniques to ensure patients' stress management and to continue it throughout the process.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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