Original Research

Evaluation of the Results of Intracytoplasmic Sperm Injection and Microdissection Testicular Sperm Extraction Treatments in Patients with Nonobstructive Azoospermia According to Etiological Factors: A Retrospective Analysis

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Received: 2024-05-14

Accepted: 2024-07-09

Published Online: 2024-08-07

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INTRODUCTION

Infertility is observed in 8-12% of the population and azoospermia occurs as a cause of this condition in some

ABSTRACT

Objective: This study aimed to retrospectively compare the results of microdissection testicular sperm extraction (microTESE) and Intracytoplasmic sperm injection (ICSI) treatments in nonobstructive azoospermia (NOA) patients with different aetiologies. Determinants (clinical characteristics) for microTESE outcomes were compared between patients with successful sperm retrieval (SSR) and sperm retrieval failure (SRF).

Material and Method: A total of 510 NOA patients who underwent microTESE between January 2015 and January 2024 were included in this study. Patients were classified according to the cause of NOA and SSR, fertilisation rate, clinical pregnancy, and overall live birth rate were evaluated.

Results: The SSR rate was 44.1% in the whole population. The idiopathic patient group had the lowest SSR rate (X^2 : 34.81; p<0.01). There was no difference between the groups in terms of fertilisation rate, clinical pregnancy and overall live birth rate. There was a negative correlation between age and SSR rates in patients with idiopathic NOA (t:-0.27; p<0.01). SSR rates were higher in patients with cryptorchidism (right: t:0.8; P:0.003; left: t:0.72; p:0.002) and mumps orchitis (right: t:0.76; P<0.01; left: t:0.76; p=0.003).

Conclusion: Etiology has a significant role in terms of SSR in patients with NOA. SSR was found to be significantly less in patients with idiopathic NOA compared to other causes. In addition, age and testicular volume were significant predictive factors for SSR in patients with idiopathic and acquired NOA.

Keywords: nonobstructive azoospermia, microtese, intracytoplasmic sperm injection, male infertility

patients [1]. Azoospermia may result from obstructive and nonobstructive causes [2]. Nonobstructive azoospermia (NOA) is the absence of spermatozoa in semen [3]. Although there are many factors among the etiologies of NOA, Klinefelter syndrome (KS), Y chromosome microdeletions (YCMDs) cryptorchidism, idiopathic factors and mumps orchitis are the most common etiologies [4].

Intracytoplasmic sperm injection (ICSI) technique is widely used in patients with NOA. The main aim is to extract live spermatozoa for assisted reproductive techniques in these patients [5]. Conventional testicular sperm extraction (cTESE) and microdissection testicular sperm extraction (microTESE) are the methods used to obtain viable spermatozoa [5]. MicroTESE has a higher sperm retrieval rate (SSR) than cTESE. In the literature, the results of microTESE and ICSI treatments in NOA patients differ according to etiologic factors [6-8].

In our study, we aimed to compare the results of microTESE and ICSI treatments in NOA patients according to the etiologic factor.

MATERIALS AND METHODS

Ethics committee approval was obtained from the ethics committee of our hospital with decision number 2024/02-19 on 04.03.2024. Our study was conducted according to the ethical standards of the 1964 Declaration of Helsinki.

A total of 510 NOA patients who underwent microTESE between January 2015 and January 2024 for ICSI were included in this study. Inclusion criteria were absence of sperm in at least 2 spermiogram tests, obstructive azoospermia, lack of radiologic and genetic testing, and hormonal evaluation. Exclusion criteria were defined as the presence of any disease that may

Main Points:

- Azoospermia may result from obstructive and nonobstructive etiological factors.
- Etiology has a significant role in terms of SSR in patients with NOA.
- MicroTESE has a higher sperm retrieval rate (SSR) than cTESE
- Idiopathic NOA patients have the lowest SSR rate.
- Age and testicular volume are important parameters for SSR in idiopathic and acquired NOA patients.

be associated with infertility in the woman and patients with incomplete data.

In the study, patients were divided into 5 groups according to the cause of NOA. The patient groups were idiopathic, KS, YCMDs, cryptorchidism and mumps orchitis. A detailed medical history and physical examination were performed in all patients. Semen analysis, hormonal evaluation and scrotal ultrasound were performed to exclude obstructive pathologies. All patients in the study underwent genetic testing after NOA was considered, and patients who could not be diagnosed despite these tests were defined as idiopathic NOA. The study collected microTESE results (SSR ratio) and ICSI results including fertilization, clinical pregnancy and live birth rates. All NOA patients with KS in the study group were non-mosaic Klinefelter males. All patients with YCMD had a partial mutation in the AZFc region on the Y chromosome. In all patients with cryptorchidism, testicular descent to the inguinal region was observed.

Surgical Procedure of MicroTESE

Following the midline incision, the tissues were crossed with blunt and sharp dissections and the tunica albugenia was reached. The tunica albuginea was opened with a sagittal incision of approximately 1,5 cm from the avascular line. The testicular tissue was examined under a microscope at 20 magnification and samples from the seminiferous tubules, which were fuller and more whitish, were taken and sent for examination by the embryologist. If no sperm was found in the examination of the tissues sent from the opened testicle, local anesthesia was applied to the contralateral vas deferens, the testicle was opened and samples were sent from the testicle on that side in the same way and sperm were searched. One sample was taken in pathology without scapating both testes and sent in a bovine solution. Tunica albuginea was closed with 4/0 monocryl. The scrotum skin was closed separately with 3/0 monocryl.

Sperm Processing

The tissues obtained from the microTESE procedure were dissected by the embryologist using two needles. The dissected tissues were analyzed in a micromanipulator under 200 or 400 times magnification. The tissues with spermatozoa were dissected thoroughly and taken into a tube with the help of a pipette. The tube was then vortexed for 35 minutes. The vortexed tube was removed from the incubator until the medium was warmed up. Two tubes were prepared in two layers by placing 90% and 45% gradient solutions (1ml each from bottom to top) in a 15ml conical falcon tube. TESE tissue in the previously

incubated tube was added to the heated conical tube with the help of a pipette without shaking the layers. The conical tubes were centrifuged at 2000 rpm for 20 minutes and the supernatant was removed with a pipette until 0.5 ml remained at the bottom of the tubes. The remaining 0.5ml at the bottom was mixed with 23ml of wash medium. Centrifuged at 1800 rpm for another 10 minutes. The supernatant portion was discarded with a pipette until 0.4ml remained at the bottom of the tube. The remaining portion was placed in the incubator until ICSI.

Intracytoplasmic Sperm Injection Prosedure

Following the hormone protocol, ovulation induction was performed with a single dose of hCG approximately 36 hours before ovum retrieval. Oocyte cumulus complexes were collected by puncture of follicles under ultrasound guidance and placed in a universal IVF medium. After 30 seconds of hyaluronidase (80IU/ml) application, the cumulus was separated from the oocyte by up and down movements with a Pasteur pipette. Oocytes were incubated at 37°C and 5% CO2 until injection. A pool was created with the help of mediums to put sperm in the sterile polystyrene IVF container. The prepared sperm was added to the pool with a pipette. The spermatozoa were placed in PVP (a liquid that slows down sperm movement and allows the micropipette to draw sperm under control) solution with the help of a micropipette. The sperm whose tail was broken and immobilized with the help of a micropipette was removed from the PVP solution and an ICSI procedure was performed.

Definitions of ICSI Outcomes

Clinical outcomes were determined as fertilization, clinical pregnancy and live birth rates. Fertilization was defined as the presence of two pronuclei (2pn) and two polar bodies after the ICSI procedure. Pregnancy was defined as a spontaneous increase in HCG levels after >10 days. Clinical pregnancy was defined as the appearance of a gestational sac on USG >5 weeks after ICSI.

Statistical Analysis

Statistical analysis in this study was performed with SPSS version 22.0 (SPSS Inc, Chicago, IL, United States of America). Continuous variables were analyzed as mean \pm standard deviation (SD) and categorical variables were expressed as proportion (%). Data distribution was analyzed using the Kolmogorov-Smirnov test. Group differences in demographic

and clinical data were compared with one-way analysis of variance (ANOVA), and post hoc contrasts were made with chisquare test for categorical variables. Furthermore, associations between clinical characteristics and SSR rates were analyzed by Kendall's correlation analysis.

RESULTS

Results of MicroTESE Results According to Aetiologies

Non-clinical characteristics according to different aetiologies are given in Table 1. The results of patients who underwent microTESE for ICSI are given in Table 2. The overall SSR rate was 44.1% (225/510). When SSR rates were analyzed, the idiopathic group had the lowest SSR rate compared to the other groups (36.4%, 125/343). SSR rates in other groups were as follows: KS: 49.3%, YCMDs: 60%, cryptorchidism: 77.1%, mumps orchitis: 70.5% (X^2 : 34.81; p<0.01). Predictors of successful sperm retrical by aetiology are given in Table 3. In SSR patients, age was significantly lower in the idiopathic group (t:-1.92; p<0.05). Mean testicular volume was higher in patients with cryptorchidism (left: t:5.3, p<0.001; right: t:4.23, p<0.001) and mumps orchitis (left: :2.8, p:0.003; right: t:2.72, p:0.002). No significant difference was found in hormone levels (FSH, LH, T) in patients with SSR and SRF.

Comparison of ICSI Results According to Aetiologies

Fertilisation rate was determined as the number of patients with successful sperm retrieval. Clinical pregnancy was calculated according to the fertilisation rate. Live birth was calculated according to the clinical pregnancy rate. In our study, the overall fertilisation rate was 73.3% (165/225). No difference was found in fertilisation rates according to etiology (idiopathic: 76%, KS: 72.9%, YCMDs: 62.5%, cryptorchidism: 70.3%, mumps orchitis: 75%, X^2 : 0.72; p:0.691) (Table 2).

The clinical pregnancy rate was 66.67% (110/165). No difference was found in clinical pregnancy according to etiology (idiopathic: 68.4%, KS: 66.6%, YCMDs: 46.4%, cryptorchidism: 68.4%, mumps orchitis: 77.7%, X² : 3,76; p:0.404) (Table 2).

The overall live birth rate was 68.2% (75/110). No difference was found in overall live birth according to etiology (idiopathic: 73.8%, KS: 50%, YCMDs: 42.8%, cryptorchidism: 76.9, mumps orchitis: 71.4%, X² : 2.04; p:0.428) (Table 2).

	Whole Cohort (n=510)	Idiopathic (n=343)	Klinefelter (n=75)	Y chromosome micro deletion (n=40)	Cryptorchidism (n=35)	Mumps orchitis (n=17)
Age (years)	32.7 ± 4.61	33.1 ± 3.7	30.8 ± 4.2	33.7 ±6.1	27.5 ± 4.3	29.5 ± 2.8
FSH (IU/L)	19.2± 14.1	13.9 ± 11.8	39.2±15.8	17.2 ±8.1	18.3 ± 6.2	21.7 ± 11.3
LH (IU/L	10.4 ± 7.9	8.1 ± 5.3	22.1 ± 10.4	8.8 ± 3.8	11.9 ± 4.1	13.2 ± 5.2
Testesteron (ng/mL)	9.2 ± 5.8	10.3 ± 6.6	5.8 ± 4.23	11.8 ±4.2	11.1 ± 1.3	10.9 ± 5.6
Left Testis Volume (mL)	6.4 ± 3.4	7.6 ± 3.3	2.1 ± 0.6	7.2 ± 2.3	4.9 ± 1.5	4.9 ± 1.8
Right Testis Volume (mL)	6.3 ± 3.1	7.4 ± 3.2	2 ± 0.6	7.4 ± 2.4	5.1 ± 1.3	4.8 ± 1.7

Table 1. Demographic, Laboratory and Radiological Data

Table 2. Results of microTESE and ICSI according to Etiological Factors

(n/%)	Whole Cohort (n=510)	Idiopathic (n=343)	Klinefelter (n=75)	Y chromosome micro deletion (n=40)	Cryptorchidism (n=35)	Mumps orchitis (n=17)
Successful sperm retrieval	225 (44.1%)	125 (36.4%)*	37 (49.3%)	24 (60%)	27 (77.1%)	12 (70.5%)
Fertilization	165 (73.3%)	95 (76%)	27 (72.9%)	15 (62.5%)	19 (70.3%)	9 (75%)
Clinical pregnancy	110 (66.6%)	65 (68.4%)	18 (66.6%)	7 (46.6%)	13 (68.4%)	7 (77.7%)
Live birth	75 (68.2%)	48 (73.8%)	9 (50%)	3 (42.8%)	10 (76.9%)	5 (71.4%)

Table 3. Predictors of SSR success according to ethylogical factors

	Whole Cohort (44.1%) SSR (225) / SRF (285)	Idiopathic (36.4%) SSR (125) / SRF (218)	Klinefelter (49.3%) SSR (37) / SRF (38)	Y chromosome micro deletion (60%) SSR (24) / SRF (16)	Cryptorchidism (77.1%) SSR (27) / SRF (8)	Mumps orchitis (70.5%) SSR (12) / SRF (5)
Age (years)	$\begin{array}{c} 30.96 \pm 4.27 * \\ 32.92 \pm 3.96 * \end{array}$	30.8 ± 3.6*/ 34.43 ± 3.4*	$30.9 \pm 4.1/$ 30.9 ± 5.2	$31.9 \pm 5.8/$ 31.6 ± 5.2	$30.8 \pm 3.6/$ 32.1 ± 5.2	$31.3 \pm 3.7/$ 32.3 ± 2.1
FSH (IU/L)	$\begin{array}{c} 20.9 \pm 16.7 / \\ 18.6 \pm 14.8 \end{array}$	$15.5 \pm 11.8/$ 12.7 ± 10.8	$37.6 \pm 13.9/$ 40.5 ± 14.8	$17.1 \pm 7.8/$ 15.4 ± 8.5	$20.6 \pm 6.1/$ 18.5 ± 3.2	$21.7 \pm 11.8/$ 21.5 ± 13.3
LH (IU/L)	12.3 ±8.3/ 10.5 ± 8.2	7.7 ± 4.8/ 7.8 ± 5.3	$24.8 \pm 8.4/$ 22.2 ± 9.6	9.1 ± 4.4/ 8.6 ± 4.1	$11.9 \pm 4.4/$ 12.5 ± 1.7	11.7 ± 5.6/ 12.9 ± 4.7
Testesteron (ng/mL)	$9.8 \pm 5.2/$ 9.4 ± 6.3	9.8 ± 6.1/ 9.4 ± 6.2	$5.5 \pm 4.2/$ 5.5 ± 4.1	$\begin{array}{c} 13.1 \pm 4.3 / \\ 12.7 \pm 4.6 \end{array}$	$10.5 \pm 1.6/$ 11.3 ± 1.1	$\begin{array}{c} 10.3 \pm 4.1 / \\ 9.8 \pm 6.7 \end{array}$
Left Testis Volume (mL)		$7.9 \pm 2.91/$ 7.3 ± 3.4	$2.1 \pm 0.6/$ 2.2 ± 0.7	8 ± 2.4/ 7.3 ± 2.2	5.3 ± 1.4*/ 2.6 ± 0.7*	5.4 ± 1.6*/ 3.2 ± 1.2*
Right Testis Volume (mL)	$6.3 \pm 3.7/$ 6.1 ± 3.5	7.7 ± 3/ 7.2 ± 3.4	$2.3 \pm 0.6/$ 2.1 ± 0.7	8.4 ± 2.3/ 7.1 ± 2.5	6.1 ± 1.3*/ 3.4 ± 0.7*	5.5 ± 1.7*/ 2.4 ± 1.2*

SSR, successful sperm retrieval; SRF, sperm retrieval failure

Results Between Age, Testicular Volume and SSR in Patients Undergoing Microtese

There was a negative correlation between age and SSR rates in the idiopathic patient group (t:-0.27; p<0.01). There was a positive correlation between testicular volume and SSR rates in patients with cryptorchidism (right: t:0.8; p=0.003; left: t:0.72; P:0.002) and mumps orchitis (right: t:0.76; p<0.01; left: t:0.76; p:0.003).

DISCUSSION

The factors affecting the treatment in NOA patients who underwent ICSI after TESE treatment have always been a subject investigated by researchers interested in infertility [9]. In the studies performed, microTESE is considered to be the most successful of the TESE methods performed for ICSI. While the SSR rate is between 16.7-45% in patients who underwent C-TESE, this rate is between 42.9-63% in patients who underwent microTESE and the rate of finding live spermatozoa is approximately 1.5 times higher compared to C-TESE [9]. In our study, SSR rate was found to be 44.1%. SSR was found to be lowest in the idiopathic group and highest in the cryptorchidism group.

In one study, it was found that age had no effect on SSR in microTESE, whereas in other studies, it was shown that TESE performed at an early age had better SSR rates than TESE performed at an older age [10,11]. In our study, early TESE in patients with idiopathic NOA resulted in better SSR rates.

In the literature, it has been shown that a testicular volume has no effect on sperm detection rates and that similar success can be achieved even in testicular volumes below 2 ml [12]. Nevertheless, many studies have reported that microTESE success is higher in patients with larger testicular volume. Corona et al. reported that the SSR rate was significantly higher in NOA with testicular volume >12 cc compared to patients with testicular volume <12 cc [13]. In our study, it was observed that SSR rate was affected by testicular volume. This was especially significant in patients with cryptorchidism and mumps orchitis. We think that age and testicular volume are important factors for SSR.

Studies on the factors affecting the results of microTESE have been conducted primarily on SSR. In this study, we evaluated the results of ICSI and microTESE treatments in NOA patients according to the etiological factors. The overall fertilization, clinical pregnancy and live birth rates for all NOA patients were 73.3%, 66.6%, and 68.2%, respectively, with no difference between groups. In another study in which these factors were analyzed, clinical pregnancy rates were 39% and live birth rates were 39%. No effect of clinical characteristics and hormone levels on ICSI was found [14]. In a study related to fertilization, clinical pregnancy, and live birth rates, these rates were found to be higher in patients with orchitis among the etiological factors, whereas these rates were found to be the lowest in patients with YCMDs [15]. In our study, SSR rates were higher in patients with YCMD and KS compared to other similar studies in the literature.

There is a relationship between deletion localisation and SSR rate in YCMD patients. No sperm is observed in AZFa and AZFb microdeletion patients. In patients with AZFc microdeletion, there is a possibility of spermatozoa [16]. SSR is 30-50% in patients with KS [17]. In our study, all patients with KS were non-mosaic KS and the SSR rate in patients with YCMD and KS was found to be similar to the literature.

Zang et al. [15] reported that clinical pregnancy and live birth rates of 46.9% and 40.6% in patients with idiopathic NOA, 54.4% and 50.4% in patients with KS, 20.3% and 18.8% in patients with YCMDs, 53.9% and 46.2% in patients with cryptorchidism, respectively. In our study, the clinical pregnancy rate in the general cohort was 66.6% and the live birth rate was 68.2%. When analyzed between groups, the highest clinical pregnancy rate was observed in mumps orchitis at 77.7%, and the lowest was observed in the YCMDs group at 46.6%. In terms of live birth rate, the highest pregnancy rate was observed in patients with cryptorchidism at 76.9% and the lowest was observed in the YCMDs patient group at 42.8%. The higher clinical pregnancy and live birth rate in YCMDs patients compared to the literature is due to the fact that, unlike other studies, both fresh and frozen microTESE were performed in NOA patients instead of only fresh MTESE. We think that this led to higher clinical pregnancy and live birth rates.

There are some limitations in our study. The data of the patients were collected retrospectively. In addition, etiological factors were classified under only 5 main groups. Other rare factors that cause NOA were not included in the study.

CONCLUSION

Etiological factors have an important role in terms of SSR in NOA patients. Among the etiological factors, idiopathic NOA patients have the lowest SSR rate. Age and testicular volume are important parameters for SSR in idiopathic and acquired NOA patients. Our study showed that the etiological factors affect the success of microTESE and ICSI in NOA patients.

Consent to Participate: For this type of retrospective study, formal consent is not required.

Inform of Publication: The results of the study were not published in full or in part in the form of an abstract.

Research Involving Human Participants and/or Animals: This article does not contain any studies with animals performed by any of the authors. All procedures performed in studies involving human participants were by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of Interest: The authors declare no competing interests.

No artificial intelligence was used in the writing of our study.

Ethics Approval: The study was approved by The University of Health Sciences, IzmırTepecik Training and Research Hospital Ethical Committee, Izmır, Türkiye (Decision No: 2024/02-19, Date: 04.03.2024).

Authors Contributions; Conception: YA, MZK, AHİ; Design: YA, MZK, AHİ; Supervision: YA, MZK; Fundings: -; Materials: -; Data Collection: ED,YA; Analysis: MZK, ED; Literature Review: YA, ED; Writer: YA, ED; Critical Review: MZK, YA, AHİ.

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How to Cite;

Arikan Y, Dumanlı E, İnan AH, Keskin MZ (2024) Evaluation of the Results of Intracytoplasmic Sperm Injection and Microdissection Testicular Sperm Extraction Treatments in Patients with Nonobstructive Azoospermia According to Etiological Factors: A Retrospective Analysis. Eur J Ther. 30(5):645-651. <u>https://doi.org/10.58600/eurjther2193</u>