ORIGINAL RESEARCH

Outcomes of Surgical Sperm Retrieval for Non-obstructive Azoospermia: A Single-Center Experience

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Objective: To evaluate the sperm retrieval rate and factors influencing its success among patients who undergo conventional or microsurgical testicular sperm extraction (TESE) for non-obstructive azoospermia.
Methods: Data were from 223 consecutive patients who underwent conventional or microsurgical TESE from August 2011 to January 2021 under two urologists of the center. Data regarding age, follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, estradiol, testicular size, histopathology, surgical technique, and sperm retrieval were collected. Patients with obstructive azoospermia, repeated TESE procedure, and those who underwent TESE for oncofertility were excluded. Using simple logistic regression analysis, the relationship of the different factors to successful sperm retrieval was computed as odds ratio.
Results: The overall surgical sperm retrieval rate was found to be 65.71%. The odds ratio of successful sperm retrieval were 1.04 (95% CI 1.00-1.09) for age, 0.94 (95% CI 0.91-0.97) for FSH, 0.93 (95% CI 0.87-0.99) for LH, 1.24 (95% CI 0.99-1.55) for testosterone, and 0.93 (95% CI 0.88-0.98) for estradiol. Decreased testicular size was also associated significantly with lower sperm retrieval rate (OR 0.22, 95% CI 0.09-0.56). Histopathologic pattern and surgical technique were also significantly associated with successful sperm retrieval.
Conclusion: The surgical sperm retrieval rate in this institution is comparable to the global surgical sperm retrieval rate. Age, FSH, LH, estradiol, testicular size, histopathologic pattern and surgical technique were found to have significant association to successful surgical sperm retrieval.

Key words: Non-obstructive azoospermia, surgical sperm retrieval, male infertility, testicular sperm extraction (TESE), micro-TESE

Introduction

Azoospermia affects 1% of men and 10 to 15% of infertile males.[1] It is defined as the absence of sperm in the semen. There are many etiologic causes of azoospermia but the condition is generally divided into obstructive and non-obstructive types. As the name implies, surgical sperm retrieval is defined as the retrieval of sperm from the epididymis or testicles and the procedure is used to assist conception in cases of male factor infertility. The retrieved sperm is then used for fertilization or cryopreserved for future fertilization treatment through intra-

cytoplasmic sperm injection (ICSI). In obstructive azoospermia, surgical sperm retrieval rate (SSRR) is nearly 100%,[2,3] but is not the case for non-obstructive azoospermia (NOA). A systematic review done by Corona, et al.[4] showed that the mean surgical sperm retrieval rate (SSRR) for testicular sperm extraction (TESE) was 47%.

Schoor, et al.[5] reported that in 89% of men with NOA, follicle stimulating hormone (FSH) was greater than 7.6 mIU/mL and a testicular long axis of less than 4.6 cm. Multiple factors have also been implicated in predicting the successful retrieval of sperm among men with NOA. Initial endocrine screening tests for azoospermia include total testosterone, sex-hormone binding globulin, albumin, luteinizing hormone (LH), FSH, and estradiol. However, there have been conflicting results regarding the associated factors affecting the SSRR. For example, Corona, et al.[4] showed that SSRR was not associated with age and hormonal factors, but associated with testicular size. Meanwhile, Wang, et al.[6] showed that FSH and testicular volume had low predictive values for SSRR. Salehi, et al.[7] classified histopathological findings into three groups, namely, sertoli-cell only (SCO), maturation arrest (MA), and hypospermatogenesis (HS). They also found that increased FSH and small testicular size were associated with decreased SSRR, while age, testosterone, and prolactin were not associated with SSRR.

There have been several surgical techniques described to recover sperm from men with non-obstructive azoospermia. These include testicular sperm aspiration, open or conventional testicular sperm extraction (cTESE), and microdissection testicular sperm extraction (mTESE).[8,9] More recently, cTESE and mTESE have been compared to determine which is the more efficient technique in the recovery of sperm from NOA.[4,10] Although the latest meta-analysis has shown no superiority of mTESE over cTESE, more robust studies and well-designed randomized controlled trials are required to give a more judicious interpretation of results.[4,10] On the other hand, Bernie, et al. reported in their meta-analysis that SSRR was higher for mTESE compared to cTESE.[11] The American Urological Association (AUA) and the American Society for Reproductive Medicine jointly recommended that mTESE should be performed for men with NOA undergoing surgical sperm retrieval.[12]

In the local setting, Salvaña, et al.[13] reviewed 46 patients who underwent cTESE in this institution from 2012 to 2016. They found no significant relationship between successful TESE and age, FSH, LH and total testosterone. Furthermore, a successful SSRR of 80.4% was reported. There are no other local studies SSRR among men with azoospermia.

The primary objective of this study was to determine the SSRR among patients who underwent cTESE or mTESE for NOA. Secondary objectives were to determine the SSRR for each of the different histopathological findings and the factors that are associated with successful sperm retrieval among patients who undergo cTESE or mTESE for NOA.

Methods

This is a retrospective cross-sectional study of patients who underwent cTESE or mTESE for NOA from August 2011 to January 2021 in the Institute under two urologists. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the hospital's Institutional Ethics Review Committee (SL-21019).

The presence of azoospermia was confirmed by at least two semen analyses. All patients without any age restriction who underwent cTESE or mTESE at the institution from August 2011 to January 2021 under two urologists were included in the study. Exclusion criteria were the following: 1. Patients with obstructive azoospermia; 2. those who underwent a previous TESE; and 3. those who underwent TESE for oncofertility (e.g. underwent TESE for fertility preservation prior to, during, or after chemotherapy or radiation therapy for any reason). The latest serum FSH, LH, testosterone and estradiol levels prior to TESE were included which were collected through patient's medical records. Testicular size measurement, histopathology, surgical technique, sperm retrieval, were collected through medical records.

Testicular size was measured through an orchidometer, a caliper or through intraoperative

measurement. An orchidometer can be used as a practical and economical alternative to ultrasound measurement as it is rapid, accurate, and with values correlating significantly to ultrasound and intraoperative measurement.[14,15] Doria, et al.[16] reported on the average testicular sizes of Filipino young adults and found that the lower limit for the average testicular size was 3.50 cm. Testicular size was thus classified as normal if long axis was greater than 3.5 cm, and decreased, if otherwise.

There are a number of different TESE techniques which depend on the surgeon's judgment and preference. The most common TESE procedures done in this institution are cTESE and mTESE. In cTESE, the patient is placed supine. Scrotum is opened and testis is exposed. Avascular area of the tunica is incised and testicular tissue is excised, crushed, and examined under a microscope. This is repeated in multiple sites all over the testis until sperm is found or the entire testicular surface has been explored. Testicular tissue is also sent for histopathology. Another option is to make a long incision in the tunica and the testis is bivalved to expose the testicular parenchyma, and the testis is explored in an orderly fashion. If no sperm is retrieved after adequate exploration, the same procedure is repeated on the contralateral testis, followed by hemostasis and closure. In mTESE, the scrotum is incised and testis is exposed. The tunica is bivalved and dilated tubules seen in the protruding parenchyma is biopsied and checked for sperm with the aid of an operating microscope. If now sperm is found, the contralateral testis is explored the same way. The procedure was considered positive if sperm was retrieved, and negative if otherwise.[8] Pathological diagnosis was determined by an experienced pathologist and categorized as HS, MA or SCO.

A minimum sample size of 132 was required to achieve 80% power and 95% confidence level to address the objectives of this study, given an expected frequency of 47%[4], 5% precision, and finite population correction factor of 200. This sample size would have at least 80% power for detecting the differences in sperm retrieval between the different factors (e.g. age, FSH, LH, total testosterone, estradiol, testicular size, histopathologic findings and surgical technique) included in the study. Overall SSRR was determined by dividing the total number of procedures with successful surgical sperm retrieval by the total number of procedures, which was also done for the different histopathologic findings. For the relationship of the different factors to SSRR, simple logistic regression analysis was used. Alpha is 0.05 and p-values less than 0.05 was considered as statistically significant. Stata SE version 14.2 for Windows was the statistical software used.

Results

Characteristics of Participants

From August 2011 to January 2021, a total of 287 patients underwent cTESE or mTESE, and of these, 223 patients underwent cTESE or mTESE under two urologists. After excluding 83 patients who underwent repeat SSR, and those who underwent SSR for obstructive azoospermia or oncofertility, a total of 140 patients were analyzed (Figure 1). Table 1 shows the characteristics of the study participants. The mean age of the study participants was 39.5±10.2. The mean FSH, LH, testosterone and estradiol were 17.86±14.1, 8.38±5.89, 3.58±1.88 and 28.21±10.14, respectively. For testicular size, 74/128 (62.7%) had decreased testicular size while 44/128 (37.3%) had normal testicular size. On testicular biopsy, 75/137 (54.7%) showed HS, 46/137 (33.6%) showed SCO, 2/137 (1.5%) showed MA, and 14/137 (10.2%) showed a mixed histology. For the mixed histology, all were mixed HS and SCO, except for one case which was mixed MA and SCO. For the surgical technique, overall, 92/140 (65.7%) and 48 (34.29%) underwent cTESE and mTESE, respectively.

Surgical Sperm Retrieval Rate Overall, by Histopathology and Surgical Technique

The overall SSRR was found to be 65.71% (95% CI 57.38-73.18) (Table 2). Based on histopathology, the SSRR were 96% (95% CI 88.13-98.73), 19.57% (95% CI 10.37-33.84), 50% (95% CI 1.88-98.12) and 64.29% (95% CI 36.43-84.97) for HS, SCO, MA, and mixed histology, respectively. Based on surgical technique, the SSRR were 73.91% (95% CI 63.86-81.96) and 50%

(95% CI 35.97-64.03) for patients who underwent cTESE and mTESE, respectively.

Factors Associated with Surgical Sperm Retrieval Rate

The factors associated with SSRR were age, FSH, LH, estradiol, testicular size, histopathology and surgical technique ($p<0.05$; see Table 3). Of the continuous factors explored, there was positive association between age (years) and successful surgical sperm retrieval, while there was negative association between FSH, LH, estradiol and surgical sperm retrieval. On the other hand, the odds of successful surgical sperm retrieval was lower among those with decreased testicular size compared to those with normal size (OR 0.22, 95% CI 0.09-0.56). By histopathology, compared to those with HS, the odds of successful sperm retrieval was lower among those with SCO (OR 0.01, 95% CI 0.002-0.04), MA (OR 0.04, 95% CI 0.002-0.84) and mixed (OR 0.08, 95% CI 0.02-0.37). Lastly, by surgical technique, the odds of SSRR was lower among those with mTESE than cTESE (OR 0.35, 95% CI 0.17-0.73).

Table 1. Characteristics of participants.

Characteristics	Total (N=140)
Age in years (mean, [SD])	39.5 [10.2]
FSH in mIU/mL (mean, [SD])	17.86 [14.10]
LH in mIU/mL (mean, [SD])	8.38 [5.89]
Testosterone in ng/mL (mean, [SD])	3.58 [1.88]
Estradiol in pg/mL (mean, [SD])	28.21 [10.14]
Testicular size (n, [%])	
Decreased	74 [62.7]
Normal	44 [37.3]
Histopathology (n, [%])	
Hypospermatogenesis	75 [54.7]
Sertoli-cell only	46 [33.6]
Maturation arrest	2 [1.5]
Mixed	14 [10.2]
Surgical technique (n, [%])	
cTESE	92 [65.7]
mTESE	48 [34.3]

Abbreviations: TESE, Testicular Sperm Extraction; FSH, Follicle Stimulating Hormone; LH, Luteinizing hormone

Table 2. Surgical sperm retrieval rate according to study variable (%, [95% CI])

Variables	Surgical Sperm Retrieval Rate
Overall (N=140)	65.71% (57.38-73.18)
By histopathology	
Hypospermatogenesis (n=75)	96.00% (88.13-98.73)
Sertoli-Cell Only (n=46)	19.57% (10.37-33.84)
Maturation Arrest (n=2)	50.00% (1.88-98.12)
Mixed (n=14)	64.29% (36.43-84.97)
By surgical technique	
cTESE (n=68)	73.91% (63.86-81.96)
mTESE (n=48)	50.00% (35.97-64.03)

Abbreviations: cTESE, Conventional Testicular Sperm Extraction; mTESE, Microdissection Testicular Sperm Extraction

Discussion

The overall SSRR at this institution under two urologists was 65.71%. This was lower than the previously reported SSRR of 80.4% by another study[13] also done in this institution. In their study, a large number of patients were excluded because of incomplete data which could have affected their reported increased SSRR. Nonetheless, current SSRR was still higher than the reported mean SSRR in the systematic review by Corona et al. of 47%.[4]

For the different histopathological types, current SSRR of 19.57%, 50% and 96% for SCO, MA and HS, respectively, were comparable to those reported by Salehi, et al.[7] which were 21.6%, 43.5% and 94% for SCO, MA and HS, respectively. Oddly, most of the histopathological findings of current patients were of HS and SCO, and only two patients had MA as histopathologic diagnosis. Additional studies to investigate the association of epidemiological factors and histopathology can be done but are outside the scope of this study.

Another unusual finding in this study was the relationship of age to SSRR. Patients who were sperm retrieval positive had a higher mean age than patients who were sperm retrieval negative (40.77 vs 37.06, OR 1.04, $p=0.46$), which means that success rate increases per unit increase in age. This seems counterintuitive, as there is data that semen parameters worsen with increased age. However, in the present study, the median age was 37 years

Table 3. Relationship of factors to surgical sperm retrieval rate.

Characteristics	OR (95% CI)	p-value
Age in years (mean, [SD])	1.04 (1.00-1.09)	0.046
FSH in mIU/mL (mean, [SD])	0.94 (0.91-0.97)	<0.001
LH in mIU/mL (mean, [SD])	0.93 (0.87-0.99)	0.025
Testosterone in ng/mL (mean, [SD])	1.24 (0.99-1.55)	0.061
Estradiol in pg/mL (mean, [SD])	0.93 (0.88-0.98)	0.005
Testicular size (n, [%])		
Decreased	0.22 (0.09-0.56)[a]	0.002
Normal	REFERENCE	
Histopathology (n, [%])		
Hypospermatogenesis	REFERENCE	
Sertoli-cell only	0.01 (0.002-0.04)[b]	<0.001
Maturation arrest	0.04 (0.002-0.84)[b]	0.038
Mixed	0.08 (0.02-0.37)[b]	0.001
Surgical technique (n, [%])		
cTESE	REFERENCE	
mTESE	0.35 (0.17-0.73)[c]	0.005

Abbreviations: TESE, Testicular Sperm Extraction; FSH, Follicle Stimulating Hormone; LH, Luteinizing hormone
[a] reference: normal
[b] reference: hypospermatogenesis
[c] reference: cTESE

old, and majority (88/140) of participants were less than 40 years old, 23.6% (33/140) were in their forties, and only 13.6% (19/140) were aged fifty and above. Decreased semen parameters, sperm concentration and sperm DNA fragmentation were found in men 50 years and above.[17] Although age was a significant predictor in this study, majority of participants are not yet in the advanced paternal age in which decreased fertility rates are associated with.

Other studies have also shown the relationship of increased FSH and LH to SSRR, and is also reflected in the present study. As LH and FSH show the status of spermatogenesis from the feedback mechanism between the testis and hypothalamus and pituitary axis, elevated levels of FSH and LH indicate abnormal spermatogenesis. In the current study, the baseline mean FSH of all participants was elevated at 17.86 mIU/mL, which is expected as study population included patients who are diagnosed with NOA. However, there is a statistically significant difference between the FSH levels of patients who were sperm retrieval positive and patients who were sperm retrieval negative and success rates decreased by 6% for every unit increase in FSH. Likewise, baseline mean LH was also elevated at 8.38 mIU/mL and the difference of mean LH between sperm retrieval positive and sperm retrieval negative patients were also statistically significant.

Estradiol's relationship to sperm retrieval is controversial and previous studies show conflicting results. The current study shows that there is a significant difference between the levels of Estradiol between sperm retrieval positive and sperm retrieval negative patients, and SSRR decreases by 7% per unit increase in Estradiol. This might mean that to optimize TESE outcomes, lowering the estradiol levels of patients must be attempted. It should be noted, however, that the estradiol levels of these patients are within normal limits, and the optimal level of estradiol might need further investigation. A study by Salama, et al.[18] divided patients with non-obstructive azoospermia into those with

high, normal, and low estradiol levels, and they recommended that estradiol should be included in the evaluation of male infertility because not only will it aid in diagnosis, it also has an impact in treatment decisions in hormonal therapy. For patients with a testosterone/estradiol ratio of <10 with elevated estradiol and low testosterone, aromatase inhibitors are usually recommended, while infertile men with normal estradiol would be candidates for clomiphene citrate rather than aromatase inhibitors.

The relationship between testicular volume and male infertility is also well-known, and is also reflected in the present data. Based on those results, a patient with normal testicular volume is 4.5 times more likely to have successful sperm retrieval. Although low testicular volumes are associated in NOA,[19] the meta-analysis done by Li, et al.[20], showed testicular volume low predictive value for successful surgical sperm retrieval and suggest that low testicular volume should not be a contraindication for mTESE. Meanwhile, cTESE had a higher surgical sperm retrieval rate of 73.91% vs 50% in mTESE, with cTESE 2.86 times more likely to have positive sperm retrieval compared to mTESE. A possible explanation might be that the decision to do cTESE versus mTESE is surgeon dependent. Patients whom they deem clinically to less likely be successful in cTESE will be planned to undergo mTESE instead (e.g. patients with Klinefelter's syndrome, small testicular size, highly elevated FSH levels, etc.). Therefore, this selection bias may be one reason why the SSRR is lower in mTESE than cTESE in the present study. Additional randomized controlled trials are suggested to prove unbiased results.

For histopathology, patients with HS are 100 times more likely to have successful sperm retrieval compared to SCO, and 25 times more likely to have successful sperm retrieval than patients with MA. The clinical implication of this result is that patients with SCO or MA might be better candidates for mTESE rather than cTESE. Li, et al.[20] also described that histopathology might be predictive of successful surgical sperm retrieval, where patients with HS had high SSRR, while patients with SCOS had low likelihood of successful sperm retrieval. Despite these findings, they still do not consider the presence of severe histopathological patterns as contraindications for performing mTESE, as there could still be normal spermatogenesis in other parts of the testis.

The aurhors also recommend testicular biopsy during TESE for three reasons: 1) to confirm if the patient has NOA rather than obstructive azoospermia (OA); 2) to predict successful sperm retrieval in future TESE procedures; 3) to rule out CIS of the testis as infertility is a risk factor.[21]

Strengths of this study include an adequate sample size to meet the primary objective of the study and inclusion of different hormones as study variables. However, as this is a cross-sectional study, causal relationship is difficult to establish. Additional prospective studies to establish causal relationship is recommended. It is also interesting that when multiple regression analysis was done on present data, when adjusted for the effects of other factors, only FSH, estradiol and histopathologic diagnosis were related to sperm retrieval. Ideally, this can be done but due to limited sample size, adjusted analysis will be underpowered. Another study with greater sample size is recommended to be able to do adjusted analysis. Other areas of possible research include outcome of fertility treatments using the retrieved sperm which would further establish the efficiency of these surgical retrieval procedures.

Conclusion

The SSRR at this institution is comparable to the global SSRR. Age, FSH, LH, estradiol, testicular size, histopathologic pattern and surgical technique were found to have significant association to successful surgical sperm retrieval.

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