ORIGINAL RESEARCH

Predictive Factors of Sperm Retrieval in Non-obstructive Azoospermia Using Conventional Testicular Sperm Extraction (TESE) - A Retrospective, Single Center Study

Jethro Salvaña, MD; Jerome Kyle San Jose, MD, FPUA
Nikko J. Magsanoc, MD, FPUA and Dennis G. Lusaya, MD, FPUA

Institute of Urology, St. Luke's Medical Center Global City

Testicular sperm extraction (TESE) allows for the possibility of intracytoplasmic sperm injection (ICSI) to achieve fertility but is an invasive procedure, and failed testicular sperm extraction has brought significant emotional and financial consequences to couples.

Objective: This study aims to determine the relationship of pre-operative work-up variables such as age, FSH, LH, total testosterone in the success or failure of TESE in patients by 2 urologists with non-obstructive azoospermia in St. Luke's Medical Center-Global City.

Materials and Methods: This is a retrospective chart review of patients presenting with infertility, diagnosed to have non-obstructive azoospermia and underwent conventional TESE from 2012 to 2016 at St. Luke's Medical Center-Global City. Patients were adult males presenting with infertility undergoing conventional TESE, known to have non-obstructive azoospermia. TESE outcomes of 46 patients with complete parametric laboratory exams warranted for this study were used for statistical analysis.

Results: T-test results showed no sufficient evidence to conclude that there is significant difference in mean age (p-value = 0.509), mean LH (p-value = 0.549), mean FSH (p-value = 0.81), and total testosterone (p-value = 0.824) between patients who had successful and failed TESE. Fisher's exact test showed that most patients (90.3%) who have successful TESE outcome have normal FSH values. Logistic regression results showed no sufficient evidence to conclude that there is significant relationship between TESE outcome and age (p-value = 0.503), LH (p-value = 0.542), FSH (p-value = 0.098), and TT (p-value = 0.819). Patients with normal FSH values are 6.22 times more likely to have successful TESE outcomes compared to patients with elevated FSH values. However, logistic regression results showed no sufficient evidence to conclude that there is significant relationship between successful TESE outcome and normal LH values (OR = 2.0, p-value = 0.493).

Conclusion: The preoperative factors for predicting success and failure of sperm retrieval during TESE, including total testosterone, FSH and LH levels, were examined in this study, may not fully give an estimation of the chances of obtaining spermatozoa in patients with NOA. Accordingly, the combination and simultaneous interpretation of the other factors not present in this study, such as testicular volume, histopathological patterns, and karyotyping, would likely help to provide a more accurate prediction of success and failure and subsequently help the clinician to pursue the appropriate methods of treatment for these patients.

Key words: sperm retrieval, non-obstructive azoospermia, testicular sperm extraction

Introduction

Azoospermia is defined as the complete absence of the sperm in the ejaculate. For couples affected with azoospermia, the surgical extraction of sperm has provided new possibilities for achieving pregnancy. While TESE allows for the possibility of intracytoplasmic sperm injection (ICSI) to achieve fertility, it still is an invasive procedure, and failed testicular sperm extraction has brought significant emotional and financial consequences to couples. The prediction of success in testicular sperm extraction has therefore become increasingly important. There are no local studies that have reviewed predictive factors in the use of TESE among patients with nonobstructive azoospermia. This study aimed to determine the relationship of pre-operative work-up variables in predicting the success or failure of TESE among patients with non-obstructive azoospermia in St. Luke's Medical Center - Global City.

Review of Related Literature

Assisted reproduction techniques have changed the approach to evaluation and management of couples with azoospermia as a cause of infertility. Intracytoplasmic sperm injection (ICSI) is now possible with sperm extracted from the patient rather than relying exclusively on donor sperm. Azoospermia, the inability to detect spermatozoa in the ejaculate after centrifugation at x400 magnification in two separate occasions[1] is said to be present in 1% of all men and 10-15% of infertile males.[2] Surgical sperm retrieval methods have been described for application in cases of either obstructive or non-obstructive azoospermia. Percutaneous epididymal sperm aspiration, microsurgical epididymal sperm aspiration and testicular sperm aspiration (TESA) are used in obstructive azoospermia cases, while TESA and testicular sperm extraction (TESE) are used in non-obstructive azoospermia (NOA).[3] Non-obstructive azoospermia, accounting for 60% of azoospermic men[4], may be due to a variety of etiologies, including genetic disorders, cryptorchidism, or exposure to radiation and toxins.[2] The existence of minute foci of active spermatogenesis has made it possible to retrieve testicular spermatozoa from some men afflicted with NOA. As such, multiple focal testicular sperm retrieval may be done to ensure the presence of sperm in testicular samples.[5] An open single biopsy TESE is known as the main procedure for NOA because of the assumption of multiple foci of spermatogenesis distributed throughout the testis. A single incision is done, resulting in a large volume of tissue and presumably a high retrieval rate, but results in loss of testicular volume. Multiple TESE has therefore been strongly recommended to increase the retrieval yield, and has been shown to be more effective than needle biopsy in patients with NOA[6,7], although the most appropriate number of samples to be taken has remained controversial.[3]

In one study of testicular sperm extraction with ICSI in NOA, it was shown that 6 of 16 (38%) of couples will not have sperm retrieved with TESE and may undergo an unnecessary ICSI procedure.[8] In another study concerning microsurgical TESE, it was reported that sperm retrieval rates were still at around 50% for patients with NOA.[9] A reliable prediction method for successful sperm retrieval is needed to avoid unnecessary surgeries.

Multiple studies have already attempted to describe the diagnostic and predictive value of non-invasive preoperative parameters in predicting successful sperm retrieval. In a study for microsurgical TESE, FSH, total testosterone and serum inhibin B were found to be the most influential preoperative factors.[9] Another study of 85 patients who underwent multiple TESE for NOA concluded that serum FSH and serum inhibin B are useful markers, and that the latter has a high specificity when combined with the former.[10] A literature review of prognostic factors for sperm retrieval in NOA, conducted by Glina and Vieira[11] yielded no reliable positive prognostic factors that guarantee sperm recovery for such patients, although it concluded that above a cut-off value of 19.4mIU/mL of FSH, sperm was not found. The mean inhibin B levels were not found to differ significantly between successful and failed sperm retrieval groups studied. The authors also concluded that the only negative prognostic factor

is the presence of AZFa and AZFb microdeletions in the long arm of the Y chromosome. In a study of 123 patients with NOA, Friedler et al. also concluded that there is a lack of efficient noninvasive parameters to predict sperm retrieval in NOA.[12]

Materials and Methods

This is a retrospective chart review of patients presenting with infertility, diagnosed to have non-obstructive azoospermia and underwent conventional TESE from 2012 to 2016 at St. Luke's Medical Center, Global City. Patients should be adult males presenting with infertility undergoing conventional TESE, known to have non-obstructive azoospermia. Patients will be limited to patients managed by two selected Urologists. One hundred one (101) patient charts were collected initially for the study, however, only 46 of them underwent the complete parametric laboratory exams needed for this study. Patients with known genetic abnormalities and those who underwent other procedures such as microTESE, TESA, percutaneous epididymal sperm aspiration were excluded in this study. TESE was rendered as follows: Under local or regional anesthesia, TESE was done with an incision on the scrotum, down to the scrotal sac. The testis was exposed and excision of seminiferous tubules and the specimen was viewed under microscopy for the presence of motile sperm. If the specimen was negative for sperm, then subsequent samples were taken from other locations. The procedure was terminated on retrieval of sperm or if samples from all quadrants had been examined for the presence or absence of testicular sperm. TESE Success is defined as demonstration of at least one (1) spermatozoa count via light microscope whereas TESE failure is defined as non demonstration of spermatozoa or zero (0) count via light microscope.

Results

There were 46 patients with Non-obstructive Azoospermia who had recorded TESE outcomes and information on their laboratory values on luteinizing hormone (LH), follicle stimulating hormone (FSH), and total testosterone (TT). Of these, 9 patients had failed TESE outcome. T-test results showed no sufficient evidence to conclude that there is significant difference in mean age (p-value = 0.509), mean LH (p-value = 0.549), mean FSH (p-value = 0.81), and total testosterone (p-value = 0.824) between patients who had successful and failed TESE. (Table 1)

Fisher's exact test showed significant relationship between status of FSH and TESE outcomes (p-value = 0.042). This means that most patients (90.3%) who have successful TESE outcome have normal FSH values (Table 2).

Table 1. Mean pre-operative workup variables by TESE outcome

Variables	TESE outcome	n	Mean	Mean Difference	P-value
Age	success	37	44 years old	2.77	0.509
	fail	9	42 years old		
Luteinizing hormone	success	28	9.72 m/U/mL	2.86	0.549
	fail	5	12.58 m/U/mL		
Follicle stimulating hormone	success	37	14.09 m/U/mL	10.66	0.81
	fail	9	24.75 m/U/mL		
Total testosterone	success	36	3.64 ng/ml	0.1997	0.824
	fail	9	3.44 ng/ml		

Table 2. Proportion of patients with successful TESE outcomes by status of workup variables (Normal versus Elevated)

	Success n (%)	Failure n (%)	Fisher's Exact Test (p-value)
Luteinizing hormone			
Normal	21 (87.5%)	3 (12.5%)	0.597
Elevated	7 (77.8%)	2 (22.2%)	
Follicle stimulating hormone			
Normal	28 (90.3%)	3 (9.7%)	0.042
Elevated	9 (60.0%)	6 (40.0%)	
Total testosterone			
Normal	34 (79.1%)	9 (20.9%)	1
Elevated	2 (100.0%)	0 (0.0%)	

Logistic regression was also done per individual variable to test if significant relationship exists between each Pre-operative workup variable and TESE outcome. Logistic regression results showed no sufficient evidence to conclude that there is significant relationship between TESE outcome and age (p-value = 0.503), LH (p-value = 0.542), FSH (p-value= 0.098), and TT (p-value = 0.819). (Table 3)

Table 3. Logistic regression on TESE outcome and pre-operative workup variables

Variables	Odds Ratio	p-value
Age	1.027	0.503
Luteinizing hormone	0.974	0.542
Follicle stimulating hormone	0.967	0.098
Total testosterone	1.039	0.819

Logistic regression was also done per based on status of Pre-operative Workup Variable to test if significant relationship exists between normal hormone values and success of TESE. Logistic regression results showed that there is significant relationship between successful TESE outcome and normal FSH (OR = 6.22, p-value = 0.023). This means that patients with normal FSH values are 6.22 times more likely to have successful TESE outcomes compared to patients with elevated FSH values. However, logistic regression results showed no sufficient evidence to conclude that there is significant relationship between successful TESE outcome and normal LH values (OR = 2.0, p-value = 0.493). (Table 4)

Table 4. Logistic regression on successful TESE outcome and normal pre-operative workup variables

Variables	Odds Ratio	p-value
Luteinizing hormone	2.0	0.493
Follicle stimulating hormone	6.22	0.023

The regression model for normal total testosterone and successful TESE outcome cannot be established since all patients who failed TESE have normal total testosterone levels. Multiple logistic regression also showed no significant relationship between TESE outcome and all Pre-work operative Work-up Variables (Table 5).

Table 5. Multiple logistic regression on TESE outcome

Variables	Odds Ratio	p-value
Age	1.001	0.970
Luteinizing hormone	0.996	0.940
Follicle stimulating hormone	0.978	0.475
Total testosterone	1.117	0.668

Discussion

In this study, the authors determined the relation of the following factors to failed or successful sperm retrieval: FSH, LH, total testosterone. Patients who had recorded TESE outcomes with preoperative workup values of concern demonstrate no significant difference in relation to the success or failure of TESE. This would mean that initial request for LH and FSH workup prior to TESE is not imperative in order to predict either the success or failure of this procedure, rather needed for diagnostic and monitoring purposes. However, present data demonstrated that a normal FSH finding would predict the success of TESE. An elevated level of FSH was observed on patients with failed TESE outcomes. This increase in the observed concentrations of the hormone was related to the spermatogenetic defect and decrease in total number of testicular germ cells in patients with NOA.

Since this is an initial study for its kind in the involved institution, it is recommended that further studies that involve more subjects be conducted in order to increase the power of the study. It is also recommended to provide standardized methods of record-keeping for patients who undergo TESE. Since this study lacks data on the final outcome which is ability of the male to impregnate, it is recommended that a long term follow up study be made. Such study should entail monitoring of pregnancy outcomes of those who underwent successful TESE.

Conclusion

In conclusion, preoperative factors for predicting success and failure of sperm retrieval during TESE, including total testosterone, FSH and LH levels, were examined in this study, may not fully give an estimation of the chances of obtaining spermatozoa in patients with NOA, but rather used as diagnostic tools for baseline monitoring purposes as well as to determine any other primary reason for being infertile. Accordingly, the combination and simultaneous interpretation of the other factors not present in this study, such as testicular volume, histopathological patterns, and karyotyping, would likely help provide a more accurate prediction of success and failure and subsequently help the clinician to pursue the appropriate methods of treatment for these patients.

References

1. Jungwirth A, et al. European Association of Urology guidelines on Male Infertility: the 2016 update. Eur Urol 2016; 62(2): 9-11.
2. Cocuzza M, Alvarenga C, Pagani R. The epidemiology and etiology of azoospermia. Clinics 2013; 68: 15-26.
3. Ishikawa T. Surgical recovery of sperm in non-obstructive azoospermia. Asian J Androl 2012; 14(1): 109-15.
4. Jarow JP, Espeland MA, Lipshultz LI. Evaluation of the azoospermic patient. J Urol 1989; 142(1): 62-5.
5. Hauser R, et al. Multiple testicular sampling in non-obstructive azoospermia-is it necessary? Hum Reprod 1998; 13(11): 3081-5.
6. Donoso P, Tournaye H, Devroey P. Which is the best sperm retrieval technique for non-obstructive azoospermia? A systematic review. Hum Reprod Update 2007; 13(6): 539-49.
7. Tournaye H, et al. Recent concepts in the management of infertility because of non-obstructive azoospermia. Hum Reprod 1995; 10 suppl 1: 115-9.
8. Schlegel PN, et al. Testicular sperm extraction with intracytoplasmic sperm injection for non-obstructive azoospermia. Urology 1997; 49(3: 435-40.
9. Tsujimura A, et al. Prediction of successful outcome of microdissection testicular sperm extraction in men with idiopathic nonobstructive azoospermia. J Urol 2004; 172.5: 1944-7.
10. Ziaee SA, et al. Prediction of successful sperm retrieval in patients with non-obstructive azoospermia. Urology J 2009; 3(2): 92-6.
11. Glina S, Vieira M. Prognostic factors for sperm retrieval in non-obstructive azoospermia. Clinics 2013; 68: 121-4.
12. Friedler S, et al. Factors influencing the outcome of ICSI in patients with obstructive and non-obstructive azoospermia: a comparative study. Hum Reprod 2002; 17(12): 3114-21.
13. Aydin T, Sofikerim M, Yucel B, Karadag M, Tokat F. Effects of testicular histopathology on sperm retrieval rates and ICSI results in non-obstructive azoospermia. J Obstet Gynaecol 2015; 35: 829-31.