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ORIGINAL ARTICLE

Micro-testicular sperm extraction outcomes for non-obstructive azoospermia in a single large clinic in Victoria

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Aims: To evaluate the results of microdissection testicular sperm extraction (micro-TESE) and intracytoplasmic sperm injection (ICSI) for treatment of non-obstructive azoospermia (NOA).

Materials and methods: We retrospectively analysed data of 88 consecutive patients with clinical NOA who were treated with micro-TESE by a single surgeon, between August 2014 and September 2020, in Melbourne, Victoria. Upon a successful sperm retrieval, sperm was either used fresh for ICSI, frozen for future use or both. The outcome measures were sperm retrieval rate (SRR), and in vitro fertilisation (IVF)/ICSI results. Furthermore, SRR was calculated for the predominant causes and histopathological patterns.

Results: The overall SRR was 61.2%. It was significantly higher in patients with a history of cryptorchidism and other childhood diseases (100%) than in the other NOA groups ($P < 0.05$). Patients with Klinefelter syndrome had a 75% SRR. Among the different types of testicular histology, the highest SRR were noted in patients with complete hyalinisation (100%) and hypospermatogenesis (92.9%), and low with Sertoli cell-only syndrome (46.3%). The SRR has significantly increased from 33.3% in 2015–2016 to 73.6% in 2019–2020 ($P = 0.009$). Of the 52 patients with SSR, 47 underwent IVF/ICSI. Fertilisation rate was 42.4%. Twenty-nine couples achieved at least one good-quality embryo and had embryo transfer. Nineteen achieved pregnancy (40.4%), and in three patients a miscarriage resulted.

Conclusions: This is the first report from Australia showing that micro-TESE is an effective treatment for NOA with high SRR. The increasing success rates over several years indicate the importance of surgical skill and laboratory staff experience.

KEYWORDS

azoospermia, non-obstructive [supplementary concept], infertility, male, reproductive techniques, sperm injections, intracytoplasmic, sperm retrieval

INTRODUCTION

Infertility affects about 15% of couples trying to conceive. In half of them, it may be attributed to a male factor.[1] Azoospermia occurs in 1% of men and in 10–15% of the infertile male population.[2] Non-obstructive azoospermia (NOA) is caused by testicular failure, which may be primary (testicular) or secondary to hypothalamic-pituitary dysfunction (pre-testicular). It constitutes 60–70% of all cases of azoospermia.[3]

NOA is a heterogeneous condition, with impaired spermatogenesis resulting from hypospermatogenesis, maturation arrest or Sertoli cell-only syndrome (SCOS).[1,4] Klinefelter's syndrome (KS)

and Y-chromosome microdeletions represent the most common congenital causes of NOA.[5] Acquired causes of NOA include testicular torsion, mumps orchitis, cryptorchidism and iatrogenic causes such as medications, chemotherapy and radiotherapy.[6]

Fertility management of patients with NOA relies on surgical sperm retrieval techniques. Devroey et al were the first to describe conventional testicular sperm extraction (TESE) for NOA patients in 1995.[7] Microdissection TESE (micro-TESE) followed by intracytoplasmic sperm injection (ICSI) was first described in 1999 by Schlegel et al.[8] Although some suggest that conventional TESE may yield similar overall 50% sperm retrieval rate,[9,10] micro-TESE has been associated with improved sperm retrieval rate (SRR) compared to conventional TESE[11,12] and has been adopted by international guidelines to be to the preferred method of surgical sperm retrieval.[13,14]

The ability to predict those patients with a high probability of achieving a successful sperm retrieval remains a challenge. The current literature is limited by low number of reported cases as well as lack of randomised controlled trials, and there is no single clinical finding or investigation that can accurately predict the outcome of micro-TESE.[15]

While intraoperative features using a high-powered operating microscope can predict SRR with a greater accuracy, there are a few pre-operative conditions that can reliably predict the presence of sperm in the testis. Several studies have failed to identify good prognostic factors. Follicle-stimulating hormone (FSH) level, inhibin level and scrotal duplex perfusion tests have been suggested, but all have demonstrated a relatively low predictive value for a successful TESE.[16-18] The evidence concerning the predictive value of testis volume for SRR success in patients with NOA remains equivocal. Recent data suggest that testicular volume >12.5 mL is associated with a higher SRR[12] and smaller testicular volume is associated with worse prognosis.[15]

Surgeon skill and experience (particularly when micro-TESE is used) has shown improved outcomes.[19] Furthermore, different tissue processing methods, the time, skills, and effort dedicated to the identification of spermatozoa in the testicular specimen may greatly affect the sperm retrieval rates.[20]

The aim of this study was to describe the first Australian experience with micro-TESE at a single large referral clinic in Victoria, and to identify predicting factors of successful sperm retrieval. We hypothesised that micro-TESE would be demonstrated as an effective method for the treatment of NOA and that success rates would be influenced by increased surgical experience, histological pattern and aetiology.

MATERIALS AND METHODS

We conducted a retrospective analysis of 88 consecutive patients with clinical NOA who underwent a micro-TESE by a single surgeon (author 3) in Melbourne, Australia, between August 2014 and April 2020. August 2014 is when the surgeon commenced the micro-TESE program. We chose a very strict definition of NOA with all patients meeting three criteria: (i) normal volume azoospermia on at least two semen analyses; (ii) elevated FSH; and (iii) histology consistent with NOA. Relevant clinical history was recorded, including age, history of an undescended testis, mumps orchitis, previous genito-urinary infection, radiotherapy, chemotherapy, surgical procedures or exposure to gonadotoxic agents. A clinical examination included secondary sexual characteristics, testicular size and consistency, epididymal distension, the presence of the vas deferens and varicocele. All patients had blood tests for baseline serum FSH, luteinising hormone and testosterone concentrations. The study was approved by the local institutional review board (IRB) of the Western Health Office for Research in Victoria (Project Reference: QA2021.73_RO).

As the last author was trained and mentored by Dr Peter Schlegel hence the surgical technique was as per Dr Schlegel's previously described micro-TESE operation.[21] Under general anaesthesia, a median raphe incision was made in the scrotum, the tunica vaginalis opened and the testis delivered. An equatorial incision involving the circumference was made using the surgical microscope to avoid vascular injury. Microdissection at ×15-20 magnification was then performed to expose the seminiferous tubules and select samples of testicular tissue from areas that appeared favourable for spermatogenesis. Specimens were examined by an embryologist in the operating room and analysed for the presence of sperm for live feedback to the surgeon. If viable sperm was confirmed in the laboratory, the partner's eggs were thawed and injected using ICSI. Excess sperm was cryopreserved. If there were no eggs, available sperm was cryopreserved. During the operation, a random histopathology specimen was sent for analysis and classified based on most predominant histopathological pattern by a uro-pathologist: normal spermatogenesis, hypospermatogenesis, maturation arrest, Sertoli cell-only and complete hyalinisation. Three patients with normal histology, despite clinical and biochemical suggestion of NOA, were excluded from final analysis. No major complications were noted on patient follow-up including re-operations, re-admissions, large haematoma or testicular loss.

Statistical analysis was performed using SPSS software v27 (IBM, USA). Continuous variables were compared by Student's *t*-test. Nominal variables were compared by the χ^2 test. Multivariate logistic regression analysis was performed to detect independent predictors of sperm retrieval. Successful sperm retrieval (yes/no) served as the dependent variable. Age (continuous), baseline FSH <20 (yes/no), mean testicular size <15 cc (yes/no) and aetiology one of the following, KS, Y-micro deletion, history of cryptorchidism, mumps orchitis, or gonadotoxic treatment (yes/no), served as independent variables. The significance threshold was set as $P < 0.05$.

RESULTS

During the study period, 88 men with NOA underwent micro-TESE. Three patients with clinical NOA were excluded from analysis as

their histology revealed normal spermatogenesis. Sperm was successfully retrieved in 52/85 (61.2%) men. Baseline characteristics were similar between men with and without successful sperm retrieval (Table 1).

Table 2 presents the aetiologies for azoospermia and the SRR for each aetiology. Successful sperm retrieval was achieved in all men with azoospermia due to cryptorchidism (undescended testis) and childhood diseases, such as mumps orchitis. Men with KS were also found to have high SRR (75%), while men with Y-chromosome microdeletions (AZFc) and men who were previously treated with chemotherapy had a lower SRR. Furthermore, Table 2 presents the histology results and the SRR for each histologic type. SRR was 100% in men with complete hyalinisation and very high (92.9%) in men with hypospermatogenesis.

The number of micro-TESEs has increased over the years from only eight in 2015 to 21 in 2019 and 17 in 2020 (until 31 August). The SRR has significantly increased from 33.3% (6/18) in 2015–2016 to 73.6% (28/38) in 2019–2020 (P = 0.009) (Fig. 1).

On multivariate logistic regression analysis, baseline FSH less than 20 and aetiology (childhood diseases and KS vs other diagnoses) were independent predictors of successful sperm retrieval, whereas age and testicular size less than 15 cc were not (Table 3).

Overall, 80 men underwent micro-TESE with the aim of using the sperm for in vitro fertilisation (IVF)/ICSI, while five men have undergone the procedure with the aim of freezing sperm for future fertility preservation. Sperm was successfully retrieved in 47 (58.8%) men who intended to use sperm for IVF/ICS. Overall, 29 couples achieved at least one good-quality embryo and had embryo transfer, and 19 couples achieved at least one pregnancy. Three pregnancies ended in miscarriages. Eight are ongoing and in eight a live birth occurred (Table 4).

DISCUSSION

Patients with NOA can benefit from micro-TESE in order to achieve a biological offspring. Given the variability in clinical presentations, surgical techniques and partner factors, from the literature it is difficult to identify the role of each parameter and isolate predictors of successful sperm retrieval and IVF/ICSI in patients with NOA. In the absence of uniformity in approach to selection of patients, surgical techniques and prospective trials, conclusions with regard to variables associated with SRR remain in dispute.

This is the first cohort of published micro-TESE outcomes performed in Australia by a single surgeon. Overall, our SRR of 61.2% represents higher than most reported success rates which are in the realms of 50% SRR.[22] Furthermore, it should be noted that we followed a very strict inclusion criteria to ensure purity of the data. While many papers included patients based on clinical criteria alone, we ensured that the cohort for this study included patients with abnormal histology as well. There were three patients with clinical NOA (abnormal FSH and normal volume azoospermia) in our initial cohort which were excluded due to normal spermatogenesis being found on histology. It is possible though that due to the heterogeneity of this condition, other parts of the testicle may have demonstrated other pathologies such as hypospermatogenesis. These three patients had sperm retrieved and all ended up having live births. Therefore, our success rate for sperm retrieval from a clinical standpoint is slightly higher at 62.5%.

Surgical experience may play a significant role in sperm retrieval success. It is notable that even though this particular surgeon has been trained by the inventor of the micro-TESE technique (Peter Schlegel), a learning curve exists. As previously reported by Ishikawa et al,[19] our series demonstrated that with an increase in surgical experience, success rates have improved from 33.3% in the first two years to 73.6% SRR in the last two years. Moreover, this procedure relies heavily on the skills and experience of the laboratory scientific team and embryologists. The laboratory-related technical expertise in dealing with very small amounts of tissue and identifying the rare individual sperm among the tissue cannot be underestimated. The embryology staff often spends hours searching for sperm. These skills take time to develop and so there is almost certainly a learning curve from a laboratory perspective. Patient selection is unlikely to be a factor here given that all consecutive patients with NOA who presented for treatment and consented to have surgical treatment were included in this study.

Although histopathology is considered very predictive for SRR,[23] in order to obtain it, a prior diagnostic biopsy is required. The authors, and other expert opinions, suggest that this is not recommend routinely for several reasons.[21] First, there will be

TABLE 1 Patient demographics

	Unsuccessful sperm retrieval *n* = 33	Successful sperm retrieval *n* = 52	*P*-value
Age, years	35.7 ± 5.8	35.2 ± 6.2	0.71
Mean testicular volume, mm	9.6 ± 4.8	8.7 ± 4.9	0.39
Baseline LH, IU/mL	12.9 ± 9.4	12.9 ± 8.8	0.97
Baseline FSH, IU/mL	26.3 ± 12.4	24.8 ± 14.7	0.61
Baseline testosterone, nmol/L	13.2 ± 5.3	12.7 ± 7.0	0.72

Data are presented as mean ± SD, or *n* (%).
Abbreviations: FSH, follicle-stimulating hormone; LH, luteinising hormone.

some testicular fibrosis created by the biopsy. This can make subsequent micro-TESE more difficult and is associated with a lower SRR.[21,24] Second, the small testicular tissue specimen obtained may not represent the whole testicular tissue, and different areas may have different histological patterns. Third, even a negative predictive histology of Sertoli-cells only will still result in a 47.2% SRR according to our data. Finally, it is recommended that if a diagnostic biopsy is undertaken, and subsequent micro-TESE is needed, it is best to wait 4–6 months before this is undertaken. This delay may cause further psychological distress, and may be detrimental if there is a female age factor to consider.

TABLE 2 Aetiology and histopathology of non-obstructive azoospermia patients

	Total number of patients	Number of successful sperm retrievals	SRR
Aetiology			
Cryptorchidism	6	6	100%
Childhood diseases	5	5	100%
Testicular cancer	1	1	100%
Chromosomal translocation 9/17	1	1	100%
Klinefelter's syndrome	12	9	75%
Idiopathic	49	25	51%
AZFc	6	3	50%
Previous chemotherapy	5	2	40%
Histology			
Complete hyalinisation	5	5	100%
Hypospermatogenesis	14	13	92.9%
Maturation arrest	11	8	72.7%
SCO	55	26	47.2%

SCO, Sertoli cell-only syndrome; SRR, sperm retrieval rate.

Histopathology of hyalinised or hypospermatogenesis had shown very high sperm retrieval of 100% and 92.9% respectively, compared to patients with maturation arrest and Sertoli-cells only who had SRR of 72.7% and 47.2%, respectively. Our data is consistent with previous publications demonstrating that hypospermatogensis is associated with the best outcome of 50–100% SSR followed by maturation arrest (10.8–77.3%), and that SCOS demonstrates the lowest SSR (29.1–60%).[12,25]

KS is the most common genetic abnormality causing infertility and approximately 90% of KS patients have NOA. Micro-TESE has been demonstrated to be an effective sperm retrieval technique in men with KS with SRR reported to be in the ranges of 22.5–66% in retrieving testicular spermatozoa.[12,26] Although the latest meta-analysis demonstrated a rather lower SSR in patients with KS compared to other secondary cause NOA, our SRR was 75%.[5,12] For IVF/ICSI attempts in which sperm was retrieved in KS patients, the clinical pregnancy and live birth rates have been reported to be 57% and 45%, respectively.[26] Of six KS patients trying to conceive, two achieved a clinical pregnancy, one of which has already ended with a live birth.

Cryptorchidism is found in 3% of full-term infants and is more prevalent among preterm infants.[27] It was associated with better SRR in our cohort. Previous studies have shown that SRR was similar in men with a history of unilateral or bilateral cryptorchidism[28] and was as high as 74%. In our cohort, all patients with a

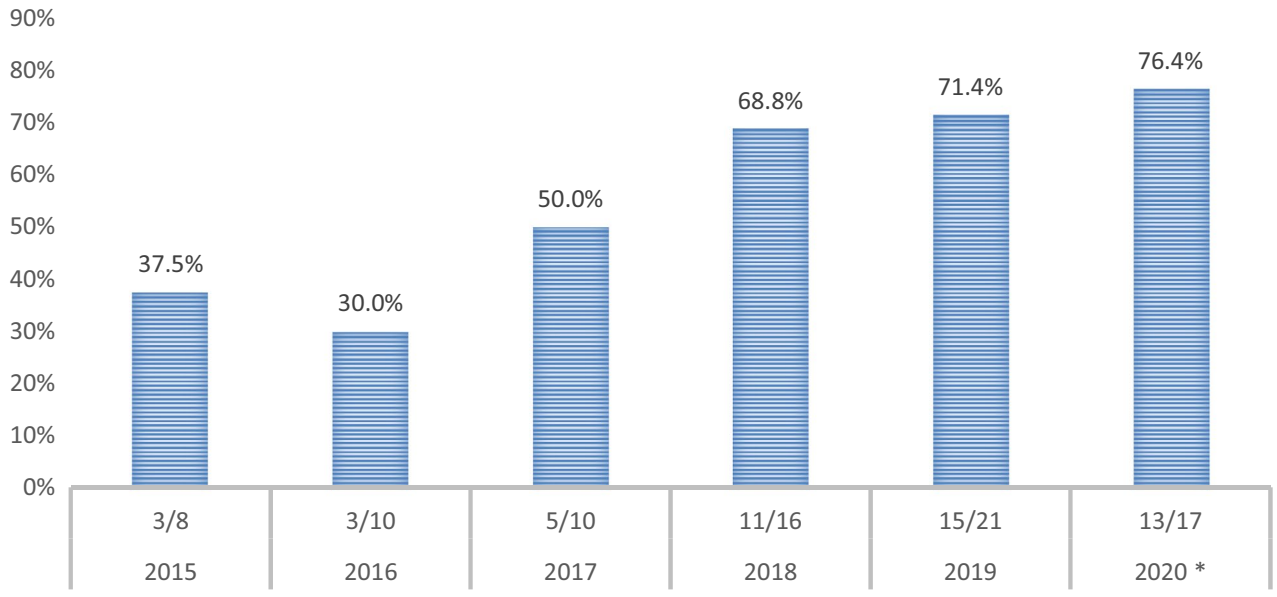

FIGURE 1 Sperm retrieval rate from 2015 to 2020. The horizontal axis presents the number of successful sperm extractions out of the total number of micro- testicular sperm extraction procedures performed each year (*n*/*N*). 2014 not shown as only three procedures were performed that year. *Data extracted until 31 August 2020.

TABLE 3 Multivariate logistic regression model–odds ratios for successful sperm retrieval

Factor	Adjusted OR (95% CI)†	*P*-value
Age	0.99 (0.91–1.08)	0.91
Mean testicular size <15 cc	1.33 (0.34–5.22)	0.67
Baseline FSH <20	3.74 (1.34–10.45)	0.012
Diagnosis of childhood disease or Klinefelter's syndrome	8.48 (2.12–33.88)	0.002

CI, confidence interval; FSH, follicle-stimulating hormone; OR, odds ratio.
†Odds ratios are adjusted for all variables listed in the table.

TABLE 4 IVF outcome following micro-TESE for non-obstructive azoospermia

	Confirmed NOA*
Number of men with successful sperm retrieval	52/85 (61%)
Number of men who attempted micro-TESE with the aim of using the sperm for IVF/ICSI	80
Number of men with successful sperm retrieval and IVF/ICSI attempt	47/80 (58.8%)
Number of 2pn embryos out of total number of eggs (fertilisation rate)	257/606 (42.4%)
Number of couples with at least one good-quality embryo who had embryo transfer	29 (61.7%)
Number of clinical pregnancies per started IVF/ICSI cycle	19/47 (40.4%)
Number of miscarriages per clinical pregnancies	3/19 (15.8%)
Number of ongoing pregnancies and live births	16/19 (84.2%)
Rate of ongoing pregnancies and live births per started cycle of IVF/ICSI	16/47 (34.0%)
Rate of ongoing pregnancies and live births per micro-TESE procedure	16/80 (20.0%)

Abbreviations: ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilisation; NOA, non-obstructive azoospermia; TESE, testicular sperm extraction.
*Three patients not included in this table had clinical NOA but normal histology. All three patients had live births.

history of unilateral or bilateral cryptorchidism had a successful sperm retrieval.

Y-chromosome microdeletions in regions AZFa/b are associated with a negligible sperm retrieval success.[12] By contrast, AZFc microdeletions most commonly present with severe oligospermia. When these patients are presented with NOA, the expected SSR is around 55%,[29] similar to the 50% SRR in our cohort.

Several limitations of our study must be acknowledged. First, our data is retrospective; second, we did not consider some variables such as inhibin B, Johnsen score, smoking and lifestyle, which have been shown to have a relevant albeit controversial predictive value. Furthermore, the outcome measure utilised, SRR, does not encompass the final goal which is live birth. As some pregnancies are still ongoing and some patients with retrieved sperm that has been frozen have partners still undergoing IVF, we cannot provide a cumulative live birth from all retrieved sperm at this stage and we hope to publish this in the future. Nevertheless, our findings are useful for clinicians and patients, offering realistic data, and stress the importance of gaining experience and expertise in order to improve outcomes.

This study confirms that in an Australian context, micro-TESE is an effective method for the treatment of NOA, and its combination with ICSI can help NOA patients obtain genetic offspring. SRR rates are influenced by increased surgical experience, histological pattern and aetiology.

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