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REVIEW ARTICLE

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Outcome of microdissection TESE compared with conventional TESE in non-obstructive azoospermia: a systematic review

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SUMMARY

Retrieval of spermatozoa is unfortunately still only successful in a subset of patients suffering from non-obstructive azoospermia (NOA) by conventional testicular sperm extraction (TESE). Microdissection TESE may have some theoretical benefits over conventional TESE, but uncertainty exists about its superiority. The objective of this systematic review was therefore to compare the efficacy and safety of microTESE with conventional TESE in men with NOA. The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. Literature was searched for studies comparing outcome of conventional TESE with microdissection TESE. Primary outcome was sperm retrieval rate (SRR). Secondary outcomes were clinical predictors of sperm retrieval as well as complication rate. Of 62 articles, a total of seven studies were included in the final analysis. Overall SRR was significantly higher in the microTESE group in comparison with conventional TESE in five of these studies. Overall sperm retrieval ranged from 16.7 to 45% in the conventional TESE vs. 42.9 to 63% in the microTESE group. A sub-analysis of the SRR according to testicular histology was available in four of the selected articles. MicroTESE in men with Sertoli cell only syndrome and hypospermatogenesis carried a small but significant more favourable outcome according to, respectively, two and one of the studies. Correlation of serum follicle stimulating hormone and testicular volume with positive outcome was variable. Fewer complications were observed on ultrasound examination after microTESE procedure. Clinical randomized studies comparing microTESE with conventional TESE in NOA are still lacking to date. Pseudo-randomized prospective data, however, show more favourable sperm retrieval in NOA for microTESE, especially in histological patterns of patchy spermatogenesis such as Sertoli cell only syndrome. However, in patients with uniform histological patterns such as maturation arrest outcome of microTESE seems less favourable.

INTRODUCTION

In contrast to obstructive azoospermia in which there is an obstruction in the ductal system, non-obstructive azoospermia (NOA) is characterized by a complete absence of spermatozoa in semen because of minimal or no spermatogenesis. Possible aetiologies are genetic disorders such as sexual chromosomal abnormalities, translocation and microdeletions of the Y chromosome, cryptorchidism, testicular torsion, radiation and toxins (Ezeh, 2000; Raman & Schlegel, 2003). Approximately 10% of all male infertility is because of NOA (Jarow *et al.*, 1989). Different options are available for obtaining viable spermatozoa in these patients: fine needle aspiration (FNA), which is potentially ultrasound guided, conventional testicular sperm extraction (TESE) and microdissection TESE. TESE in combination with intracytoplasmatic sperm injection has become the first line treatment for patients with NOA. Testicular biopsy appears more effective than FNA for the retrieval of spermatozoa in NOA (Friedler *et al.*, 1997; Ostad *et al.*, 1998). Until recently, conventional TESE was considered gold standard for retrieving spermatozoa in these men. During a conventional TESE procedure, the testis is exposed through a small incision and one or multiple biopsies are taken blindly. According to Donoso *et al.* (2007), conventional TESE has an average retrieval rate around 50% in NOA men. Possible complications are low but include loss of significant amount of testicular tissue, haematoma, inflammatory changes and permanent devascularization (Schlegel & Su, 1997).

MicroTESE was first introduced in 1999 (Schlegel, 1999). In this technique, the tunica albuginea is widely opened and examination of the testicular tissue is carried out at 20–25× magnification under an operating microscope allowing visualization

of whitish, larger and more opaque tubuli. The concept of this technique is that these tubuli are more likely to contain active spermatogenesis. Another possible benefit is better identification of sub-tunical vessels reducing risk of devascularization. To date several studies have been conducted comparing the efficacy of conventional and microTESE. The aim of this review was to compare the outcome of conventional TESE with microTESE through a systematic review of the literature comparing these two methods.

METHODS

The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (Moher *et al.*, 2009). Eligible for inclusion were all (pseudo-) randomized, observational and descriptive studies comparing the outcome of conventional TESE with microdissection TESE in patients with NOA. MEDLINE, EMBASE and Cochrane Controlled Trial Register were searched in July 2013 using the search terms 'TESE', 'Microdissection sperm extraction', 'TESE' and 'NOA'. A bibliography search of the available literature was also performed. A total of 62 abstracts were screened. After assessing the articles for eligibility seven studies were included in the qualitative synthesis.

Primary outcome was sperm retrieval rate (SRR) in the microTESE group and the conventional TESE group. Secondary outcomes were other clinical predictors of positive sperm retrieval and complication rate.

RESULTS

The literature search is described in Fig. 1. A total of 69 records were screened of which 60 were excluded because of irrelevancy; these excluded studies had other objectives than directly comparing SRR s between conventional and microTESE, or were review articles. Nine full-text articles (Schlegel, 1999; Amer *et al.*, 2000; Okada *et al.*, 2002; Tsujimura *et al.*, 2002; Mulhall *et al.*, 2005; Ramasamy *et al.*, 2005; Colpi *et al.*, 2009; Turunc *et al.*, 2010; Ghalayini *et al.*, 2011) were assessed for eligibility of which two were excluded. Reasons for exclusion are listed in the flow chart.

Of the seven included studies two were prospective, non-randomized studies (Schlegel, 1999; Amer *et al.*, 2000). Three studies were retrospective (Okada *et al.*, 2002; Tsujimura *et al.*, 2002; Ramasamy *et al.*, 2005) and the two remaining studies were pseudo-randomized controlled studies (Colpi *et al.*, 2009; Ghalayini *et al.*, 2011); these last two studies were randomized based on the waiting list for the operative theatre. Characteristics of the included studies are documented in Table 1. Single biopsy conventional TESE was used in the study of Amer *et al.* (2000) and Colpi *et al.* (2009) where in the other study protocols multiple biopsies were taken. In the study of Amer *et al.* (2000), 100 patients with bilateral identical histopathology were operated on one testis with conventional TESE procedure and on the other side with microdissection TESE.

Comparison of overall sperm retrieval rate

All seven included studies compared the overall SRR (Schlegel, 1999; Amer *et al.*, 2000; Okada *et al.*, 2002; Tsujimura *et al.*, 2002; Ramasamy *et al.*, 2005; Colpi *et al.*, 2009; Ghalayini *et al.*, 2011). The SRR in the conventional TESE group ranged from 16.7 to 45% and from 42.9 to 63% in the microTESE group. Results are presented in Table 2. Five of the seven studies showed a significant difference ($p < 0.05$) in favour of microTESE (Amer *et al.*, 2000; Okada *et al.*, 2002; Ramasamy *et al.*, 2005; Colpi *et al.*, 2009; Ghalayini *et al.*, 2011). Results of the study of Colpi *et al.* were omitted. In this article, a testis that had been operated by microTESE was randomly paired to a testis operated by TESE. Therefore, it is impossible to compare results of this single study with the other articles.

Comparison of sperm retrieval rate according to testicular histology

Five of the included studies made a comparison of sperm retrieval according to testicular histology (Okada *et al.*, 2002; Tsujimura *et al.*, 2002; Ramasamy *et al.*, 2005; Colpi *et al.*, 2009; Ghalayini *et al.*, 2011). Four studies directly compared SRR s between conventional and microTESE in patients with Sertoli cell only syndrome (SCOS) and patients with maturation arrest. For hypospermatogenesis this was studied in three of the selected articles. Results are listed in Table 2.

Sertoli cell only syndrome, a histological condition characterized by absence of germ cells with only normal Sertoli cells lining the seminiferous tubules predicted a significant better result in the microTESE group according to two studies (Okada *et al.*, 2002; Ghalayini *et al.*, 2011). Results ranged from 22.5 to 41% in the microTESE and from 6.3 to 29% in the conventional TESE group.

In patients with the histological diagnosis of maturation arrest, which is characterized by failure of meiosis of tetraploid pachytene spermacytes to haploid spermatids (Nagpal *et al.*, 1993), all four studies failed to show a significant difference. SRR were highly variable and ranged from 36.4 to 75% in the microTESE group and 0 to 37.5% in the conventional TESE group.

For hypospermatogenesis, which is associated with reduced number of germ cells although all stages of spermatogenesis are present (McDougal *et al.*, 2011), the study of Ramasamy *et al.* is the only one to show a significant difference in favour of the microTESE group. Results ranged from 81 to 100% in the microTESE group and from 50 to 84% in the conventional TESE group.

Other clinical predictors of positive sperm retrieval

Besides testicular histology, other frequent proposed predictors for sperm retrieval are plasma Follicle Stimulating Hormone (FSH) concentration and testicular volume. Three of the included studies assessed pre-operative plasma FSH concentration as a predictor of positive sperm retrieval (Okada *et al.*, 2002; Colpi *et al.*, 2009; Ghalayini *et al.*, 2011). In the study of Okada *et al.* no FSH cut-off value was apparent for successful sperm recovery. In the studies of Colpi *et al.* and Ghalayini *et al.*, however, increased FSH levels were associated with significant more failure of sperm retrieval in both groups.

Two studies assessed testicular volume as a predictor of successful sperm retrieval (Colpi *et al.*, 2009; Ghalayini *et al.*, 2011). In the study of Colpi *et al.*, increase in testicular volume showed no significant increase in sperm retrieval, whereas in Ghalayini *et al.* (2011) testicular volume was positively correlated with sperm retrieval for both methods.

Comparison of complication rate

The study of Okada *et al.* was the only to report clinical complications in the conventional TESE group; one patient with

Figure 1 PRISMA Flow Diagram.

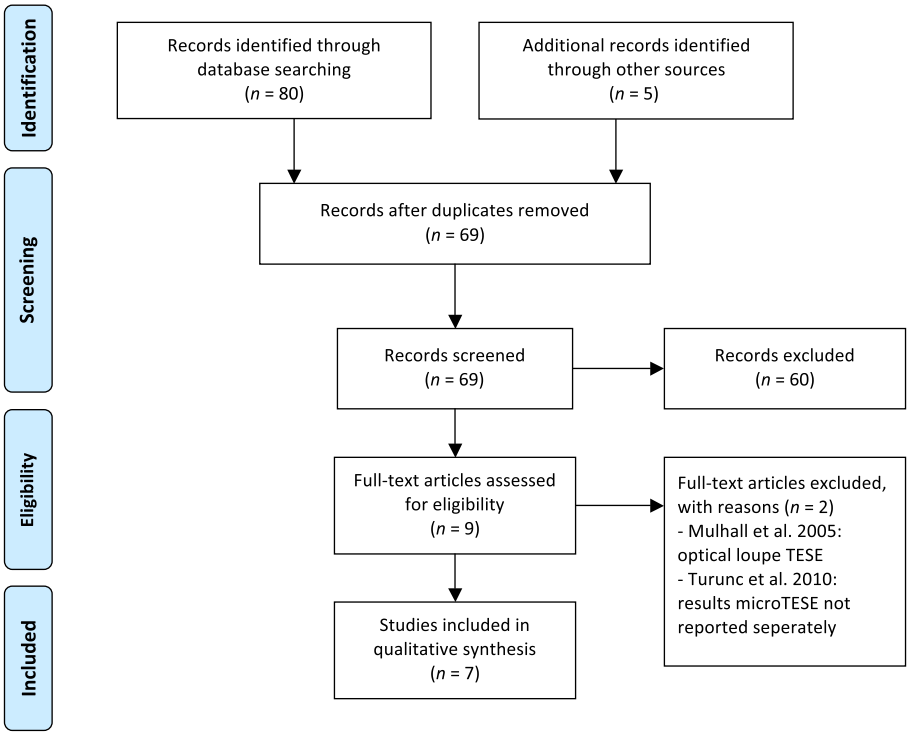

Table 1 Summary of characteristics of included studies

Study	Design	Participants	Intervention	Outcome
Schlegel (1999)	Prospective, non-randomized	49 NOA patients	Conventional multiple TESE (n = 22 attempts) MicroTESE (n = 27 attempts)	Sperm retrieval rate (SRR), average retrieval per sample, fertilization rate
Amer *et al.* (2000)	Prospective, non-randomized	100 NOA patients with bilateral identical histopathology	On one side conventional single TESE (n = 100 testes) On other side microTESE (n = 100 testes)	SRR, weight of testicular tissue, sonographic FU at 1, 3 and 6 months
Okada *et al.* (2002)	Retrospective	98 NOA patients	Conventional multiple TESE (n = 24 attempts) MicroTESE (n = 74 attempts)	SRR according to histology, sonographic FU at 1 and 6 months
Tsujimura *et al.* (2002)	Retrospective	93 NOA patients	Conventional multiple TESE (n = 37 attempts) MicroTESE (n = 56 attempts)	SRR, mean operating time, SRR according to histology, microscopical findings during operation
Ramasamy *et al.* (2005)	Retrospective	435 NOA patients	Conventional multiple TESE (n = 83 attempts) MicroTESE (n = 460 attempts)	SRR according to histology, sonographic and endocrine FU at 3 and 6 months
Colpi *et al.* (2009)	Controlled, pseudo-randomized	154 NOA patients	Conventional single TESE (n = 117 testes) MicroTESE (n = 78 testes)	SRR according to histology, testicular volume and FSH
Ghalayini *et al.* (2011)	Controlled, pseudo-randomized	133 NOA patients	Conventional multiple TESE (n = 68 attempts) MicroTESE (n = 65 attempts)	SRR according to histology, testicular volume and endocrine factors

wound infection and one hypogonadism secondary to ischemic atrophy were reported. The other studies reported no clinical complications in both groups.

Three of the included studies systematically compared the sonographical changes at different months of follow-up (Amer *et al.*, 2000; Okada *et al.*, 2002; Ramasamy *et al.*, 2005). Haematoma was less frequent in the microTESE group after 1 and 3 months. Fibrosis and decreased testicular volume (>2 mL) were also less frequent in the microTESE group at 6 months.

In the study of Okada *et al.*, a significant decrease in serum testosterone after 6 months was observed in two patients in the conventional TESE group, whereas none occurred in the microTESE, although this was not statistically significant. Ramasamy *et al.* reported no significant difference in return to baseline testosterone levels between the two procedures.

DISCUSSION

MicroTESE offers the potential advantage of direct visualization of zones of testicular tissue whereas conventional TESE is a blind procedure. For obvious reasons, it has been thus far not possible to set up fully randomized comparative studies comparing microTESE versus conventional TESE in NOA patients.

Table 2 Comparison of sperm retrieval rates (SRR)

Study	Overall SRR (%) cTESE (*n*) microTESE (*n*)	SRR in SCO (%) cTESE (*n*) microTESE (*n*)	SRR in maturation arrest (%) cTESE (*n*) microTESE (*n*)	SRR in hypospermatogenesis (%) cTESE (*n*) microTESE (*n*)
Schlegel (1999)	45 (*n* = 22) 63 (*n* = 27)			
Amer *et al.* (2000)	30 (*n* = 100 testes) 47 (*n* = 100 testes)*			
Okada *et al.* (2002)	16.7 (*n* = 24) 44.6 (*n* = 74)*	6.3 (*n* = 16) 33.9 (*n* = 56)*	37.5 (*n* = 8) 75 (*n* = 12)	
Tsujimura *et al.* (2002)	35.1 (*n* = 37) 42.9 (*n* = 56)	13 (*n* = 23) 22.5 (*n* = 40)	0 (*n* = 1) 75 (*n* = 4)	76.9 (*n* = 13) 100 (*n* = 12)
Ramasamy *et al.* (2005)	32 (*n* = 83) 57 (*n* = 460)*	29 (*n* = 24) 41 (*n* = 237)	20 (*n* = 10) 44 (*n* = 62)	50 (*n* = 14) 81 (*n* = 73)*
Ghalayini *et al.* (2011)	38.2 (*n* = 68) 56.9 (*n* = 65)*	6.2 (*n* = 32) 26.9 (*n* = 26)*	27.3 (*n* = 11) 36.4 (*n* = 11)	84 (*n* = 25) 92.9 (*n* = 28)
Mean SRR weighed by sample size	33 54	14 37	27 49	73 85

*Statistically significant ($p < 0.05$).

Nevertheless, available retrospective as well as prospective pseudo-randomized studies reporting on both procedures tend to show higher SRR following microTESE. It is highly unlikely that this better outcome is related to patient selection. Nevertheless, the relatively small number of studies comparing both methods makes it difficult to draw definitive conclusions

MicroTESE seems most beneficial in Sertoli cell only syndrome. The better outcome may be because of presence of patchy spermatogenesis in some of these patients, as already suggested by Donoso *et al.* (2007). It is well established that some men suffering with NOA still have some patchy spermatogenesis whereas others have complete absence of germ cells and/or full block of maturation of spermatozoa in all tubuli. Contrary to expectations, a histological diagnosis of SCOS may indeed still be associated with patchy spermatogenesis. This finding explains why poor histological classification has been not predictive for outcome of conventional TESE. Moreover, in two included studies microTESE in SCOS was associated with higher sperm retrieval suggesting that proper identification of zones of spermatogenesis by microscopic magnification had indeed been realized. In maturation arrest, where all tubuli are microscopically uniform despite the presence of active spermatogenesis (Silber, 2000) and in hypospermatogenesis microTESE seems less favourable.

Although elevated FSH levels tended to reduce outcome for both procedures in two included studies, it is questionable that serum FSH levels are really predictive for successful sperm retrieval. A large retrospective study by Ramasamy *et al.* (2009) demonstrated that chances of sperm retrieval are just as common for NOA men with elevated FSH than for men with lower FSH. Testicular volume has a poor prognostic value because of patchy spermatogenesis.

Fewer sonographical complications such as haematoma and fibrosis were observed after microTESE procedure. However, these findings seem to have minimal clinical impact as no significant difference in clinical complication rate is reported in any of the included articles. After both procedures there is a return to baseline serum testosterone levels.

A further question that needs to be addressed is the health cost evaluation of microTESE vs. conventional TESE. MicroTESE procedures are much more time-consuming and require the purchase of an operating microscope. Moreover, the learning curve of a microTESE operation is steeper than that of a conventional TESE procedure, underlining the importance of a high turnover of microTESE operations (Ishikawa *et al.*, 2010). Also so far no clinical studies have compared birth rate between cycles using spermatozoa retrieved through conventional and microdissection TESE procedures.

CONCLUSIONS

In current literature, there is a tendency towards higher SRR in microTESE procedures when compared with conventional TESE, although good clinical randomized studies are still lacking to date. Pseudo-randomized prospective data, however, show more favourable sperm retrieval in NOA for microTESE, especially in histological patterns of patchy spermatogenesis such as Sertoli cell only syndrome. However, in patients with uniform histological patterns such as maturation arrest outcome of microTESE seems less favourable. No secure clinical predictors of sperm retrieval are demonstrated for both procedures and although fewer sonographical complications occur after microTESE, clinical complication rate between both procedures seems not to differ.

AUTHOR CONTRIBUTIONS

Y.D., F.V. and D.V. have all given substantial contributions to conception and design of the present review. Y.D. has drafted the manuscript and F.V. and D.V. have revised the content critically. All authors have made final approval of the version to be published.

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

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