When their first antimuscarinic has failed, why not take a different path?

astellas

Prescribing another antimuscarinic may be of minimal benefit after the first has failed.[1] So why not choose another route? BETMIGA is in a different class, relaxing the bladder via β_3-adrenoceptors.[2] It can be just as effective as an antimuscarinic, but it doesn't have the same side-effect profile.[3]

BETMIGA is indicated for symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.[2]

Prescribing information: BETMIGA™ (mirabegron)

For full prescribing information, refer to the Summary of Product Characteristics (SPC)

Presentation: BETMIGA prolonged-release tablets containing 25 mg or 50 mg mirabegron.

Indication: Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

Posology and administration: The recommended dose is 50 mg orally once daily in adults (including elderly patients). Mirabegron should not be used in paediatrics. A reduced dose of 25 mg once daily is recommended for special populations (please see the full SPC for information on special populations). The tablet should be taken with liquids, swallowed whole and is not to be chewed, divided, or crushed. The tablet may be taken with or without food.

Contraindications: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC. Severe uncontrolled hypertension defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg.

Warnings and Precautions: Renal impairment: BETMIGA has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m^2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2); based on a pharmacokinetic study (see section 5.2 of the SPC) a dose reduction to 25 mg is recommended in this population. This medicinal product is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2) concomitantly receiving strong CYP3A inhibitors (see section 4.5 of the SPC). Hepatic impairment: BETMIGA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. This medicinal product is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors (see section 4.5 of the SPC). Hypertension: Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with mirabegron, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg). Patients with congenital or acquired QT prolongation: BETMIGA, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies (see section 5.1 of the SPC). However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients. Patients with bladder outlet obstruction and patients taking antimuscarinics medicinal products for OAB: Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medicinal products for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with BETMIGA; however, BETMIGA should be administered with caution to patients with clinically significant BOO. BETMIGA should also be administered with caution to patients taking antimuscarinic medicinal products for the treatment of OAB.

Interactions: Caution is advised if mirabegron is co-administered with medicinal products with a narrow therapeutic index and significantly metabolised by CYP2D6. Caution is also advised if mirabegron is co-administered with CYP2D6 substrates that are individually dose titrated. In patients with mild to moderate renal impairment or mild hepatic impairment, concomitantly receiving strong CYP3A inhibitors, the recommended dose is 25 mg once daily. For patients who are initiating a combination of mirabegron and digoxin (P-gp substrate), the lowest dose for digoxin should be prescribed initially (see the SPC for full prescribing information). The potential for inhibition of P-gp by mirabegron should be considered when BETMIGA is combined with sensitive P-gp substrates. Increases in mirabegron exposure due to drug-drug interactions may be associated with increases in pulse rate.

Pregnancy and lactation: BETMIGA is not recommended in women of childbearing potential not using contraception. This medicinal product is not recommended during pregnancy. BETMIGA should not be administered during breast-feeding.

Undesirable effects: Summary of the safety profile: The safety of BETMIGA was evaluated in 8433 patients with OAB, of which 5648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received BETMIGA for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 88% of the patients completed treatment with this medicinal product, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity. The most common adverse reactions reported for patients treated with BETMIGA 50 mg during the three 12-week phase 3 double blind, placebo controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving BETMIGA 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving BETMIGA 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving BETMIGA 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving BETMIGA 50 mg. Serious adverse reactions included atrial fibrillation (0.2%). Adverse reactions observed during the 1-year (long term) active controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week phase 3 double blind, placebo controlled studies. Adverse reactions: The following list reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies. The frequency of adverse reactions is defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (cannot be established from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The adverse events are grouped by MedDRA system organ class. *Infections and infestations:* Common: Urinary tract infection, Uncommon: Vaginal infection, Cystitis. *Psychiatric disorders:* Not known (cannot be estimated from the available data): Insomnia*, Confusional state*. *Nervous system disorders:* Common: Headache*, Dizziness*. *Eye disorders:* Rare: Eyelid oedema. *Cardiac disorders:* Common: Tachycardia, Uncommon: Palpitation, Atrial fibrillation. *Vascular disorders:* Very rare: Hypertensive crisis*. *Gastrointestinal disorders:* Common: Nausea*, Constipation*, Diarrhoea*, Uncommon: Dyspepsia, Gastritis, Rare: Lip oedema. *Skin and subcutaneous tissue disorders:* Uncommon: Urticaria, Rash, Rash macular, Rash papular, Pruritus, Rare: Leukocytoclastic vasculitis, Purpura, Angioedema*. *Musculoskeletal and connective tissue disorders:* Uncommon: Joint swelling. *Renal and urinary disorders:* Rare: Urinary retention*. *Reproductive system and breast disorders:* Uncommon: Vulvovaginal pruritus. *Investigations:* Uncommon: Blood pressure increased, GGT increased, AST increased, ALT increased. * signifies adverse reactions observed during post-marketing experience. Prescribers should consult the SPC in relation to other adverse reactions.

Overdose: Treatment for overdose should be symptomatic and supportive. In the event of overdose, pulse rate, blood pressure, and ECG monitoring is recommended.

Basic NHS Cost: BETMIGA 50 mg x 30 = £29, BETMIGA 25 mg x 30 tablets = £29

Legal classification: POM

Marketing Authorisation number(s): EU/1/12/809/001 – 018

Marketing Authorisation Holder: Astellas Pharma Europe B.V. Sylviusweg 62. 2333 BE Leiden. The Netherlands.

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Job bag number: BET_2019_0023_UK

Further information available from: Astellas Pharma Ltd, Medical Information: 0800 783 5018. For full prescribing information, please see the Summary of Product Characteristics, which may be found at www.medicines.org.uk

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Astellas Pharma Ltd. on 0800 783 5018

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Salvage micro-dissection testicular sperm extraction; outcome in men with non-obstructive azoospermia with previous failed sperm retrievals

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Objective

To assess the outcome of micro-dissection testicular exploration sperm extraction (m-TESE) as a salvage treatment in men with non-obstructive azoospermia (NOA) in whom no sperm was previously found on single/multiple TESE or testicular sperm aspiration (TESA).

Patients and Methods

In all, 58 men with NOA underwent m-TESE. All the patients had previously undergone either single/multiple TESE or TESA with no sperm found. All the patients underwent an m-TESE using a standard technique. Serum follicle-stimulating hormone (FSH), testosterone and histopathological diagnosis were examined as predictive factors for sperm recovery. All patients underwent preoperative genetic screening. One patient was found to have an azoospermic factor c (AZFc) micro-deletion and five were diagnosed with Kleinfelter's syndrome.

Results

The mean (range) patient age was 39.0 (26–57) years. Spermatozoa were successfully retrieved in 27 men by m-TESE (46.5%). The mean (range) FSH level was 19.4 (1.6–58.5) IU/L. There was no correlation in age (mean age retrieved 38.1 years, not retrieved 39.7 years, $P = 0.38$), FSH levels (mean FSH retrieved 21.4 IU/L, not retrieved 17.7 IU/L, $P = 0.3$) and the ability to find sperm by m-TESE. However, there was a significant difference in testosterone levels and sperm retrieval (mean testosterone retrieved 14.99 nmol/L, not retrieved 11.39 nmol/L, $P < 0.05$). Patients with a diagnosis of Sertoli-cell-only (SCO) syndrome [14/35 (40%)] and maturation arrest [four of 11 (36%)] had lower sperm retrieval rates than those in the hypospermatogenesis group [nine of 12 (75.0%)] ($P < 0.05$). There were no significant complications after m-TESE.

Conclusions

In men with NOA who have undergone previous attempts at sperm retrieval with negative results, a salvage m-TESE offers a significant chance of finding sperm even in SCO syndrome. There does seem to be a correlation between preoperative testosterone levels and the ability to successfully find sperm.

Keywords

salvage, non-obstructive azoospermia, m-TESE, success

Introduction

In non-obstructive azoospermia (NOA), testicular sperm can be retrieved using a conventional open testicular sperm extraction (TESE) technique in 10–50% [1,2] or testicular sperm aspiration (TESA) in 10–20% [3]. The microsurgical TESE procedure or micro-dissection TESE (m-TESE) was first introduced by Schlegel and Li [4] and may allow for better visualisation of the larger tubules of increased opacity. These tubules are postulated to contain the greatest number of active germ cells. It has previously been reported that the sperm retrieval rate is higher with m-TESE than with open TESE, in which multiple samples are obtained (conventional TESE) [4–6] and TESA [7]. The m-TESE procedure appears to be safe, resulting in minimal complications but with a higher yield of sperm [8]. As a result, the number of patients who request m-TESE after failed conventional TESE or TESA has been increasing.

Further sperm retrieval may also be performed in patients with a history of successful sperm collection after the exhaustion of the cryopreserved testicular sperm for intracytoplasmic sperm injection (ICSI), or in those with unsuccessful previous TESE outcome who do not wish to use donor sperm. A repeat procedure has historically been performed with great caution because of the potential for

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testicular damage after previous operations [9,10]. However, there is now evidence that sperm retrievals may be successfully and safely repeated several times if required [2].

The most commonly used histopathological scoring system for spermatogenesis is the one proposed by Johnsen in 1970 [11]. A registration of the most mature cell type present was taken as an index of tubule quality. A number of historical studies suggest that there may be a correlation between the histology and the chances of finding sperm, although using the m-TESE technique, testicular histology does not appear to be a significant factor in predicting outcome.

A management dilemma occurs when patients with NOA have undergone negative sperm retrieval with less exhaustive sperm retrieval techniques, such as TESA and multiple biopsy TESE or single biopsy TESE in attempting to retrieve sperm for ICSI. In these cases sperm may not be found and the patient remains in a dilemma as whether or not to proceed to a m-TESE to try and maximise the chances of finding sperm or potentially go down the route of adoption or use donor sperm. Currently there exists very little published data on the outcome of patients in this difficult group.

The aim of the present study was to determine the outcome of m-TESE as a salvage treatment in men with NOA in whom no sperm was seen on initial single/multiple TESE or TESA and to determine what factors may predict successful sperm retrieval including testicular histopathology, FSH and testosterone levels.

Patients and Methods

The case records of 58 men with NOA between 2008 and 2013 were evaluated retrospectively. All patients had previously undergone single or multiple TESE or TESA where no sperm were found. No patients had previously had a m-TESE procedure. Some of these patients were non-UK residents and therefore we were unable to ascertain correctly the number of procedures that had been performed in the form of single or multiple TESA, although some patients had had this procedure performed up to four times. All patients underwent a preoperative clinical evaluation including a physical examination, hormonal assessment (FSH, LH, and testosterone), testicular ultrasound, and genetic analysis (karyotype and Y chromosome micro-deletion). Sperm retrieval was not performed for at least 6 months following the primary procedure. This period was chosen based upon evidence that sperm retrieval rates are reportedly higher if a period of 3–6 months has elapsed since primary surgery, as the ultrastructural changes induced by biopsy can take up to 6 months to resolve [10,12].

No patients were operated on if they had an azoospermic factor (AZF) region a or b micro-deletion detected preoperatively, as successful sperm retrieval in these patients has been reported to be zero [13,14]. All other patients including those with AZFc deletions were offered either sperm retrieval in isolation (and any sperm found were cryopreserved), or sperm retrieval on the day of their partners oocyte retrieval. Any postoperative complications were noted and all patients were followed up for ≥6 weeks after surgery.

The technique has previously been described [8]. Briefly, under general anaesthesia, a mid-line scrotal incision was made on the median raphe of the scrotum. A transverse equatorial incision was made on each testis, with a surgical haemostat then placed on either side of the tunical incision and gently pulled apart. Care was taken to protect the underlying subtunical vessels and then under an operating microscope at ×25, tubular dissection was undertaken. Using the operative microscope, opaque and more dilated tubules were removed and immediately placed within a sperm buffer. At the same time as performing the m-TESE, biopsies were sent for histopathological examination. The patients were usually discharged on the day of surgery with analgesia and prophylactic antibiotics were given for 7 days. The patients were then followed up in out-patients.

The descriptive statistics are presented as the mean (SEM), as well as percentages. Analytical tests used include Student's *t*-test (two-tailed) for comparing the retrieval rates in paired groups and chi-squared test for contingency table analysis.

Results

All 58 patients were sub-classified into patients with Sertoli-cell-only (SCO) syndrome (35 patients), maturation arrest (11 patients) or hypospermatogenesis (12 patients). The mean serum FSH in the SCO group was 21.05 IU/L. In the maturation arrest group FSH was 13.63 IU/L and inpatients with hypospermatogenesis 15.99 IU/L. Patients with SCO syndrome diagnosis (14/35, 40%) and maturation arrest (four of 11, 36%) had lower sperm retrieval rates compared with the hypospermatogenesis group (nine of 12, 75%) and are shown in Tables 1 and 2. The mean Johnson's score in each sub-category was 2.1, 2.37 and 3.87, respectively.

Spermatozoa were successfully retrieved from 27 men by m-TESE (46.55%) (Tables 1 and 2). The mean (range) age of patients was 39.0 (29–57) years. The mean (range) FSH level was 19.4 (1.6–58.5) IU/L. There was no correlation in age (retrieved 38.1, not retrieved 39.7 years, $P = 0.38$) and FSH levels (mean FSH retrieved 21.4, not retrieved 17.7 IU/L, $P = 0.3$) and the ability to find sperm by m-TESE. However, there was a positive correlation between preoperative testosterone level (mean testosterone retrieved 14.99, not retrieved 11.39 nmol/L, $P < 0.05$) and a previous histological diagnosis of hypospermatogenesis ($P = 0.001$) and successful sperm retrieval.

All patients underwent a genetic evaluation preoperatively including karyotyping and Y chromosome micro-deletion

Table 1 The sperm retrieval rate using m-TESE as a salvage technique in the present series

Variable	Histological diagnosis			Overall	*P*
	SCO syndrome	Maturation arrest	Hypospermatogenesis		
No. of patients	35	11	12	58	NA
Mean (SEM) age, years	38.6 (1.22)	38 (2.63)	40.3 (1.21)	39 (0.92)	NS
Sperm retrieval rate, n/N (%)	14/35 (40)	4/11 (36)	9/12 (75)	27/58 (46.55)	0.001
Mean (SEM) FSH level, IU/L	21.05 (1.79)	13.63 (3.72)	15.99 (3.55)	19.39 (1.69)	NS
Mean Johnsen score	2.1	2.75	3.87	NA	NA

NA, not applicable; NS, statistically not significant, P > 0.05.

Table 2 Comparison between the successful and unsuccessful groups after a salvage m-TESE in the present series

	Successful	Not successful	*P*
No. of patients (%)	27 (46.55)	31 (53.45)	NA
Mean (SEM) age, years	38.1 (1.38)	39.7 (1.21)	0.38
Mean (SEM) FSH level, IU/L	21.44 (2.59)	17.75 (2.15)	0.3
Mean (SEM) testosterone level, nmol/L	14.99 (1.48)	11.39 (0.67)	0.035
Histology, n/N (%)			
SCO syndrome	14/35 (40)	21/35 (60)	
Maturation arrest	4/11 (36)	7/11 (63)	
Hypospermatogenesis	9/12 (75)	3/12 (25)	

NA, not applicable; NS: statistically not significant, P > 0.05.

Table 3 Sperm retrieval rates using m-TESE after previously failed sperm retrievals in NOA

Reference	Type of retrieval	Type of previous procedure	N	Sperm retrieval rate, %	Sperm retrieval rate (%) by histology
Okada et al. 2002 [16]	m-TESE	TESE	13	30.7	Not known
Tsujimura et al. 2006 [17]	m-TESE	TESE	46	45.7	SCO syndrome (39.1) Maturation arrest (41.7) Hypospermatogenesis (100)
Ramasamy and Schlegel 2007 [18],	m-TESE	TESE	20	45	SCO syndrome (34.3) Maturation arrest (61.55) Hypospermatogenesis (93.3)
Present series	m-TESE	TESE or TESA	58	46.55	SCO syndrome (40) Maturation arrest (36) Hypospermatogenesis (75)

analysis. Of the 58 patients one patient had an AZFc micro-deletion. Histologically he had SCO syndrome and had previously undergone a TESA but was not found to have sperm on m-TESE. Five patients were found to have a non-mosaic Kleinfelter's preoperatively and sperm was successfully retrieved in one of five cases. There were no significant complications after m-TESE.

Discussion

The present study reports that in men with NOA who have previously undergone unsuccessful multiple biopsy TESE or TESA sperm retrieval rates using salvage micro-dissection, are comparable to those undergoing a primary procedure. In the present study, sperm was retrieved in 46.5% of patients, which is comparable to the results of men undergoing m-TESE as a primary procedure [5,6,8,15,16]. There are only three other studies that have reported m-TESE as a salvage procedure in men who have previously failed sperm retrieval, with reported sperm retrieval rates of 30–45.7% (Table 3) [16–18]. However, the number of patients in these studies was small (13, 46 and 20 patients) and this present study represents the largest series of patients reporting the application of m-TESE as a salvage treatment in these men. There were no significant complications reported in the present study, indicating that a salvage procedure is safe in this group of patients.

Several medical treatments have been used empirically for male infertility including hormone manipulation with

clomiphene and hCG. However, in randomised placebo-controlled studies, none of these treatments have been clinically proven [19–22].

Several authors have advocated hormone manipulation before surgical sperm retrieval. However, the level of evidence for this is low and so this was not used in our present cohort of patients. Furthermore, the mean testosterone levels in our present study for both the retrieved and non-retrieved groups were within the published normal ranges. Despite this, our present study did show a statistical difference between the two groups for sperm retrieval and testosterone levels. There may well therefore be a threshold level of testosterone below which hormonal manipulation before surgical sperm retrieval may be of benefit. The options which seem to have both theoretical and published support are the use of either hCG, recombinant FSH, clomiphene or aromatase inhibitors either alone or in combination before m-TESE. Clomiphene is a selective oestrogen receptor modulator that prevents negative feedback by sex hormones and, as a result, increases the expression of gonadotrophins. hCG is an analogue of the gonadotrophin LH that stimulates Leydig cell production of testosterone. Anastrozole and testolactone increase the effective concentration of endogenous testosterone by preventing its conversion to oestradiol by aromatase.

In a study by Shiraishi et al. [23], 48 men with NOA who had negative sperm retrieval from a m-TESE procedure had a second m-TESE and were divided into two groups; 20 were not treated by any hormonal therapy, and 28 received daily injections of hCG for 4–5 months before the second m-TESE procedure. Recombinant FSH was added if endogenous gonadotrophin levels decreased during the hCG stimulation. Sperm was successfully obtained at the second m-TESE from six men of the 20 who had received hormonal therapy (21%), whereas no sperm were retrieved from the untreated men. Consistent with our present findings, success at the second m-TESE was more likely if histology at the first m-TESE showed hypospermatogenesis. In a further study, patients were classified into four groups according to their response to clomiphene citrate [24]. If there was no increase in the level of FSH or testosterone then these patients discontinued clomiphene citrate and commenced hCG and human menopausal gonadotropin (hMG). Using this protocol, sperm was found in 54 patients (10.9%) in the ejaculate after treatment (mean concentration of 2.3 million/mL). Furthermore, successful sperm retrieval was significantly higher (57%) than in the control group who had no hormonal manipulation (33.6%). A criticism of that study includes the observation that the sperm retrieval rate of the control group is very low and indeed lower than the success rate of many reported primary m-TESE studies. These results may suggest a role for hormonal modification in patients with NOA. However, in contrast to this a large retrospective review by the group at Cornell has suggested that there is no overall benefit of hormonal manipulation either on sperm retrieval or live birth rates [25]. In their analysis of 736 men, 388 (53%) had baseline testosterone levels of >300 ng/dL with a sperm retrieval rate of 56%. In the other 348 men with pre-treatment testosterone levels of <300 ng/dL, the sperm retrieval rate showed no statistical difference (52%, $P = 0.29$). Of the patients with a low testosterone level, only 88% of patients responded (testosterone level >300 ng/dL) to the hormonal manipulation preoperatively. Despite this there was no statistical difference in sperm retrieval between patients that responded (51%), did not respond (51%) or were not treated preoperatively (61%) [25].

It has been debated whether or not preoperative histopathology correlates with sperm retrieval rates [26,27]. A recent UK study has suggested that preoperative histopathology is the most important factor in predicting sperm retrieval rates in men on repeat biopsy [28]. However, an isolated testicular biopsy is an invasive procedure that can cause inflammatory changes, haematoma, fibrosis or atrophy [10]. As a result of this even that recent study has suggested that an isolated diagnostic biopsy should not be performed and that testicular biopsy should be performed concurrently with the surgical sperm retrieval. In the present study, concurrent biopsy was performed at the time of m-TESE and it is interesting to note that even in the 40% of patients with SOC syndrome, sperm was retrieved, irrespective of the histopathological diagnosis of SCO syndrome and suggests that a significant number of patients will have sperm found despite an adverse histopathological diagnosis. Furthermore, nine of 12 men (75%) with hypospermatogenesis had sperm found compared with only four of 11 men (36%) with maturation arrest. Therefore we do not recommend a diagnostic testicular biopsy preoperatively.

Earlier studies using random biopsy TESE have reported that elevated FSH levels are associated with a lower success rate for successful sperm retrieval [27,29,30] and lower pregnancy rates in their female partners [31]. These results have historically been used to counsel patients against undergoing TESE if they have abnormal FSH values, because their chances of sperm retrieval will be lower. In general terms, the serum concentration of FSH is inversely correlated with impairment of overall spermatogenesis as it is inversely related to the total number of germ cells present. There is evidence to suggest that there is a correlation between FSH and the ability to predict the presence of sperm at random biopsy using conventional TESE techniques [32,33]. The m-TESE procedure on the other hand is based on the principle of identifying the most advanced pattern, not necessarily the predominant pattern, of spermatogenesis in the testis. Therefore, the FSH level may not be a good predictor for the determination of isolated areas of mature

spermatogenesis within the testis, as FSH levels are not related to the advanced stages of spermatogenesis [34]. Previous studies using m-TESE have shown that there is poor correlation between the FSH level and the ability to retrieve sperm [8,35]. The results of the present study further support this, as the group in which sperm was retrieved had a higher mean level compared with the group that were unsuccessful (21.44 vs 17.75 IU/L). Further support for this is provided by a recent study in which sperm retrieval was higher in men with NOA with FSH levels of >15 IU/mL than those men with FSH levels of <15 IU/L. It is known that different areas of the testis can have varying histological patterns, and a single biopsy may miss areas of spermatogenesis and not be representative of the most advanced histology. The m-TESE technique is based on the principle of being able to analyse the testes more thoroughly and systematically than the random biopsy TESE. The finding that sperm may be retrieved more successfully in patients with a higher rather than lower FSH level may highlight a subset of infertile men with azoospermia and maintenance of the of the hypothalamic-pituitary-gonadal feedback (normal FSH levels) but where spermatogenesis remains impaired. This subset of patients (normal FSH level, maturation arrest, with lower sperm retrieval rates) have also been found to have a higher prevalence of chromosomal abnormalities and Y chromosome micro-deletions compared with other patients with NOA (45% vs 17%), and sperm retrieval success was lower (41% vs 60%) [36].

There were no significant complications after m-TESE, indicating that as a salvage procedure it appears to be safe even in men who have undergone multiple biopsies previously. Patient counselling about the possible risk of hypogonadism is very important preoperatively; however, we found that there were no patients that required hormone replacement therapy in the group available for follow-up. This seems to also be confirmed in previous studies where the testosterone level does return to 80–93% of the preoperative value but may take up to 12 months. However, this does also seem to be partially dependent on the histology and their Kleinfelter's status. We therefore recommend that all patients who have had m-TESE should undergo postoperative hormone evaluation and it is currently our protocol to assess LH, FSH and testosterone levels at 6–9 months after m-TESE [37].

One of the limitations of the present study is that the primary endpoint used was that of sperm retrieval as opposed to pregnancy or delivery rates. There currently remains very little published data about pregnancy rates after the use of cryopreserved sperm vs fresh sperm, although more recently we have published a series of patients where we found no difference in those patients with NOA as opposed to obstructive azoospermia in terms of outcome. The argument of course is that the quantity and quality of sperm may be poor in such patients and therefore the cryopreservation process may damage sperm in a significant portion of patients such that they may require further sperm retrieval on the day of the ICSI cycle.

In summary the present study has shown that salvage m-TESE is a safe technique with minimal long-term risk in men with NOA who have undergone previous TESA or TESE. Sperm can be retrieved in a significant portion of patients using this technique with the results being comparable with a primary procedure. The role of preoperative hormonal manipulation is still yet to be established but there does seem to be a difference with respect to preoperative testosterone level and the success of sperm retrieval.

Conflicts of Interest

None disclosed.

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Abbreviations: AZF, azoospermic factor; ICSI, intracytoplasmic sperm injection; NOA, non-obstructive azoospermia; SCO, Sertoli-cell-only (syndrome); TESA, testicular sperm aspiration; (m-)TESE, (micro-dissection) testicular sperm extraction.