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ORIGINAL PAPER

Varicocelectomy for nonobstructive azoospermia should be considered only in carefully selected patients: Opinions based on treatment experience at Dokkyo Medical University

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Summary *Introduction: The need for varicocelectomy for varicoceles complicated by nonobstructive azoospermia (NOA) has long been debated in the field of male infertility. In this study, we analyzed the clinical outcomes of varicocelectomies for varicoceles in patients with NOA.*
Methods: We retrospectively reviewed the following data of 11 patients with NOA and varicoceles who underwent varicocelectomies: age at admission, right and left testicular volumes, operative varicocele grades, operative site, body mass index, endocrine and genetic examination results, number of semen analyses before and after varicocelectomy, sperm appearance rate in ejaculated semen after varicocelectomy, sperm retrieval rate (SRR) with microdissection testicular sperm extraction (MD-TESE), and histopathological analysis results of testicular tissue.
Results: Varicocelectomies were performed bilaterally and on the left side in 1 and 10 patients, respectively. The number of pre- and postoperative semen analyses was 1-3 and 1-7, respectively. Ejaculated semen analysis after varicocelectomy did not reveal sperm in any patient. Ten patients underwent MD-TESE; however, sperm was retrieved from only two patients (20%). Pathological examination of seminiferous tubular tissue collected by MD-TESE revealed hyalinization in one patient, Sertoli cells in eight, and hypospermatogenesis in two.
Conclusions: Sperm could not be retrieved from the ejaculated semen of patients with NOA and varicoceles who underwent varicocelectomies, and the SRR of MD-TESE was suboptimal. These results suggest that varicocelectomy should be performed cautiously in patients with NOA.

KEY WORDS: *Varicocelectomy; Sperm retrieval; Non-obstructive azoospermia; Ejaculated semen; Microdissection testicular sperm extraction.*

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INTRODUCTION

The association between *nonobstructive azoospermia* (NOA) and varicoceles represents a significant clinical concern and has been the focus of clinical research for a considerable period. These diseases are occasionally encountered during the evaluation of infertility in men. As per previous reports, varicocelectomy improves the *sperm retrieval rate* (SRR), clinical pregnancy rate, and live birth rate after intracytoplasmic sperm injection in patients with NOA, and sperm was retrieved in the ejaculated semen of 14-55% of patients (1-7). These cases also involved successful instances of spontaneous pregnancy (1-5). However, these reports remain controversial because of a low level of evidence. Based on these results, varicocelectomy has been performed in patients with NOA and varicocele at our hospital only after adequate informed patient consent for surgery.
There are various opinions regarding varicocele treatment in patients with NOA. Some opinions suggest that varicocelectomy is a useful treatment option for patients with NOA to obtain sperm in ejaculated semen (8), while others suggest that it may be effective in very limited cases, such as sperm maturation arrest; however, in all cases, surgery should be performed with caution (5, 9, 10). In this article, we discuss the indications for treatment based on our experience and outcomes.

METHODS

Patients

We analyzed the data of all patients with NOA who underwent varicocelectomies for *sperm retrieval* (SR) at our hospital between April 2014 and April 2022. All patients were diagnosed with infertility and azoospermia, and palpation and ultrasonography did not confirm spermatic tract obstruction, indicating a varicocele. Patients who underwent prior cancer treatment, including chemotherapy and radiotherapy, were excluded from the study. The clinical information of these patients was obtained from their medical records and was retrospectively reviewed and analyzed.

Data collection

We retrospectively investigated patients' background information, including age at admission, right and left testicular volumes, operative varicocele grades, operative sites, *body mass indexes* (BMI), endocrine examination

results (*luteinizing hormone* (LH), *follicle-stimulating hormone* (FSH), prolactin, and testosterone levels), genetic test results such as G-banding and AZF deletion, number of semen analyses before and after varicocelectomy, sperm appearance rate in ejaculated semen after varicocelectomy, SRR through *microdissection testicular sperm extraction* (MD-TESE), and histopathological analysis results of testicular tissue during MD-TESE by reviewing medical charts.

Operative varicocelectomy procedures

We performed varicocelectomies using an operating microscope under local and intravenous anesthesia. A 2 cm skin incision was made over the spermatic cord, 3-4 cm below the external inguinal ring. The spermatic cord was externalized through the wound, and the dilated internal and external spermatic veins were ligated and dissected, ensuring no damage to the vas deferens. During surgery, lymphatic vessels were preserved to the greatest extent possible.

Operative MD-TESE procedures

We performed MD-TESE using an operating microscope under local and intravenous anesthesia, which involved making a 5 cm incision on the scrotal skin to access the tunica albuginea and harvest a small amount of testicular tissue, including the seminiferous tubules. An embryologist immediately examined the excised testicular tissue microscopically for the presence of sperms. If spermatozoa could not be retrieved via MD-TESE on one side, the same surgical procedure was repeated on the contralateral side.

Results

Patient characteristics

Tables 1 and 2 provide a summary of the results of this study. Eleven patients with NOA complicated by varicocele were enrolled in this study. The ranges of serum values obtained for various hormones were 4.2-19.3 mIU/mL for LH, 4.5-51.1 mIU/mL for FSH, 5.5-27.2 ng/mL for prolactin, and 1.1-7.4 ng/mL for testosterone. The left and right testicular volumes were 6-14 mL and 6-16 mL, respectively. Age and BMI at the time of hospital attendance ranged from 22-46 years and 17.6-33.3 kg/m^2, respectively. Genetic examination revealed that G-banding was 46XY in all patients, with no *azoospermia factor* (AZF) loss in four patients, AZFc: Ym-12 gr/gr deletion in six, and AZFc: Ym-11 b2/b4 deletion in one.

Operation site and operative varicocele grade

Varicocelectomy was performed on the left side in 10 patients and bilaterally in 1. Varicoceles were classified as grade 3 in nine patients and grade 2 in 3 (n = 2, varicocelectomy performed on the left side; n = 1, varicocelectomy performed on the right side) (Table 1).

Outcomes of pre- and postoperative semen analyses

The median (range) numbers of pre- and postoperative semen analyses were 2 (1-3) and 4 (1-7), respectively. Ejaculated semen analysis after varicocelectomy failed to identify sperm in any patient.

Table 1.

Patient characteristics. Characteristics of patients with NOA before varicocelectomy enrolled in this study. All parameters are presented as median and range values.

	NOA with varicocele repair (n = 11)
Age	35 (22-46)
Left testis volume (ml)	10 (6-14)
Right testis volume (ml)	12 (6-16)
Left operative varicocele grade: III/II/I	9/2/0
Right operative varicocele grade: III/II/I	0/1/0
Operation site: Left/Right/Bilateral	10/0/1
BMI	22.8 (17.6-33.3)
LH	7.7 (4.2-19.3)
FSH	18.5 (4.5-51.1)
Prolactin	12.9 (5.5-27.2)
Testosterone	5.4 (1.1-7.4)
G-banding	46XY: 11
AZF deletion	No: 4 cases
	AZFc: Ym-12 gr/gr: 6 cases AZFc: Ym-11 b2/b4: 1 case

Outcomes of MD-TESE

Of the 11 patients who underwent varicocelectomy, MD-TESE was performed in 10 patients. The time from varicocelectomy to MD-TESE ranged from 4 to 27 months (median, 8.5 months). Sperm was retrieved using MD-TESE in only two (20%) patients. Histopathological examination of seminiferous tubular tissue collected using MD-TESE revealed hyalinization in 1 patient, Sertoli cells in 8 patients, and hypospermatogenesis in 2 patients. SR was possible in 2 patients with histopathological findings of hypospermatogenesis (Table 2).

Table 2.

Details of semen analysis and outcomes of MD-TESE. Number of semen analyses before and after varicocelectomy, pre-and post-operative sperm identification rate in ejaculated semen, and outcomes of MD-TESE.

	NOA with varicocele repair (n = 11)
Number of semen analysis (Number of cases for each) Pre-varicocelectomy	Once (1 case), Twice (8 cases), 3 times (2 cases)
Number of semen analysis (Number of cases for each) Post-varicocelectomy	Once (1 case), Twice (1 case), 3 times (3 cases), 4 times (5 cases), 7 times (1case)
Sperm in ejaculated semen Pre-varicocelectomy	0% (0/11)
Sperm in ejaculated semen Post-varicocelectomy	0% (0/11)
Sperm Retrieval Rate with MD-TESE (%)	20% (2/10)
Duration from surgery to TESE (months)	8.5 (4-27)
Pathology in MD-TESE	Hyalinization: 1, SCO: 7, HS: 2
SCO: Sertoli cell only; HS: Hypo-spermatogenesis.	

Discussion

In this study, it was difficult to determine whether varicocelectomy contributed to SR in patients with NOA. Previous reports on varicocelectomy in patients with NOA have shown favorable SRR outcomes (1-7). In a systematic review of varicocele treatment in patients with NOA, *Jensen et al.* (8) described varicocelectomy for NOA as the only treatment capable of reviving sperm in ejaculated semen. This study showed that 13 studies had an average sperm presence rate of 27% in the ejaculated semen after varicocelectomy, while only two showed motile sperm. Further analysis of the MD-TESE outcomes after varicocelectomy revealed an average SRR of 48.9%, which was better than the average SRR of 32.1% in the untreated cohort group. *Ustuner et al.* (11) reported improved histopathological findings after varicocelectomy in patients with NOA.

However, a dilemma arises: should we aggressively recommend varicocelectomy for all patients with NOA complicated by varicocele? Some reports have shown varicocelectomy to only benefit a limited proportion of patients with NOA, including those with sperm maturation arrest or hypospermatogenesis, whereas patients with *Sertoli cell-only syndrome* (SCOS) do not benefit as much (5, 9, 10).

If varicocelectomy benefits only a limited population of patients with NOA and varicocele, such as those with sperm maturation arrest or hypospermatogenesis, it is important to select patients carefully. However, identifying patients who will benefit from varicocelectomy is difficult without a preoperative invasive testicular biopsy. Further, even if a testicular biopsy is performed, only a small portion of the testis is evaluated, making it impossible to reach a conclusive diagnosis. Regarding sperm maturation arrest, which is characterized by the maintenance of normal FSH levels and no evidence of seminal tract obstruction on physical examination and ultrasonography, the disease can be predicted from blood sampling results. Therefore, patients with NOA with normal FSH levels may be good candidates for varicocelectomy.

Our findings conflict with those of previous studies. A possible reason for this discrepancy may be problems with semen analysis accuracy during NOA diagnosis in previous studies. Uemura et al. reported that when they performed a thorough semen analysis of patients who had been diagnosed with azoospermia at another hospital and were referred for consultation, they were able to identify sperm in the ejaculated semen in 15.8% of the patients (12). In that report, patients with sperm identified in their ejaculated semen had FSH levels within a slightly higher or normal range. Among patients with FSH levels exceeding 15.3 mIU/mL, only 4.5% had identified sperm, representing a low rate. The World Health Organization semen analysis guidelines from the 2010 edition (13) clearly recommend including a centrifugation step if sperm cannot be identified via routine or repeated semen analysis. The likelihood of detecting sperm in the ejaculated semen depends on the quality of the semen analysis and skill of the embryologist. Consequently, a significant problem is that depending on the institution that performs the semen analysis, some patients may be diagnosed with NOA, while others may be classified as having cryptozoospermia or severe oligozoospermia. If patients with cryptozoospermia and severe oligozoospermia were included in the group of patients diagnosed with NOA, the chance of identifying sperm in the ejaculated semen of patients who underwent varicocelectomy would be relatively high. Thus, it is possible that these patients were included in the successful group in previous reports.

Varicocelectomy may be inefficient in cases where spermatogenesis is disrupted, such as SCOS. The diagnosis of NOA should be carefully made in accordance with guidelines, and surgical indications for varicocelectomy should be thoroughly considered. Our opinion on the indications for varicocelectomy in patients with NOA is that it is preferable to distinguish patients with genuine NOA and perform it only under exceptional circumstance, including maturation arrest.

This study has several limitations, including the small number of patients and its retrospective nature. In addition, the patients had varying medical backgrounds. We reiterate the need for more prospective studies with larger numbers of patients with well-matched backgrounds.

Conclusions

We found that varicocelectomies for varicoceles in patients with NOA did not lead to the identification of sperm in postoperative ejaculated semen samples or demonstrate good MD-TESE outcomes. These data indicate that varicocelectomy may contribute to an improved SRR in patients with limited NOA; however, these findings should be validated in future studies.

Declarations

Ethical approval and consent for participate: *The study protocol was approved by the Ethics Review Committee of the Dokkyo Medical University (Approval number: 21123). The need for written informed consent was waived owing to the retrospective nature of the study.*

Availability of data and material: *The datasets generated and/or analyzed during the current study are not publicly available for privacy protection but are available upon reasonable request from the corresponding author.*

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