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Therapeutic strategy after microsurgical varicocelectomy in the modern assisted reproductive technology era

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Abstract In this study, we searched for prognostic factors at preoperative examination for the improvement in spermatogenesis of patients undergoing varicocelectomy. Eighty patients with varicocele testis underwent microsurgical varicocelectomy. Before surgery, the seminogram, testicular volume, varicocele grade, and serum FSH, LH, testosterone, prolactin, and estradiol were evaluated. Postoperatively, semen analysis was performed every 3 months. We assessed the associations between the preoperative variables and postoperative seminogram improvement. of 80 patients, 37 showed improvement, usually by 6 months. Patient age, duration of sterility, testicular volume, sperm motility, morphology, semen volume, serum LH, testosterone, prolactin, and estradiol showed little difference between responders and non-responders. A small left testis, or a grade III varicocele decreased the likelihood of improvement. Patients with a sperm count of $10–20\times10^6$/ml were significantly more likely to respond to varicocelectomy than those with sperm counts $< 5\times10^6$/ml. Patients with elevated FSH were less likely to respond, as were those with a Johnsen score below 6. Varicocelectomy alone is unlikely to improve sperm counts of patients with a sperm count below 5×10^6/ml, high FSH, small left testes, or Johnsen scores below 6. In conclusion, for couples in this situation, assisted reproductive technology coupled with varicocelectomy should be proposed.

Keywords Varicocele testis · Microsurgical varicocelectomy · Prognostic factors

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Introduction

Controversy continues concerning the degree of negative impact of varicocele on male fertility and the ability of varicocelectomy to improve the fertility of affected men [5, 6]. Nonetheless, patients with varicocele have shown improved seminal characteristics and achieved increased pregnancy rates after this operation [1]. Recently, some infertile couples have been offered an early option of intrauterine insemination or use of artificial reproductive technology, even though the husband had a varicocele testis, because some patients show no improvement of an unfavorable seminogram after varicocelectomy. In such circumstances an intracytoplasmic injection is most likely to be required. Thus, since varicocele repair is apparently of limited value for some men, the patients most likely to benefit from varicocelectomy need to be identified. Patients will then require optimal follow-up after surgery. Accurately predicting who will respond to varicocelectomy is difficult. Attempts to define the patient subgroups most likely to benefit from the operation are worthwhile, but such studies have been affected by the heterogeneity of varicoceles and lack of control subjects. Previous authors have recommended varicocelectomy based upon size of the varicocele [7, 15], size of the testis [9], and, more recently, provocative endocrine testing [11, 21].

We studied oligozoospermic patients with clinically palpable varicocele to examine factors affecting the likelihood of sperm count improvement after varicocelectomy and to determined the criteria for the application of assisted reproductive technology (ART).

Materials and methods

All 80 patients were referred for infertility evaluation. Semen analysis was performed at least three times preoperatively after collection by masturbation following a 5-day abstinence period. All specimens were analyzed within 1 h of collection for determination of the volume of ejaculate, sperm count, and the percent motility using a Makler chamber (Sefi Medical, Haifa, Israel). When

azoospermia was diagnosed in all three specimens, patients were excluded from the study. Serum concentrations of FSH, LH, testosterone, prolactin, and estradiol were examined in the morning. Varicoceles were graded by physical examination in a warm room with the patient standing, using the guidelines of the World Health Organization [24]. The numbers of patients with grade I, II and III were 20, 27 and 33, respectively. Varicocelectomy was performed using a microsurgical technique [17]. Patients were followed up every 3 months for more than 6 months. The mean follow-up period was 11.0 ± 3.7 months (mean $\pm$ SD). Improvement in the seminogram after 6 months was evaluated according to criteria described previously [3]. Preoperative and postoperative semen analysis after 6 months or more were compared to identify improvement according to our criteria shown in Table 1. The rest were considered non-responders. Fertility problems in female partners were ruled out by a thorough gynecological examination. Patients whose wives had gynecological problems were excluded from the study. The mean age of female partners was 30.2 ± 3.1 years.

The statistical comparison of clinical parameters between responders and non-responders was performed by analysis of variance (ANOVA) followed by Scheffe multiple comparison testing, or, where appropriate, by an unpaired Student's *t*-test. Comparisons between responders and non-responders in relation to variables potentially influencing outcome were made using a χ^2 test or a Kruskal-Wallis test adjusted for multiple comparisons. Multivariate analysis (age, testicular volume, varicocele grade, preoperative sperm concentration, motility, morphology, total sperm count, semen volume, and hormone level) was performed to determine improvement in the seminogram. P values < 0.05 indicated significance.

Results

Of 80 patients, 37 (46.3%) were responders to varicocelectomy in terms of improvement in the seminogram, usually within 6 months (31 patients; 83.8%). Pregnancy by natural intercourse was achieved by 15.8% of all patients. All patients who caused a spontaneous pregnancy showed an improvement of the seminogram. When we compared demographic, clinical, and laboratory variables between responders and non-responders (Table 2), age of patients, duration of sterility, testicular volume, preoperative sperm concentration, motility, morphology, total sperm count, semen volume, serum LH, testosterone, prolactin, and estradiol showed no significant difference between responders and non-responders. However, preoperative sperm concentration, total sperm count and the Johnsen score determined from the testicular biopsy specimens tended to be higher in responders than non-responders, while FSH in responders appeared to be lower than in non-responders.

We analyzed potential preoperative prognostic factors for sperm count improvement by grouping patients according to testicular volume, varicocele grade, sperm count, preoperative serum hormone concentrations, and Johnsen score (Table 3). A small left testis relative to the right was associated with less likelihood of improvement than similar right and left testicular sizes (33.3% vs 62.5%; $P = 0.0267$). Improvement rates in patient groups with varicocele grade I, II, and III were 50, 66.7, and 27.3%, respectively, and the rate of grade III was significantly lower than grade II ($P = 0.0095$). The rate of improvement in patients with a sperm count of $< 5\times10^6$/ml, 5–10×10^6/ml, and 10–20×10^6/ml were 25.0, 56.5, and 55.2%, respectively, being significantly higher for the highest- and intermediate-count groups vs the lowest-count group ($P = 0.0320$). Serum concentrations of LH, testosterone, prolactin, and estradiol did not show a relationship to improvement. In contrast, patients with abnormally high FSH concentrations had a lower improvement rate (29.2%) than those with normal FSH concentrations (53.8%; $P = 0.0448$). As for the histopathological analysis of testicular biopsy specimens, patients with a Johnsen score < 6 (18.8%) had a significantly lower response rate than those with scores ≥ 6 but < 7 (54.5%) or scores > 7 (57.1%) ($P = 0.0354$).

Using all of the variables described above, multivariate regression analysis was carried out to identify the factors that independently predict therapeutic benefit form varicocelectomy. Sperm count ($P = 0.0122$)

Table 2. Patients' characteristics. Some data are missing in testicular volume and Johnsen score

	Responders ($n = 37$)	Non-responders ($n = 43$)
Term of sterility (months)	32 ± 4.1	33 ± 4.4
Age (years)	30.9 ± 18.5	43.5 ± 38.8
Testis volume (ml) ($n = 71$)		
Rt	19 ± 3.5	17 ± 4.6
Lt	18 ± 3.7	16 ± 4.9
Seminogram		
Sperm conc ($\times10^6$/ml)	11.0 ± 6.0	7.0 ± 5.3
Sperm motility (%)	40.0 ± 17.0	39.0 ± 17.0
Sperm morphology (% of abnormality)	42.7 ± 13.8	48.8 ± 12.0
Total sperm count ($\times10^6$)	35.0 ± 26.1	22.1 ± 25.8
Volume (ml)	3.6 ± 1.4	3.4 ± 1.4
Hormones		
FSH (mlU/ml)	7.0 ± 4.2	11.0 ± 10.0
LH (mlU/ml)	4.4 ± 2.2	5.0 ± 3.3
Testosterone (ng/ml)	6.2 ± 7.6	4.5 ± 1.4
PRL (ng/ml)	9.5 ± 6.7	11.0 ± 8.0
E_2 (pg/ml)	26.0 ± 8.5	26.0 ± 12.0
Johnsen score (n = 66)	6.95 ± 1.1	6.22 ± 1.4

Table 1. Criteria for the improvement of spermiogram after surgery. * indicates compared with concentration or motility before surgery

	Improvement	
	Before surgery	After surgery
Sperm concentration	$< 1\times10^6$/ml	Increase $> 5\times10^6$/ml
	1×10^6/ml $\leq$ SD $< 5\times10^6$/ml	Increase $> 10\times10^6$/ml
	5×10^6/ml $\leq$ SD $< 10\times10^6$/ml	Increase $> 20\times10^6$/ml
	10×10^6/ml $\leq$ SD $< 20\times10^6$/ml	Increase more than two times*
Sperm motility		Increase more than two times*

Table 3. Results for patients according to their clinical parameters. Some data are missing because each test could not be performed in all patients.* indicates a significant difference ($P < 0.05$) by χ^2 test or Kruskal-Wallis test. P values of testicular volume, grade, sperm concentration, FSH, and Johnsen score were 0.0267, 0.095, 0.0320, 0.0448, and 0.0354, respectively

	n	Responders (%)	Non-responders
Testicular volume*			
Right > left	39	13 (33.3)	26
Right = left	32	20 (62.5)	12
Grade*			
I	20	10 (50.0)	10
II	27	18 (66.7)	9
III	33	9 (27.3)	24
Sperm concentration*			
$< 5\times10^6$/ml	28	7 (25.0)	21
$5–10\times10^6$/ml	23	3 (56.5)	10
$10–20\times10^6$/ml	29	16 (55.2)	13
FSH*			
Normal (1.6–9.2 mlU/ml)	54	29 (53.7)	25
High (> 9.2 mlU/ml)	24	7 (29.2)	17
LH			
Normal	72	34 (47.2)	38
High	6	2 (33.3)	4
Johnsen score*			
Score < 6	16	3 (18.8)	13
6 ≤ score < 7	22	12 (54.5)	10
Score≥7	28	16 (57.1)	12

independently predicted improvement of the seminogram.

Discussion

Several attempts have been made to predict which patients with varicocele are likely to benefit from varicocelectomy in terms of an improved seminogram. Such prediction has proven very difficult. Reasons include the absence of objective criteria for evaluating varicocelectomy candidates and the lack of universally standardized criteria for improvement. In this study we performed varicocelectomy in oligozoospermic men with clinically palpable varicoceles and later analyzed those factors potentially related to the outcome.

Patients with sperm counts $> 5\times10^6$/ml, normal FSH concentrations, small varicoceles, no testicular hypotrophy, or a Johnsen score ≥6 were most likely to show postoperative improvement.

Many studies have considered factors possibly related to the surgical outcome in varicocele. In various previous reports, the response was positively related to varicocele size, showing a greater improvement in semen parameters following the repair of larger varicoceles [20, 22]. In other studies varicocele size had no relationship to seminal improvement [14]. We found larger varicoceles to be associated with less improvement in the postoperative seminogram, presumably because a large varicocele can irreversibly damage testicular function [23]. We found a lower Johnsen score (6.27 ± 1.37) associated with grade III varicocele than with grade I (6.98 ± 1.04) or II (6.61 ± 1.43). Uyger et al. [23] also reported lower Johnsen scores in grade III than in grade I or II cases. Su et al. [21] reported that the primary effect of varicocelectomy is to normalize serum testosterone levels and that this especially appears to benefit patients in whom varicoceles have a more detrimental effect on the hormonal function of the testis. Lecomte et al. [13] concluded that among hormones FSH was the best indicator of male reproductive function, with elevated FSH predicting a low likelihood of achieving pregnancy after varicocelectomy. In agreement, our study showed FSH level to be an important prognostic factor. In a detailed examination of serum hormones by Hadziselimovic et al. [6], patients with low plasma testosterone, but normal LH and FSH showed a significant improvement in sperm count after surgery. Recently, inhibin B was reported to be a good marker for spermatogenesis [9]. In a previous study, we also reported that preoperative serum inhibin B concentration could not reliably predict a response to varicocelectomy. However, a change in serum inhibin B concentration after varicocelctomy may be helpful in evaluating the improvement of testicular function after varicocelectomy [4].

With respect to the histological findings, Uygur et al. [23] reported that their varicocelectomy patients had Johnsen scores for both testes that fell below the lowest normal value of 8.9 [10]. They also found a positive correlation between Johnsen score and preoperative sperm counts in these patients [23]. The analysis of testicular biopsy specimens suggests that a certain threshold of spermatogenesis, requiring the presence of at least spermatids, is necessary for a good reproductive result after varicocele repair [12]. This is consistent with our finding that a score of at least 6 was needed for a good outcome. In another study, pregnancies occurred after surgery only when the preoperative Johnsen score for at least one testis exceeded 7.0 [8].

One study has suggested that pregnancy rates were higher when sperm counts exceeded 10×10^6/ml, being lower in severely oligozoospermic cases in which sperm counts were less than 10×10^6/ml [2]. However, another study reported a good outcome despite counts below this value [18]. In our study, patients with sperm counts $< 5\times10^6$/ml had a poorer outcome than those with sperm count $\geq 5\times10^6$/ml. Therefore, sperm count appears to be related to the outcome, though the threshold count permitting success was somewhat lower than in some reports.

A small left testis (relative to the right) is a finding suggesting varicocele in some men [14, 16, 19]. Marks et al. [14] reported that testicular atrophy in an infertile patient indicated a decreased potential for seminal improvement and pregnancy after varicocele repair [14, 16]. In our study, patients with no difference in size between the right and left testes had better outcomes than those showing such differences.

In conclusion, the prognostic factors identified in this study of varicocele patients may be used as a guide

to subsequent clinical management. Those unfortunate patients who are unlikely to show postoperative improvement of the seminogram should be informed of this preoperatively and also should be told that careful follow-up assessment and early consideration of intrauterine insemination or other assisted reproductive technology will be needed. Such counseling should include a presentation of the relative risks and benefits of each treatment, and must be individualized for each couple, with particular consideration of the spouse's age.

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