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ORIGINAL PAPER

Microsurgical varicocelectomy efficacy in treatment of men with primary and secondary infertility (retrospective study)

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Summary ***Introduction and objectives: Varicocele is the most common treatable cause of male infertility. The study aimed to compare varicocelectomy efficacy in men with primary (PI) and secondary infertility (SI).***
Patients and methods: Medical records of 100 men suffering from PI and SI and having varicocelectomy at the Republican Specialized Scientific-Practical Medical Center of Urology were retrospectively selected and analyzed. Patients were divided into 2 groups. Group I included 58 men with PI and Group II 42 men with SI. Preoperative clinical characteristics and semen parameters before and after varicocelectomy were analyzed and compared between groups.
Results: Analysis revealed that the mean age of patients of group I was significantly lower ($p < 0.001$) and the duration of infertility was accurately shorter ($p < 0.01$) than those of group II. Main semen parameters increased significantly in group I (e.g., sperm concentration increased by 50%, from 62.2 ± 8.7 to 93.5 ± 10.0 M/ml, and total motile sperm count increased by 113%, from 76.7 ± 17.1 to 163.4 ± 27.8 M $p < 0.05$), while in group II only rate of progressive motile sperm increased significantly (by 107%, from 13.5 ± 2.6 to 28.0 ± 5.2% $p < 0.05$).
We identified a significant difference in varicocelectomy efficacy between group I and group II in change of total motile sperm count (by 113% vs. 74% respectively, $p < 0.01$). We also revealed a discrepancy between groups in correlation ratio (r) between initial and post-surgical percent of progressive motile sperm.
Conclusions: Patients with SI were older and had longer infertility period. Varicocelectomy resulted in significant semen parameters improvement in patients with PI. In patients with SI, only percent of progressively motile sperm improved significantly. It indicates that advanced male age and long infertility duration may have a negative impact on varicocelectomy success.

KEY WORDS: *Varicocele; Varicocelectomy; Primary infertility; Secondary infertility.*

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INTRODUCTION

Currently, research are conducted actively on possible causes of male infertility. Varicocele is the most common cause of primary and secondary infertility in men. In this regard, varicocele repair remains the most frequently performed surgery to correct male factor infertility (1, 2). Analysis of the literature demonstrated that among men with primary infertility, the proportion of patients with varicocele is 33-40%, and among those who suffer from secondary infertility it is up to 81% (1).

According to data from many authors, in varicocele, the testis suffers from venous overflow and it is supplied with blood poor in oxygen and nutrients, leading to atrophy of its tissue (1, 6). Another pathogenetic factor is the increase of testicular temperature to + 37°C due to the overflow of venous blood. Most men with varicocele are fertile, but the prevalence of infertility in this group is increased compared with the general population. However, more than 40% of patients with varicocele have reduced sperm quality (1). The relationship between varicocele and semen parameters may be different. Microcirculation disorders evolving with varicocele leads to an increase in the testis cells' concentration of reactive oxygen species and oxidative stress. The latter is nowadays considered a leading pathophysiological mechanism of pathozoospermia with varicocele (6).

Recent *randomized controlled trials* (RCTs) have demonstrated that varicocele repair (varicocelectomy) in patients with clinical varicocele and pathologies of semen analysis leads to a significant increase in pregnancy rates (3) and improvement of semen quality in relation to observation group (control) (4). Other authors in RCTs revealed low efficiency of varicocelectomy in cases of subclinical varicocele and normal semen parameters (5).

Persad et al. and *Cayan et al.* referring to a large number of studies indicated that microsurgical (inguinal and subinguinal) ligation of spermatic cord veins is the most appropriate surgery for the treatment of clinical varicocele with infertility (6, 7).

Fukuda et al. conducted a study of 71 infertile men who underwent microsurgical varicocelectomy. The subjects had their semen analysis taken 3 times (before and after the intervention, at 3 and 12 months). The results showed that the quality of semen analysis at 3 months after surgery was significantly better than that before surgery. No statistically significant differences were detected between semen parameters taken at 3 and 12 months after surgery (8).

Walsh et al. in their study came to the conclusion that

men with primary and secondary infertility with varicocele may have different clinical characteristics including semen parameters, i.e. males with secondary infertility had significantly better parameters of the semen (sperm concentration) (9).
In this regard, we aimed to assess initial semen parameters and varicocelectomy efficacy in men with primary and secondary infertility dividing them into two separate groups.

Patients and methods

During the study, we evaluated the main semen parameters: semen volume (ml), sperm concentration (million/ml) and total sperm count (million), % of sperm with progressive motility, total sperm motility (%), and *total motile sperm count* (TMC) according to WHO 2010 Manual (10).
The presence of varicocele was determined by visual and palpation methods, as well as using Doppler ultrasound of the testis according to the 2000 WHO classification of varicocele (subclinical varicocele, I, II, III) (11).

Patient selection

We used the following inclusion and exclusion criteria for recruiting appropriate patients for our study.

Inclusion criteria

- patients had their semen analysis taken before and after varicocelectomy (at 3 - 12 months);
- patients with a pathological deviation of at least one of the studied parameters of semen analysis;
- patients with clinical varicocele (grade I-III);
- patients with complaints of pregnancy absence in their partners for 12 months and longer period.

Exclusion criteria

- patients with azoospermia and normozoospermia (according to WHO 2010 Manual);
- patients with other infertility causes.

Patients

According to those criteria we selected for the study and carefully explored the medical cards of 100 men aged from 21 to 46 years, who suffered from infertility and varicocele.
Patients were divided into 2 groups: 58 men with primary infertility (aged from 21 to 38 years) were included in group I and 42 ones with secondary infertility (aged from 24 to 46 years) were recruited into group II.

Ethical approval

The collection and the analysis of these data were approved by the Republican Specialized Scientific-Practical Medical Center of Urology local ethics committee.

Surgical procedure

All patients underwent microsurgical subinguinal/inguinal varicocelectomy. Procedures were performed by three experienced surgeons following the techniques described below. A 4-5 cm incision was made inferior to the external inguinal ring in the subinguinal technique and over the inguinal canal in the inguinal technique.
The spermatic cord was isolated, and the veins were dissected away from the arteries, lymphatics, vas deferens, and ligated under special surgical loupes or microscope.

Statistical analysis

Statistical data were analyzed by MS Excel 2019 and IBM SPSS© Statistics 21.0 statistical packages. The significance of differences between groups was calculated using Student's t test for means; differences were considered significant at $p < 0.05$.

Results

Analysis revealed that the mean age of patients in group I was significantly lower ($p < 0.001$) and the mean duration of infertility was significantly shorter ($p < 0.01$) than those of patients of group II (Table 1). Most patients had left-sided varicocele (76 patients, 76%) (Table 1).
BMI of 36 (36%) patients was slightly higher than normal (25.0-30.0), which was evaluated as pre-obese, BMI of 18 (18%) was significantly higher than normal (> 30.0), which was assessed as obesity, and BMI of 46 (46%) patients was within normal range (18.5-25.0) (12).

Table 1.
Key features of group of patients.

Groups	Age M ± G	Anthropometric data			Varicocele *						Duration of infertility (in months) M ± G
					Side			Grade			
		Height	Weight	BMI **	Left	Right	Bilaterlal	I	II	III	
Group I	27.4 ± 0.6	1.7	81.2	26.8	40	-	2	8 (29)	19 (68)	1 (3)	28.7 ± 4.6
Group II	31.0 ± 0.6	1.7	79.9	26.5	36	2	4	5 (23)	15 (68)	2 (9)	51.8 ± 5.6
P	< 0.001	-	-	-	-	-	-	-	-	-	< 0.01
TOTAL	-	-	-	-	76 (76)	2 (2)	6 (12)	8 (20)	34 (68)	3 (6)	-

** Data are given in absolute numbers in relation to the group.*
*** Body mass index.*

Following Table 2 shows the main semen parameters of patients of both groups before surgery for statistical comparison.
As it is seen from Table 2, no statistically significant differences in the initial semen parameters were revealed between groups.

Table 2.
Main parameters of semen analysis in both groups in preoperative period for their comparative estimation.

Groups	Semen volume. ml M±m	Sperm concentration (M/ml) M±m	Total sperm count (M) M±m	Sperm with progressive motility (%) M±m	Total sperm motility (%) M±m	Total motile sperm count (M) M±m
First	3.4 ± 0.3	62.2 ± 8.7	213.6 ± 35.9	11.4 ± 2.3	30.8 ± 3.6	76.7 ± 17.1
Second	3.7 ± 0.3	47.2 ± 8.6	171.9 ± 33.5	13.5 ± 2.6	35.1 ± 4.6	76.3 ± 19.2
P	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

Table 3.
Comparative assessment of main semen parameters of both groups in pre- and post-surgical period.

Groups	Semen volume. ml M±m	Sperm concentration (M/ml) M±m	Total sperm count (M) M±m	Sperm with progressive motility (%) M±m	Total sperm motility (%) M±m	Total motile sperm count (M) M±m
Group I [1]	3.4 ± 0.3	62.2 ± 8.7	213.6 ± 35.9	11.4 ± 2.3	30.8 ± 3.6	76.7 ± 17.1
Group I [2]	3.4 ± 0.2	93.5 ± 10.0	341.8 ± 46.6	20.0 ± 3.1	46.1 ± 4.5	163.4 ± 27.8
P [3]	> 0.05	**< 0.05**	**< 0.05**	**< 0.05**	**< 0.05**	**< 0.05**
Group II [1]	3.7 ± 0.3	47.2 ± 8.6	171.9 ± 33.5	13.5 ± 2.6	35.1 ± 4.6	76.3 ± 19.2
Group II [2]	3.9 ± 0.3	65.7 ± 10.2	246.9 ± 40.8	28.0 ± 5.2	46.0 ± 6.0	132.7 ± 31.3
P	> 0.05	> 0.05	> 0.05	**< 0.05**	> 0.05	> 0.05
P [4]	> 0.05	> 0.05	> 0.05	**< 0.01**	> 0.05	**< 0.01**

[1] Preoperative period; [2] Postoperative period; [3] Statistically significant changes; [4] Statistically significant differences between groups.

Preoperative and postoperative semen parameters of patients of both groups are given in Table 3 for comparison of varicocelectomy efficacy before and after repair, as well as between groups.

In the postoperative period, the following changes were observed in average counts of studied semen parameters in both groups:

- semen volume in both groups remained unchanged ($p > 0.05$);
- sperm concentration increased significantly in group I (by 50% $p < 0.05$), while in group II it increased not significantly (by 39% $p > 0.05$);
- total sperm count increased by 60% ($p < 0.05$) in group I, whereas in the second one this parameter increased by 44% ($p > 0.05$);
- percent of sperm with progressive motility increased more in group II (by 107% $p < 0.05$) than in group I (by 75% $p < 0.05$) and the difference between groups was significant ($p < 0.01$);
- total sperm motility also increased significantly (by 50% $p < 0.05$) in group I, while in group II this parameter also increased, but not significantly (by 31% $p > 0.05$);
- total motile sperm count in group I increased more significantly ($p < 0.01$) than in group II (113% $p < 0.05$ *vs.* 74% $p > 0.05$ respectively).

As it was shown above, statistically significant differences were revealed between groups in changes in some postoperative semen parameters. In patients of group I varicocelectomy resulted in significant improvements in all semen parameters. In contrast to group I in group II, statistically accurate improvement occurred for only percent of sperm with progressive motility, which increased more significantly than in group I.

We also revealed a significant discrepancy between groups in correlation ratio (r) between the initial and post-operative % of sperm with progressive motility. In patients of group I there was no correlation ($r = -0.02$), whereas in patients of group II correlation was direct and strong ($r = 0.71$). In general, differences between groups in mean correlation ratios between initial and postsurgical semen parameters were not significant ($r = 0.4$ for group I and $r = 0.5$ for group II).

Discussions

Currently, a varicocele is the most common surgically curable cause of male infertility. Although the vast majority of research supports the opinion of the beneficial effect of surgical treatment of varicocele on sperm parameters (3, 4, 13), the question of the true effect of surgery on testicular function remains unresolved (1). Although the exact relationship between improvements in indicators of semen analysis and surgical treatment of varicocele has not been finally determined, a meta-analysis of RCTs conducted by *Agarwal et al.* showed significant improvement in semen parameters after varicocelectomy (13), which corresponds to the results of our research.

However, interesting is the fact that greater significant changes occurred in patients with primary infertility and varicocele than those in patients with secondary infertility and varicocele, although in patients with secondary infertility a positive effect of intervention was also determined.

There are a number of reports on the association between initial semen parameters and the efficacy of the varicocele repair. These studies assumed that men with higher preoperative semen parameters are more likely to see an improvement in their semen parameters after varicocelec-

tomy (14, 15). Our study partially confirmed this statement because the association between initial and postsurgical semen parameters was moderate.
According to some authors, varicocele is more common in men with SI than in men with PI, but the difference is not so high (+3.5%, $p < 0.05$) (16). They also noted that patients with PI and SI were almost of the same age which finding does not agree with our results.
It is also worth noting that according to some authors, the average age of men with secondary infertility is older, which corresponds to our data. However, they also state that there is no significant difference in the duration of infertility, whereas our study revealed a significant difference in this parameter between primarily and secondarily infertile men (9, 17). In addition, the above-mentioned authors claim the presence of differences in initial semen parameters of patients with secondary infertility, although to our knowledge no statistically significant differences were revealed between baseline semen parameters of men with primary and secondary infertility.
The main limitation of our study was the small sample size that in turn resulted in the differences between groups in mean patient's age and infertility duration.

Conclusions

The mean age and duration of infertility in patients with SI were higher than those in patients with PI. Varicocelectomy resulted in significant improvement of main semen parameters in patients with PI. In patients with SI varicocelectomy resulted in significant improvement of only a percent of progressively motile sperm. It indicates that advanced male age and long infertility duration may have a negative impact on varicocelectomy success. Further large-scale clinical trials are needed to confirm this statement.

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Conflict of interest: The authors declare no potential conflict of interest.