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Comparison of DNA fragmentation index and fertility rate after unilateral and bilateral microsurgical varicocelectomy

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Abstract

Varicoceles and their impact on sperm quality are considered one of the most common causes of male infertility. This study aims to examine the outcomes of unilateral and bilateral microsurgical varicocelectomy concerning DNA Fragmentation Index (DFI), different sperm parameters, and overall fertility. This is a cross-sectional study in which we analyzed 100 male patients who were diagnosed with varicocele by ultrasound and had a history of infertility of at least one year. Fifty patients had unilateral varicocele and 50 had bilateral varicocele (left side clinical plus right side subclinical) who underwent microsurgical varicocelectomy from March 21, 2022, to March 21, 2023. We compared the DFI before and after surgery, and fertility rates between the two groups were assessed. The median age of participants was 32 years, with a body mass index (BMI) of 25 kg/m² and an average infertility duration of 2 years. A comparative analysis revealed a statistically significant difference in the median years of infertility between the unilateral and bilateral groups before surgery ($p=0.03$). Both unilateral ($p<0.001$) and bilateral ($p<0.001$) microsurgical varicocelectomy significantly reduced DFI. However, the bilateral approach was better at lowering DFI than the unilateral method in microsurgical varicocelectomy ($p<0.05$). The pregnancy rates after surgery were 36.0% for the unilateral and 58.0% for the bilateral group; this difference was statistically significant, favoring bilateral microsurgical varicocelectomy ($p=0.04$). Microsurgical varicocelectomy is a viable treatment option for couples facing oligospermia, especially for those with bilateral varicoceles.

Key Words: varicocele, infertility, microsurgical varicocelectomy, sperm DNA fragmentation index, oligospermia.

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Varicocele is an important cause of male infertility, affecting approximately 10-15% of the general male population, 30-35% of those with primary infertility, and 69-81% of men experiencing secondary infertility.[1] The mechanisms through which varicocele causes testicular dysfunction and infertility are complex and involve multiple factors. These include small vessel blockage and blood pooling, which raise scrotal temperature and cause testicular hypoxia, reflux of toxic substances from the adrenal or kidney disruption of the hypothalamic-pituitary-gonadal axis; oxidative stress and decreased antioxidant capacity.[2-6]

The evidence points out the important link between varicocele, oxidative stress, and sperm dysfunction in infertile men. Increased levels of ROS and reduced TAC have been associated with DNA damage in sperm, including single- and double-strand breaks. This oxidative stress is critical in impairing sperm DNA integrity, which correlates with reduced fertility potential in assisted reproduction techniques.[7-10]

The Sperm Chromatin Structure Assay (SCSA) is a clinically relevant technique for assessing sperm DNA fragmentation through the DNA Fragmentation Index (DFI), which reflects the percentage of sperm with denatured nuclei.[11] High DFI levels, particularly at 20% or more, are linked to lower success rates in Assisted Reproductive

Technologies (ARTs) like Intracytoplasmic Sperm Injection (ICSI). A DFI value of more than 25% serves as a clue to the degree of DNA fragmentation and a main predictor of reproductive outcomes following ARTs. This threshold underlines the importance of DNA integrity assessment in the male partner because high fragmentation levels are statistically related to increased reproductive challenges.[12] DFI assessment is thus critical to determining male fertility and predicting reproductive outcomes, making it a significant tool in fertility investigations.

Varicocelectomy is widely recognized as an effective treatment for varicocele, particularly for men with infertility. Whereas the initial interest was mainly focused on improvement in natural conception rates following the surgery, growing evidence highlights the benefits of varicocelectomy on semen quality, including DNA quality, sperm DNA fragmentation, and overall sperm parameters.[13-16]

While guidelines currently recommend the treatment of varicoceles in selected cases of infertility, the effects of varicocelectomy on DFI are less clear due to limited research. This study aimed to elucidate the relationship between varicocelectomy and sperm DFI, hence contributing to the management of male infertility.

Materials and Methods

Study design

This cross-sectional study enrolled 100 microsurgical varicocelectomy candidates, comprising 50 males with unilateral varicocele and 50 males with bilateral varicocele (including subclinical cases). Participants were referred to Baqiyatallah Hospital in Tehran, Iran, from March 21, 2022, to March 21, 2023.

Inclusion criteria include eligible males who have been diagnosed with varicocele based on preoperative clinical assessments, ultrasound examinations, and a history of at least one year of infertility. The following were excluded from participating in the study: Individuals with a history of cigarette smoking, alcohol consumption, radiotherapy, cancer, the use of cytotoxic agents, chemotherapeutic agents, and acute or chronic infections.

The sample size was determined using previous studies[17,18] utilizing a disease prevalence of 45%, an alpha of 0.10, a power of 90%, and an attrition rate of 20%. The sample size was calculated using the following formula

$$n = \frac{z\left(1-\frac{\alpha}{2}\right)PQ}{d^2}$$

Socio-demographic and anthropometric measurements

Participants completed a comprehensive questionnaire assessing socio-demographic characteristics, including age, duration of infertility, and educational attainment before surgery. Anthropometric measurements (weight and height) were obtained to calculate body mass index (BMI) using the standard formula: BMI=weight (kg) / (height [m²]). Postoperative follow-up was conducted at one year to evaluate pregnancy outcomes (dichotomized as successful or unsuccessful).

Evaluation of laboratory findings

Laboratory parameters were evaluated using pre- and postoperative data extracted from hospital records. For each participant, we analyzed semen volume (mL), sperm concentration ($\times 10^6$/mL), total sperm count (million/mL), sperm morphology (normal forms, %), and DNA fragmentation index (DFI, %). Varicocele diagnosis (unilateral or bilateral) was confirmed through standardized scrotal ultrasonography.

Statistical analysis

All statistical analyses were performed using SPSS version 26 (SPSS Inc., Chicago, IL, USA). Significance was considered to be at $P < 0.05$. Quantitative variables were assessed for normal distribution using the Kolmogorov-Smirnov test.

Intergroup comparisons of quantitative variables were performed using either independent samples t-tests (for normally distributed data) or Mann-Whitney U tests (for non-normally distributed data). Qualitative variables were compared using either χ^2 tests or Fisher's exact tests, as appropriate. Intragroup differences between baseline and postoperative measurements were assessed using paired t-tests.

Results

As presented in Table 1, the participants had a median age of 32 years, a BMI of 25 kg/m², and an average infertility duration of 2 years. When a comparison analysis was done between the unilateral and bilateral varicocele groups before surgery, the difference in the median years of infertility between these groups was statistically significant (p=0.03). However, no significant difference was found between the groups for other socio-demographic and anthropometric characteristics before intervention ($p > 0.05$).

Men who underwent bilateral varicocelectomy had a significantly higher pregnancy rate than those who opted for unilateral varicocele repair. Moreover, the naturally spontaneous pregnancies were very high in the group that underwent bilateral varicocelectomy.

Table 2 presents the comparative outcomes of DFI and pregnancy rates between unilateral and bilateral microsurgical varicocelectomy procedures. The mean DFI was 20.3% ±7.5 for the unilateral group (n=50) and 24.1% ±7.0 in the bilateral group (n=50). After surgeries, the DFI in the unilateral group was 16.5% ±6.1, and that of the bilateral group was 18.5% ±6.0.

Both surgical approaches demonstrated significant reductions in DFI compared to controls (unilateral: $p < 0.001$; bilateral: $p < 0.001$). Moreover, the bilateral approach demonstrated statistically superior outcomes compared to unilateral varicocelectomy, reflecting a clinically meaningful improvement in success rates (mean change: -5.5 vs. -3.9, respectively; $p < 0.05$).

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Table 1. *General characteristics of the participants in unilateral and bilateral groups before surgery.*

Variable	Total (n=100)	Unilateral group (n=50)	Bilateral group (n=50)	*P-value
Age (y)	32.0 (28.0, 35.0)	32.0 (28.0, 35.0)	32.5 (29.0, 35.0)	0.42
Body mass index (kg/m^2)	25.0 (23.0, 27.0)	26.0 (23.1, 27.7)	24.7 (23.0, 27.0)	0.23
Infertility (year)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	3.0 (2.0, 3.3)	0.03
Semen volume (ml)	2.9 (1.8, 4.0)	3.0 (1.0, 4.5)	2.7 (1.8, 3.4)	0.20
Sperm concentration (× 10^6/ml)	33.0 (15.0, 68.3)	32.0 (13.5, 57.3)	35.0 (16.0, 71.8)	0.28
Total sperm (million/ml)	91.3 (28.5, 229.8)	95.8 (27.7, 221.3)	90.0 (28.8, 232.8)	0.86
Sperm morphology	2.0 (1.0, 5.0)	2.0 (1.0, 3.8)	2.0 (1.0, 5.3)	0.97
DNA fragmentation index (%)				0.15
DFI ≤15	22 (22.0)	15 (30.0)	7 (14.0)	
15<DFI<30	59 (59.0)	27 (54.0)	32 (64.0)	
DFI ≥30	19 (19.0)	8 (16.0)	11 (22.0)	
Education				0.74
Diploma and under diploma	10 (10.0)	4 (8.0)	6 (12.0)	
Above diploma	90.0)	46 (92.0)	44 (88.0)	

*Data are presented as median (P25, P75) for quantitative and number (%) for qualitative variables; *Mann-Whitney U test was used for comparison of quantitative variables and chi-square or Fisher's exact tests were used for comparison of qualitative variables between the two groups; P<0.05 was considered statistically significant.*

Table 2. *Comparing DNA fragmentation index and successful pregnancy after unilateral and bilateral microsurgical varicocelectomy.*

Variables	Unilateral group (n=50)	Bilateral group (n=50)	*P-value	Mean change	**P-value	***P-value
DFI (%)						
Before surgery	20.3±7.5	24.1±7.0	0.01	-3.9±3.5	0.01	–
After surgery	16.5±6.1	18.5± 6.0	0.09	-5.5±2.6		
*P-value****	<0.001	<0.001				
Successful pregnancy						
Yes	18 (36.0)	29 (58.0)	–	–	–	0.04
No	32 (64.0)	21 (42.0)	–	–	–	

*Values are expressed as means±SD or number (percent); *Independent sample t-test was used for comparisons between groups before and after the surgery; **Mean change of DFI was compared between the groups using independent sample t-test; ***Chi-square or Fisher's exact tests were used for comparison of qualitative variables between the two groups; ****Paired t-test was used to compare within group difference before and after the surgery. P<0.05 was considered statistically significant.*

Furthermore, our results indicated that pregnancy rates following surgery were 36.0% for the unilateral varicocelectomy group and 58.0% for the bilateral group. There was a higher rate of unsuccessful pregnancies in the unilateral group, with 64% (32 out of 50), compared to only 42% (21 out of 50) in the bilateral group. This difference was statistically significant, indicating that bilateral microsurgical varicocelectomy resulted in a higher success rate compared to unilateral varicocelectomy (p=0.04).

Discussion

Varicocele repair is associated with significant improvements in male reproductive health, particularly in semen quality, despite individual outcome variations.[19,20] Varicocele negatively affects sperm morphology, concentration, and motility, contributing to male factor infertility. Varicocelectomy offers a viable and less invasive option for couples seeking to enhance fertility potential while preventing further decline in seminal parameters.[19,20] The effectiveness of varicocelectomy among infertile patients with normal semen parameters and with subclinical varicocele is still debated. No significant improvement in pregnancy rates after varicocele repair among such populations has been reported in the meta-analyses.[21] Varicocelectomy is still controversial for men with nonobstructive azoospermia.[22] However, there is some evidence to suggest that previous varicocele repair may improve sperm retrieval rates,[5] and thus more research is needed to establish the real benefits and limitations of this surgical intervention in different infertility scenarios. The lack of clear guidelines about the benefits and indications of varicocelectomy for male infertility may raise confusion regarding the application of this treatment in daily practice. The American Society for Reproductive Medicine's Practice Committee advises waiting one year for semen characteristics to improve. However, limited studies assess the optimal waiting period after VC repair, which is the main focus of our research.

Our study further supports the role of microsurgical varicocelectomy as an effective treatment for men with infertility associated with palpable varicoceles and abnormal sperm analysis. The significant reduction in sperm DFI observed following both bilateral and unilateral varicocelectomy underscores the potential of these surgical interventions to improve sperm quality and enhance reproductive outcomes. In the current study, after the procedures, the unilateral group had a mean DFI of 16.5%±6.1, and the bilateral group had a DFI of 18.5%±6.0. Furthermore, enhanced biomarkers related to male infertility have been established, such as those that pertain to semen quality.

The evidence from various studies, including those by Mohamed *et al.* and Zampieri *et al.*, indicates that varicocelectomy can significantly enhance semen parameters in both primary and secondary infertile men.[23,24] These findings are further supported by Alhathal *et al.*, who noted improvements in DFI and sperm progressive motility post-surgery.[25] The consistency of these results across several studies is further shown by Lima *et al.* and La Vignera *et al.*, thus proving that varicocele treatment is effective in improving reproductive health and could be a good option for men experiencing infertility problems associated with the disorder.[26,27] There is an established relationship between varicocele and sperm DNA fragmentation. Repairing varicoceles has been associated with decreased SDF, possibly improving fertility potential in such individuals.[28,29] DFI is an important indicator of sperm DNA integrity and damage, as studies indicate the value of DFI as a predictor of ART outcome. A DFI threshold of 25% is clinically significant, as levels above this are associated with an increased risk of reproductive issues in men.[30]

Concerning the optimum time of waiting following varicocele repair that is considered optimal for improving sperm DFI and normal semen parameters, a study by Hamidi Madani *et al.* demonstrates a significant reduction in sperm DFI following varicocelectomy, which is more evident in the first four months following surgery.[31] A meta-analysis involving a larger population with varicocele supports this study, with increased DFI before surgery and significant reductions at 3, 6, and 12 months thereafter. However, no further reductions in DFI were observed between 6 and 12 months, highlighting the sustained positive impact of varicocelectomy on sperm DFI in varicocele patients.[32]

In particular, the present study showed that the bilateral approach was more effective than the unilateral method, not only in reducing DFI but also in yielding higher pregnancy rates of 36.0% for unilateral and 58.0% for bilateral surgery. Men with a diagnosis of bilateral varicoceles showed a more significant improvement in both sperm concentration and motility following bilateral varicocelectomy when compared to those with unilateral left varicocele who underwent left varicocelectomy. Couples who underwent bilateral varicocelectomy had a more significant improvement in semen quality and a significantly higher pregnancy rate compared to those who underwent unilateral varicocele repair. Those who underwent bilateral varicocelectomy also had a significantly higher spontaneous pregnancy rate. These results indicate that bilateral microsurgical varicocelectomy may be the surgery of choice to optimize fertility among men with varicoceles.

Consequently, a prospective randomized controlled trial in agreement with the results of this study illustrated that in infertile men with left clinical and right subclinical varicocele, the outcomes of bilateral varicocelectomy were better compared to unilateral varicocelectomy. It also corresponded to significant improvements in sperm concentration, normal sperm morphology, progressive motility, and spontaneous pregnancy rates after surgery were noted.[33] This finding was inconsistent with some previous studies, which may be attributed to various factors. First, advancements in color Doppler ultrasound have revealed higher varicocele detection rates, suggesting that previous studies based solely on physical examination may underestimate the prevalence in subfertile men. Moreover, the lack of correlation between varicocele size and testicular pathology, along with the potential for further complications such as subclinical progressive deterioration leading to sterility, necessitates evaluation in all cases. Lastly, in subfertile males, the duration of a varicocele was reportedly to influence seminiferous tubular function. Hence, the longer duration might be associated with poorer fertility.[33]

On the other hand, several studies have identified that bilateral varicocelectomy has significant effects on sperm parameters and male fertility.[34-36] Bilateral varicocele may lead to the insufficiency or absence of gonadal venous valves, allowing blood to flow back into the mammary venous plexus. A left-sided varicocele can affect right-side spermatogenesis.[34] Based on the literature, the incidence of right varicocele with palpable left varicocele has been reported to be as high as 60%. Currently, advanced diagnostic techniques like color Doppler ultrasonography have altered diagnosis rates, leading to an increased incidence of bilateral varicocele.[37]

Our surgical approach is microsurgical, offering the benefit of enhanced magnification compared to non-microsurgical techniques, which is highly significant. Results of a systematic review and meta-analysis provide strong evidence that microsurgical varicocelectomy is an effective intervention for improving spermatogenesis in infertile men. The procedure not only significantly reduces sperm DNA fragmentation, with a mean decrease of 5.46%, but also improves critical semen parameters, including increases in sperm concentration (+8.23%), motility (+7.17%), progressive motility (+2.77%), and morphology (+0.64%). These improvements in both DNA integrity and sperm quality underscore the potential of microsurgical varicocelectomy as a valuable treatment option for male infertility.[38] Microsurgical low ligation for varicocele repair is likely to continue being the gold standard of surgical treatment for varicocele. A body of evidence from systematic reviews and meta-analyses has dispelled much skepticism regarding its efficacy, especially in the context of male infertility. Although most of the existing studies focus on improvements in semen parameters and non-ART pregnancy rates, the positive outcomes associated with this surgical approach underscore its relevance and effectiveness.[39] Furthermore, when focusing exclusively on semen improvement, parameters obtained from scrotal Doppler Ultrasound (DUS), DFI, and the performance of bilateral varicocelectomy emerge as reliable indicators of the success of microsurgical varicocelectomy.[40]

Conclusions

Our study has identified that bilateral and unilateral microsurgical varicocelectomy can be effective interventional means for male infertility, with bilateral varicocelectomy demonstrating superior efficacy, based on DFI significantly lowered and a notable improvement in semen quality. Our findings underscore a potential indication of varicocelectomy as a quite viable treatment alternative for couples struggling with oligospermia, particularly for those with microsurgical bilateral varicoceles.

List of abbreviations

DFI, DNA Fragmentation Index
SCSA, Sperm Chromatin Structure Assay
ARTs, Assisted Reproductive Technologies
BMI, Body Mass Index
DUS, Doppler Ultrasound
ICSI, intracytoplasmic sperm injection

Ethics approval

This study has been approved by the Baqiyatallah University of Medical Sciences (ethics code IR.BMSU.BAQ.REC.1403.146). All the experiments of this study were conducted in accordance to the relevant guidelines and regulations or in accordance to the Declaration of Helsinki.

Informed consent

All patients participating in this study signed a written informed consent form for participating in this study.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Conflict of interest

The authors declare no potential conflict of interest, and all authors confirm accuracy.

Authors' contributions

All authors designed the study and wrote the manuscript, data and helped to draft the manuscript. All authors have read and approved the final manuscript.

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