Semen parameter improvements after microsurgical subinguinal varicocele repair are durable for more than 12 months

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Abstract

Introduction: Varicoceles account for the most common correctable cause of male infertility, with varicocele repair leading to improvements in semen quality. However, there is little evidence to establish the durability of varicocele repair. We analyzed the durability of improvements in postoperative semen parameters following microsurgical subinguinal varicocele repair.

Methods: We evaluated all men who underwent microscopic subinguinal varicocelectomy from 2015–2019. Patients were included if they desired fertility and had a followup of at least 12 months. We assessed the baseline characteristics of these patients, as well as semen volume, total motile sperm count (TMSC), concentration, percent motility, and morphology. Semen parameters were analyzed at baseline (preoperative) and at approximately three months and ≥12 months postoperatively.

Results: Of 105 men who underwent varicocelectomy, 18 men had a followup of at least 12 months. These men presented with median age of 34.5 (27–38) years for a median followup duration of 14.5 (13–22.5) months. TMSC levels increased from 6.4 (1.1–24.5) million at baseline to 11.1 (2.4–38.4) million at approximately three months and remained similar at 12.5 (1.6–31.5) million at ≥12 months. The study is limited by its retrospective nature and limited sample size.

Conclusions: Microscopic subinguinal varicocele repairs can result in durable improvements of semen quality beyond one year, as demonstrated by upgrade in median TMSC. Further studies should be performed to confirm our findings.

Introduction

A varicocele is a dilation of the pampiniform venous plexus. This pathology has a prevalence equivalent to approximately 15% of males and can be clinically relevant in up to 20% of that population.[1-3] Its effect on semen parameters was first described in 1965 by Macleod, and although largely asymptomatic, it stands as the most common correctable cause of male infertility, affecting up to 41% of men with primary infertility, up to 81% of men with secondary infertility, and up to 45% of men with dyspermia.[1-3]

It is largely agreed upon that varicoceles can result in testicular hypotrophy, gonadotropin level changes, and impaired spermatogenesis.[2,3] Most investigations of varicocele pathophysiology propose a mechanism of impaired testicular blood flow, which can result in increased scrotal temperature. Although the specific pathophysiology leading to impaired spermatogenesis remains elusive, numerous studies have shown varicocele repair to be effective in improving pregnancy rate through improvements in semen quality, especially with regards to semen motility and concentration.[2]

For adults presenting with infertility and varicocele, the benefit of varicocelectomy is clear.[4] Repairing clinical varicoceles in oligospermic and non-obstructed azoospermic men prior to in vitro fertilization (IVF) can be beneficial and has been shown to decrease levels of assisted reproductive technology (ART) necessary to achieve successful pregnancy in both subclinical and clinical varicoceles.[5-7] However, for adolescents, the decision to treat is controversial, as the goal of management becomes preventing testicular injury and maintaining function for future fertility.[4] Techniques for repair include retroperitoneal, laparoscopic, inguinal, and subinguinal approaches; subinguinal approaches, specifically when aided by an operating microscope, are favored in adults while laparoscopic approaches are favored in adolescents.[2,4,8] In both adults and adolescents, identifying who will likely benefit from repair and for how long, remains a topic of further investigation.[4]

Despite the wealth of evidence demonstrating the clinical benefit of varicocele repair, most studies follow patients at three-month intervals for a maximum of 6–12 months.[8,9] Scant literature exists to qualify durability of such improvement at periods ≥12 months. The aim of this study is to analyze the durability of improvements in postoperative semen parameters following microsurgical varicocele repair. We hypothesized subinguinal varicocelectomy will yield durable results at one-year postoperative.

Methods

An institutional review board approval was acquired and a retrospective chart review was performed, including all patients who underwent microsurgical subinguinal varicocelectomy between August 2015 and October 2018. All procedures were performed by a single surgeon, and varicoceles for repair were clinically palpable or subclinical (i.e., detected by ultrasound).

All patients underwent a thorough evaluation that consisted of a physical exam, hormonal profile (follicular stimulating hormone, luteinizing hormone, and testosterone) and semen analysis. Physical exam was used to determine testicular volume, orchidometer-based measurement in cubic centimeters (cc), laterality, and varicocele grade in accordance with the physical exam. Patients underwent two preoperative semen analyses, the mean of which was used to establish baseline preoperative semen parameters. The following semen analysis parameters were recorded: volume, total motile sperm count (TMSC), concentration, percent motility, and morphology. On followup after surgery, semen analyses were obtained at approximately three-month intervals. Prior to providing semen analysis samples, patients were instructed to remain abstinent for a minimum of two days. A single lab technician performed both semen analyses for all patients to minimize inter-observer variability.

Patients included in the study presented with chronic orchialgia or desired fertility with varicocele, and those with a recorded followup with semen analyses <12 months were excluded. These patients were subsequently studied to observe changes in their semen parameters over time — at baseline (preoperative), approximately three months, six months, nine months and any followup ≥12 months postoperatively; however, due to inconsistent postoperative followup, we have only presented here results from baseline, followup at approximately three months, and followup ≥12 months. TMSC at each period was of interest due to its utility in grading patient eligibility for ART, and morphology was omitted from results due to the inconsistent collection at followup.

For the statistical analysis, continuous variables were presented as means and standard deviations (±SD) or medians and interquartile ranges (IQR) according to the data distribution. Comparison of semen parameter values was performed using the Mann-Whitney U or Kruskal-Wallis test as required. Categorical variables were presented as absolute values and frequencies. For this research, $p<0.05$ was considered statistically significant.

Results

The study analyzed 18 men who underwent microscopic subinguinal varicocelectomy. For these men, the median age at surgery was 34.5 (27–38) years, mean testicular volume was 14 (12.5–14.8) cc, bilateral varicocele was present in five (27.8%) of patients, and the distribution of varicoceles by grade were subclinical (n=2, 11.1%), I (n=2, 11.1%), II (n=7, 38.9%), and III (n=7, 38.9%). The median followup duration of the cohort was 14.5 (13.0–22.5) months (Table 1).

When comparing semen parameters at these followup intervals, we note an improvement in TMSC, concentration, and total motility from baseline to approximately three months, but the same was not observed of semen volume. TMSC and concentration were greater at approximately three months and ≥12 months postoperatively than at baseline. TMSC levels increased from 6.4 (1.1–24.5) million at baseline to 11.1 (2.4–38.4) million at approximately three months and 12.5 (1.6–31.5) million at ≥12 months (Figs. 1, 2). Median and IQR of TMSC at both postoperative followup periods remain higher than that at baseline (Fig. 2). Concentration increased from 10.7 (3.5–21.3) million sperm/cc semen at baseline to 14.5 (4.0–22.6) million sperm/cc semen at approximately three months, and 16 (1.4–20.0) million sperm/cc semen at ≥12 months.

It should be noted, however, that these improvements in TMSC and semen concentration were not statistically significant. The comparative analysis did not find statistically significant differences for either approximately three-month or ≥12-month followups in comparison to baseline, with $p=0.650$ for baseline vs. TMSC ≥12 months (Table 2).

Discussion

In our study, we retrospectively evaluated 18 men desiring fertility who underwent subinguinal microsurgical varicocele repair and were followed up at three-month intervals for at least 12 months. These patients were presented in terms of their baseline characteristics, baseline and postoperative semen parameters, and duration of followup. We found that varicocele repair resulted in an improvement of semen quality, with improvement of both motility and concentration, that

Table 1. Demographic and clinical characteristics

	Overall n=18
Age at surgery in years	33.6±8.9
Laterality	
Left (%)	13 (72.2)
Bilateral (%)	5 (27.8)
Higest grade	
Subclinical (%)	2 (11.1)
I (%)	2 (11.1)
II (%)	7 (38.9)
III (%)	7 (38.9)
Testes volume	13.9±3.7
Last followup in months	14.5 (13–22.5)

Mean ± standard deviation, median (interquartile range).

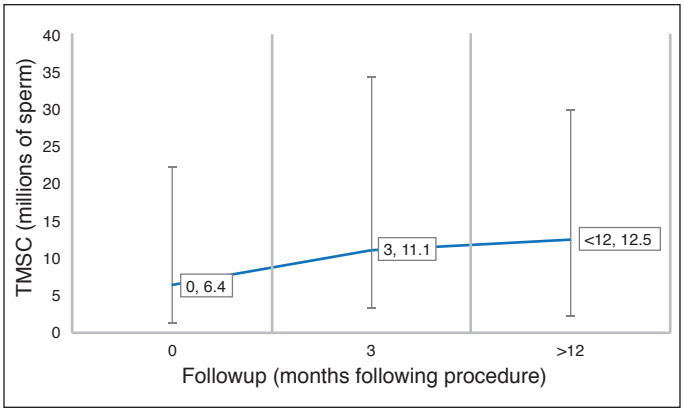

Fig. 1. Median total motile sperm count (in millions), with error bars representing interquartile range, observed at baseline, postoperative three months and postoperative ≥12 months.

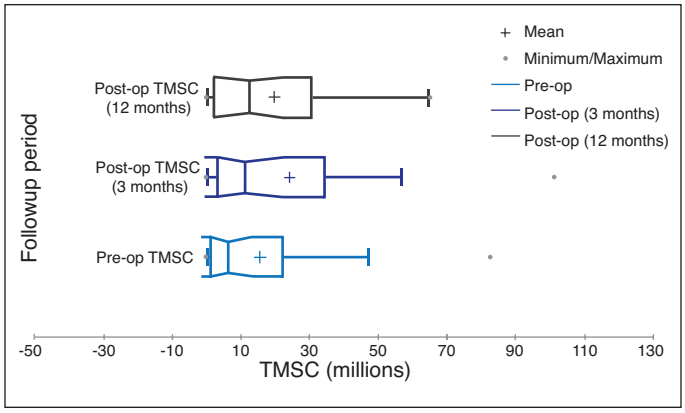

Fig. 2. Median and interquartile range of total motile sperm count (in millions) at baseline (preoperative) vs. postoperative ≥12 months.

was maintained for a median duration of 14.5 months postoperatively. However, it should be noted that due to the small sample size, these changes were not statistically significant.

The clinical benefit of varicocele repair for clinical and subclinical varicoceles lies in its ability to improve spermatogenesis, and thereby reduce the need for ART.[5-7] Previous studies have primarily used motility and concentration as markers for improvement in semen quality.[2] Our study emphasizes these findings. In this study, TMSC improved from 6.4 (1.1–24.5) million at baseline to 11.1 (2.4 – 38.4) million at three months, and concentration improved from 10.7 (3.5–21.3) million sperm/cc semen at baseline to 14.5 (4.9–22.6) million sperm/cc semen at three months. These improvements were maintained at followup periods ≥12 months, with TMSC of 12.5 (1.6– 31.5) million and concentration of 16 (1.4–20.0) million sperm/cc semen.

These results showcase that varicocele repair can effectively improve TMSC from a median level at baseline indicating IUI (5–9 million sperm), to a median level at three and 12 months postoperatively indicating natural pregnancy (>9 million sperm).[5] It similarly demonstrated improvement in median semen concentration (10.7 million sperm/cc semen) that was well under normal (≥15 million sperm/cc semen) at baseline to normal (16 million sperm/cc semen) at long-term followup (≥12 months). The p-value of these changes in TMSC (p=0.65) and concentration (p=0.56) from baseline to long-term followup did not indicate statistical significance, but this should not be confused with clinical relevance, which has been established through "upgrade" in median TMSC and normalization of median concentration.[5]

Literature on the durability of post-varicocelectomy improvements in semen parameters is scarce. Existing studies focus on improvement of semen quality and pregnancy rate within 3–12 months of the repair. Masterson et al described that men with TMSC <5 million can expect the largest improvement in TMSC within 3–6 months postoperatively, but only minimal improvement thereafter.[8] Fukuda et al found that after improvement from baseline to three months postoperatively, there was no significant difference between semen parameters at three and 12 months post-varicocelectomy.[10] The importance of our study lies in suggesting that these improvements in spermatogenesis are not transient. Although they may not increase substantially from levels at three months, they are certainly maintained well past this period, and past one year postoperatively.

Although our study has some strengths, which include that physical exams and surgical procedures were performed by a single surgeon and that the semen analysis was done by a single lab technician, some limitations include the inherent boundaries of a retrospective study and a small sample size, in which several patients were lost to followup at either three or six months. This decreases the power of the study and affects its ability to reach statistically significant results.

Moreover, this study may have a selection bias, as patients with longer followup may have been persistently concerned

Table 2. Comparation analysis between all the measurements and from baseline to the measurements performed at baseline and ≥12 months

Semen analysis	Baseline n=18	~ 3 months n=18	≥12 months n=18	Overall, p	Baseline vs. ≥12, p
Volume	2.6 (2–3.4)	2.5 (1.9–4.4)	3 (1.2–4.2)	0.988	0.791
TMSC	6.4 (1.1–24.5)	11.1 (2.4–38.4)	12.5 (1.6–31.5)	0.849	0.650
Concentration	10.7 (3.5–21.3)	14.5 (4–22.6)	16 (1.4– 20)	0.728	0.563
Total motility	36.7 (10–52.5)	38.5 (12.3–60)	49.5 (31–62)	0.395	0.143

Median (interquartile range). TMSC: total motile sperm count.

with their fertility and patients who failed to follow up with semen analysis for a period ≥12 months might be those with the best response to the varicocelectomy or may have achieved pregnancy. It is worth mentioning that, from the patients that were excluded (n=39) due to incomplete followup, the median TMSC at three months postoperatively was 13.4 (5.0–18.2) million sperm, which was not statistically significant compared to the analyzed cohort (p=0.948). Although the TMSC reported during the same period was similar to that the 18 patients presented in our study, the semen parameter values and fertility rate are difficult to assess, and it might be possible that the excluded patients had a significant semen improvement after three months that was not measured. We expect other studies that include a wider range of semen parameters (i.e., semen reactive oxygen species and DNA fragmentation) to help better assess this.[11]

Furthermore, an improvement in semen quality may not translate into improved pregnancy rate. Thus, further multicentric studies that use a prospective methodology should be performed to assess microsurgical subinguinal varicocelectomy long-term changes in semen parameter (i.e., volume, TMSC, concentration, and total motility), semen reactive oxygen species and DNA fragmentation, pregnancy rate (both natural and assisted), and the effect on the hypothalamic-pituitary-gonadal axis.[11]

Conclusions

Our study suggests that microscopic subinguinal varicocele repair can result in clinically relevant improvements of semen quality that are durable in quality and maintained for periods ≥12 months postoperatively. Further studies should be performed to confirm our findings.

Competing interests: Dr. Patel has been an advisory board member for Aytu BioScience. Dr. Ramasamy has been a consultant for Acerus, Aytu BioScience, and Boston Scientific. The remaining authors report no competing financial or personal interests related to this work.

This paper has been peer-reviewed

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