The Impact of Varicocele Microsurgical Ligation on The Testicular Hormonal Cells: Sub-Saharan Country Experience

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Abstract

Background: Varicocele is one of the most common causes of infertility. Various modalities, such as retrograde blood flow accumulation of metabolites and the disturbance of thermoregulation in the testicles, mediate it. This study aimed to evaluate the effect of varicocele on hormonal cells (Sertoli and Leydig cells) by measuring the semen parameters and hormones before and after microsurgical varicocele ligation. **Methods**: A cross-sectional study was conducted among patients who underwent microsurgical subinguinal varicocele ligation from January 2023 to December 2023 at Gezira Hospital for Renal Disease and Urology (GHRDS). Any patient with abnormal semen analysis, grade-II or grade-III varicocele (palpable or visible) with reflux who underwent microscopic sub-inguinal varicocele ligation was included in this study. **Results**: The sample size was 54 patients. The mean age of them was 36±7 years. Most of the patients had left-sided and grade-III varicocele (n=42; 78%). The degree of reflux was severe in most cases (n=25; 46%). The semen parameters including count, motility, and morphology were improved postoperatively (P=0.031). There was a significant increase in testosterone levels postoperatively (pre= 3.6±1.6 ng/ml V post= 5±1.9 ng/ml, mean difference= 1.4 ng/ml; P= 0.001) and decreasing in FSH levels postoperatively (pre= 17±15 mlu/ml V post= 13.6±12.1mlu/ml, mean difference= 3.4 mlu/ml; P= 0.000). **Conclusion**: Varicocele had an obvious effect on hormonal cells, confirmed by the good outcomes following microsurgical varicocele ligation, which led to an increased level of testosterone, reduction of FSH, and improvement of semen parameters.

Keywords: Varicocele, microsurgical ligation, testicular hormonal cells

Introduction

Varicocele is a pathological scrotal condition that arises after a dilated pampiniform plexus, with a prevalence of 15% among males (**Pastuszak & Wang,2015**). The effect of varicocele on spermatogenesis has been a matter of debate. Its importance is a common pathology that leads to infertility from two points of view. It is one of the most common causes of infertility and it is considered the most common correctable cause of male infertility **(Alsaikhan et al.,2016)**. Regarding pathophysiological mechanisms behind varicocele-induced infertility it seems to be no single theory can explain the differential effect of varicocele on infertility **(Alsaikhan et al.,2016)**.

Microsurgical varicocele ligation results in seminal improvement in 60-80% and natural pregnancy in 20% of couples **(Jensen et al.,2017)**. The prevailing theories such as retrograde blood flow and accumulation of metabolites, in addition

to the thermoregulation disturbance in the testicles, explain impairments in testicular function (**Pastuszak & Wang,2015**; **(Durairajanayagam et al. 2015; Boman et al., 2008)**. The varicocele impairs the function of testicular Leydig cells and likely affects semen alteration, leading to a significant decrease in testosterone production **(Bellastella et al.,2022)**. Although the consequences of varicocele and its resolution have been documented for decades, only a few studies have been conducted in this area **(Li et al.,2012; Öztekin et al.,2020).**

Different studies demonstrated the relationship between varicocele repair and testosterone levels, suggesting that varicocelectomy enhances testosterone production for men of all age groups **(Tanrikut et al.,2011)**. The varicocele affected the hormonal cells; hence, there is marked improvement in the hormone level and semen component following microsurgical varicocele ligation.

No published study discussed the context of this article in Sudan. This study aimed to evaluate the effect of varicocele on testicular hormonal cells among Sudanese patients.

Methodology

Design:

This is a cross-sectional hospital-based study. Conducted from January 2023 to December 2023. It is a total coverage study.

Inclusion and exclusion criteria*:*

Any patient aged more than 16 years with abnormal semen analysis, grade-II or grade-III varicocele (palpable or visible) with reflux, who underwent microscopic sub inguinal varicose ligation at GHRDS was included in this study. In contrast, any patient with other causes of abnormal seminal analysis, testicular atrophy, recurrent varicocele, or who refused to participate in this study was excluded.

Tools*:*

Patients' information was extracted from medical records and entered into a computer Excel sheet. Information collected included Demographic and clinical data, comorbidities, and characteristics of varicocele. Testosterone and FSH measurements before and after microsurgical varicocele ligation. Semen analysis was done using masturbation as a method of collection with 4-6 days of sexual abstinence, analysis was done by using the CASA technique (Computer Assisted Semen Analysis) for all patients

Setting*:* This study was conducted at Gezira Hospital for Renal Diseases and Surgery (GHRDS), Sudan,

Procedures: The indicators for the affection of Leydig cells were reflected in the improvement of serum testosterone level and Sertoli cells by reducing FSH and improvement of semen parameters postoperatively. A blood sample for testosterone and FSH was taken in the early morning—a normal range for testosterone (2.6 to 7.8 ng/ml) and FSH (1.7 to 12.0 mlu/ml). Preoperatively the following workup was done as a routine (1) clinical assessment and (2) investigations for patient fitness e.g. complete hemogram, renal functions test …etc. (3) semen analysis (4) hormones e.g. Morning testosterone, FSH, LH …etc. (5) Scrotal ultrasound was performed for all patients to confirm the diagnosis (diameter of dilated veins plus degree of reflux).

(6) Cryopreservation was done for a semen count of 5 million per milliliter or less. Three months postoperatively semen analysis and hormones were requested again.

Data Analysis:

Data was analyzed by using the computer program Statistical Package for Social Sciences (SPSS V. 21.0). The analyzed data was presented in tables and figures designed by Microsoft Excel Software.

Ethical approval:

Ethical approval was obtained from the ethical committee of the Faculty of Medicine - University of Gezira and GHRDS. All methods were carried out following relevant guidelines and

regulations" in the methods section. A written consent was obtained from all subjects.

Result:

The total number of patients enrolled in this study was 54, with a mean age of 36±7 years. Most of them, 28 (51.9%), belonged to the age group of 30-39 years. Thirty-seven patients (68.5%) were employed as free workers. Most patients, 51(94.4%), were married, with a mean duration of 7±5 years. Seven patients (13%) had comorbidities, including hypertension in 5 (9.3%) and diabetes mellitus in 2 (3.7%) patients. Smoking was reported in 17 patients (31.5%) and snuffing in 12 patients (22.2%), which were the main social habits. Detailed characteristics of the other patients are shown in Table 1. Most patients, 42(78%), had left-sided varicocele, while the remaining 12 patients had bilateral varicocele. Forty-two patients (78%) had grade-III varicocele. The degree of reflux was severe in 25 (46%), moderate in 19 (35%), and mild in 10 (19%) patients (Table 1).

The seminal analysis of study patients before and after the intervention is shown in Table 2. Twenty-two patients (40.7%) had azoospermia both pre- and post-operatively (P value = 0.363), but regarding hormonal function for those cases, they were studied within the sample.

Table 3 showed a significant increase in testosterone levels (pre= 3.6±1.6 ng/ml V post= 5±1.9 ng/ml, mean difference= 1.4 ng/ml; P value= 0.001) and decreasing in FSH levels postoperatively (pre= 17±15 mlu/ml V post= 13.6±12.1mlu/ml, mean difference= 3.4 mlu/ml; P value= 0.000). Postoperative semen analysis was not significantly affected by the degree of reflux (P value=0.084), showed in Table 4. Postoperative levels of testosterone and FSH were not significantly affected by the degree of reflux (P value=0.799 for testosterone and 0.385 for FSH) shown in Table 5.

Table 1: patients character with abnormal semen analysis underwent varicocele ligation (patient= 54)

Variables		Frequency	Percentage
Age	20-29 years	8	14.8%
	30-39 years	28	51.9%
	40-49 years	16	29.6 %
	More than 50 years	2	3.7 %
Occupations	Worker	37	68.5 %
	Employee	12	22.2 %
	Farmer	2	3.7 %
	Student	3	5.6 %
Marital status	Married	51	94.4 %
Comorbidities	HTN	5	9.3 %
	DM	2	3.7 %
Social habits	Smoking	17	31.5 %
	Snuffing	12	22.2 %
	Alcohol	1	1.8 %
Side of varicocele	Left	42	78%
	Bilateral	12	18%
Degree of reflux	Mild	10	19%
	Moderate	19	35%
	Severe	25	46%
Severity of reflux	Grade-I	1	1.8%
	Grade-II	11	20.4%
	Grade-III	42	77.8%

Table 2: The pre and postoperative semen analysis among patients with abnormal semen analysis underwent varicocele ligation (patient= 54)

Semen analysis	Before Surgery		After Surgery		P value
	patient	%	patient	%	
Normal	0	0	1	1.9	
Oligozoospermia	6	11.1	13	24.1	
Oligoas then ozoospermia	11	20.4	5	9.3	
Oligoas then oteratozoospermia	10	18.5	7	13.0	0.363
Azoospermia	22	40.7	22	40.7	
As then ozoospermia	2	3.7	3	5.6	
Teratozoospermia	3	5.6	3	5.6	

Table 3: The pre and postoperative testosterone and FSH levels among patients with abnormal semen analysis underwent varicocele ligation (patient= 54)

	Before surgery	After surgery	Mean dif	P value
	Mean ± SD	Mean ± SD		
Testosterone (ng/ml)	3.6±1.6	5±1.9	1.4	0.001
FSH (mlu/ml)	17±15	13.6±12.1	3.4	0.000

Table 4: The correlation between reflux degree and semen analysis among patients with abnormal semen analysis underwent varicocele ligation (N=54)

Semen analysis	Degree of Reflux			P value
	Mild	Moderate	Severe	
Normal	0(0%)	1(5.3%)	0(0%)	
Oligozoospermia	1(10%)	3(15.8%)	9(36%)	
Oligoasthenozoospermia	3(30%)	0(0%)	2(8%)	
Oligoasthenoteratozoospermia	1(10%)	3(15.8%)	3(12%)	0.084
Azoospermia	3(30%)	11(57.9%)	8(32%)	
Asthenozoospermia	2(20%)	0(0%)	1(4%)	
Teratozoospermia	0(0%)	1(5.3%)	2(8%)	

Table 5: The correlation between reflux degree with testosterone and FSH levels among patients with abnormal semen analysis underwent varicocele ligation (patient= 54)

	Degree of Reflux			P value
	Mild	Moderate	Severe	
Testosterone (ng/ml)	5±2.6	5.1±1.8	4.7±1.7	0.799
FSH (mlu/ml)	9.7±7.3	16.3±13.8	13.2±12.4	0.385

Discussion

The incidence of varicocele is approximately one-third of the infertile males affected by this pathology **(Alsaikhan et al.,2016)**. The current study showed that the mean age was 36±7 years, with most participants in the third decade of life. Similar

findings were reported by Boman J et al**.(2008)** (mean age 36.7 years), Esteves S et al. **(2010)** (mean age 35.3 years), Pasqualotto F et al**.(2012)** (mean age 37.2 years), and Haydardedeoglu B et al. **(2010)** (mean age 35.2 years).

While left-sided varicocele predominates, asynchronous contralateral varicocele may present in 30%–80% of cases **(Masson & Brannigan, 2014).** In contrast, isolated right-sided varicocele comprises <5% of cases and should raise concern for a retroperitoneal mass effect **(Raman et al., 2005)**. In the present study, most of the patients had left-sided varicocele, and less than five percent had right-sided varicocele. The high incidence of varicocele on the left side is justified by numerous factors, including (a) upright posture resulting in venous congestion, (b) venous valves are more commonly absent on the left side, right-sided testicular venous drainage is directly into the inferior vena cava, whereas the left spermatic vein drains into the left renal vein, which drains more slowly than the vena cava due to its smaller diameter, and (c) left-sided spermatic vein drainage increases the chances of renal vein compression between the superior mesenteric artery and aorta or obstruction of the left common iliac vein by the left common iliac artery as it crosses above the vein (**Pastuszak & Wang,2015**).

A recent study revealed grade-III varicocele in clinical examination in 78% of the patients, this may be due to the late presentation, which can be explained by varicocele causing a testicular sensation of heaviness rather than severe pain which is always making the patient seek early medical consultations. A consistent finding was reported by Daria M et al **(2021)**, who reported most of the patients (49.5%) had a grade-III varicocele.

In a recent study, microsurgical varicocele ligation showed a significant improvement in semen parameters (sperm count, motility, and morphology). This result was in agreement with several studies, including meta-analyses by Agarwal et al., **(2007)**, Kim et al., **(2013)**, and Baazeem et al., **(2011)** as well as the studies by Boman et al.**(2008)**, Mansour Ghanaie et al.,(2012), Al Bakri et al. **(2012)**, and Japari et al**.,(2025)** , all of which reported the benefits of varicocele ligation on semen parameters in infertile or sub-fertile men undergoing the procedure, providing high-level evidence in favor of treatment.

This study demonstrated a significant increase in testosterone levels and decreasing in FSH levels postoperatively after microsurgery. These findings were supported by the studies of Su et al., **(1995)**, Gat et al**. (2004),** Grober et al**.,(2004),** Pasqualotto et al., **(2005)**, Ramasamy et al. **(2006)**, Hsiao et al., **(2013)** those demonstrated improvements in testosterone levels following varicocele repair. However, some studies have failed to demonstrate significant improvement in testosterone levels after surgeries **(Ishikawa& Fujisawa,2004; Zheng et al.,2009)**

Moreover, this study illustrated that the degree of reflux did not statistically affect the postoperative improvement in semen analysis, testosterone, and FSH. This finding supports the possibility of indirect damage to the spermatogenic cells due to the reduction of Leydig and Sertoli cell functions, which might result in impaired spermatogenesis. On the other hand, it diminishes the likelihood of direct testicular injury from the accumulation of metabolites, or it supports the multifactorial effect. Correspondingly, Mostafa B et al. did not find any significant correlation between venous reflux and semen parameters **(Babai et al.,2019)**.

Limitations of the study

There were several limitations, such as a small sample size, and the determination of the reflux degree being more subjective because ultrasonic findings were operator-dependent over the study. Lastly, the follow-up was short only 6 months.

Conclusion and recommendations

There was an obvious effect of varicocele on hormonal cells, confirmed by the good outcomes after microsurgical varicocele ligation, which led to increased levels of testosterone, reduction of FSH, and

improvement of semen parameters. The sexual function and paternity improvement depend on the improvement of the hormonal environment of the testis.This testicular stability usually occurs following surgery. Accordingly, we recommend early microsurgical varicocelectomy when indicated to improve sexual dysfunction and paternity

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