Title: Varicocelectomy Versus Antioxidants Medication for Cryptozoospermic men. Randomized Control Trial

Protocol N: 4,799/1/24

Date: 01/01/2024

Patients and methods

This randomized study is a prospective comparative analysis of male infertility patients who were referred to our tertiary center February 2024 and December 2025.

After Institutional ethical approval (IRB 4,799/1/24), eligible patients were evaluated and written informed consent was obtained from patients according to the Good Clinical Practice guidelines and the Declaration of Helsinki, The study will be retrospectively registered in the clinicalTrials.Gov.

Patients were included if they had at least a 1-year history of male factor subfertility, normal female factor evaluation, a clinically palpable varicocele and cryptospermia. Exclusion criteria were men with hypogonadism (total testosterone < 8nmol/L), subclinical varicoceles, recurrent varcicoceles, cryptorchidism, men with previous genital surgery, previous sexually transmitted diseases or significant genital infection, alcohol or drug abuse and previous exposure to chemotherapy. A total of 69 patients met the eligibility criteria and randomly allocated into two groups using closed envelope technique.

1- Group A (N=35) Patients underwent subinguinal microsurgical varicoceles ligation. Microsurgical subinguinal varicocelectomy was performed by the same surgical team using a Karl Zeiss operating microscope with a magnification of ×10–20, according to the standard surgical technique.
2- Group B (N= 34). Patients were offered life style modifications only and follow up semen test in 6 months.

Patients were referred to us with at least two abnormal semen analysis performed at our assisted conception unit. All patients had a detailed history and examination including examination of genitalia in the sitting and standing position. Fasted and morning (before 11 am) serum testosterone, FSH, and LH were done routinely for all patients. Genetic testing (Karyotype and

Y deletion) was done to exclude any associated abnormalities that might affect the outcome or need genetic counselling. Scrotal doppler ultrasound scan was performed to assess the degree of varicoceles and for exclusion of any associated pathology. Varicoceles diagnosed based on the clinical criteria introduced by Dubin and Amelar (3). Repeat semen analysis was performed at our IVF unit, and patients were subclassified according to the results into (a)- Azoospermia, (b) cryptozoospermia not suitable for Intracytoplasmic sperm injection (ICSI) and (c) cryptozoospermia suitable for ICSI.

Patients follow up and outcome measures:

Repeat semen analysis was arranged 4months after the surgery. The primary outcome was the improvement of semen parameters, while the secondary outcomes were the number of ICSI cycles and the percentage of biochemical pregnancy after ICSI.

Statistical analysis methodology

Data were recorded using Microsoft Excel program (Microsoft Co, USA) and analyzed using R Studio Pro software (version 2026.01.1, Posit PBC, Boston, USA). The normality of data distribution was checked using the Shapiro-Wilk test. Continuous normally distributed variables were presented as mean ± standard deviation (SD) and compared using the Welch Two Sample t-test, while continuous non-normally distributed variables were presented as median and interquartile range (IQR) and compared using the Wilcoxon rank-sum test. Categorical variables were presented as frequencies and percentages, and compared using Pearson's Chi-squared test or Fisher- Exact test. Univariate and multivariate generalized linear regressions with mean differences and 95% confidence intervals (CIs) were used to investigate potential predictors of improvement in semen profile after one year. Statistical significance was considered when the two-tailed P value <0.05.