

INPLASY PROTOCOL

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The effect of varicocele repair for sperm DNA fragmentation: a protocol for systematic review and meta-analysis

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The authors report no conflicts of interest in this work.

Review question / Objective: The effect of varicocele repair for sperm DNA fragmentation.

Condition being studied: Sperm DNA integrity has been considered as one of the important determinants of normal fertilization and embryonic development in natural and assisted pregnancy. It is difficult for men with high levels of sperm DNA fragmentation(SDF) in semen to conceive their partners naturally and assist in conception. The studies have found that the level of SDF in the semen of patients with varicocele(VC) was on the high side. In recent years, the effect of varicocele surgery on DNA fragmentation index(DFI) has attracted the attention of researchers. In this study, we will evaluate the effectiveness of varicocele repair as a way to alleviate SDF and improve male fertility.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 July 2020 and was last updated on 27 July 2020 (registration number INPLASY202070119).

INTRODUCTION

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DNA fragmentation(SDF) in semen to conceive their partners naturally and assist in conception. The studies have found that the level of SDF in the semen of patients with varicocele(VC) was on the high side. In recent years, the effect of varicocele surgery on DNA fragmentation index(DFI) has attracted the attention of researchers. In this study, we will evaluate the effectiveness of varicocele repair as a way to alleviate SDF and improve male fertility.

METHODS

Participant or population: Patients have been diagnosed with varicocele by physical examination and color Doppler ultrasonography of the male reproductive system. Patients who were tested before the operation and showed high SDF.

Intervention: The patients in the treatment group received varicocelectomy (no restriction on the methods of operation and course of treatment).

Comparator: The control group could gain a placebo, no treatment, exercise, or guideline-recommended conventional treatment.

Study designs to be included: All the RCTs will be included without publication status restriction or writing language.

Eligibility criteria: Electronic databases including English databases (PubMed, MEDLINE, EMBASE, Web of Science, Cochrane Library) and Chinese databases (China National Knowledge Infrastructure, China Biology Medicine Database, Wanfang Database, VIP Database) will be searched from their inception to December 2020 to recognize related studies. All the randomized controlled trials (RCTs) of microsurgical varicocelectomy for the management of varicocele patients will be included. The potential outcome will include Improvement in sperm DNA fragmentation, oxidative stress markers (reactive oxygen species, nitric oxide, and lipid peroxidation products) ,

sperm chromatin compaction, other advanced sperm function characteristics, follow-up of fertility results. We will conduct this study strictly according to the Cochrane Handbook for Systematic Reviews of Interventions.

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Main outcome(s): 1) Improvement in sperm DNA fragmentation index. (The sperm chromatin structure assay (SCSA), terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), sperm chromatin dispersion test (SCD), and single gel electrophoresis (Comet) are the most commonly used methods to measure SDF.

Quality assessment / Risk of bias analysis: The risk of bias will be independently assessed by two reviewers and any differences will be resolved through consultation or the participation of a third reviewer. The RCTs will be evaluated using the Cochrane "risk of bias assessment" tool. The tool assesses the risk of bias mainly in the following 7 aspects: random sequence generation, allocation concealment, the blinding method for patients, researchers and outcomes assessors, incomplete result data, and

selective reports. As recommended by the Cochrane manual, the risk of bias in each of these areas will be assessed as low or high depending on whether the criteria were met or not met, and the lack of information will be recorded as unclear. In most cases, disagreements will be settled by discussion between the 2 reviewers. If disagreement remained after discussion, a third reviewer will be consulted before taking the final decision on the disagreements.

Strategy of data synthesis: We will use RevMan5.3 software for meta-analysis. For dichotomous data (e.g., effective and ineffective), we will calculate risk ratio (RR) and 95% confidence intervals (CIs). For continuous data, when the measurement method and unit are consistent, we will calculate the weighted mean difference (WMD) and 95% CIs. When the measurement methods and units are inconsistent or the mean values of different experiments differ greatly, we will use the standardized mean difference (SMD) and 95% CIs as the composite statistics.

Subgroup analysis: If there is significant heterogeneity in the included trials, we will identify the source of heterogeneity through subgroup analysis and manage the heterogeneity: 1) The duration and severity of VC. 2) Intervention features: unilateral varicose vein surgery or bilateral varicose vein surgery. 3) High duration of sperm DNA fragmentation. 4) demographic characteristics of the patients: age, marital and family status, region, race, and ethnicity. 5) follow-up time.

Sensibility analysis: A sensitivity analysis will be performed to test the robustness of the review result and to detect the source of heterogeneity. This can be done by excluding trials with a high risk of bias or eliminating each study individually. And, the impact of methodological quality, sample size, and missing data will be assessed. Then the analysis will be repeated after the exclusion of low methodological quality studies and the results compared with the previous meta-analysis.

Country(ies) involved: China.

Keywords: Sperm DNA damage; Sperm DNA fragmentation; DNA fragmentation index; Varicocele ; Varicocele repair.

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