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Review Article

Treatment of varicocele in children and adolescents: A systematic review and meta-analysis of randomized controlled trials

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Summary

Background
The prevalence of varicoceles is as high as 15% in children and adolescents. Optimal management of varicoceles has not been consolidated. Options include observation, radiological intervention, or surgical varicocelectomy.

Objective
Herein, we aim to assess the outcomes of radiological and surgical interventions for varicocele in children and adolescents evaluated by RCTs.

Study design
The study subjects were children and adolescents up to 21 years old, diagnosed with varicocele and allocated to receive either "surgical or radiological intervention" or "no treatment".

Materials and methods
We searched MEDLINE and EMBASE (Ovid platform), Web of Science, CINAHL, Cochrane Central Register of Controlled Trials, Google Scholar, Clinical-Trials.gov, and the World Health Organization International Clinical Trials Registry Platform for RCTs reporting on varicocele treatment in children and adolescents up to June 23, 2016. Only RCTs with patients aged under 21 years were included. Main outcomes of interest included changes in testicular size, semen analysis parameters, surgical adverse events and failures.

Results
Nine eligible studies were included in the systematic review. Meta-analysis based on available outcomes data demonstrated an improvement in testicular volume (mean difference 3.18 mL, 95% CI 1.94–4.42) and in sperm count (mean difference 25.54 $\times$ 10^6/mL, 95% CI 12.84–38.25) in patients who underwent radiological or surgical treatment compared with conservative management.

Conclusions
Based on current available randomized controlled trials, there is low to moderate level of evidence that radiological or surgical treatment of adolescent varicocele is associated with improved testicular size/growth and sperm concentration. The ultimate effects on fertility and paternity rates are not known.

Introduction

The prevalence of varicoceles is as high as 15% in children and adolescents [1,2]. Varicocele is the result of an abnormal enlargement of the pampiniform venous plexus, the structure responsible for venous drainage to the testicular, pudendal, and cremasteric veins [3]. The grading system for detection of a varicocele consists of grade 1: palpable only on Valsalva maneuver, grade 2: palpable with no Valsalva maneuver, and grade 3: visible with no need for palpation. Management options include monitoring, radiographic intervention, or surgical varicocelectomy. The main effect of varicocele is its potential role in male infertility. Current guidelines recommend testicular volume loss or growth lag as the main indication for intervention to preserve or improve fertility. Other indications include pain, co-existing testicular anomalies, and abnormal semen analysis [4]. However, evidence supporting best treatment practices is lacking. Our literature search found several reviews on the optimal management strategy in children and adolescents with varicoceles [5–10]. Nevertheless, the authors of these reviews included several various types of studies not as rigorous as randomized controlled trials (RCTs). It is well known that uncontrolled and non-randomized studies can overestimate the effect of interventions [11]. Furthermore, because of the variable inclusion criteria and different outcome measurements reported in these reviews there was significant

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heterogeneity leading to no overall consensus on optimal management strategy. Other shortcomings included limited number of targeted databases and exclusion of non-English language articles.

Objectives

We hypothesize that active treatment of pediatric and adolescent varicocele is associated with better outcomes such as testicular size and semen analysis parameters compared with conservative management. Our objective is to assess the effect of active treatments (radiological or surgical) compared with each other or conservative follow-up for varicoceles in children and adolescents up to age of 21 evaluated by randomized controlled trials.

Material and methods

Eligibility criteria

A literature search protocol was developed based on the Cochrane recommendations for systematic reviews. Criteria for considering studies for this review were formed in PICO (Participants, Interventions, Comparisons and Outcomes) format (Appendix 1). The study participants were children and adolescents up to 21 years old, diagnosed with varicocele and allocated to receive either "surgical or radiological intervention" or "no treatment." Only randomized or quasi randomized trials were included. The studies should have reported at least one of the primary outcomes of interest including persistence or recurrence of varicocele, changes in testicular volume and changes in semen parameters (volume, concentration, % motility, morphology, and vitality). Changes in testicular status can be measured by resolution of testicular asymmetry, absolute or relative changes in testicular volume as measured by ultrasound or physical examination, and changes in testicular atrophy index. Secondary outcomes included post-operative complications (hydrocele, wound complication, damage to genitofemoral nerve, testicular/scrotal edema, testicular atrophy, umbilical hernia), incisional pain, analgesic requirements, operating time, length of stay, and patient satisfaction.

Information sources

A search was performed for all RCTs reporting on varicocele treatment in children and adolescents up to June 23, 2016 in MEDLINE and EMBASE (Ovid platform), Web of Science, CINAHL, Cochrane Central Register of Controlled Trials, Google Scholar, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform for ongoing trials. A cross-reference hand search was performed to identify additional studies not found in the computerized search. Furthermore, reference lists from all other relevant systematic reviews were searched to locate any possible missing publications.

Search strategy

We designed a highly sensitive search strategy for MEDLINE that included relevant MeSH (medical subject headings) terms, common keywords, and combinations of them (Appendix 2). Search was limited to humans, children and adolescents, and randomized controlled trials (RCTs). No exclusions were made on the basis of language.

Study selection and data collection process

Titles and abstracts were screened by two investigators (JL and MN), using the predefined criteria for inclusion. Afterwards the two investigators independently examined the full-text articles of the selected studies for inclusion in the review. For the one study published in a language other than English, Google translator was used to translate the article into English prior to review. A study selection form was completed to document the reason for exclusion/inclusion of each study. Any disagreement was resolved by discussion with the senior author (KA).

Data extraction for included studies was performed independently by two investigators using pre-defined data extraction forms. Data including details of the studies (e.g. types of interventions), characteristics of the participants, and outcomes after at least 6 months of follow-up were entered in Review Manager software (RevMan version 5.2.7 Cochrane Collaboration, Oxford, UK).

Risk of bias

Two reviewers independently assessed the methodological qualities for each study using the "seven evidence-based domains" table from the Cochrane Collaboration (random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting, and other possible sources of bias). Risk of bias for included studies was assessed as high, low, or unclear, with the last category indicating either lack of information or uncertainty over the potential for bias. Publication bias was not assessable in these trials because of the small number of included studies in the meta-analysis (less than 10). Any disagreements between reviewers regarding extracted data or risk of bias were resolved by discussion with the senior author.

Summary measures and synthesis of results

All extracted data were pooled and analyzed by RevMan software, version 5.2.7. Dichotomous variables were pooled to estimate the risk ratio (RR) and continuous variables were pooled to calculate the mean difference (MD). The results were reported with 95% CI. The Cochrane Q statistic and I^2 statistic were used to evaluate statistical heterogeneity. A fixed effects model was used for this review as pooled studies showed low statistical heterogeneity.

Proportions for post-operative hydrocele occurrences and varicocele recurrences were calculated in open and laparoscopic surgery sub-groups as well as for lymphatic sparing (LS) and non-lymphatic sparing (NLS) approaches using SPSS version 23 (IBM Corp.)

All results were assumed statistically significant at the $p = 0.05$ level.