MEDS Clinical Medicine (2024)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2024.050217
ISSN 2616-1907 Vol. 5 Num. 2

A Systematic Review and Meta-Analysis Comparing Endovascular, Laparoscopic, and Open Surgical Therapies for Varicocele

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Keywords: Varicocele, Laparoscopic, Open Surgical Therapies, Meta-Analysis

Abstract: Varicocele is a common vascular disease, which can seriously affect the physiological function of testis and lead to male infertility. The present study aims to systematically collect evidence on the treatment and observational outcomes of varicocele in infertile adult males, and to excavate the optimal treatment. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement and included only prospective randomized and non-randomized studies between January 1977 and September 2022. The outcomes of our observation included postoperative recurrence rate, major surgical complications, and postoperative pregnancy, the men with any-grade of varicocele were included as objects. We examined the outcomes of varicocele embolization with open surgery, laparoscopic embolization treatment, and laparoscopic treatment with open surgery in 2427 patients among 893 eligible articles and 21 trials. Offer guidelines for clinical practice.

1. Introduction

Varicocele is a condition in which the vein valves above the testicles fail to function properly, leading to an obstruction of blood and the dilatation of veins around the testicles [1]. However, varicocele can cause blood retention and overheating of the testicles, leading to increased venous pressure, oxidative stress, and testosterone imbalance, all of which will seriously decrease the count and quality of sperm [2,3]. Treatment strategies and indications for varicocele have long been divergent, and there also exists a wide range of differences in clinical guidelines and management practices [4,5]. However, it remains unclear which type of treatment is the safest and most effective option. In this systematic review and meta-analysis, we summarized current prospective randomized and non-randomized trials on the three main treatment options for varicocele, aiming to

update clinical management decisions and recommend the best treatment for varicocele patients.

2. Evidence acquisition

2.1 Search strategies and selection criteria

The present meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [6].

PubMed, Embase and Cochran Library databases were queried with following keywords: varicocele*, embolization*, surgery*, as well as relevant "MeSH" terms, to identify studies which comparing the efficacy of endovascular and surgical treatments for varicocele. The deadline for publication of literature included in our analysis was limited to September 2022. Titles and abstracts of all retrieved manuscripts were screened for initial inclusion and a full-text review was performed in case where the abstract was insufficiently conclusive. Three authors completed the selection of articles independently, and differences were resolved through interactive discussion.

2.2 Inclusion and exclusion criteria

Studies were included if they had presented comprehensive data of the three different treatment modalities for varicocele on the incidence of adverse events, pregnancy rate, and recurrence rate. The surgical success rate (disappearance of varicocele) of all included studies must be at least 80%. Case reports, reviews, opinion articles, conference abstracts or studies lacked sufficient data were excluded. The detailed selection process of the study is presented in Figure 1 A.

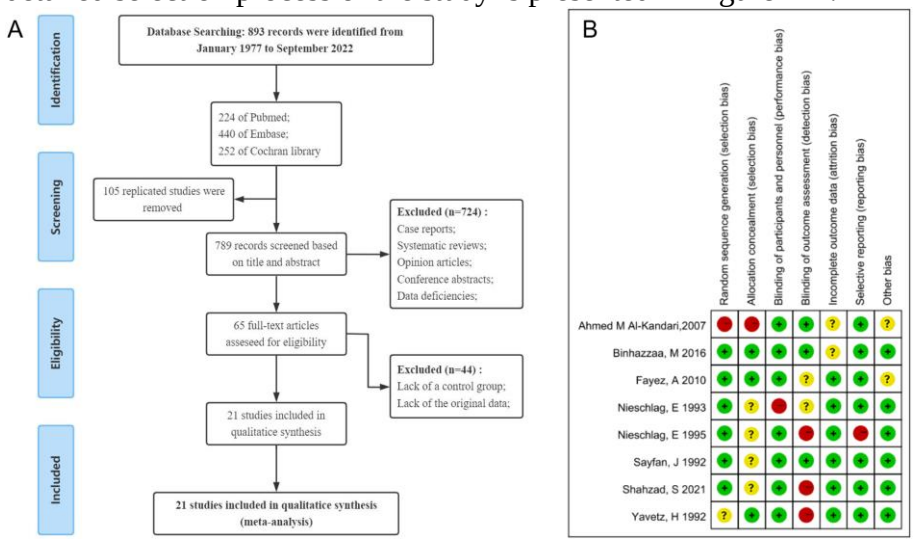

Figure 1: (A) PRISMA flow chart—study selection with inclusion and exclusion criteria of reviewed studies. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses. (B) Risk of bias summary for 8 RCTs. RCT = randomized controlled trial

2.3 Variables and outcome definition

The major information of included articles was presented in proforma that included year of publication, name of first author, study design, number of differential treated patients, and major clinical outcomes (Table 1). Observational outcomes of our analysis included comparison of varicocele recurrence rates, surgical adverse events, and postoperation pregnancy rates with different treatments. Pregnancy is defined as a natural or unnatural (medically assisted) event.

Major adverse events after surgery included hydrocele of testis, epididymitis, hematoma, bloating, atrophic testis, wound infection, and scrotal pain.

Table 1: Basic characteristics of the studies included in the meta-analysis

Author (year)	Study design	Endovascular embolization	Open surgery	Laparoscopic surgery	Outcomes
Nieschlag E.(1995)[7]	RCT	33	38	-	Pregnancy
Shahzad S.(2021)[8]	RCT	75	75	-	Improvement of semen parameters
Sayfan J.(1992)[11]	RCT	36	83	-	Recurrence
Mongio ìL. M. (2019)[14]	RCT	50	44	-	Recurrence / Pregnancy
Pintus C.(2001) [16]	retrospective analysis	18	20	-	Recurrence
Fayez A.(2010)[17]	RCT	49	106	-	Recurrence / Pregnancy
Nishio S.(1995)[9]	retrospective analysis	52	30	26	Recurrence
Ouanes Y.(2022)[10]	retrospective analysis	63	79	65	Recurrence / Complication
Sep úlveda L. (2018)[12]	retrospective analysis	41	48	72	Recurrence / Complication
Yavetz H.(1992)[13]	RCT	51	43	43	Recurrence / Pregnancy
Abdulmaaboud M. R.(1998)[15]	retrospective analysis	120	131	87	Recurrence
Jing Y. X.(2020)[18]	retrospective analysis	26	9	34	Recurrence / Complication
Feng R.(2022)[19]	retrospective analysis	40	-	19	Recurrence / Complication
Motta A.(2019)[20]	retrospective analysis	48	-	50	Recurrence
Sautter T.(2002) [21]	retrospective analysis	34	-	33	Recurrence / Complication
Wickham A.(2021)[22]	retrospective analysis	48	-	8	Recurrence / Complication
Binhazzaa M.(2016)[23]	RCT	49	-	27	Improvement of semen parameters
May M.(2006)[24]	retrospective analysis	122	-	108	Complication
Al-Kandari A M.(2007) [25]	RCT	-	59	52	Recurrence / Complication
Watanabe M.(2005)[26]	retrospective analysis	-	50	33	Recurrence / Complication

2.4 Statistical Analysis

All statistical analyses were performed using Review Manager 5.4. The heterogeneity of the study trial was evaluated using the I^2 test and Chi-squared, and the appropriate model for analysis (random-effect model or fixed-effect model) was determined. When the I^2 test p-value was less than 0.05 and the I^2 test value was greater than 50%, heterogeneity was considered high, and the random-effects model was used to assess the studies.

3. Evidence synthesis

3.1 Results of the meta-analysis

After removing 105 duplicative articles from the initial screen of 893 abstracts and titles (224 PubMed, 440 Embase, 252 Cochrane Library) , a total of 65 relevant studies were retrieved for full-text screening and 21 eligible studies were finally selected for the analysis (Figure 1). Among the included 8 RCTs [7-8], [11], [13,14], [15], [21], [23] and 13 retrospective studies [9,10], [12], [13-14], [16-20], [22], [24] in this analysis, the earliest was published in 1992 and the latest in 2022, covered 2,427 patients performed treatments over a 30-year span.

Varicocele was treated with vascular intervention in 18 studies, open surgery in 14 studies, and laparoscopic surgery in 13 studies. All of the studies selected in this analysis had included outcomes of postoperative recurrence rates, major adverse surgical complications, and postoperative pregnancy. Detailed information of study characteristics and contrasts are shown in Table 1.

3.2 Risk of bias summary for the included studies

Figure 1B summarizes the risk of bias and confounding assessment of the eight included randomized controlled trials. Our data showed that a low-risk selection bias was present for the majority of the studies, while a high risk was present only for one study. There was one study with high-risk performance bias and one with high-risk reporting bias. Three studies with a high-risk of decision bias. All included randomized controlled trials showed a low or unknown risk of attrition bias and other biases. Overall, the risk of bias according to the Cochrane Collaboration's tool and the Newcastle and Ottawa Scale was low/intermediate.

3.3 Complication of endovascular embolization / open surgery

Of the twelve studies that included endovascular versus open surgery, eight compared disease recurrence rates after treatment, three compared postoperative adverse events, and six reported postoperative pregnancy rates. Using the random effect model, our analysis showed that endovascular embolization was a protective factor for postoperative pregnancy compared with open surgery, with a lower pregnancy rate after treatment (odds ratio [OR] 0.57, 95% confidence interval [CI] 0.41-0.78, $p < 0.001$; Fig.2C). Endovascular embolization was associated with a lower rate of recurrence (OR 0.88, 95% CI 0.60-1.29, $p = 0.51$; Fig.2A) and adverse events (OR 0.69, 95% CI 0.32-1.49, $p = 0.35$; Fig.2B) than open surgery, although these differences were not statistically significant. Heterogeneity was high in the included studies, and I^2 was higher than 60% in all outcomes except the recurrence rate.

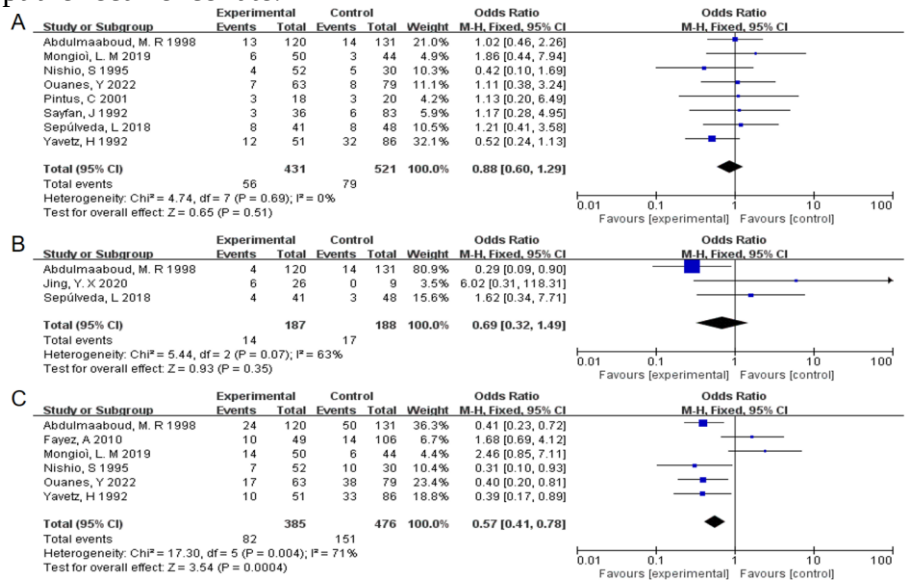

Figure 2: Pooled analysis of the included studies on endovascular embolization versus open surgery: (A) Forest plot demonstrating recurrence risk of varicocele, (B) Forest plot demonstrating occurrence of adverse events, (C) Forest plot demonstrating relative risk for pregnancy. CI = confidence interval; M-H = Mantel-Haenszel; df = degree of freedom.

3.4 Complication of laparoscopic surgery / endovascular embolization

Of the eleven studies comparing laparoscopic versus endovascular therapy included in the analysis, eight compared disease recurrence rates after treatment, seven compared postoperative adverse events, and three reported postoperative pregnancy rates. Our analysis showed that laparoscopic therapy was a risk factor for all outcomes compared to endovascular embolization,

with a higher risk of varicocele recurrence (OR 1.15, 95% CI 0.67-1.95, p = 0.62; Fig.3A), surgical adverse events (OR 2.90, 95% CI 1.73-4.86, p < 0.01; Fig.3B), and post-treatment pregnancy (OR 1.16, 95% CI 0.78-1.71, p = 0.46; Fig.3C), although these differences were not statistically significant except for adverse events. Heterogeneity was low in this included study, and the value of I^2 for all outcomes was lower than 10%.

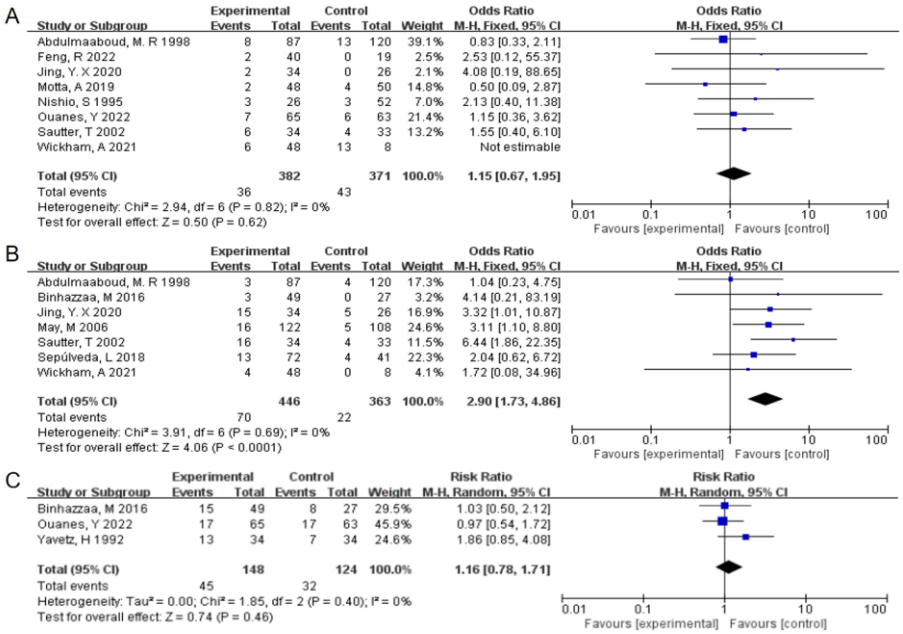

Figure 3: Pooled analysis of the included studies on endovascular embolization versus laparoscopic surgery: (A) Forest plot demonstrating recurrence risk of varicocele, (B) Forest plot demonstrating occurrence of adverse events, (C) Forest plot demonstrating relative risk for pregnancy. CI = confidence interval; M-H = Mantel-Haenszel; df = degree of freedom.

3.5 Complication of laparoscopic surgery / open surgery

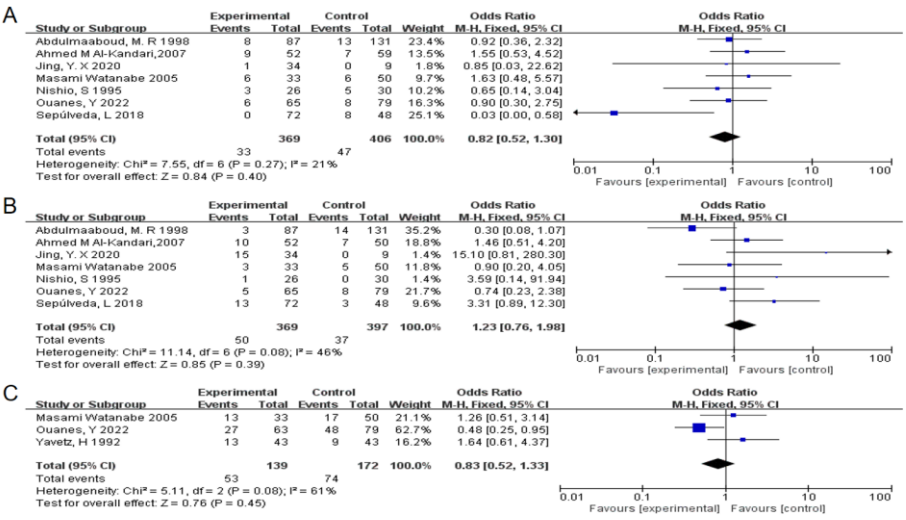

Figure 4: Pooled analysis of the included studies on open surgery versus laparoscopic surgery: (A) Forest plot demonstrating recurrence risk of varicocele, (B) Forest plot demonstrating occurrence of adverse events, (C) Forest plot demonstrating relative risk for pregnancy. CI = confidence interval; M-H = Mantel-Haenszel; df = degree of freedom.

In the final comparative analysis, a total of eight studies investigated the relationship between laparoscopic and open surgery. Of these, seven studies each compared recurrence rates and adverse events, and three reported postoperative pregnancy rates. Laparoscopic treatment was a risk factor for all outcomes compared to open surgery, with a higher risk of varicocele recurrence (OR 0.82, 95% CI 0.52-1.30, p = 0.40; Fig.4A), surgical adverse events (OR 1.23, 95% CI 0.76-1.98, p = 0.39; Fig.4B), and post-treatment pregnancy (OR 0.83, 95% CI 0.52-1.33, p = 0.45; Fig.4C), although these differences were also not statistically significant. The studies included in the pregnancy analysis had high heterogeneity, with I^2 greater than 60%, while the studies included in the recurrence rate and adverse events had low heterogeneity, both with I2 less than 50%.

4. Discussion

With the popularity of minimally invasive concept, more and more attention has been paid to the development of interventional instruments and surgical techniques for endovascular therapy of varicocele. It is important to note that not all of these differences were statistically significant for our study limitations, meaning that our results are consistent with previous studies [25,26], but Based on the results of our meta-analysis and systematic review of previous studies, we recommend interventional technology as the first standard treatment potion to improve sperm parameters, increase pregnancy rate, reduce the recurrence rate, shorten the hospitalization time, and avoid postoperative adverse events. The treatment of varicocele has long been divisive, but with the development of methods and the mature of technology, more and more studies have shown that endovascular embolization is a more advantageous option.

5. Conclusion

Current evidence does not confirm which kind of treatment for varicocele possesses the greatest clinical value, and higher quality RCTs are needed to determine the benefits of each method in increasing pregnancy rates in the same setting. The results of our analysis, combined with recent evidence, suggest that patients may benefit most from vascular embolization.

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