Asian Journal of Andrology (2015) 17, 74–80

www.asiaandro.com; www.ajandrology.com

Open Access

ORIGINAL ARTICLE

Male Health

Inguinal and subinguinal micro-varicocelectomy, the optimal surgical management of varicocele: a meta-analysis

Jun Wang, Shu-Jie Xia, Zhi-Hong Liu, Le Tao, Ji-Fu Ge, Chen-Min Xu, Jian-Xin Qiu

Conventional meta-analyses have shown inconsistent results for the efficacy of various treatments of varicoceles. Therefore, we performed a multiple-treatment meta-analysis to assess the effectiveness and safety of 10 methods of varicocelectomy and embolization/sclerotherapy. We systematically reviewed 35 randomized controlled trials and observational studies, from 1966 to August 5, 2013, which compared any of the following treatments for varococeles: laparoscopic, retroperitoneal, open inguinal and subinguinal varicocelectomy, microsurgical subinguinal and inguinal varicocelectomy, percutaneous venous embolization, Tauber antegrade sclerotherapy, retrograde sclerotherapy and expectant therapy (no treatment). Inguinal and subinguinal microsurgery, open inguinal, laparoscopic varicocelectomy showed a significant advantage over expectant therapy in terms of pregnancy rates (odds ratio (OR): 3.48, 2.68, 2.92 and 2.90, respectively). Compared with retroperitoneal open surgery, inguinal microsurgery showed an improvement of sperm density (mean difference (MD): 10.60, 95% confidence interval (CI): 1.92–19.60) and sperm motility (MD: 9.09, 95% CI: 4.88–13.30). Subinguinal and inguinal microsurgery outperformed retroperitoneal open surgery in terms of recurrence (OR: 0.05, 0.06 respectively). Tauber antegrade sclerotherapy and subinguinal microsurgery were associated with the lowest risk of hydrocele formation. The odds of overall complication, compared with retroperitoneal open varicocelectomy, were lowest for inguinal microsurgery (OR = 0.07, 95% CI: 0.02–0.19), followed by subinguinal microsurgery (OR = 0.09, 95% CI: 0.02–0.19). Inguinal and subinguinal micro-varicocelectomy had the highest pregnancy rates, significant increases in sperm parameters, with low odds of complication. These results warrant additional properly conducted randomized controlled clinical studies with larger sample sizes.
Asian Journal of Andrology (2015) **17**, 74–80; doi: 10.4103/1008-682X.136443; published online: 09 September 2014

Keywords: meta-analysis; varicocele; varicocelectomy

INTRODUCTION

A varicocele is defined as abnormal dilated and tortuous veins in the scrotum. They are present in 15%–20% of the male population, and in up to 35% of patients with male infertility.[1] Varicoceles are now recognized as the most surgically correctable cause of male infertility.[2] The exact pathophysiologic association between reduced male fertility and varicocele is still unknown. Several postulated causes include increased reactive oxidative species, sperm DNA damage, increased scrotal temperature, and reduced the supply of oxygenated blood and nutrients.[3–6]

Several surgical approaches have been used for varicocele including open surgical ligation of the spermatic vein, and microsurgical and laparoscopic varicocelectomy. Each technique has its own advantages and disadvantages, and conflicting results have been reported in various studies.[7–9] Until date, there is no consensus as to which technique should be considered the "gold standard."

In recent times, new meta-analytic methods–network or mixed treatment comparisons meta-analysis have become available that allow complete assessments across various treatments.[10–12] Network meta-analysis is a fairly new statistical technique that allows both direct and indirect comparisons to be undertaken, even when two of the strategies have not been directly compared.

The aim of the current study was to use a network meta-analysis on data from randomized comparative clinical trials (RCT) and nonrandomized clinical trial studies to assess the efficacy and safety of currently used treatment for varicoceles in order to provide better guidance for treatment choices.

MATERIALS AND METHODS

Criteria for study inclusion and search strategy

Systematic reviews were done according to the preferred reporting items for systematic reviews and meta-analysis statement.[13] Inclusion criteria were similar to the analysis by Kroese *et al.*[14] men with varicocele (any grade) who had semen analyses, who were part of a couple with otherwise unexplained subfertility.[14] Subfertility is defined by 1 year of infertility and no identifiable female factors. Types of outcome measures included pregnancy rate, semen parameters, overall complications, recurrent varicocele, postoperative hydrocele. Exclusion criteria for pregnancy rates were: follow-up <9 months, patients with azoospermia, crypto-ozospermia, obstructive oligospermia or urinary infection, couples with additional fertility drugs or assisted reproduction techniques such as *in vitro* fertilization or intrauterine insemination. Exclusion criteria for semen parameters were: semen parameters are

Department of Urology, Shanghai First People's Hospital, Medical College of Shanghai Jiao Tong University, Shanghai, China.
Correspondence: Prof. JX Qiu (jianxinqiu@126.com)
Received: 13 January 2014; Revised: 11 March 2014; Accepted: 14 May 2014

tested <3 times, patients with azoospermia, crypto-ozospermia. Exclusion criteria for complications were: follow-up <3 months, not confirmed by proper examination, insufficient data, more than one treatment per arm. All patients with prior surgery for varicoceles or congenital diseases (e.g. Klinefelter, Y chromosome deficiency) or endocrine diseases (e.g. Kallmann syndrome, hypercorticoidism) were excluded.

We identified RCTs and non-RCTs that evaluated the efficacy and safety of surgical ligation, therapeutic embolization and sclerotherapy treatment methods for varicocele reported from 1966 to August 5, 2013. Observational studies were pooled into the analysis only when there were complications or particular treatment. We searched PubMed, Embase, the Cochrane Collaboration's Database of Systematic Reviews, and Scopus using the MeSH terms: "varicocele," "varicocelectomy," "ligation," "embolization," "therapeutic," "sclerotherapy," "human." In addition, we reviewed the reference lists of all the previous meta-analyses. Studies published in any language were eligible for inclusion.

Study selection

Study eligibility was independently determined by two authors. Titles and abstracts were used to screen for initial study inclusion. Full-text reviews were carried out on the remaining papers. Discrepancies were resolved by discussion.

Evaluation for bias

We scored these non-RCT studies using a modified Newcastle–Ottawa Quality Assessment Scale[15] and assessed risk of bias from for each included RCTs by Cochrane Collaboration's tool which includes the selection, performance, attrition, detection, and reporting bias. Evaluation was done by two independent assessors to improve the validity.

Data extraction and management

Two reviewers performed data extraction independently. Disagreements were resolved by discussion and consensus. Population information and study characteristics such as the specific intervention were extracted independently using standard data extraction forms. For multiple reports of the same study, duplicated data were removed. We imputed missing standard deviations (s.d.) of mean changes for each treatment using the largest s.d. reported in the set of included studies for each outcome.

Subgroup analysis

Where data were available, we conducted a subgroup analysis with more strictly defined inclusion criteria: studies that included men with abnormal semen, clinical varicocele to determine the efficacy of various types of varicocelectomies and other modalities.

Statistical analysis

We did network meta-analyses within a Bayesian framework using Markov chain Monte Carlo (MCMC) methods in Just Another Gibbs Sampler and programming language R, version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria.).[16] We modeled the binary outcomes in each treatment group of every study, and specified the relationships among odds ratios (ORs) across studies making various comparisons. This method combines direct and indirect evidence for any given pair of treatments. Convergence was checked after every outcome analysis using diagnostic tools as described by Raftery and Lewis[17] and diagnostic plots (trace, density, autocorrelation) from MCMC simulations. Heterogeneity was evaluated using I^2-statistics. Inconsistency was estimated within each outcome analysis. We did sensitivity analyses according to age range (including only studies with patient age >14) and study designs (RCTs only).

RESULTS

A total of 157 articles were identified through the electronic and manual searches of references (**Figure 1**). Of these, 95 were judged to be relevant according to the review of the abstracts and titles. More studies were eliminated because of use of inadequate study designs, and lack of relevance of measured outcomes. RCTs were assessed using a risk of bias table, and non-RCT studies were scored by the Newcastle–Ottawa Quality Assessment Scale.[15] After scoring, 35 studies (12 observational studies and 23 RCTs) qualified for inclusion (**Figure 2** and **Supplementary Table 1**). The characteristics of the studies are shown in **Table 1**. The types of intervention were laparoscopic retroperitoneal, open inguinal varicocelectomy, microsurgical subinguinal and inguinal varicocelectomy, percutaneous venous embolization, Tauber antegrade sclerotherapy, retrograde sclerotherapy. Because subinguinal antegrade sclerotherapy was reported only in one study is not widely used clinically, this study was excluded from the analysis.

Randomization was achieved by a random number generator in five studies (Abdel-Maguid and Othman 2010, Barbalias *et al*. 1998, Krause *et al*. 2002, Nieschlag *et al*. 1995/1998, Pan *et al*. 2013), and was not stated in the other studies. Normozoospermic men from infertile couples (normal semen density, motility and morphology) were evenly distributed in different groups. Blinding is difficult to implement in surgical trials, and only one trial stated that it was double-blinded. However, blinding is not likely to have a great effect on objective outcomes such as pregnancy rates, semen parameters, recurrence and hydrocele formation rates. Although semen analysis results may be influenced by testicular volume and female age, unfortunately, the original articles did not report on these data, and that is a limitation of the current study.

Efficacy outcomes

Pregnancy rate

Seventeen studies and 2042 subjects were eligible for analyses of pregnancy rates.[7,8,18–32] The networks are provided in the online appendix (**Supplementary Figure 1**). Patients who had undergone

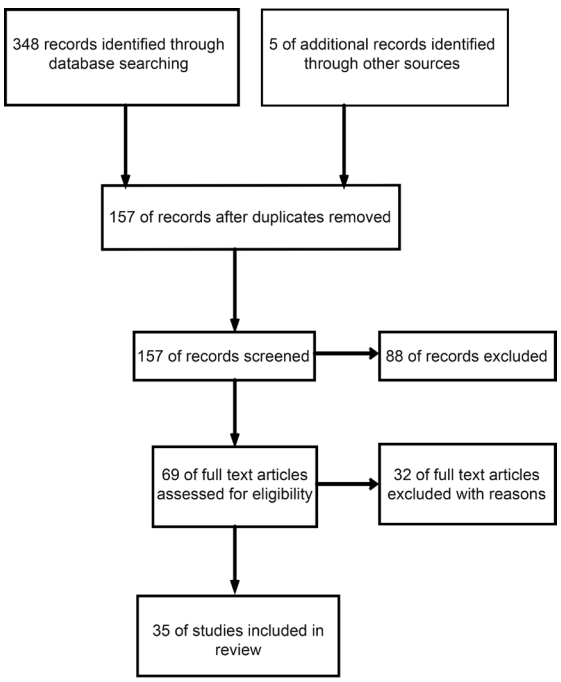

Figure 1: A study workflow diagram.

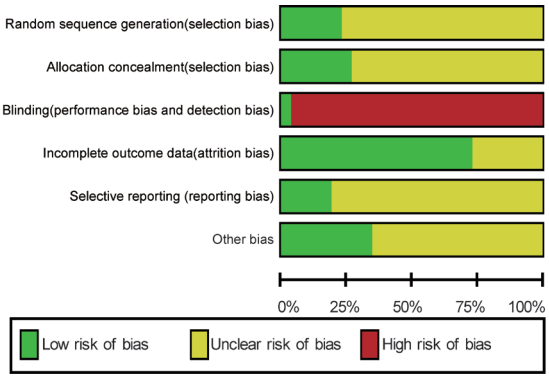

Figure 2: A risk of bias graph.

subinguinal, inguinal microsurgery, inguinal open surgery and laparoscopic surgery had a significant advantage over those who had undergone expectant therapy in terms of pregnancy rates (OR: 3.48, 2.68, 2.92 and 2.90, respectively). However, there was no significant difference between inguinal microsurgery, inguinal open surgery, laparoscopic surgery and subinguinal varicocelectomy. The rank probability plot suggested that inguinal, subinguinal microsurgery, inguinal open surgery and laparoscopic surgery were the top four techniques (**Figure 3**).

Sperm density and sperm motility

Twelve studies[7,8,18,20,22,23,26,28,30,31,33,34] with 1900 subjects, and 13 studies[7,8,18,20,22,23,26,28,30,31,33,35,36] with 1964 subjects were included in the network meta-analysis of sperm density and sperm motility. Because Zucchi *et al.*[36] reported sperm density in a median (range) form, and sperm motility in mean (s.d.) form, that study was not included in the analysis of sperm density. **Figure 4** shows forest plots of each treatment assessed against expectant therapy or no treatment in terms of sperm density and sperm motility. Inguinal, subinguinal microsurgery, laparoscopic techniques ranked among the top three. Compared with retroperitoneal open surgery, inguinal microsurgery showed noticeable improvement of sperm density (mean difference (MD): 10.6, 95% confidence interval (CI): 1.92–19.6) and sperm motility (MD: 9.09, 95% CI: 4.88–13.3). Subinguinal microsurgery also improved sperm motility by 7.98% (95% CI: 2.28–11.5).

Subgroup analysis of pregnancy rate, sperm density and sperm motility

This subgroup analysis was restricted to men with clinical varicoceles, and abnormal semen analyses (azoospermia excluded) (**Supplementary Figure 2**). Patients who had undergone subinguinal and inguinal microsurgery, inguinal open surgery and laparoscopic surgery had a significant advantage over those who had undergone expectant therapy in terms of pregnancy rate. However, the precision was low. The semen parameters also demonstrated similar results. Overall, this subgroup analysis also favored inguinal and subinguinal microsurgery over other treatment, but the difference was not statistically significant due to a small number of studies.

Adverse events outcomes

Twenty-three studies[7,8,18,20,21,26,28,29,31,33,35–48] were included in the network meta-analysis of recurrent varicocele. The odds of recurrent varicocele were significantly lower after subinguinal and inguinal microsurgery compared with retroperitoneal open surgery (OR = 0.05, 95% CI: 0.01–0.19 and OR = 0.06, 95% CI: 0.01–0.16). There were no significant differences between various other treatments and retroperitoneal varicocelectomy (**Figure 5a**).

Twenty-three studies[7,8,18,20,21,26,28,29,33,35–47,49] were included in the network meta-analysis of hydrocele formation. The incidence of hydrocele was relatively low. There was no hydrocele formation reported with inguinal microsurgery according to two studies. The upper 95% CI of OR against retroperitoneal open surgery was 0.08. The incidence of hydrocele after retrograde sclerotherapy was reported in only one study. Because the sample size was limited, this study was excluded from this section of the analysis. Subinguinal microsurgery again outperformed retroperitoneal open varicocelectomy (**Figure 5b**). Tauber antegrade sclerotherapy was found to be associated with the lowest risk of hydrocele formation compared with retroperitoneal open varicocelectomy.

Twenty-three studies[7,8,18,20,21,26,28,29,31,33,35–46,48,49] with 5851 subjects were included in the network meta-analysis of overall complication (**Figure 5c**). The odds of overall complications, compared with retroperitoneal open varicocelectomy, were lowest for inguinal microsurgery (OR = 0.07, 95% CI: 0.02–0.19), followed by subinguinal microsurgery (OR = 0.09, 95% CI: 0.02–0.19). Inguinal open and laparoscopic surgery were associated with lower risks of overall complications. Although there was a tendency for relatively low risks of overall complications for Tauber sclerotherapy, the failure rate is not negligible.

A sensitivity analysis of the study type, and the patient age did not show any major change in recurrence, hydrocele formation, or overall complications (**Supplementary Table 2**). However, the difference was not statistical significant due to the small number of studies.

Overall, heterogeneity was found to be moderate, although, in the direct comparisons of overall complications, we found I^2 values higher than 70% for the comparisons of laparoscopic surgery and Tauber sclerotherapy (I^2 = 79.8%). Only three studies were included in that meta-analysis.

DISCUSSION

Recent meta-analyses have raised interest in the choice of treatment for varicocele. Cayan *et al.*[50] reviewed pregnancy rates, recurrence and hydrocele formation rates among various techniques, and found that open microsurgical inguinal or subinguinal varicocelectomy techniques resulted in higher pregnancy rates, and fewer recurrences and postoperative complications compared with conventional varicocelectomy techniques in infertile men. These data are consistent with the current results.

In the current network analysis, microsurgical inguinal varicocelectomy showed a slight advantage over the subinguinal technique. Hopps *et al.*[51] concluded that the anatomy using a subinguinal approach is far more complicated, and is associated with a greater number of internal spermatic veins and arteries compared with the inguinal approach. Any damage to the lymphatic drainage during the excess dissection of the cord structures may increase the possibility of hydrocele. However, the subinguinal approach still outperformed conventional open retroperitoneal surgery in terms of rates of development of hydrocele. Microsurgical inguinal surgery is technically easier, but some reports have stated that the opening of the aponeurosis of the external oblique results in more pain, and a longer recovery period.[28]

The most important issue is whether patients with subclinical varicocele and one or more abnormal semen parameters benefit from surgical repair. A prospective randomized trial compared the effect of unilateral surgical repair of left clinical varicoceles. Subclinical varicocelectomy had an improvement in sperm density ($P < 0.006$), and total motile sperm counts ($P < 0.008$), but had no beneficial

Table 1: Study and patient characteristics

Studies	*Treatment group*	*Sample size*	*Grade*	*Patient age (range or mean±s.d.)*	*Outcome measure*	*Design*
Abdel-Maguid and Othman 2010[18]	Subinguinal open/subinguinal micro	80/82	I–III	34±8.51/33.7±8.77	Complications/pregnancy rate/sperm parameters	RCT
Abdel-Meguid *et al.* 2011[19]	Control/subinguinal micro	72/73	NA	20–39	Pregnancy rate	RCT
Al-Kandari *et al.* 2007[8]	Laparoscopic/inguinal open/ subinguinal micro	40/40/40	NA	14–45	Complications/pregnancy rate/sperm parameters	RCT
Al-Said *et al.* 2008[20]	Laparoscopic/subinguinal micro/ inguinal open	94/112/92	NA	20–55	Complications/pregnancy rate/sperm parameters	RCT
Barbalias *et al.* 1998[35]	Retro open/Pv embolization/inguinal open/subinguinal open	20/20/20/20	I–III	22–39	Complications/sperm parameters	RCT
Cayan *et al.* 2000[7]	Retro open/laparoscopic	232/236	I–III	20–35	Complications/pregnancy rate/sperm parameters	RCT
Fayez *et al.* 2010[21]	Tauber sclerotherapy/inguinal open/ subinguinal antegrade	51/55/49	NA	Not given	Complications/pregnancy rate	RCT
Mansour Ghanaie *et al.* 2012[22]	Control/inguinal micro	68/68	I–III	36.1±4.2/36.8±4.6	Pregnancy rate/sperm parameters	RCT
Grasso *et al.* 2000[23]	Retro open/control	34/34	I	30–38	Complications/pregnancy rate/sperm parameters	RCT
Gontero *et al.* 2005[49]	Inguinal open/subinguinal micro	50/49	I–III	25.13±6.58/24.86±6.00	Complications/pregnancy rate	RCT
Madgar *et al.* 1995[25]	Control/inguinal open	20/25	NA	21–45	Pregnancy rate	RCT
Nieschlag *et al.* 1993/1998[26,27]	Pv embolization/retro open	62/63	I–III	32.8±0.5/33.1±0.4	Complications/pregnancy rate/sperm parameters	RCT
Nilsson *et al.* 1979[32]	Control/retro open	45/51	NA	21–52	Pregnancy rate	RCT
Pan *et al.* 2013[28]	Subinguinal micro/inguinal micro	56/59	I–III	29.5±4.6/29.1±4.1	Complications/pregnancy rate/sperm parameters	RCT
Podkamenev *et al.* 2002[37]	Laparoscopic/retro open	434/220	II–III	7–17	Complications	RCT
Sautter *et al.* 2002[38]	Tauber sclerotherapy/laparoscopic	35/34	I–III	16–45	Complications/pregnancy rate	RCT
Sayfan *et al.* 1992[29]	Pv embolization/retro open/inguinal open	36/55/28	NA	23–44	Complications/pregnancy rate/semen	RCT
Sun *et al.* 2012[33]	Inguinal open/retro open/laparoscopic	51/51/51	NA	13–33	Complications	RCT
Telkar *et al.* 2012[48]	Laparoscopic/retro open	15/15	I–III	18–45	Complications	RCT
Yamamoto *et al.* 1996[30]	Control/Pv embolization	45/47	NA	24–37	Pregnancy rate	RCT
Yavetz *et al.* 1992[31]	Retro open/Pv embolization/inguinal open	43/51/43	NA	Not given	Complications/pregnancy rate/sperm parameters	RCT
Zucchi *et al.* 2005[36]	Inguinal open/Tauber sclerotherapy	32/32	I–III	16–44	Complications/sperm parameters	RCT
Krause *et al.* 2002[24]	Tauber sclerotherapy/control/ retrograde Sclerotherapy/control	11/11/22/23	NA	32.2±5.8	Pregnancy rate	RCT
Ghanem *et al.*, 2004[44]	Subinguinal micro/retro open	304/109	I–III	36.7±4.9/35.8±4.3	Complications/ pregnancy rate	Cohort
Watanabe *et al.* 2005[39]	Retro open/laparoscopic/subinguinal micro	50/33/61	I–III	32.2±4.2/33.5±4.2/33.1±5.9	Complications/ pregnancy rate	Cohort
Shlansky-Goldberg *et al.* 1997[57]	Inguinal open/Pv embolization	149/197	NA	20–56	Complications/ pregnancy rate	Cohort
Vermeulen *et al.* 1986[58]	Pv embolization/control	90/25	I–III	29.1±3.8/28.2±3.4	Pregnancy rate	Cohort
Khouni *et al.* 2011[40]	Retro open/laparoscopic/Tauber sclerotherapy	42/41/45	I–III	Mean age 28	Complications/ pregnancy rate	Cohort
Abdulmaaboud *et al.* 1998[42]	Inguinal open/retrograde Sclerotherapy/laparoscopic	94/120/87	I–III	30±7/29±5/28.7±5.8	Complications/ pregnancy rate	Cohort
Orhan1 *et al.* 2005[41]	Subinguinal micro/inguinal micro	65/147	NA	19–41	Complications/ pregnancy rate	Cohort
Rageth *et al.* 1992[59]	Retro open/control	55/31	NA	Not given	Pregnancy rate	Cohort
Beutner *et al.* 2007[45]	Laparoscopic/Tauber sclerotherapy/Pv embolization	122/108/126	I–III	9–59	Complications	Cohort
May *et al.* 2006[46]	Laparoscopic/Tauber sclerotherapy	122/108	II–III	20±8.5	Complications	Cohort
Mazzoni *et al.* 2001[47]	Retro open/Tauber sclerotherapy	45/44	I–III	9–18	Complications	Cohort
Riccabona *et al.* 2003[43]	Laparoscopic/inguinal/retro open	19/21/88	II–III	4–15	Complications	Cohort

Retro open: retroperitoneal open; Pv embolization: percutaneous venous embolization; NA: not available; RCT: randomized clinical trial

effect on pregnancy rates.[30] Trial including male patients >30 years, demonstrated that open retroperitoneal surgery did not improve either sperm quality nor pregnancy rates.[23] Another randomized trial compared surgical repair in infertile men with clinical left and subclinical right varicoceles.[52] Left and bilateral repairs resulted in improvements in sperm concentration, motility, but no significant

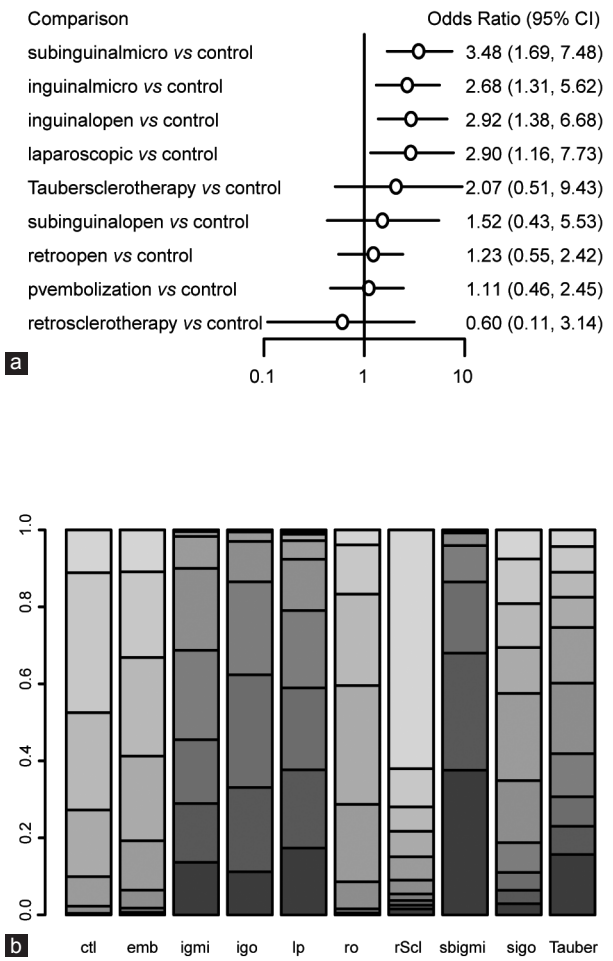

Figure 3: A comparison of pregnancy rates after various surgical/radiological treatments. (**a**) A forest plot of pregnancy rates. (**b**) A rank probability plot of pregnancy rates. Ctl: control; emb: percutaneous venous embolization; igmi: inguinal microsurgery; igo: inguinal open; lp: laparoscopic; ro: retropertional open; rScl: retrograde sclerotherapy; sbigmi: subinguinal microsurgery; sigo: subinguinal open; Tauber: Tauber sclerotherapy; CI: confidence interval.

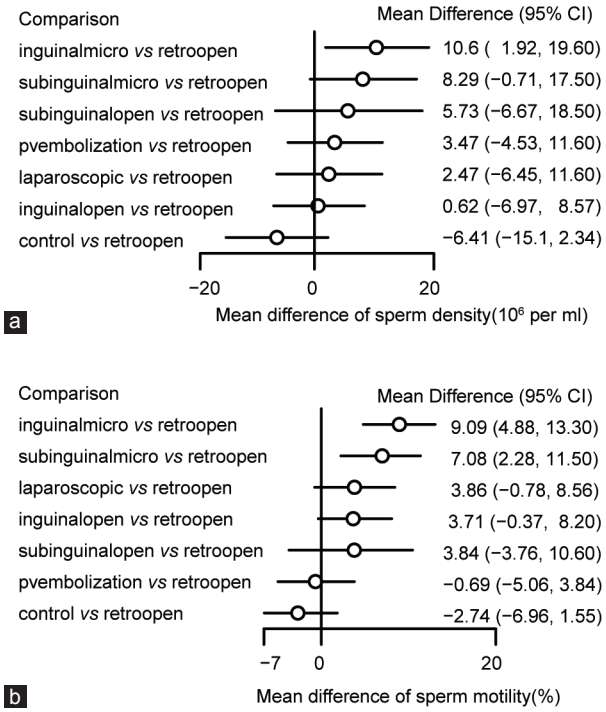

Figure 4: A comparison of semen parameters after various surgical/radiological treatments. (**a**) A forest plot of sperm density (10^6 ml^{-1}). (**b**) A forest plot of sperm motility (%). CI: confidence interval.

difference of pregnancy rates. In the current analysis, retroperitoneal ligation method did not achieve an average efficacy. Pregnancy rates can be easily biased by the influence of female partners in the infertile couple population. The studies, however, are not sufficiently conclusive to recommend for or against subclinical varicocele repair.[53]

Postoperative hydrocele formation with its associated accumulation of high-protein fluid can be a potential problem with any technique used for varicocele ligation. Liang *et al.*[54] found that lymphatic-sparing laparoscopic varicocelectomy is valuable in reducing the incidence of the postoperative hydrocele, with similar incidences in children and adolescents. However, the most important clinical implication of the results is the low odds of hydrocele formation using minimally invasive procedures like Tauber antegrade sclerotherapy, and embolization. Radiologic embolization (balloon or coil) or sclerotherapy of spermatic veins was found to have a failure rate of 19.8%, 17% respectively in the current studies. We did not include unsuccessful interventions in the overall complication rates. Radiation exposure is another disadvantage of the procedure.

Retroperitoneal (Palomo's) technique is one of the most widely used methods. However, the current study showed that it is also the least efficacious treatment, with relative high risk of recurrence and hydrocele formation. That treatment of varicocele aims to block the internal spermatic vein. However, the external spermatic vein has been found to be dilated in 16%–74% of cases.[55] This vein cannot be approached by retroperitoneal or laparoscopic techniques and therefore, subinguinal or inguinal approaches are preferred. In addition, varicocelectomy performed without using magnification may result in recurrence because of the difficulty in visualization of small branches of the internal spermatic vein, proven to be present radiologically.[56]

There are several limitations to the current study. We did not investigate some important complications such as testicular atrophy, prolonged pain, epididymoorchitis. Some complications like inferior epigastric arterial bleeding, subcutaneous emphysema are only associated with laparoscopic procedures. According to Cayan *et al.*[50] a pooled complication rate with laparoscopic approaches was found to be 7.45%. As for Tauber's technique, the complication rates reported were between 0% and 14%. The common complications were scrotal hematoma (1.5%–2.2%) and epididymoorchitis (0.5%–2%). Postembolization complications included contrast extravasation, vascular perforation, coil migration, and allergy to contrast agents.

Due to ethical limitations and characteristics of surgical trials, most trials were not blinded. In addition, some trials did not disclose methods of randomization. Most of RCTs included were not of good quality. With limited information, we could not evaluate the impact of the learning curve, which may have potentially biased the results. For semen parameters, many studies did not report s.d. of mean changes. We imputed missing s.d. of mean changes for each treatment using the largest s.d. reported in the set of included studies for each outcome.

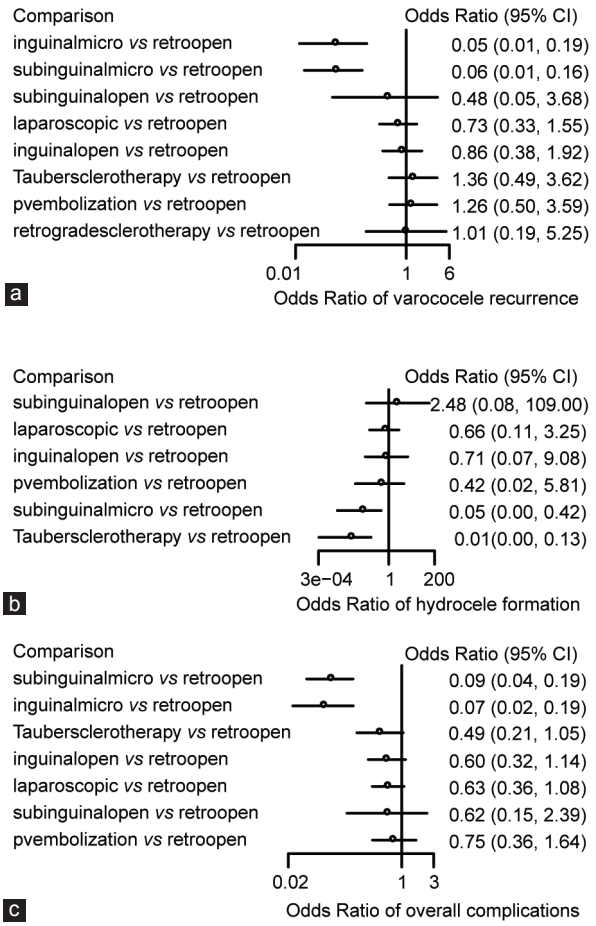

Figure 5: A comparison of complications after various surgical/radiological treatments. (**a**) A forest plot of recurrence of varicoceles. (**b**) A forest plot of hydrocele formation. (**c**) A forest plot of overall complications. CI: confidence interval.

As a consequence, conservative results had poor precision. Another limitation of our analysis is that the method for detecting publication bias is not well established. In one study which used a crossover design, only the data before crossover were used. The effectiveness and safety of several surgical techniques were well estimated. However, retrograde sclerotherapy was evaluated in only two trials. Thus, the result of retrograde sclerotherapy may not be as robust as that of other techniques. The studies included in the present analysis of varicocele treatment were moderately heterogeneous. Restriction to men with clinical varicoceles, an abnormal semen analysis did not lower the heterogeneity.

In patients with subfertility or abnormal sperm parameters, various surgical approaches and embolization/sclerotherapy have led to improvements in pregnancy rates, and sperm counts and motility. Inguinal and subinguinal micro-varicocelectomy had the highest pregnancy rates, and significant increases in sperm parameters. In all patients after various varicocelectomy or embolization/sclerotherapy, inguinal and subinguinal micro-varicocelectomy were associated with low odds of recurrence, hydrocele formation and overall complications. Tauber antegrade sclerotherapy was associated with lower odds of hydrocele formation. Larger properly conducted RCTs of varicocele treatment in men with varicocele and sperm defects are needed to confirm these results.

AUTHOR CONTRIBUTIONS

JW, SJX and JXQ conceived of the study, participated in its design and coordinated and drafted the manuscript. CMX, JW and ZHL participated in the evaluation for bias. ZHL, LT and JFG collected the data. JW and JFG performed the statistical analyses. CMX, JW and ZHL participated in critical revision of the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

ACKNOWLEDGMENTS

The authors thank Dr. Gert van Valkenhoef (Department of Epidemiology, University Medical Center Groningen) for his consultation in statistics.

Supplementary information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

REFERENCES

1 Gorelick JI, Goldstein M. Loss of fertility in men with varicocele. *Fertil Steril* 1993; 59: 613–6.
2 Schlesinger MH, Wilets IF, Nagler HM. Treatment outcome after varicocelectomy. A critical analysis. *Urol Clin North Am* 1994; 21: 517–29.
3 Merla A, Ledda A, Di Donato L, Di Luzio S, Romani GL. Use of infrared functional imaging to detect impaired thermoregulatory control in men with asymptomatic varicocele. *Fertil Steril* 2002; 78: 199–200.
4 Hauser R, Paz G, Botchan A, Yogev L, Yavetz H. Varicocele: effect on sperm functions. *Hum Reprod Update* 2001; 7: 482–5.
5 Blumer CG, Fariello RM, Restelli AE, Spaine DM, Bertolla RP, *et al*. Sperm nuclear DNA fragmentation and mitochondrial activity in men with varicocele. *Fertil Steril* 2008; 90: 1716–22.
6 Sakamoto Y, Ishikawa T, Kondo Y, Yamaguchi K, Fujisawa M. The assessment of oxidative stress in infertile patients with varicocele. *BJU Int* 2008; 101: 1547–52.
7 Cayan S, Kadioglu TC, Tefekli A, Kadioglu A, Tellaloglu S. Comparison of results and complications of high ligation surgery and microsurgical high inguinal varicocelectomy in the treatment of varicocele. *Urology* 2000; 55: 750–4.
8 Al-Kandari AM, Shabaan H, Ibrahim HM, Elshebiny YH, Shokeir AA. Comparison of outcomes of different varicocelectomy techniques: open inguinal, laparoscopic, and subinguinal microscopic varicocelectomy: a randomized clinical trial. *Urology* 2007; 69: 417–20.
9 Unal D, Yeni E, Verit A, Karatas OF. Clomiphene citrate versus varicocelectomy in treatment of subclinical varicocele: a prospective randomized study. *Int J Urol* 2001; 8: 227–30.
10 Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004; 23: 3105–24.
11 Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat Med* 2002; 21: 2313–24.
12 Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, *et al*. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 2009; 373: 746–58.
13 Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151: 264–9, W64.
14 Kroese AC, de Lange NM, Collins J, Evers JL. Surgery or embolization for varicoceles in subfertile men. *Cochrane Database Syst Rev* 2012; 10: CD000479.
15 Wells GA, Shea B, O'Connell D, Peterson J, Welch V, *et al*. The Newcastle-Ottawa scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. [Last accessed on 2013 Sep 20].
16 van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, *et al*. Automating network meta-analysis. *Res Synth Methods* 2012; 3: 285–99.
17 Raftery AE, Lewis SM. One long run with diagnostics: implementation strategies for Markov chain Monte Carlo. *Stat Sci* 1992; 7: 493–7.
18 Abdel-Maguid AF, Othman I. Microsurgical and nonmagnified subinguinal varicocelectomy for infertile men: a comparative study. *Fertil Steril* 2010; 94: 2600–3.
19 Abdel-Meguid TA, Al-Sayyad A, Tayib A, Farsi HM. Does varicocele repair improve male infertility? An evidence-based perspective from a randomized, controlled trial. *Eur Urol* 2011; 59: 455–61.
20 Al-Said S, Al-Naimi A, Al-Ansari A, Younis N, Shamsodini A, *et al*. Varicocelectomy for male infertility: a comparative study of open, laparoscopic and microsurgical approaches. *J Urol* 2008; 180: 266–70.
21 Fayez A, El Shantaly KM, Abbas M, Hauser S, Müller SC, *et al*. Comparison of

inguinal approach, scrotal sclerotherapy and subinguinal antegrade sclerotherapy in varicocele treatment: a randomized prospective study. *Urol Int* 2010; 85: 200–3.
22 Mansour Ghanaie M, Asgari SA, Dadrass N, Allahkhah A, Iran-Pour E, *et al*. Effects of varicocele repair on spontaneous first trimester miscarriage: a randomized clinical trial. *Urol J* 2012; 9: 505–13.
23 Grasso M, Lania C, Castelli M, Galli L, Franzoso F, *et al*. Low-grade left varicocele in patients over 30 years old: the effect of spermatic vein ligation on fertility. *BJU Int* 2000; 85: 305–7.
24 Krause W, Müller HH, Schäfer H, Weidner W. Does treatment of varicocele improve male fertility? Results of the 'Deutsche Varikozelenstudie', a multicentre study of 14 collaborating centres. *Andrologia* 2002; 34: 164–71.
25 Madgar I, Weissenberg R, Lunenfeld B, Karasik A, Goldwasser B. Controlled trial of high spermatic vein ligation for varicocele in infertile men. *Fertil Steril* 1995; 63: 120–4.
26 Nieschlag E, Behre HM, Schlingheider A, Nashan D, Pohl J, *et al*. Surgical ligation *vs* angiographic embolization of the vena spermatica: a prospective randomized study for the treatment of varicocele-related infertility. *Andrologia* 1993; 25: 233–7.
27 Nieschlag E, Hertle L, Fischedick A, Abshagen K, Behre HM. Update on treatment of varicocele: counselling as effective as occlusion of the vena spermatica. *Hum Reprod* 1998; 13: 2147–50.
28 Pan F, Pan L, Zhang A, Liu Y, Zhang F, *et al*. Comparison of two approaches in microsurgical varicocelectomy in Chinese infertile males. *Urol Int* 2013; 90: 443–8.
29 Sayfan J, Soffer Y, Orda R. Varicocele treatment: prospective randomized trial of 3 methods. *J Urol* 1992; 148: 1447–9.
30 Yamamoto M, Hibi H, Hirata Y, Miyake K, Ishigaki T. Effect of varicocelectomy on sperm parameters and pregnancy rate in patients with subclinical varicocele: a randomized prospective controlled study. *J Urol* 1996; 155: 1636–8.
31 Yavetz H, Levy R, Papo J, Yogev L, Paz G, *et al*. Efficacy of varicocele embolization versus ligation of the left internal spermatic vein for improvement of sperm quality. *Int J Androl* 1992; 15: 338–44.
32 Nilsson S, Edvinsson A, Nilsson B. Improvement of semen and pregnancy rate after ligation and division of the internal spermatic vein: fact or fiction? *Br J Urol* 1979; 51: 591–6.
33 Sun HB, Liu Y, Yan MB, Li ZD, Gui XG. Comparing three different surgical techniques used in adult bilateral varicocele. *Asian J Endosc Surg* 2012; 5: 12–6.
34 Song T, Wang CY, Zhang L, Zhang F, Chen WZ, *et al*. Microscopic versus laparoscopic varicocelectomy in the treatment of varicocele: effects and complications. *Zhonghua Nan Ke Xue* 2012; 18: 335–8.
35 Barbalias GA, Liatsikos EN, Nikiforidis G, Siablis D. Treatment of varicocele for male infertility: a comparative study evaluating currently used approaches. *Eur Urol* 1998; 34: 393–8.
36 Zucchi A, Mearini L, Mearini E, Costantini E, Bini V, *et al*. Treatment of varicocele: randomized prospective study on open surgery versus Tauber antegrade sclerotherapy. *J Androl* 2005; 26: 328–32.
37 Podkamenev VV, Stalmakhovich VN, Urkov PS, Solovjev AA, Iljin VP. Laparoscopic surgery for pediatric varicoceles: randomized controlled trial. *J Pediatr Surg* 2002; 37: 727–9.
38 Sautter T, Sulser T, Suter S, Gretener H, Hauri D. Treatment of varicocele: a prospective randomized comparison of laparoscopy versus antegrade sclerotherapy. *Eur Urol* 2002; 41: 398–400.
39 Watanabe M, Nagai A, Kusumi N, Tsuboi H, Nasu Y, *et al*. Minimal invasiveness and effectivity of subinguinal microscopic varicocelectomy: a comparative study with retroperitoneal high and laparoscopic approaches. *Int J Urol* 2005; 12: 892–8.
40 Khouni H, Bouchiba N, Khelifa MM, Ben Ali M, Sebai A, *et al*. Treatment of idiopathic varicocele: comparative study of three techniques about 128 cases. *Tunis Med* 2011; 89: 929–34.
41 Orhan RO, Semercïöz A, Firdolas F, Ardicoglu A, Köksal IT. Comparison of two different microsurgical methods in the treatment of varicocele. *Syst Biol Reprod Med* 2005; 51: 213–20.
42 Abdulmaaboud MR, Shokeir AA, Farage Y, Abd El-Rahman A, El-Rakhawy MM, *et al*. Treatment of varicocele: a comparative study of conventional open surgery, percutaneous retrograde sclerotherapy, and laparoscopy. *Urology* 1998; 52: 294–300.
43 Riccabona M, Oswald J, Koen M, Lusuardi L, Radmayr C, *et al*. Optimizing the operative treatment of boys with varicocele: sequential comparison of 4 techniques. *J Urol* 2003; 169: 666–8.
44 Ghanem H, Anis T, El-Nashar A, Shamloul R. Subinguinal microvaricocelectomy versus retroperitoneal varicocelectomy: comparative study of complications and surgical outcome. *Urology* 2004; 64: 1005–9.
45 Beutner S, May M, Hoschke B, Helke C, Lein M, *et al*. Treatment of varicocele with reference to age: a retrospective comparison of three minimally invasive procedures. *Surg Endosc* 2007; 21: 61–5.
46 May M, Johannsen M, Beutner S, Helke C, Braun KP, *et al*. Laparoscopic surgery versus antegrade scrotal sclerotherapy: retrospective comparison of two different approaches for varicocele treatment. *Eur Urol* 2006; 49: 384–7.
47 Mazzoni G, Spagnoli A, Lucchetti MC, Villa M, Capitanucci ML, *et al*. Adolescent varicocele: Tauber antegrade sclerotherapy versus Palomo repair. *J Urol* 2001; 166: 1462–4.
48 Telkar S, Goudar BV, Lamani YP, Ambi U, Koppal R. Laparoscopic versus open varicocelectomy a prospective study. *J Clin Diagn Res* 2012; 6: 271–3.
49 Gontero P, Pretti G, Fontana F, Zitella A, Marchioro G, *et al*. Inguinal versus subinguinal varicocele vein ligation using magnifying loupe under local anesthesia: which technique is preferable in clinical practice? *Urology* 2005; 66: 1075–9.
50 Cayan S, Shavakhabov S, Kadioglu A. Treatment of palpable varicocele in infertile men: a meta-analysis to define the best technique. *J Androl* 2009; 30: 33–40.
51 Hopps CV, Lemer ML, Schlegel PN, Goldstein M. Intraoperative varicocele anatomy: a microscopic study of the inguinal versus subinguinal approach. *J Urol* 2003; 170: 2366–70.
52 Zheng YQ, Gao X, Li ZJ, Yu YL, Zhang ZG, *et al*. Efficacy of bilateral and left varicocelectomy in infertile men with left clinical and right subclinical varicoceles: a comparative study. *Urology* 2009; 73: 1236–40.
53 Baazeem A, Belzile E, Ciampi A, Dohle G, Jarvi K, *et al*. Varicocele and male factor infertility treatment: a new meta-analysis and review of the role of varicocele repair. *Eur Urol* 2011; 60: 796–808.
54 Liang Z, Guo J, Zhang H, Yang C, Pu J, *et al*. Lymphatic sparing versus lymphatic non-sparing laparoscopic varicocelectomy in children and adolescents: a systematic review and meta-analysis. *Eur J Pediatr Surg* 2011; 21: 147–53.
55 Beck EM, Schlegel PN, Goldstein M. Intraoperative varicocele anatomy: a macroscopic and microscopic study. *J Urol* 1992; 148: 1190–4.
56 Murray RR Jr, Mitchell SE, Kadir S, Kaufman SL, Chang R, *et al*. Comparison of recurrent varicocele anatomy following surgery and percutaneous balloon occlusion. *J Urol* 1986; 135: 286–9.
57 Shlansky-Goldberg RD, VanArsdalen KN, Rutter CM, Soulen MC, Haskal ZJ, *et al*. Percutaneous varicocele embolization versus surgical ligation for the treatment of infertility: changes in seminal parameters and pregnancy outcomes. *J Vasc Interv Radiol* 1997; 8: 759–67.
58 Vermeulen A, Vandeweghe M, Deslypere JP. Prognosis of subfertility in men with corrected or uncorrected varicocele. *J Androl* 1986; 7: 147–55.
59 Rageth JC, Unger C, DaRugna D, Steffen R, Stucki D, *et al*. Long-term results of varicocelectomy. *Urol Int* 1992; 48: 327–31.