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Original Article

Laparoendoscopic single-site versus conventional multiport laparoscopic varicocelectomy: a meta-analysis

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Abstract: Recently, several studies assessed the effectiveness of laparoendoscopic single-site (LESS) varicocelectomy for varicoceles, but the efficacy and potential advantages of LESS compared with conventional multiport laparoscopic (CML) remained controversial. Therefore, the purpose of this systematic review is to evaluate the current evidence regarding the efficiency, safety, and potential advantages of LESS compared with CML in the treatment of patients with varicoceles. Relevant articles published in English were identified by searching PubMed, EMBASE, Cochrane Library, and the ISI Web of Knowledge databases up to October 2015. The Related Articles function was also used to identify relevant manuscripts and references were explored to broaden the search. Primary outcomes (operative time, hospital stay, return to normal activities time, pain score, and cosmetic satisfaction rate) and secondary outcomes (improvements of semen parameters and postoperative complications) were pooled. The odds ratio (OR) and weighted mean difference (WMD) with 95% confidence intervals (CIs) were used to compare dichotomous and continuous variables. Two randomized controlled trials (RCTs) and four non-randomized controlled trial (NRCTs) were eligible. 407 patients were treated, 169 with LESS and 224 with CML. LESS was superior to CML in postoperative pain within 24 h (VAS in 6 h, WMD: -0.56; 95% CI, -0.93, -0.20; P=0.0003; VAS in 24 h, WMD: -0.60; 95% CI, -0.80, -0.39; P<0.00001), return to normal activities time (WMD: -1.31; 95% CI, -2.21, -0.40; P=0.005), and cosmetic satisfaction rate (OR 6.76, 95% CI 2.17, 21.07, P=0.001). Other outcomes were similar. LESS offered a safe and efficient alternative to CML with a less postoperative pain, shorter return to normal activities time and better cosmetic result for patients with varicocelectomy. Due to the inherent limitations of the included studies, future well-designed and high quality RCTs are awaited to confirm and update the findings of this analysis.

Keywords: Laparoendoscopic single-site surgery, conventional multiport laparoscopic, varicocelectomy, meta-analysis

Introduction

Varicoceles are considered to be a major cause of male infertility [1]. Ligation of the internal spermatic vein can improve testicular Leydig cell function, reduces sperm DNA damage and seminal oxidative stress, leading to remarkable improvement of basic sperm parameters [2]. Several surgical procedures have been used to varicocelectomy, including retroperitoneal, inguinal, microscopic, and laparoscopic [3-5]. Laparoscopic varicocelectomy has been recommended as one method of effective and safe to correct the varicocele [6, 7]. Minimally invasive surgery has continued to evolve. To strive for further reduce the morbidity and scarring, laparoscopic single-site surgery (LESS) is currently under active investigation.

Many studies reported that LESS patients benefit from less postoperative pain, shorter hospital stay, faster recovery time, and a better cosmetic outcome [8, 9]. Nevertheless, some studies found no significant advantage of LESS [9-11]. Thus, LESS is still to be defined in the field of minimally invasive urologic surgery. Recently, several studies comparing LESS varicocelectomy and conventional multiports laparoscopic (CML) varicocelectomy have been reported, most are small series [12-17]. Therefore, we systemically searched and analyzed the available studies to evaluate the surgi-

cal efficacy and potential advantages of LESS compared with CML in the treatment of patients with varicoceles.

Methods

Search strategy

A systematic review of the literature was performed in October 2015, without restriction to publication types, or regions, using PubMed, EMBASE, Cochrane Library, and the ISI Web of Knowledge databases. The language was restricted in English. The relevant medical subject heading (MeSH) terms and their combinations were searched in [Title/Abstract]: single site/port/incision, natural orifice transumbilical, and laparoscopic/laparoendoscopic varicocelectomy. The Related Articles function was also used to identify relevant manuscripts and references were explored to broaden the search.

Study selection

The process of study selection was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Selected studies met all of the following criteria: (1) randomized controlled trails (RCTs) or non-randomized controlled trials (NRCTs); (2) compared LESS and CML; (3) revealed at least one of the outcomes: operative time, hospital stay, postoperative abdominal pain, cosmetic satisfaction, return to normal activities time, Semen parameters, hydrocele rate, and recurrence rate. The studies were excluded if: (1) the surgery was not varicocelectomy; (2) single incision was not mentioned; (3) the studies were reported without detailed information of outcomes. When multiple articles describing the same population were published, the article with the most recent or detailed information was selected. The eligibility of all retrieved articles was evaluated by two authors independently. All the disagreements were resolved by discussion or in consultation with a third author.

Data extraction

Data were extracted from all the eligible studies by two of the authors. Primary outcomes between the two surgical approaches were compared including operative time, hospital stay, postoperative abdominal pain, cosmetic satisfaction rate, and return to normal activities time. Pain scores from using a visual analogue scale (VAS) were pooled to evaluate postoperative abdominal pain. Three postoperative time points (6 h, 24 h, and 48 h) were used to evaluate pain. Secondary outcomes evaluated included improvements of semen parameters and postoperative complications. The sperm analyses were collected to assess for improvement of semen parameters. Postoperative complications included postoperative hydrocele rate and recurrence rate.

Quality assessment

The level of evidence was rated for the included studies according to the criteria provided by the Center for Evidence-Based Medicine in Oxford, UK. The methodological quality of RCTs was assessed by Jadad scale (score ranging between 0 and 5, with 0-2 being low, 3-5 high) [18]. The methodological quality of NRCTs was assessed by the Newcastle-Ottawa Scale, which consist of three factors: patient selection, comparability of the study groups, and assessment of outcome; and score ranging between 0 and 9, with 0-2 being low, 3-5 moderate, and 6-9 high [19].

Statistical analysis

All the meta-analyses were performed using Cochrane Review Manager software (Cochrane Collaboration, Oxford, UK, Version 5.2). The odds ratio (OR) and weighted mean difference (WMD) with 95% confidence intervals (CIs) were used to compare dichotomous and continuous variables, respectively. For studies that presented continuous data as means and range values, we calculated the standard deviations using the technique described by Hozo et al. [20]. The inconsistency (I^2) statistic was used to evaluate the heterogeneity. Low, moderate and high represented I^2 values of 40, 70 and 100%, respectively. Where $I^2 \leq 40\%$ indicates there was no evidence of heterogeneity, the fixed-effects model was used, otherwise the random-effects model was used. The fixed-effects model was used if $I^2 \leq 40\%$, which indicates there was no evidence of heterogeneity; otherwise, the random-effects model was used. Detailed subgroup analyses were performed based on different time points to evaluate postoperative VAS scores. The influence of single study on the overall risk estimate was investigated by sequentially removing study to test the robustness of the main results. Funnel plots were used to identify potential publication bias.

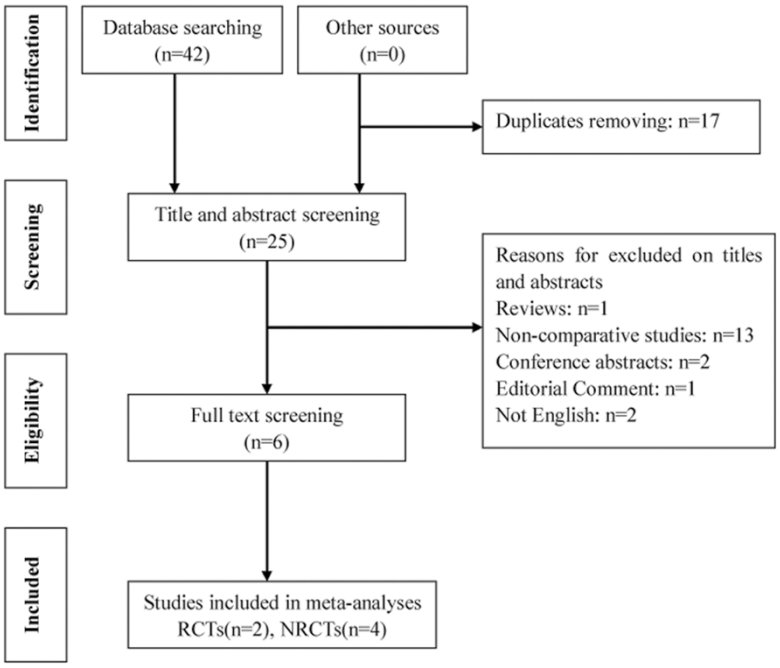

Figure 1. PRISMA flowchart of literature searches and results. PRISMA, preferred reporting items for systematic reviews and meta-analyses; RCTs, randomized controlled trials; NRCTs, non-randomized controlled trials.

Results

Literature search

The initial search obtained 42 articles. After screening the abstracts and the full texts, there were 2 RCTs [12, 13], and 4 NRCTs [14-17] were included in this meta-analysis. A detailed PRISMA flowchart of the selection process was shown in **Figure 1**.

Study characteristics

Table 1 shows the major characteristics of the 6 studies. Of the 6 studies, 2 were performed in Italy [16, 17], 1 were performed in the USA [15], 1 in Germany [14] and the remaining in China [13] and Korea [12] respectively, during the period between 2012 and 2015. The sample size of included studies ranged from 24 to 99 (407 in total). 169 patients were treated with LESS and 238 patients were treated with CML. Four studies [14-17] used commercial single-port devices (ie, X-Cone Port, TriPort, and SILS Port), and two studies [12, 13] used homemade devices. According to Jadad scale for RCTs, one study scored 4 points, and another study scored 3 points (**Table 2**). The quality of NRCTs according to Newcastle-Ottawa Scale, one study scored 5 points and another three studies scored 6 points (**Table 2**).

Primary outcome: operative time

All the 6 studies reported operative time for the 407 included patients. There was no significant difference between the LESS and CML groups (WMD: -6.71; 95% CI, -14.48 to 1.06; P=0.09) (**Figure 2**).

Primary outcome: length of hospital stay

There were 4 studies [12-14, 17] reported length of hospital stay in 295 pa tients, and the pooled data showed no significant differences between the LESS and CML groups (WMD: -0.91, 95% CI -1.95, 0.12, P=0.08) (**Figure 3**).

Primary outcome: VAS scores

Figure 4 lists the postoperative VAS scores at different time points and the result showed significant lower VAS scores in the LESS group than the CML group (WMD: -0.43; 95% CI, -0.66 to -0.20; P=0.0002). In the results of subgroup analyses, 2 studies reported [13, 16] postoperative VAS scores in 6 hour in 159 patients, and the pooled data showed a significant lower VAS scores in the LESS group than the CML group (WMD: -0.56; 95% CI, -0.93 to -0.20; P=0.0003). 4 studies [12-14, 16] compared postoperative VAS in 24 hour in 340 patients, and lower VAS scores was showed in LESS group (WMD: -0.60; 95% CI, -0.80 to -0.39; P<0.00001). The pooled data of 3 studies [12-14] showed that there was no significant statistic difference between the LESS and CML groups on postoperative VAS in 48 hour in 271 patients (WMD: -0.21; 95% CI, -0.71 to -0.29; P=0.41).

Primary outcome: return to normal activities time

There were 3 studies [12, 13, 17] reported return to normal activities time in 196 patients, and the pooled data showed a significant shorter reported return to normal activities time in the LESS group than the CML group (WMD:

Table 1. Characteristics of the studies included in the meta-analysis

Study/year	*Country*	*Surgical approach*	*Patients*	*Port*	*Instruments*	*Ligation approach*	*Outcome*
Seung 2012	Korea	LESS	39	A homemade single-port	Flexible laparoscopic instruments	Hem-o-lok clips	1, 2, 3, 4, 5, 6, 7, 8
		CML	43	Conventional multiple port			1, 2, 3, 4, 6, 7, 8
Frank 2013	Germany	LESS	20	X-Cone single-port	Prebent laparoscopic instrument	10-mm Dexon clips or Hem-o-lock clips	1, 2, 3, 4, 6, 7
		CML	79	Conventional multiport			1, 2, 3, 4, 6, 7
Wang 2014	China	LESS	45	10-mm trocar and 6-mm working channel	5-mm rigid instrument, a 2-0 silk suture and needle	Hem-o-lok clips	1, 2, 3, 5, 6, 7, 8
		CML	45	Conventional multiport			1, 2, 3, 6, 7, 8
Danesh 2014	USA	LESS	11	Olympus TriPort	5-mm flexible laparoscope EndoEye camera system	NA	1, 7, 8
		CML	32	Conventional multiport			
Antonio 2014	Italy	LESS	44	SILS port	Two curved Rochester-Pean clamps	Titanium clips	1, 3, 7, 8
		CML	25	Conventional multiport			
Salvatore	Italy	LESS	10	SILS port	5-mm flexible laparoscope EndoEye camera system	Hem-o-lok	1, 2, 4, 5
		CML	14	Conventional multiport			

LESS, laparoendoscopic single site; CML, conventional multiport laparoscopic; NA, not available; Outcome: 1 operative time, 2 hospital stay, 3 visual analogue scale score, 4 cosmetic satisfaction, 5 return to normal activities time, 6 semen parameters, 7 hydrocele, 8 recurrence.

Table 2. Quality assessment of the studies included in the meta-analysis

Study/year	*Study type*	*Quarlity assessment scale*	*Quarlity score*
Seung 2012	RCT	Jadad scale	3 out of 5 points
Frank 2013	NRCT	Newcastle-Ottawa Scale	6 out of 9★
Wang 2014	RCT	Jadad scale	4 out of 5 points
Danesh 2014	NRCT	Newcastle-Ottawa Scale	5 out of 9★
Antonio 2014	NRCT	Newcastle-Ottawa Scale	6 out of 9★
Salvatore	NRCT	Newcastle-Ottawa Scale	6 out of 9★

RCT, randomized controlled trial; NRCT, non-randomized controlled trial.

-1.31; 95% CI, -2.21 to -0.40; P=0.005) (**Figure 5**).

Primary outcome: cosmetic satisfaction

Three studies [12, 14, 17] compared cosmetic satisfaction rate in 188 patients, and a higher cosmetic satisfaction rate was associated with LESS group (95.6% and 74.2%; OR 6.76, 95% CI 2.17 to 21.07, P=0.001) (**Figure 6**).

Secondary outcome: semen parameters improvements

The semen parameters, which include sperm count, motility, and normal morphyology, were analyzed in 2 studies [12, 13]. The pooled data showed that there was no significant statistic difference on count improvement (WMD: 0.25; 95% CI, -1.40 to 1.91; p=0.76), motility improvement (WMD: -0.15; 95% CI, -2.35 to 2.05; p=0.89), and normal morphyology improvement (WMD: 0.05; 95% CI, -1.41 to 1.51; P=0.95) (**Figure 7**).

Secondary outcome: postoperative complications

Pooling the data from 5 studies [12-16] that assessed postoperative hydrocele rate in 380 patients showed no significant difference between the LESS and CML groups (2.53% and 3.6%; OR: 0.83; 95% CI, 0.26 to 2.71; p=0.76) (**Figure 8A**). 3 studies [12, 13, 16] reported postoperative recurrence rate in 238 patients, and the pooled data showed no significant statistic difference (2.36% and 2.70%; OR: 0.85, 95% CI 0.17 to 4.30, p=0.84) (**Figure 8B**).

Sensitivity analysis and publication bias

Sensitivity analysis was performed by sequentially removing each study, the result showed that when the study (Antonio 2014) was removed, the result of recurrence rate demonstrated no significant statistic difference between the two groups (OR 1.04, 95% CI 0.14-7.55, p=0.97). In addition, no other significance of pooled ORs and 95% CIs were influenced by

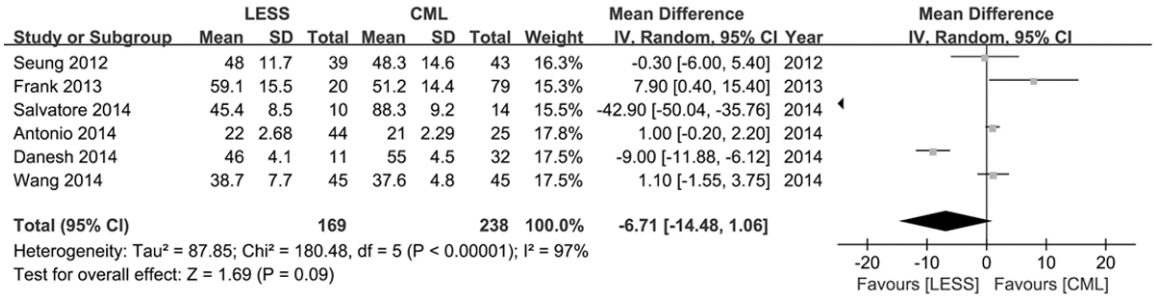

Figure 2. Forest plot and meta-analysis of operative time. LESS, laparoendoscopic single site; CML, conventional multiport laparoscopic.

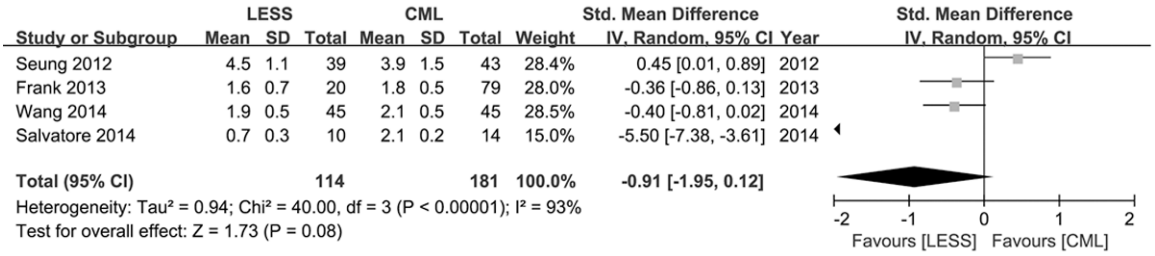

Figure 3. Forest plot and meta-analysis of length of hospital stay. LESS, laparoendoscopic single site; CML, conventional multiport laparoscopic.

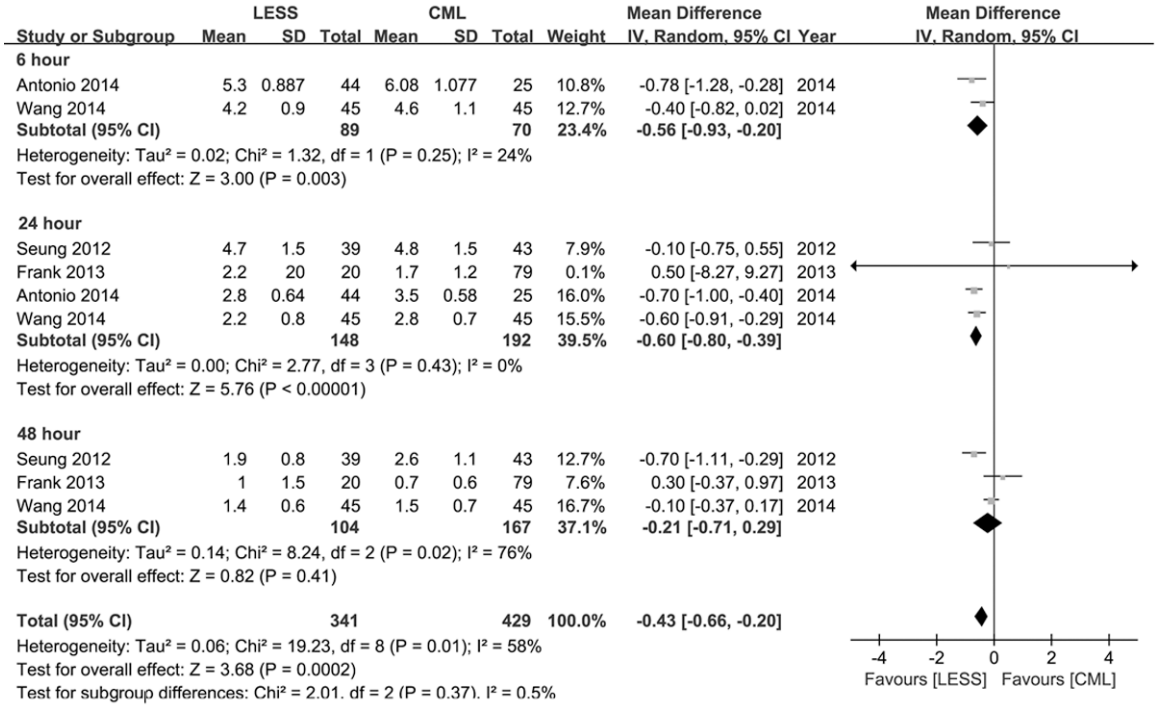

Figure 4. Forest plot and meta-analysis of VAS scores. VAS, visual analogue scale; LESS, laparoendoscopic single site; CML, conventional multiport laparoscopic.

the omission of any single study, this suggested that the results of this meta-analysis were stable. **Figure 9** shows a funnel plot of the studies included in this meta-analysis that reported

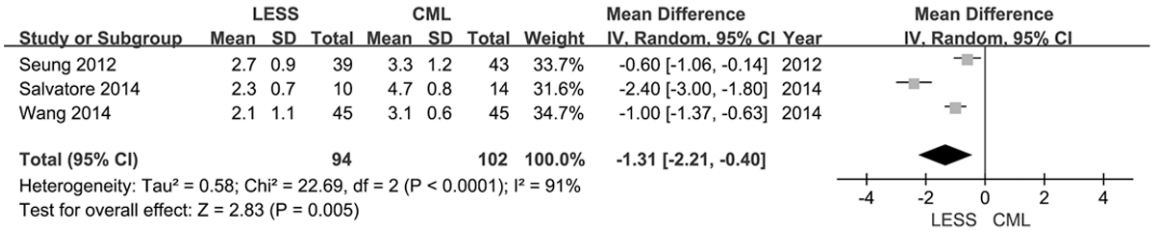

Figure 5. Forest plot and meta-analysis of return to normal activities time. LESS, laparoendoscopic single site; CML, conventional multiport laparoscopic.

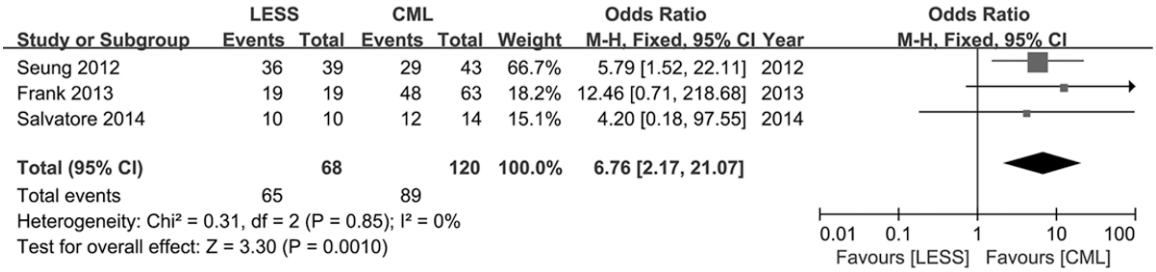

Figure 6. Forest plot and meta-analysis of cosmetic satisfaction rate. LESS, laparoendoscopic single site; CML, conventional multiport laparoscopic.

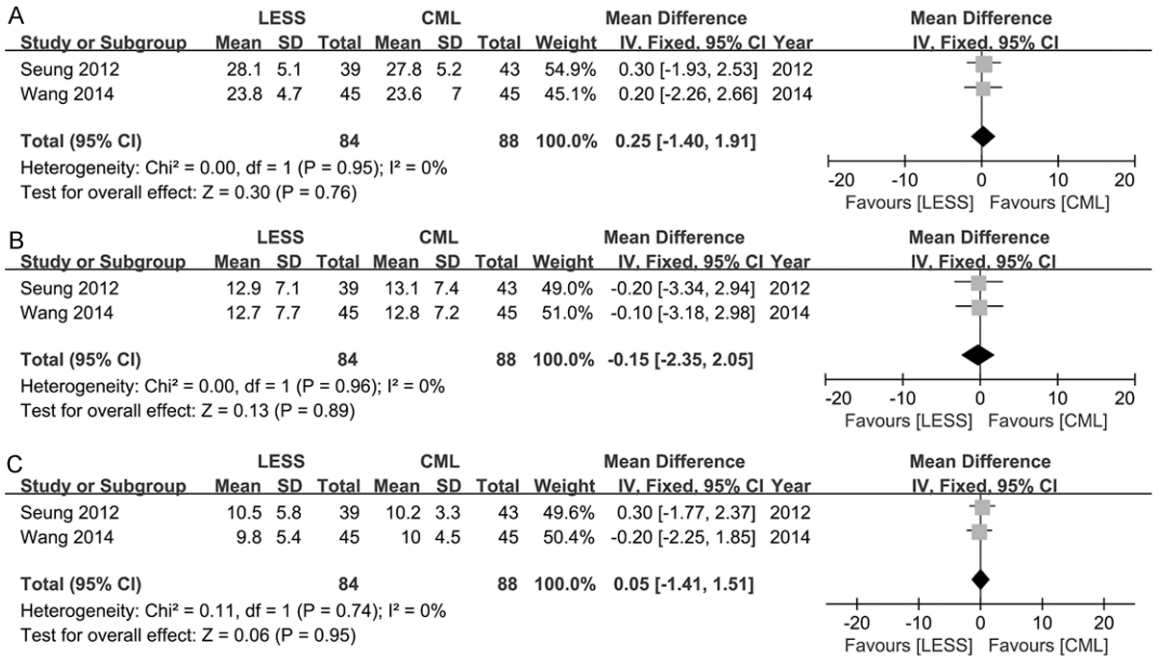

Figure 7. Forest plot and meta-analysis of semen parameters improvements, including sperm count improvements (A), motility improvements (B), and normal morphyology improvements (C). LESS, laparoendoscopic single site; CML, conventional multiport laparoscopic.

postoperative hydrocele and recurrence rate. All studies lie inside the 95% CIs, with an even distribution around the vertical, indicating no obvious publication bias.

Discussion

LESS is a minimally invasive technique that brings a revolution of technique to surgical

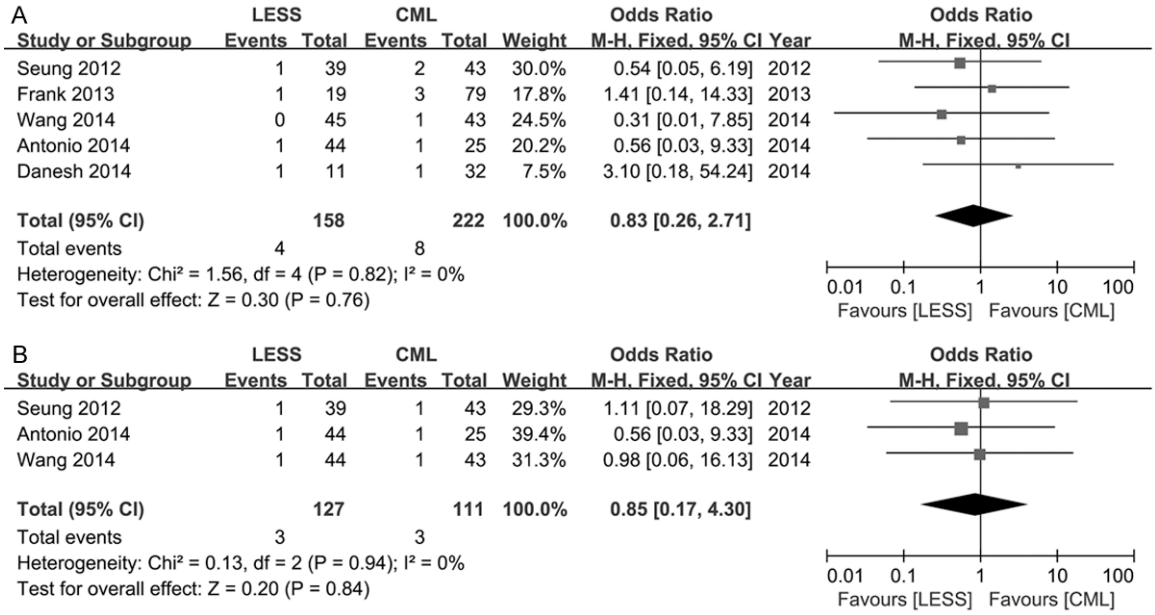

Figure 8. Forest plot and meta-analysis of postoperative complications, including postoperative hydrocele rate (A), and recurrence rate (B). LESS, laparoendoscopic single site; CML, conventional multiport laparoscopic.

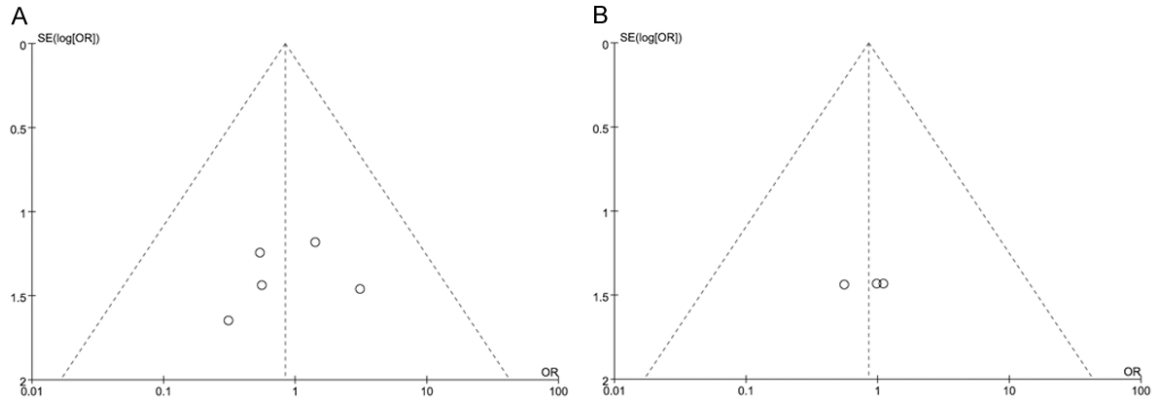

Figure 9. Funnel plots illustrating meta-analysis of postoperative hydrocele rate (A), and recurrence rate (B). SE, standard error; OR, odds ratio.

practice. During the last five years, it has been applied to many urological operations, with the aim to reduce surgical incisions [21]. Because the surgical scar was concealed within the umbilicus, LESS can improve better cosmetic results and get patient more satisfaction than CML [22]. LESS vs CML, which is safer and more effective? It is still lack of clear consensus [23]. Therefore, we present a systematic review and meta-analysis of all current available evidence of LESS and CML to compare the safety and efficacy.

This meta-analysis of 2 RCTs and 4 NRCTs including 407 patients comparing the efficacy of LESS and CML for varicoceles demonstrated that LESS was safe, with significantly reduced postoperative pain, shorter return to normal activities time and better cosmetic results. There were no significant differences in operative time, length of hospital stay, improvements of semen parameters, and postoperative complications.

In some previous studies, the operative time seems to be longer in LESS than CML, because of the much narrower space for operation, and the interference of different instruments [9-11]. Recently, some current studies reported that there were no significant differences in opera-

tive time between LESS and CML in some urologic operations [24-26]. Based on our results, similar operative time were observed between LESS and CML for varicoceles. One important reason for this result is the research and development of special ports and instruments for LESS, including TriPort, SILS port, X-Cone single-port, flexible laparoscopic instruments, and flexible laparoscope EndoEye camera system. In addition, the postoperative VAS score in 6 hour and 24 hour is lower in LESS. LESS showed a higher cosmetic satisfaction rate than CML. At least, we could believe that LESS for varicoceles is technically feasible and comparable to CML. The lower VAS score and higher cosmetic satisfaction rate are really inspiring, which may imply that LESS for varicoceles could give improved tolerance and increased acceptance.

Although the selection criteria are strict, the present meta-analysis has the following limitations that must be discussed. Firstly, the main limitation is that only two RCTs, the other studies were NRCTs. Due to the comparison intervention is surgical approach, we will inform patients of the pros and cons of two kinds of surgical approaches before the operation. Inadequate random sequence generation and blinding tended to increase the risk of bias. Secondly, heterogeneity was detected in our meta-analysis, although heterogeneity among studies is common in the meta-analysis of intervention studies. There was heterogeneity in the outcome of operative time, the heterogeneity may be associated with the different ports and surgical instruments in different studies. Thirdly, the included six studies were carried out with different levels of surgeons. The different experience of the surgical expertise with the two different approaches could influence the outcomes. Fourthly, this meta-analysis based on only six studies, and the sample size was small. Compared to those studies with large sample size, that with small sample size may do not obtain more enough power to detect the real results. In spite of these limitations, no publication bias was detected in this analysis.

This meta-analysis tries to fill a gap in the current literature on LESS for varicoceles, providing the latest information in this area. Moreover, enough data had accumulated to allow an assessment based on meta-analytical methods.

In conclusion, this meta-analysis indicates that LESS for varicoceles may be with reduced postoperative pain, shorter return to normal activities time and better cosmetic satisfaction without compromising surgical safety. The two surgical approaches appear to be equivalent in terms of operative time, length of hospital stay, improvements of semen parameters, and postoperative complications. Nevertheless, despite our rigorous methodology, the inherent limitations of included studies prevent us from reaching definitive conclusions, and the role of LESS for varicoceles remains to be defined. Future well-designed, large, prospective, randomized, multi-center RCTs are awaited to confirm and update the findings of our current meta-analysis.

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Disclosure of conflict of interest

None.

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