ABSTRACT

Introduction: Microsurgical varicocelectomy is the gold standard for varicocele therapy because it has a higher success rate and minimal complication rate than other surgical modalities. This review aims to directly compare the efficacy and safety of inguinal and subinguinal varicocelectomy microsurgery.

Method: This study conducted based on Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines. Articles examining the comparison of inguinal micro-varicocelectomy compared to subinguinal in patients with varicoceles undergoing varicocelectomy surgical procedures were systematically reviewed from the PubMed, ScienceDirect, and Scopus databases. Randomized Controlled Trials (RCT) studies’ quality was determined using the RoB Tool v2: for randomized trials. Risk Ratio with a 95% confidence interval is applied to the measurement of research outcomes. The analysis is performed with RevMan 5.4 software. This research protocol is listed in the PROSPERO register.

Result: A total of 293 study subjects were included from three articles in the study. Inguinal micro-varicocelectomy has a faster operating time outcome than the subinguinal approach (MD: -3.81 95% CI -6.41-1.21; p = 0.004) but has a higher postoperative visual analog pain scale (VAS) outcome (MD: -0.44 95% CI 0.85-0.03; p = 0.03).

Conclusion: There were no significant differences in the outcome of hydrocele incidence, the degree of recurrence, or the number of veins that were ligated after surgery. Micro-varicocelectomy with the inguinal approach has the advantage of faster operating time than the subinguinal approach but has a higher pain rate than the subinguinal approach. We suggest the sub-inguinal rather than inguinal approach because of the higher number of benefits.

Keywords: varicocele, varicocelectomy, microscopic, micro-varicocelectomy, inguinal, subinguinal, outcome.

INTRODUCTION

Varicocele is an abnormal dilatation of the venous system in the pampiniform plexus of the spermatic cord. Even in the asymptomatic, a varicocele can be felt as a lump in the scrotum or seen as a dilatation that can produce scrotal pain that limits the patient's mobility. Varicocele can also be found as a cause of subfertility and infertility in men. In general, the incidence of varicocele is 15% in the normal male population, 25% in men with abnormal semen analysis, and 30–40% in patients with infertility.

The principle of action aimed at varicocele is to correct the drainage disturbance of the internal spermatic artery and testicular lymphatic vessels. Operative management of varicocele can be done through various techniques. Surgery can be performed openly, laparoscopically, and microscopically with inguinal, subinguinal, or retroperitoneal approaches, as well as percutaneous embolization.

There are currently not many meta-analysis studies that directly compare the efficacy, postoperative complications and challenges of inguinal and subinguinal varicocelectomy microsurgery. Based on this background, a systematic review and meta-analysis of the effect of varicocelectomy microsurgery with subinguinal versus inguinal approach in patients with varicocele was conducted.

METHODS

Search strategy

This review followed the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).

A systematic search using advanced search filter was performed in Scopus, Pubmed, and Science Direct databases for studies published up to March 2023. The primary keywords used in the searching process were as follows: “varicocele”, “varicocelectomy”, “microscopic”, “micro-varicocelectomy”, “inguinal”, “subinguinal”. The independent variables in this study were subjects included in the varicocelectomy microsurgery
intervention group with a subinguinal approach compared to the inguinal approach group. The dependent variables, which are the outcomes assessed in this study, are the number of veins that can be ligated, the length of operation time, the VAS 1 month postoperatively, the incidence of recurrence, and the incidence of hydrocele.

**Inclusion and exclusion criteria**
This review included studies comparing two or more groups of patients with unilateral or bilateral varicocele, using subinguinal micro-varicocelectomy and inguinal micro-varicocelectomy as treatment arms. Studies reporting outcomes of the number of veins that can be ligated, the length of operation time, the VAS 1 month postoperatively, the incidence of recurrence, and the incidence of hydrocele were evaluated for further analysis. We only include RCT studies for our review.

**Protocol registration and guideline**
This systematic review and meta-analysis protocol has been registered in The International Prospective Register of Systematic Reviews (PROSPERO) and has been reported in line with AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines.

**RESULTS**

**Search Results**
Research databases PubMed, Scopus, and ScienceDirect returned 967 articles based on the study’s keyword search (Figure 1). There were 172 duplicate studies excluded from these articles. In addition, 795 articles were screened based on their titles and abstracts, leaving only 21 articles. Animal studies, case reports / series, studies in the form of reviews / meta-analyses, abstracts on certain posters or conferences, articles not written in English, and articles irrelevant to this meta-analysis research accounted for the exclusion of 714 articles during the screening phase. At the time of article selection based on full text, no articles were excluded because they were all accessible in full text, whereas 18 articles were excluded because they did not contain different person-intervention-control-outcome (PICO) components. The complete study search yielded three RCT articles, which will be analyzed qualitatively and quantitatively.

**References management**
The obtained results were imported and merged into the Mendeley reference manager software (version 1.19.8, 2000; Mendeley Ltd., London, UK). Duplicates were automatically identified by the software and inspected manually by the reviewers before being removed.

**Data Extraction**
Data extraction was carried out by the authors independently by filling in the pre-specified template. The supervising investigator decided on any difference in assessing study characteristics, methodology, and data extraction. The number of veins that can be ligated, the length of operation time, the VAS 1 month postoperatively, the incidence of recurrence, and the incidence of hydrocele were among the analyzed endpoints.

**Quality Assessment**
The quality assessment and the risk of bias were evaluated using RoB 2: A revised Cochrane risk-of-bias tool for randomized trials.

**Statistical analysis**
Meta-analysis was performed by determining the heterogeneity of the included studies as indicated by the Chi-square p-value and the I² percentage. The fixed-effect models were used for pooled studies with substantial heterogeneity (p < 0.05; I² > 50%); otherwise, the random-effects model was applied. A complete analysis was done using the Review-Manager (RevMan) software version 5.4 from the Cochrane Collaboration.
Studies’ characteristics

All included studies were RCT in design. The studies were performed in three different countries, one from Japan, one from Italy, and one from China. The characteristics of the included studies are outlined in Table 1. A total of 293 patients aged 13-30 years were gathered from published articles between 2013 and 2016. Mean operative time for each procedure were reported to vary, as subinguinal micro-varicocelectomy had mean operative time from 39.7 ± 9.36 minutes to 92.9 ± 25.3 minutes, while inguinal micro-varicocelectomy had mean operative time from 35.4 ± 7.92 minutes to 88.2 ± 30.0 minutes. In two trials, the subinguinal group’s mean VAS score one month after surgery ranged from 2.72 ± 2.52 to 3.73 ± 1.3, whereas the inguinal group’s score ranged from 3.32 ± 2.15 to 4.11 ± 1.2 (Table 2).

Table 1. Basic characteristic of the study included

<table>
<thead>
<tr>
<th>Author</th>
<th>Nation</th>
<th>Design</th>
<th>Number of patients</th>
<th>Age (Mean ± SD)</th>
<th>No. of Surgeon</th>
<th>Same tools</th>
<th>Same drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gontero (2005)</td>
<td>Italy</td>
<td>RCT</td>
<td>Subinguinal</td>
<td>47</td>
<td>25.13 ± 6.58</td>
<td>n</td>
<td>2</td>
</tr>
<tr>
<td>Pan (2013)</td>
<td>China</td>
<td>RCT, double-blind</td>
<td>Subinguinal</td>
<td>50</td>
<td>24.86 ± 6.0</td>
<td>n</td>
<td>1</td>
</tr>
<tr>
<td>Shiraishi (2016)</td>
<td>Japan</td>
<td>RCT</td>
<td>Subinguinal</td>
<td>59</td>
<td>29.1 ± 4.1</td>
<td>n</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Outcome characteristic of the included study

<table>
<thead>
<tr>
<th>Author</th>
<th>Nation</th>
<th>Study Design</th>
<th>Number of Patients (n)</th>
<th>Mean operative time (m)</th>
<th>Pregnancy rate (n)</th>
<th>Recurrence (n)</th>
<th>Hydrocele (n)</th>
<th>VAS</th>
<th>Mean ± SD</th>
<th>Number of Ligated Vein</th>
<th>Preserved Arteries (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gontero (2005)</td>
<td>Italy</td>
<td>RCT</td>
<td>47</td>
<td>39.7 ± 9.36</td>
<td>N/A</td>
<td>7</td>
<td>0</td>
<td>2.7 ± 2.52</td>
<td>Mean ± SD</td>
<td>5.64 ± 0.96</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inguinal</td>
<td>50</td>
<td>35.4 ± 7.92</td>
<td>N/A</td>
<td>4</td>
<td>0</td>
<td>3.32 ± 2.15</td>
<td>Mean ± SD</td>
<td>4.46 ± 1.21</td>
<td>NA</td>
</tr>
<tr>
<td>Pan (2013)</td>
<td>China</td>
<td>RCT, double-blind</td>
<td>56</td>
<td>92.9 ± 25.3</td>
<td>N/A</td>
<td>17</td>
<td>2</td>
<td>3.7 ± 1.3</td>
<td>Mean ± SD</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inguinal</td>
<td>59</td>
<td>88.2 ± 30.0</td>
<td>N/A</td>
<td>20</td>
<td>3</td>
<td>4.1 ± 1.2</td>
<td>Mean ± SD</td>
<td>N/A</td>
<td>NA</td>
</tr>
<tr>
<td>Shiraishi (2016)</td>
<td>Japan</td>
<td>RCT</td>
<td>41</td>
<td>48.8 ± 10.6</td>
<td>N/A</td>
<td>0</td>
<td>1</td>
<td>11.5 ± 1.6</td>
<td>Mean ± SD</td>
<td>7.3 ± 0.6</td>
<td>1.6 ± 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inguinal</td>
<td>40</td>
<td>45.9 ± 9.0</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Mean ± SD</td>
<td>1.2 ± 0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>
revealed that the inguinal approach required a shorter average operating time than the subinguinal approach (Mean differences: -3.81 95% CI -6.41-1.21; p = 0.004) as shown by the forest plot in Figure 4. The fixed-effect model was used in this analysis because heterogeneity between studies was high ($I^2$: 0%; p = 0.87).

**VAS post varicocelectomy**

The average VAS analysis of two inclusion studies showed that the average VAS of patients after passing varicocelectomy was significantly lower in the subinguinal technique compared to the inguinal (Mean differences: -0.44 95% CI 0.85-0.03; p = 0.03) as shown by the forest plot in Figure 5. The fixed-effect model was used in this analysis because heterogeneity between studies was high ($I^2$: 0%; p = 0.68).

**Varicocele Recurrence Rate after varicocelectomy**

Analysis of varicocele recurrences after varicocelectomy in three inclusion studies shows that the recurrence rate has no significant difference (OR: 0.71 95% CI 0.25-2.00; p = 0.52) as shown by the forest plot in Figure 6. Fixed-effect models were used in this analysis because heterogeneity between studies was low ($I^2$: 0%; p = 0.35).

**Complications of post-varicocelectomy hydrocele**

Analysis of the incidence of hydrocele complications in three inclusion studies showing that the complication of hydrocele incidence is higher in the sub-inguinal technique compared to the subinguinal technique, this incidence rate is not significant (OR: 0.32 95% CI 0.03-3.15; p = 0.33) as the forest plot shows in Figure 7. Fixed-effect models were used in this analysis because heterogeneity between studies was low ($I^2$: 0%; p = 0.98).

**DISCUSSION**

Microsurgical varicocelectomy is rated as the standard of varicocele therapy because it has a higher success rate as well as a minimal complication rate compared to other surgical modalities. Microvaricocelectomy surgery is divided into two approaches, namely, inguinal and subinguinal. Inguinal and subinguinal micro-varicocelectomy approaches were reported to have low recurrence rates and complications compared to nonmicroscopic approaches (retroperitoneal and laparoscopic).

The number of veins ligated in the inguinal and subinguinal approaches in this study found no significant difference (Mean difference: 2.70 95% CI -0.26-5.65; p = 0.07) When viewed from the average number, the subinguinal approach has a higher average number of ligated veins compared to the inguinal approach. Gontero et al. revealed a significantly higher number of ligated veins in the subinguinal approach compared to the
inguinal. Vein ligations are higher in the subinguinal region approach because the veins in that region unite to form larger veins with fewer veins in the internal ring. In addition, the collection of veins that naturally surround the arteries was discovered in 95 percent of varicocele microsurgery patients who underwent the subinguinal approach, but in only 30 percent of patients who underwent the inguinal approach.\textsuperscript{10,11}

The inguinal method takes less time or is completed in a shorter amount of time than the subinguinal approach, according to the findings of an analysis of the mean amount of time needed for the operation that was conducted in this study (Mean differences: -3.81 95% CI -6.41-1.21; \( p = 0.004 \)). Shiraishi et al. revealed that there was no significant difference between the operating time required in the two approaches, but through their research it was found that the average amount required by the subinguinal approach was higher than the inguinal approach.\textsuperscript{11} Some other studies have also revealed the same thing where the subinguinal approach takes longer than the inguinal approach, but the conclusion is not statistically significant because the time difference is not too long.\textsuperscript{8,12,13} The faster time in the inguinal approach compared to the subinguinal approach may indicate that the inguinal approach is easier when compared to the subinguinal approach.\textsuperscript{11} It's also possible that the subinguinal approach will take longer than an inguinal one because of the greater complexity of the surgery required due to the greater number of veins in the area.\textsuperscript{10}

Analysis of the mean VAS in this study concluded that it was higher in the inguinal compared to the subinguinal. (Mean differences: -0.44 95% CI 0.85-0.03; \( p = 0.03 \)). Some studies also concluded the same thing, that the pain score in the study was higher in the inguinal approach compared to the subinguinal approach.\textsuperscript{8,12} Pain in the inguinal approach is higher because the subinguinal approach requires opening the aponeurosis of the external oblique, causing disruption of the subcutaneous nerves, this causes pain to be more dominant and the healing period is longer.\textsuperscript{13,14} Research by Pan et al. also concluded that the inguinal approach requires more pain medication than the subinguinal approach.\textsuperscript{13}

Recurrence of varicocele is one of the concerns after varicocelectomy surgery. Analysis of varicocele recurrence in this study showed no significant difference for both approaches. (OD: 0.71 95% CI 0.25-2.00; \( p = 0.52 \)). Recurrence of varicocele was feared to occur in the inguinal approach, due to the presence of gubernacular and external spermatic collateral. This was dismissed by Shiraishi et al. who concluded that the incidence of varicocele recurrence in adults who performed varicocelectomy through the inguinal approach was very low and not significant (recurrence ratio 1.3-2%).\textsuperscript{11} Gontero et al. revealed that the incidence of varicocele recurrence is still controversial, where through their research the number of recurrences found the recurrence ratio of the inguinal approach was 8% and subinguinal 14.9%, which is much higher than the study by Shiraishi et al.\textsuperscript{2} However, some studies agree that varicocele recurrence in microvaricocelectomy with inguinal or subinguinal approach is lower when compared to conventional varicocelectomy. This is because the use of a loop or magnifying glass helps in identifying arteries, veins, lymph ducts and surrounding anatomical structures.\textsuperscript{8,13,16}

This study concluded that there was no difference between the subinguinal and inguinal approaches for the incidence of postoperative hydrocele. (OD: 0.32 95% CI 0.03-3.15; \( p = 0.33 \)), there were two cases of hydrocele occurring in the subinguinal approach. This contrasts with the report from Wang et al. who reported a higher number of hydrocele events found through the inguinal approach (n=40).\textsuperscript{15-17} Postoperative hydrocele can occur due to disruption of drainage caused by damage to the lymphatic channels during dissection in varicocelectomy. The incidence of post-hydrocelectomy hydrocele can be minimized by maintaining the lymphatic channels.\textsuperscript{13}

This study has several limitations, namely the RCT studies included are still relatively small, with a limited number of samples, and had a overall high bias based on RoB v2 tools. This study has not compared success rates such as pregnancy rates or sperm quality parameters due to the lack of RCT studies that discuss this. We recommend that future studies be conducted with a larger RCT sample and include sperm quality parameters or success rates that can be measured from both approaches.

**CONCLUSION**

Micro-varicocelectomy with inguinal approach has the advantage of faster operating time compared to the subinguinal approach, but has a higher pain rate than the subinguinal approach. We suggest to choose subinguinal approach rather than inguinal approach because number of benefits for patients in subinguinal approach.

**CONFLICT OF INTEREST**

The authors declare that there are no conflicts of interest.

**INFORMED CONSENT**

Informed consent not needed in this type of study.

**ETHICAL CONSIDERATION**

Not mandatory.

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**AUTHOR CONTRIBUTIONS**

Muhammad Wahyu Ali: Concepts, Design, Definition of intellectual content, Literature search, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review

Agung Ravi Saputra Sangadji: Literature search, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review

Yufi Aulia Azmi: Literature search, Data acquisition, Manuscript preparation, Manuscript review

Fikri Rizaldi: Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review

Doddy Moesbadianto Soebadi: Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review, Guarantor

Guarantor
ORIGINAL ARTICLE

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