

Therapeutic efficacy and safety of laparoscopic surgery versus microsurgery for varicocele of adult males

A meta-analysis

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Abstract

Objectives: This study aimed to systemically evaluate the efficacy and safety of laparoscopy versus microsurgery in the surgical therapy of varicocele in male adults.

Methods: Relevant literature, published between January 1995 and October 2012, were searched in Pubmed/Medline database, OVID, EMBASE, Chinese Biology Medicine disc (CBMdisc), CNKI, CEBM\CCD, and Cochrane database. The newly published papers were also manually searched. Randomized controlled trials (RCT) related to the surgical interventions of varicocele were included, and full texts were obtained. Each study was evaluated with the Cochrane Risk of Bias tool. Two investigators collected data independently to produce the meta-analysis.

Results: Five RCTs met the inclusion criteria and included 554 patients. Data were merged by the RevMan5.1 software. The sperm concentration increased significantly after surgery (WMD = 4.28; 95% CI = 4.16, 6.99; $P < .00001$, $Z = 7.72$). There was no significant difference in the postoperative hospital stay between laparoscopy and microsurgery (WMD = 0.24, 95% CI = 0.44, 0.93; $P = .49$, $Z = 0.69$). The operation time of laparoscopy was significantly shorter than that of microsurgery (WMD = 40.31, 95% CI = 37.77, 42.86; $P < .00001$, $Z = 31.03$). The incidence of hydrocele reduced significantly after microsurgery as compared to laparoscopy (WMD = 0.05, 95% CI = 0.01, 0.27; $P = .0005$, $Z = 3.49$). The postoperative recurrence rate after microsurgery was significantly lower than that after laparoscopy (WMD = 0.10, 95% CI = 0.04, 0.25; $P < .00001$, $Z = 5.01$).

Conclusion: No significant differences were found between microsurgery and laparoscopy for the increase of sperm concentration and operation time. Compared to the laparoscopy group, the microsurgery group had lower postoperative incidence of hydrocele and recurrence rate, but longer in the operation time.

Abbreviations: CCT = quasi-randomized controlled trials, CI = confidence interval, RCT = randomized controlled trials, SMD = standard mean difference, WMD = weighted mean difference.

Keywords: laparoscopy, meta-analysis, microsurgery, systemic review, Varicocele

1. Introduction

Varicocele is the leading cause of infertility in males,^[1] and patients with varicocele usually present clinical symptoms in the puberty.^[2] It is reported the prevalence of varicocele was about 9.4% in 8000 males with 80% to 90% in the left spermatic cord and less than 20% in bilateral spermatic cords.^[3] In children and

adolescents, the incidence of varicocele is about 10% to 15%.^[4] About 10% of young males had asymptomatic varicocele, of whom about 16% had reduced sperm count by semen examination and about 30% had significant abnormality in the semen. Varicocele was rare before the puberty, but its prevalence increased gradually over age, which might be ascribed to the testis enlargement and the increase in blood supply to the testis. In males, the prevalence of varicocele is about 15%.^[4] In young males which visit hospital for infertility, the incidence of varicocele is as high as 37%.^[5] and examinations display reduction in sperm count and disordered spermatogenesis.

Currently, the pathogenesis of varicocele induced infertility, but some relevant studies and experiments showed that it might be related to the following factors: (1) the metabolites of adrenal gland and kidney (such as serotonin, catecholamines, and cortisol) and other toxic metabolites may be transported into the testis via blood flow in varicocele patients, affecting the formation of sperms and resulting in infertility;^[6] (2) the testis temperature in varicocele patients is higher than normal males, which may affect the spermatogenesis and lead to infertility;^[7] (3) in varicocele, the blood backflow is obstructed, leading to focal hypoxia in the testis, which disrupts the oxygen free radical balance, and affecting the normal metabolism in the sperms;^[11] (4) in varicocele, the blood stasis and different metabolites may induce the excess synthesis of nitric oxide synthase in testicular

Editor: Ching-Sheng Hsu.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2017) 96:34(e7818)

Received: 14 August 2016 / Received in final form: 13 June 2017 / Accepted: 21 July 2017

<http://dx.doi.org/10.1097/MD.0000000000007818>

cells and endothelial cells, which significantly increases the nitric oxide in the reproductive system, leading to the disordered spermatogenesis, compromised sperm motility, and finally infertility;^[8] and, (5) the active immunomodulation and blood–testis barriers will be significantly impaired when the immune function is compromised, which increases the risk for the production of antisperm antibody when the sperms contact the immune system, affecting the spermatogenesis.^[9,10]

Some studies have shown that early treatment might achieve a favorable long-term outcome in patients with infertility due to varicocele. Currently, surgery is the most effective strategy for the therapy of varicocele, and early surgery may provide a better prognosis.^[11] There is evidence showing that surgery may improve the testicular function and sperm function,^[12,13] but opposite findings are also observed in other studies.^[14,15] Studies reveal that about two-third of patients with varicocele have no infertility,^[16,17] and not all the patients with varicocele achieve significant improvement of infertility after surgery.^[18,19] The study of Evers et al^[20] indicated that the therapy of varicocele may not benefit the pregnancy rate of the sponsors. Studies^[21–23] have shown that the testicular volume increases significantly after surgery in varicocele patients, and varicocele patients usually have reduced testicular volume.^[24] Thus, the testicular size may be used to predict the fertility. Currently, varicocele is often managed by varicolectomy via laparoscopic surgery or microsurgery. Laparoscopic surgery for varicocele is done in general anesthesia. In laparoscopic surgery, the anatomic tissues are magnified and the tissues and vessels are easy to identify which avoid the missed ligation or misligation of normal veins and the postoperative adhesion. However, the spermatic artery cannot be effectively separated from the lymphatic vessels in the laparoscopic surgery, which significantly increases the postoperative complications. In the microsurgery for spermatic vein ligation via the inguinal outer ring, the spermatic artery is easy to be differentiated from the lymphatic vessels and thus the postoperative complications reduce significantly. Microsurgery has caught increasing attention in recent years.^[25]

At present, there is still controversy on the methods of surgical intervention for varicocele. In the present study, the therapeutic efficacy of laparoscopic surgery and microsurgery was systemically evaluated in varicocele patients, which may provide evidence for the rational selection of surgical intervention for varicocele patients.

In our study, studies related to the laparoscopic surgery and microsurgery for varicocele were searched and systemically evaluated, aiming to provide evidence for the rational selection of surgical intervention for varicocele.

2. Methods

2.1. Study type

This study has been approved by the Ethics Committee of People's Hospital of Ningxiang County. Not consider the blindness between groups, randomized controlled trials (RCT) and quasi-randomized controlled trials (CCT), published between January 1995 and October 2012, were searched. Studies were conducted to compare the therapeutic efficacy of surgical interventions of varicocele in adults (laparoscopic surgery and microsurgery).

2.2. Inclusion criteria

RCT and CCT which were conducted to compare the therapeutic efficacy of surgical interventions of varicocele in adults (laparoscopic surgery and microsurgery) were searched.

2.3. Exclusion criteria

Studies that met any criteria below were excluded: (1) studies conducted in nonadult patients; (2) other therapeutic strategies employed before or during surgery; (3) studies with a small sample size (<30 cases); (4) studies conducted to summarize clinical experience.

2.4. Interventions and outcome

The therapeutic efficacy of microsurgery for varicocele was compared with that of laparoscopic surgery. The indexed included changes in sperm concentration after surgery, operation time, hospital stay, postoperative incidence of hydrocele, and recurrence rate.

2.5. Literature searching

Literatures were searched in the PubMed/MEDLINE database (1995.1–2012.10), OVID (1995.1–2012.10), EMBASE (1995.1–2012.10), China Biology Medicine disc (CBMdisc, 1995.1–2012.10), CNKI (1995.1–2012.10), CEBM\CCD, and Cochrane database. The newly published papers were also manually searched.

2.6. Selection and quality evaluation of studies

The titles of studies were reviewed to exclude irrelevant studies. Then, the abstracts of the studies were read to select eligible studies. Subsequently, the full text of each study was carefully reviewed to understand the objective and results. According to the inclusion and exclusion criteria, eligible studies were included. These procedures were done by 2 investigators independently. Discrepancy was resolved by discussion or consultation with the third part.

2.7. Data extraction

Patients' demographic information (i.e., age), number of patients in 2 groups, and therapeutic efficacy were collected and double-checked by the 2 investigators. When discrepancy was present, consultation was done with the third party, and consensus was achieved.

2.8. Statistical analysis

Relevant data were extracted from the included studies and classified. Data were then input into Cochrane Revman 5.1 for meta-analysis. Statistical analysis in the present study was performed with Revman 5.1 of Cochrane. First, we tested the consistency for selected studies. If consistent, the fixed effects model was employed; and, if not consistent, the random effects model was employed. In our study, both quantitative data and qualitative data were extracted. The weighted mean difference (WMD) and standard mean difference (SMD) as well as 95% confidence interval (CI) were calculated for quantitative data to evaluate therapeutic efficacy. The chi-square (χ^2) test was used to test heterogeneity for meta-analysis with the statistical significant level at alpha (P -value)=.1. If P -value $\geq .1$ ($I^2 \leq 50\%$), the fixed effects model was used for meta-analysis. If P -value $< .1$ ($I^2 > 50\%$), sensitivity analysis was used to resolve potential confounders. If the confounders could not be resolved, the random effects model was employed for meta-analysis.

Table 1
General characteristics of patients included in 5 studies.

Study	Publishing year	Case number	Average age, year	Microsurgery (n)	Laparoscopy (n)
Chen et al ^[28]	2009	72	30.84	32	12
Qi et al ^[29]	2009	40	31.05	20	20
Song et al ^[30]	2012	72	30 ± 5.52	36	36
Al-Kandari et al ^[26]	2007	95	33.5 ± 7.8	45	50
Al-Said et al ^[27]	2007	303	29.3 ± 7.5	155	148

Table 2
Quality evaluation of 5 included studies.

Study	Type	Quality evaluation of methodology						Score
		Randomization	Allocation concealment	Blindness	Loss to follow-up/ withdrawal	Baseline characteristics	Intention to treat	
Chen et al ^[28]	CCT	No description	No description	Unknown	No	Comparable	Unknown	B
Qi et al ^[29]	CCT	No description	No description	Unknown	No	Comparable	Unknown	B
Song et al ^[30]	CCT	No description	No description	Unknown	No	Comparable	Unknown	B
Al-Kandari et al ^[26]	RCT	No description	No description	Unknown	No	Comparable	Unknown	B
Al-said et al ^[27]	RCT	No description	No description	Unknown	No	Comparable	Unknown	B

CCT = quasi-randomized controlled trials, RCT = randomized controlled trials.

3. Results

3.1. Quantity and quality of raw data

According to the searching strategies and exclusion criteria, a total of 235 studies were identified, including 88 published in English and 147 in Chinese. Finally, 5 studies were recruited for analysis:^[26–30] 2 were RCTs^[26,27] and 3 were CCTs^[28–30]. Of the 5 included studies, there were 554 patients received surgical intervention for varicocele. The general characteristics of patients in these studies are shown in Tables 1 and 2.

3.2. Results of statistical analysis

A test for consistency in meta-analysis of sperm concentration after surgery showed the χ^2 was 281.91 ($P < .00001$, $I^2 = 99\%$). The WMD of overall effect was 4.28 (95% CI=0.69, 9.26). The Z value in test for the overall effect was 1.69 ($P = .09$). According to above results, the included 3 studies had heterogeneity ($\chi^2 = 281.91$, $P < .00001$, $I^2 = 99\%$). The overall effect was tested with the random effects model (WMD=4.28, 95% CI=0.69, 9.26; $P = .09$). This suggests that the increase in sperm concentration was comparable between the laparoscopic surgery group and the microsurgery group (Fig. 1).

A test for heterogeneity in meta-analysis of operation time showed the χ^2 was 3.58 ($P = .17$ and $I^2 = 44\%$). The WMD of

overall effect was 40.31 (95%CI=37.77, 42.86). The Z value in test for the overall effect was 31.03 ($P < .00001$). These results showed that the included 3 studies had homogeneity ($\chi^2 = 3.58$, $P = .17$, $I^2 = 44\%$). The overall effect was tested with fixed effects model, and the WMD was 40.31 (95% CI=37.77, 42.86; $P < .00001$). This suggests that there is significant difference in the operation time between laparoscopic surgery and microsurgery: the operation time of laparoscopic surgery is significantly shorter than that of microsurgery (Fig. 2).

A test for heterogeneity in meta-analysis of hospital stay showed the χ^2 was 9.28 ($P = .002$, $I^2 = 89\%$). The WMD of overall effect was 0.24 (95% CI=0.44, 0.93). The Z value in test for the overall effect was 0.69 ($P = .49$). These results showed that the included 3 studies had heterogeneity ($\chi^2 = 9.28$, $P = .002$, $I^2 = 89\%$). The overall effect was tested with random effects model, and the WMD was 0.24 (95% CI=0.44, 0.93; $P = .49$). This suggests that there is no significant difference in the hospital stay between the laparoscopic surgery group and the microsurgery group (Fig. 3).

A test for heterogeneity in meta-analysis of incidence of hydrocele showed the χ^2 was 0.04 ($P = .98$, $I^2 = 0\%$). The WMD of overall effect was 0.05 (95% CI=0.01, 0.27). The Z value in test for the overall effect was 3.49 ($P = .0005$). These results showed that the included 3 studies had homogeneity ($\chi^2 = 0.04$,

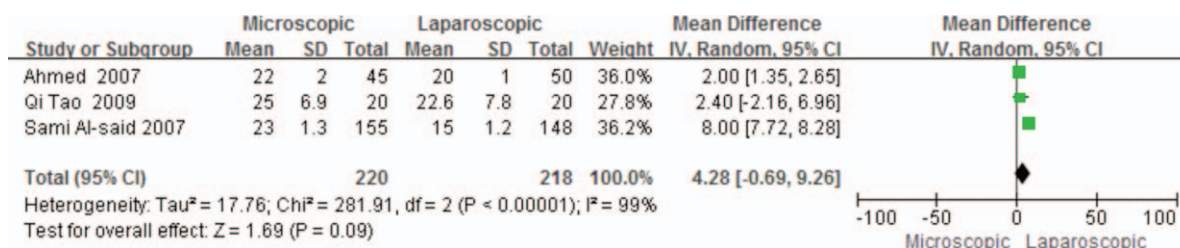


Figure 1. Sperm concentration after laparoscopic surgery and microsurgery.

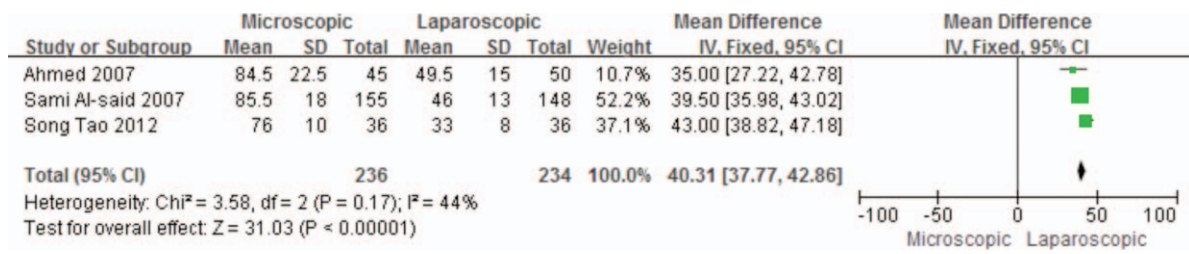


Figure 2. Operation time of laparoscopic surgery and microsurgery for varicocele.

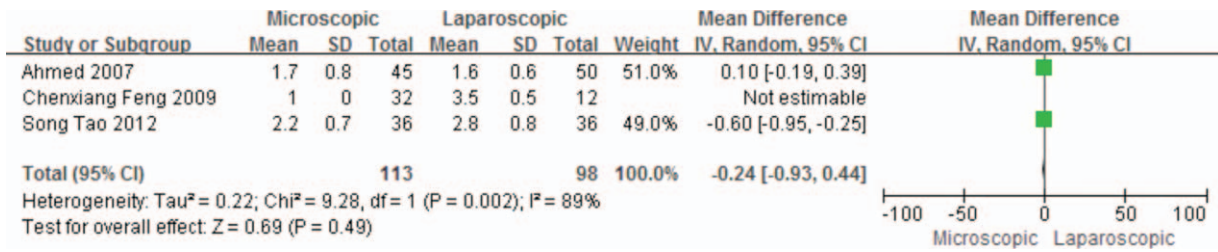


Figure 3. Hospital stay after laparoscopic surgery and microsurgery for varicocele.

P=.98, I²=0%). The overall effect was tested with the fixed effects model, and the WMD was 0.05 (95% CI=0.01, 0.27; P=.0005). This suggests that there is significant difference in the postoperative incidence of hydrocele between the laparoscopic surgery group and the microsurgery group: the incidence of hydrocele after laparoscopic surgery is significantly higher than that after microsurgery (Fig. 4).

A test for heterogeneity in meta-analysis of recurrence rate showed that the χ^2 was 0.89 (P=.64, I²=0%). The WMD of overall effect was 0.10 (95% CI=0.04, 0.25). The Z value in test for the overall effect was 5.01 (P<.00001). These results showed that the included 3 studies had homogeneity (χ^2 =0.89, P=.64, I²=0%). The overall effect was tested with the fixed effects model, and the WMD was 0.10 (95% CI=0.04, 0.25; P<.00001). This suggests that there is significant difference in the postoperative recurrence rate between the laparoscopic surgery group and the microsurgery group: the postoperative recurrence rate after laparoscopic surgery is significantly higher than that after microsurgery (Fig. 5).

4. Discussion

According to the World Health Organization, varicocele has been regarded as the leading cause of infertility in males.^[16] Surgery is still the choice of treatment for varicocele, but there are 2 different surgical interventions for varicocele: laparoscopic surgery and microsurgery. In clinical practice, there is still controversy on the therapeutic efficacy of laparoscopic surgery and microsurgery. In the present study, the increase in sperm concentration, operation time, hospital stay, incidence of hydrocele, and recurrence rate were systemically reviewed in varicocele patients after laparoscopic surgery and microsurgery. Five studies of grade B were included for meta-analysis in which there were 554 patients receiving surgical interventions. Results showed that the increase in sperm concentration and hospital stay were comparable between the laparoscopic surgery group and the microsurgery group. The incidence of hydrocele and recurrence rate after microsurgery were significantly lower than after laparoscopic surgery, but the operation time of laparoscopic surgery was significantly shorter than that of microsurgery. In microsurgery,

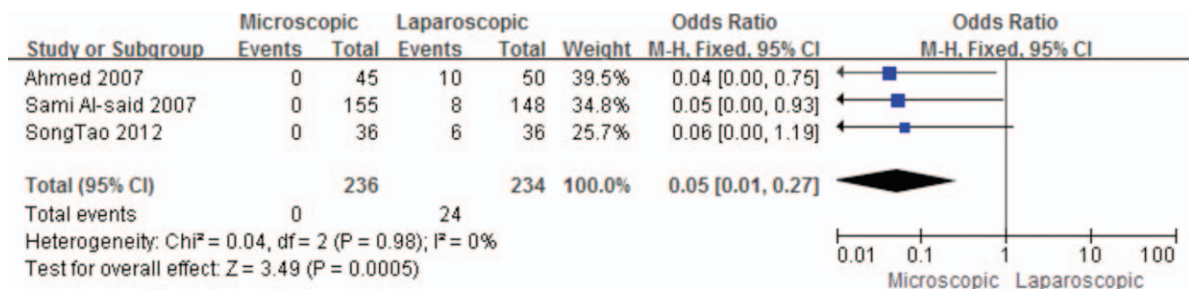


Figure 4. Incidence of hydrocele after laparoscopic surgery and microsurgery for varicocele.

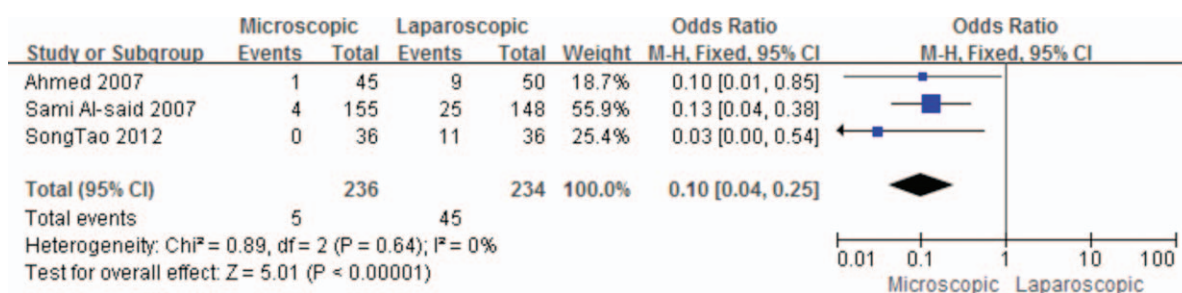


Figure 5. Recurrence rate after laparoscopic surgery and microsurgery for varicocele.

it is easy to identify the small spermatic vein for ligation, which avoids mis-ligation and also protects the testicular artery and lymphatic vessels. Thus, the testicular volume reduces, and the incidence of hydrocele and other complications and recurrence rate decreases after surgery.^[26,27,31,32]

4.1. Quality analysis and discussion

According to the inclusion and exclusion criteria, 5 studies were included for final meta-analysis,^[26–30] including 2 RCTs^[26,27] and 3 CCTs.^[28–30] In these 5 studies, a total 554 patients received surgical interventions for varicocele. Overall, the study quality was relatively high. Of note, the studies included for meta-analysis were graded B, which may avoidably have selection bias, measurement bias, and performance bias.

In the 5 included studies,^[26–30] 554 patients with varicocele were studied, including 353 patients in the laparoscopic surgery group and 288 in the microsurgery group. The sample size was relatively large, which makes the results more reliable and objective.

Allocation concealment and blindness were not mentioned in all the 5 studies.^[26–30] In clinical trials, blindness is almost impossible if involving surgery patients. This is because that the patients have the right to understand the method of surgical intervention, the whole therapeutic protocol, and the adverse effects or complications of each therapy. For patients who will receive surgery, clinicians should inform them of information and possible complications related to surgery. Thus, in the clinical randomized trials, it is hard to use the single blindness. In clinical trials, clinicians should try their best to carefully implement the procedures and aim to achieve more accurate results.

Evaluation of methodology showed the methodology was favorable in the 5 studies^[26–30] at baseline. No significant differences was observed in the age, number of patients, site of varicocele, operation time, hospital stay and recurrence rate between the 2 groups in the 5 studies. Thus, we speculated that the characteristics of patients in 2 groups were comparable at baseline in the 5 studies.

ITT analysis of patients who were lost to follow-up showed all the patients received follow up for more than 2 years and none were lost to follow-up in the 5 studies.^[26–30]

4.2. Meta-analysis and discussion

Of the 5 studies,^[26–30] the postoperative increase in sperm concentration was evaluated in the 3 studies.^[26,28,29] We assessed the operation time, postoperative recurrence rate, and incidence of hydrocele in 3 selected studies,^[28–30] and compared the hospital stay in another 3 selected studies.^[26,27,29]

1. In both groups, the WMD of overall effect of postoperative increase in sperm concentration was 4.28 (95% CI 0.69, 9.26; $P = .09$), suggesting no significant difference between 2 groups. Thus, we speculate that the postoperative increase in sperm concentration was comparable between laparoscopic surgery and microsurgery.
2. In both groups, the WMD of overall effect of operation time was 40.31 (95% CI 37.77, 42.86; $P < .00001$), suggesting significant difference between 2 groups. Thus, we speculate that the operation time of laparoscopic surgery was significantly shorter than that of microsurgery.
3. In both groups, the WMD of overall effect of hospital stay was 0.24 (95% CI 0.44, 0.93; $P = .49$), suggesting no significant difference between 2 groups. Thus, we speculate that the hospital stay was comparable between laparoscopic surgery and microsurgery.
4. In both groups, the WMD of overall effect of postoperative incidence of hydrocele was 0.05 (95% CI 0.01, 0.27; $P = .0005$), suggesting significant difference between 2 groups. Thus, we speculate that the postoperative incidence of hydrocele in the laparoscopic surgery group was significantly higher than that in the microsurgery group.
5. In both groups, the WMD of overall effect of postoperative recurrence rate was 0.10 (95% CI 0.04, 0.25; $P < .00001$), suggesting significant difference between 2 groups. Thus, we speculate that the postoperative recurrence rate in the laparoscopic surgery group was significantly higher than that in the microsurgery group.

5. Conclusion

The postoperative increase in sperm concentration and hospital stay are similar in varicocele patients after laparoscopic surgery and microsurgery. However, the postoperative incidence of hydrocele and recurrence rate after microsurgery are significantly lower than those after laparoscopic surgery, whereas the operation time of laparoscopic surgery is markedly shorter than that of microsurgery.

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