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Bilateral is superior to unilateral varicocelectomy in infertile males with left clinical and right subclinical varicocele: a prospective randomized controlled study

Xiao-lei Sun[1,2] · Jiu-lin Wang[3] · Yun-peng Peng[2] · Qing-qiang Gao[1] · Tao Song[1] · Wen Yu[1] · Zhi-peng Xu[1] · Yun Chen[1] · Yu-tian Dai[1]

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Abstract

Purpose The purpose of this study is to compare the effect of bilateral versus unilateral varicocelectomy on seminal response and spontaneous pregnancy rates in infertile male patients with left clinical and right subclinical varicocele.

Methods A total of 358 infertile men with left clinical and right subclinical varicocele were randomized to group that underwent bilateral ($n = 179$) and group that underwent unilateral microsurgical subinguinal varicocelectomy ($n = 179$). Baseline data regarding male age, female partner age, grade of varicocele body mass index, bilateral testicular volume and serum follicle-stimulating hormone, luteinizing hormone, total testosterone levels and infertility duration and semen parameters were gathered. One year after the surgery, semen parameters including sperm volume, sperm concentration, normal sperm morphology, progressive motility and sperm DNA fragmentation index were recorded and any pregnancy was also documented via telephone calls and hospital visits.

Results We found the baseline characteristics were comparable between the two groups. The seminal parameters had significant improvements 1 year postoperatively in both groups. However, the bilateral group showed significantly greater improvements than the unilateral group in sperm concentration, normal sperm morphology and progressive motility. Besides, the pregnancy rate was statistically higher in the bilateral group after the surgery (42.5 versus 26.0%, bilateral versus unilateral group).

Conclusion In conclusion, our study indicated that bilateral is superior to unilateral varicocelectomy in infertile males with left clinical and right subclinical varicocele, which is associated with greater improvements in sperm concentration, normal sperm morphology and progressive motility and spontaneous pregnancy rate after the surgery.

Keywords Pregnancy · Varicocelectomy · Subclinical · Male · Infertility · Semen

Introduction

Varicocele is defined as dilated and tortuous veins of the pampiniform plexus of spermatic veins, which is present in approximately 15% of the whole male population [1] and 21–39% of men presenting with infertility [2]. Varicocele is preferably occurred on the left side, while bilateral cases are in a smaller percentage and solitary right varicocele is rare. There are three categories of varicocele defined as grade I (palpable with valsalva), II (palpable without valsalva but not visible), III (visible) by physical examination with the subjects standing in a warm room. Subclinical varicocele is not palpable even by valsalva and refers to the presence of retrograde blood flow that can only be detected by imaging techniques, such as scrotal ultrasound [3]. However, left

Xiao-lei Sun and Jiu-lin Wang have contributed equally to this work.

✉ Yu-tian Dai
yutiandai705@126.com

[1] Department of Andrology, Drum Tower Clinical Medical School of Nanjing Medical University, Nanjing 210008, Jiangsu, China

[2] Department of Urology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou 221006, Jiangsu, China

[3] Department of Urology, Jiangsu Geriatric Hospital, Nanjing 210024, Jiangsu, China

clinical varicocele are sometimes accompanied with right subclinical varicocele [4]. On the other hand, according to the guidelines issued by the American Society for Reproductive Medicine and European Association of Urology Guideline on male infertility, infertile male patients with subclinical varicocele and normal semen quality is not indicated for varicocele correction [5, 6]. However, although isolated unilateral subclinical varicocele and normal semen quality were not indicated for varicocele correction, no consensus has yet been reached on whether the benefit of bilateral is superior to unilateral varicocele repair in patients with left clinical and right subclinical varicocele. Elbendary et al. found bilateral varicocelectomy is superior to unilateral treatment with regard to higher spontaneous pregnancy rate [7]. However, in another study, the authors found comparable postoperative semen parameters and spontaneous pregnancy rate after bilateral and unilateral varicocele repair in patients with left clinical and right subclinical varicocele [8]. These ambiguous results, can at least partly, be the effect of the small study sizes, different study design and surgical techniques of varicocelectomy applied in different studies.

Hence, in this prospective randomized controlled study, we determined to compare the surgical effect between the male infertile patients that underwent microsurgical bilateral varicocelectomy and those underwent unilateral varicocelectomy while focusing on seminal improvement and pregnancy rate. The present study helps to define the optimal treatment strategy in infertile males with left clinical and right subclinical varicocele.

Materials and methods

Patients and methods

This study complied with the ethics committee of human research of Drum Tower Clinical Medical School of Nanjing Medical University (approval number: 2015-01-04). Informed consent was also obtained from all individual participants included in the study.

The present prospective single-center study included 358 consecutive patients with left clinical and right subclinical varicocele that complained of infertility in department of Andrology of Drum Tower Clinical Medical School of Nanjing Medical University from February 2015 to June 2016. All patients had infertility duration > 1 year with unprotected sexual intercourse and impaired semen quality (sperm concentration < 20 million/ml, progressively motile sperm < 50% or sperm morphology < 4%, alone or in combination) [9]. The diagnose of clinical varicocele was based on physical examination and color Doppler ultrasound examination (Pro Focus 2202, B-K medical, Denmark). Patients with varicocele were further categorized as grade I (palpable with valsalva), II (palpable without valsalva but not visible), III (visible) by physical examination with the subjects standing in a warm room [10]. Subclinical varicocele of the right side refers to a detected retrograde blood flow with valsalva during color Doppler ultrasound examination of the spermatic cord [7]. The exclusion criteria were: normal semen parameters, azoospermia, other causes of male infertility that has been medical proven, advanced female partner age ≥ 38 years, detected female causes infertility with medical proven evidence. These included 358 patients were randomly divided into the bilateral treatment group ($n = 179$) that underwent bilateral subinguinal varicocelectomy and unilateral group ($n = 179$) that underwent unilateral subinguinal varicocelectomy.

Semen analyses

Semen analyses were conducted by the same doctor according to the World Health Organization (WHO) laboratory manual for the examination and processing of human semen [9]. The routine semen parameters included in the present study in the data synthesis were sperm volume, sperm concentration, progressive (PR%) motility, normal sperm morphology.

Semen chromatin structure assay (SCSA)

Flow cytometry SCSA method was used for sperm DNA integrity analyses by one doctor, according to the method described previously [11, 12]. The semen samples were processed with acridine orange staining and induced sperm nuclear DNA denaturation. Acridine orange binds to the fragmented sperm DNA that fluoresces red, while the double-strand DNA fluoresces green. The sperm DNA fragmentation index (DFI) refers to the percentage of the denatured sperm DNA that fluoresces red (red/(red + green)).

Endocrinological evaluation on follicle-stimulating hormone (FSH), LH (luteinizing hormone) and total testosterone (TT)

The endocrinological evaluation included measurements of serum FSH, LH and TT in a blood sample obtained between 9:00 and 10:00 am.

Serum FSH, LH and TT were measured using radioimmunoassay assays (JiuDing biomed co.ltd., Tianjin, China).

Microsurgical subinguinal varicocelectomy procedure

Microsurgical subinguinal varicocelectomy procedure was performed by the same experienced surgical team and was performed as described elsewhere [13]. Briefly, a 3–4 cm

incision was made inferior to the external inguinal ring. The spermatic cord was isolated, and the veins were ligated, while the arteries, lymphatics and the vas deferens were isolated under a surgical microscope (Carl-Zeiss, Jena, Germany). The skin was closed using 4-0 vicryl sutures after then.

Follow-up and outcome measurements

We collected and analyzed the following parameters prior to the surgery: male age, female partner age, varicocele grade of the left side, body mass index (BMI), left and right testicular size, infertility duration, which was defined as the time from unprotected sexual intercourse to hospitalization, hormonal profile (TT, FSH and LH). All patients have a mandatory 12-months follow-up. Patients were told to have sexual intercourse 1 month after the surgery. Semen analysis was also analyzed every 3 months postoperatively and one year after the surgery. Any pregnancy was documented in outpatient visit or through telephone calls.

Statistical analyses

The independent analyzed variables included categorical variables (pregnancy or not, grade of left varicocele), continuous variables (male age, female age, infertility duration, sperm volume, sperm concentration, normal sperm morphology, PR%, DFI, BMI, left and right testicular size, TT, FSH and LH levels). One-way Kolmogorov–Smirnov was used to test the normal distribution. Continuous variables were presented as mean ± standard deviation (SD) and compared using *t* test (within group comparison using paired sample t test and among group comparison using independent sample t test). The Chi-square test or Fisher's exact Chi-square test was used to for categorical variables; quantitative data non-normally distributed were presented as median (interquartile range) and compared using nonparametric test. The statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) and a two-sided p value < 0.05 was considered significant.

Results

Baseline data of the included individuals

Of the total 358 included males, 179 males underwent bilateral varicocelectomy and 179 had unilateral left varicocelectomy. The bilateral group and unilateral group had an infertility duration of 4.1 ± 1.6, 5.0 ± 1.8 years, which revealed no statistical difference ($p = 0.930$). The mean age of the male age was 32.1 ± 6.1 years in the bilateral group and 31.8 ± 5.6 years in the unilateral group ($p = 0.760$). Mean age of the female partner was 31.0 ± 5.1 years and 33.1 ± 6.5 years in the bilateral and unilateral group, respectively ($p = 0.541$). The distribution of the grade of the varicocele was also similar between the two groups ($p = 0.299$). Besides, no statistically significant differences were observed in terms of BMI, bilateral testicular volume and serum FSH, LH and TT levels between the two groups. Additionally, the baseline seminal parameters including semen volume, sperm concentration, progressive motility, normal sperm morphology and sperm DFI were also comparable between the two groups ($p = 0.550$, 0.469, 0.631, 0.540, 0.480 for sperm volume, concentration, motility, morphology and DFI, respectively). The main results are shown in Table 1.

Semen parameters and pregnancy rate

The comparisons on postoperative semen parameters 1 year after the surgery of the bilateral and unilateral group are demonstrated in Table 2. One year after the surgery, we included 160 patients in the bilateral group and 167 patients in the unilateral group, while 10 patients were excluded because they did not complete the required one year follow-up and 21 patients attempted assisted reproductive technology program after the surgery were also excluded and a total of 31 patients were therefore not included in the data synthesis procedures. For individuals that have completed the follow-up, the detailed data including semen parameters and spontaneous pregnancy occurrence was well documented. There was a statistical significant increase in sperm concentration, normal sperm morphology and progressive motility and decrease in sperm DFI in both groups, while the semen volume remained unchanged for both groups after the surgery in within group analysis. After the surgery, the mean sperm concentration increased significantly in both groups, and the bilateral group showed a significantly greater improvement than the unilateral group (increased by 19.0×10^6/ml versus 11.1×10^6/ml, bilateral versus unilateral, respectively). There were also greater improvements in normal sperm morphology (4.4 versus 2%, bilateral versus unilateral, respectively) and progressive motility spermatozoa (17 versus 11.7% for bilateral versus unilateral group, respectively), which revealed statistical significances ($p = 0.035$, 0.041 for morphology and motility increase, respectively), indicating those patients would benefit more from bilateral varicocelectomy treatment. However, the among groups comparisons regarding DFI yielded non-significant results (11.8 versus 12.1%, $p = 0.520$).

Additionally, 1 year after the surgery, 68/160 female partners (42.5%) in the bilateral group had spontaneous pregnancy with a mean time for pregnancy at 8.7 months, compared with 44/167 (26.0%) in the unilateral group, which indicated statistical difference ($p = 0.002$).

Table 1 Comparisons of baseline data of the bilateral versus unilateral varicocelectomy group

Characteristics of enrolled subjects	Bilateral group ($n = 179$)	Unilateral group ($n = 179$)	p
Male age (years)	32.1 ± 6.1	31.8 ± 5.6	0.760
Female age (years)	31.0 ± 5.1	33.1 ± 6.5	0.541
Infertility duration (years)	4.1 ± 1.6	5.0 ± 1.8	0.930
BMI (kg/m^2)	25.7 ± 2.5	26.5 ± 3.1	0.169
Testicular volume (ml)			
Left	11.4 ± 3.3	12.1 ± 3.0	0.350
Right	13.0 ± 4.0	13.8 ± 3.4	0.120
Grade of varicocele			0.299
I	44	33	
II	90	92	
III	45	54	
Semen parameters			
Volume (ml)	3.2 ± 0.1	3.4 ± 0.2	0.550
Sperm concentration (*10^6/ml)	12.3 ± 4.1	13.8 ± 5.0	0.469
Normal sperm morphology (%)	4.1 ± 2.0	3.9 ± 1.8	0.631
Progressive motility (%)	23.0 ± 6.4	22.1 ± 5.5	0.540
DFI (%)	21.6 ± 7.1	23.0 ± 8.1	0.480
Hormonal profile			
FSH (mIU/ml)	7.3 ± 2.7	6.0 ± 3.0	0.980
LH (mIU/ml)	4.1 ± 2.0	5.0 ± 3.1	0.400
TT (ng/dL)	320.6 ± 160.0	400.1 ± 218.0	0.430

Table 2 Comparisons of seminal response and spontaneous pregnancy rates of the bilateral versus unilateral group 1 year after the surgery

Characteristics	Bilateral group ($n = 160$)	Unilateral group ($n = 167$)	p
Semen volume (ml)	3.3 ± 0.1	3.3 ± 0.2	0.760
Sperm concentration (*10^6/ml)	31.3 ± 8.0	24.9 ± 7.8	0.041
Normal sperm morphology (%)	8.4 ± 3.1	5.9 ± 2.8	0.035
Progressive motility (%)	40.0 ± 13.8	33.8 ± 11.0	0.041
DFI (%)	11.8 ± 6.0	12.1 ± 6.8	0.520
SPONTANEOUS pregnancy rate	68/160, 42.5%	44/167, 26.0%	0.002

Discussion

For infertile males with infertility, the main concern is seminal improvement and natural pregnancy. Patients with varicocele in assisted reproductive program would also benefit from varicocelectomy prior to intracytoplasmic sperm injection (ICSI) with a significant increase in clinical pregnancy rate and live birth rate [14]. Non-obstructive azoospermia patients with varicocele could also benefit from varicocele correction with spermatozoa found in the ejaculate in 21–55% of the overall cases [15]. Thus, varicocele repair has several implications in male infertility treatment: natural pregnancy, improved pregnancy in ICSI program, and to down-stage the level of assisted reproductive program (ICSI to in vitro fertilization- embryo transfer).

Subclinical varicocele is not palpable or visible at rest or during valsalva maneuver, but is demonstrable by scrotal ultrasound and color Doppler examination. According to the guidelines of the American Urological Association (AUA), the American Society for Reproductive medicine (ASRM) and European Association of Urology, varicocele repair should be indicated for infertile men with a clinical varicocele and one or more abnormal semen parameters [16, 17], while subclinical varicocele repair should not be performed in patients with subclinical varicocele or normal semen parameters. However, there are many unsolved problems regarding the diagnosis and treatment of subclinical varicocele. The rationality of performing varicocele repair in subclinical varicocele cases have been under debate, while inconsistent results have been produced based on limited literature for whether to perform bilateral repair of left clinical and right subclinical varicoceles. One study with 145

infertile males included with left clinical and right subclinical varicocele and 12–45 months followed up investigated the seminal response following either unilateral or bilateral varicocele ligation. The authors found males undergoing bilateral varicocele repair had greater improvements in semen parameters (sperm concentration and progressive motility) and natural pregnancy rate (61.6 versus 31.9%) compared with men undergoing left varicocele correction [7]. However, in another study with smaller case series (104 cases), bilateral varicocele ligation have resulted in similar seminal improvements and spontaneous pregnancy rate as compared with unilateral counterpart (39.2 versus 37.7%, bilateral versus unilateral) [8].

In the present study, we determined to observe the clinical outcome using the natural pregnancy as the primary concern and the seminal improvements as the secondary in a relative large sample size cohort. This study would help to reveal the best treatment strategies for infertile men with left clinical and right subclinical varicocele. Bilateral varicocele repair resulted in greater improvements in seminal parameters as well as spontaneous pregnancy rate in the present study, indicating bilateral varicocelectomy should be performed in these patients with left clinical and right subclinical varicocele. This was not in agreement with some prior studies, which could be possibly attributed to several factors. First, the widespread application of color Doppler ultrasound in the diagnose of varicocele other than physical examination in the past could possibly partially interpret the differential result of the present study compared with some prior studies. Varicoceles are being reported in up to 91% of subfertile cases, most of whom were thought to having idiopathic etiology [18]. These data may possibly explain the limited outcome of unilateral varicocele repair on male fertility when varicocele diagnosis was based on physical examination alone. Second, convincing evidence exists that the size of a varicocele does not correlate with testicular or seminal pathology [10], while a subclinical varicocele may also have a detrimental effect on spermatogenesis. A significant proportion of subclinical varicocele may progress to clinical varicocele rather than spontaneous resolution [19]. The progressive effect rather than static effect of a varicocele indicated that subclinical varicocele may result in seminal damage and male infertility subsequently [20]. Notably, the communicating branches between the left and right testis exists, which forms the basis that a unilateral varicocele produces bilateral testicular damage [10]. In another study, 41 patients underwent left varicocelectomy failed to achieve pregnancy and had a subsequent right varicocele. However, a salvage right varicocelectomy resulted in seminal improvement in 23 patients and the spouses of 18 patients got pregnant [21]. These data may possibly explain the bilateral detrimental effect of varicocele, which indicated a toward upon bilateral repair for patients with left clinical and right subclinical varicocele. Third, the duration of varicocele could affect the seminiferous tubular function in a duration dependent manner, as evidenced in recent literature [22]. In terms of the optimal surgical approach, evidence-based proof has indicated the highest spontaneous rate after microsurgical subinguinal varicocelectomy over other procedures [23, 24]. Moreover, certain patients would benefit more from varicocele repair [13], indicating the effect of varicocelectomy on infertile males may reflect more in certain patients, in terms of the improvements of spermatogenesis and subsequent natural pregnancy.

Notably, in a recent systematic review and meta-analysis with seven trials and 548 cases enrolled, the authors found that subclinical varicocelectomy resulted in significant improvement in forward progressive sperm motility other than other sperm parameters including sperm concentration and sperm morphology, when compared to no-treatment controls. The odds ratio for pregnancy rate was 1.29 (0.99–1.67) for subclinical varicocelectomy versus no-treatment controls. Since the lower limit of the confidence interval was close to 1.0, indicating there is existence of a type II error. Although this meta-analysis was not fine enough to draw a firm conclusion, the authors concluded that patients could benefit from subclinical varicocelectomy in terms of seminal response and subsequent pregnancy chance in the era of assisted reproductive medicine [25].

There are several limitations and biases in the present study. First, the spontaneous pregnancy rate was evaluated and compared, while the pregnancy rate in assisted reproductive technology reprogram was not evaluated. The bilateral varicocele repair resulted in higher seminal parameters than unilateral varicocelectomy, indicating infertile males could possibly benefit more from varicocele repair prior to assisted reproductive program treatment, although pregnancy rate in assisted reproductive program was not analyzed in the current study. Second, the sample size was relatively small and limited, which resulted in limited statistical power.

There are also some advantages of the current study that is preferred to be mentioned. First, the present randomized controlled study provided high level evidence of the optimal treatment strategy for infertile males with left clinical and right subclinical varicocele. Second, the bilateral and unilateral group had comparable baseline characteristics including female age, male age, BMI and grade of varicocele which makes the interpretation on the results of the present study more reliable. Third, a strict inclusion and exclusion criteria was established for individuals collection procedures, including the female partner age, aiming to minimize possible confounding bias that may interfere with the outcome measurements. Based on these advantages, we believe the results of the present study reliable.

In conclusion, this single institution-based randomized controlled study demonstrated that bilateral varicocelectomy

is superior to unilateral varicocele repair infertile males with left clinical and right subclinical in terms of seminal improvements and natural pregnancy rate. More studies scientific designed with more subjects involved were warranted to confirm these findings.

Compliance with ethical standards

Conflict of interest None authors claimed any conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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