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Original Article

Surgery Section

Fertility Potential of Microsurgical Subinguinal Varicocelectomy in Non-obstructive Azoospermia, Virtual Azoospermia and Severe Oligospermia Patients in a Tertiary Care Setup

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ABSTRACT

Introduction: The role of varicocelectomy in Non-Obstructive Azoospermia (NOA) and Severe Oligospermia (SO) remains controversial with some studies reporting improvement in these patients.

Aim: To analyse the improvement in semen parameters and pregnancy outcomes after microsurgical varicocelectomy in NOA, SO and Virtual Azoospermia (VA) groups.

Materials and Methods: A single centre six year prospective study, evaluating 25 adults with primary infertility having NOA, VA (<1 million/mL) or SO (1-5 million/mL) with clinical varicocele and normal female partner evaluation was conducted at a tertiary care centre. Microsurgical varicocelectomy along with needle aspiration biopsy of bilateral testes was done in all patients. Follow-up semen analysis was done at six months' postoperatively. The improvement in sperm count and sperm motility postoperatively was compared using Wilcoxon signed rank test and paired t-test respectively.

Results: The mean age of patients were 31 years. There was significant overall improvement in both sperm count and progressive motility. Mean sperm count improved from 1.052 to 8.456 (million/mL) (mean improvement of 8.65 million/mL in VA group, and of 6.25 million/mL in SO group) while mean progressive motility improved from 15.76% to 24.4%. A total of 21 (84%) patients responded on follow-up. The non-responders' group had two patients each from VA and SO groups. Pregnancy was achieved in five patients (20%), with spontaneous pregnancy in two and Intrauterine Insemination (IUI) in three patients. All patients with early maturation arrest were non-responders.

Conclusion: Microsurgical subinguinal varicocelectomy can lead to significant increase in semen parameters in severe oligospermic men, which aids spontaneous or assisted pregnancy (IUI) in these couples. Hypospermatogenesis and late maturation arrest are favourable predictors of response after surgery.

Keywords: Primary infertility, Secondary infertility, Varicocele

INTRODUCTION

Infertility affects roughly 16% of the couples worldwide [1] with male factor (alone or with female factor) contributing to about a half of them [2]. Varicocele is present in 15% of general population, 35% of males with primary infertility and 75% of secondary infertility patients [3]. Only about 20% of all men with varicocele present with infertility [4]. But overall, it is the most frequent abnormality found in infertile men.

Azoospermia is present in 10-15% of infertile men [5]. Incidence of azoospermia and SO (sperm count <5 million/mL) is 4.3% and 13.3% in patients with varicocele [6]. First unassisted conception following surgical repair of varicocele in azoospermic man was reported by Tulloch in 1952 [7]. Since then varicocelectomy has become the most frequently performed surgery for the management of infertility in males. Improvements in semen parameters (sperm count, motility, morphology) have been reported in oligospermic men [8,9]. Some studies have reported improvement in these groups of patients [10,11]. Azoospermia makes natural pregnancy almost impossible. Treatment options available for patients with NOA are Testicular Sperm Extraction (TESE) with Intra-Cytoplasmic Sperm Injection (ICSI) and In-Vitro Fertilisation (IVF). The cost of these procedures is a major hurdle for patients from low socioeconomic background. However, role of varicocelectomy in NOA and SO remains controversial.

Hence, this study was conducted to assess the efficacy of microsurgical varicocelectomy in NOA and SO, as well as Virtual Azoospermia (VA) (sperm count <1 million/mL) patients with clinical varicocele. The primary objective was to analyse improvement in semen parameters after microsurgical varicocelectomy in NOA, VA and SO groups. The secondary objective was to assess the pregnancy outcomes in these groups.

MATERIALS AND METHODS

This was a single centre prospective study done in a tertiary care setup from August 2009 to December 2015. During this study period a total of 25 patients were reported, all of whom were recruited for the study.

The protocol described in the study was being followed by the institute for the treatment of oligospermia with varicocele since the last 15-20 years. The ethical committee approved the study protocol (IEC/19/20). A written informed consent was taken from all patients for the treatment and for enrolment in the study.

All patients with primary infertility with NOA or SO with clinical varicocele as well as normal female partner evaluation were included in the study. All patients had semen volume >1.5 mL and testicular size >10 cm^3. Patients with high serum FSH and low testosterone levels, as well as adolescents were excluded from the study.

Clinical examination of all patients was done by a single senior andrologist of the department. Clinical varicocele grading was based on the Dubin system (grade 1-varicose veins in the scrotum are palpable with the valsalva maneuver; grade 2-veins are palpable without the valsalva maneuver; grade 3-varicose veins are observed

in the scrotum without any maneuver or manipulation) [12]. It was confirmed by Colour Doppler Ultrasound (CDUS) in all cases. Semen analysis was done twice preoperatively in a single laboratory, with an interval of 3-4 weeks in between, with abstinence period of 3-5 days. The report with higher value of semen parameters was considered for statistical analysis.

Patients were operated by loupe-assisted (2.5x magnification) microsurgical subinguinal artery and lymphatic sparing varicocelectomy technique, by the same group of surgeons. All dilated internal and external spermatic veins were ligated and cut. All patients were subjected to Needle Aspiration Biopsy (NAB) of bilateral testes simultaneously (2 cores from each testis). Samples were sent in Bouin's fluid for histopathological analysis (Johnsen score) to a single laboratory. Histopathological abnormalities were categorised into hypospermatogenesis, early maturation arrest, late maturation arrest and sertoli cell only syndrome. Postoperatively, follow-up was done every six monthly with physical examination and CDUS to rule out hydrocele and varicocele recurrence. Semen analysis was done at six months postoperatively. Responders were defined as the patients having any improvement in sperm count or progressive motility. Spontaneous or assisted pregnancy {Intra-Uterine Insemination (IUI)} was considered the ultimate outcome. As all of the patients were from low socio-economic background they could not afford ICSI. Few of them could afford IUI and had success with the same.

STATISTICAL ANALYSIS

Statistical analysis was done with Microsoft Excel 2013 using XLSTAT addin version 18.06 (Addinsoft, New York, USA). Test of normalcy for various parameters was done using Shapiro-Wilk test. The age, duration of infertility, average testicular volume and grade of varicocele were compared using non-parametric tests (Kruskal-Wallis test and Mann-Whitney U-test). The improvement in sperm count and sperm mobility postoperatively was compared using Wilcoxon signed rank test and paired t-test respectively. The comparison of outcomes of each histopathology group mentioned above was done using Fisher's-Exact test.

RESULTS

A total of 25 patients were included in this study. The patient characteristics as well as distribution of patients into various sperm count and histopathology groups are shown in [Table/Fig-1]. As we had included virtual azoospermia as a separate group, the severe oligospermia group had patients with sperm count of 1-5 million/mL.

Observation	Value
Total patients	25
Age (years)	31 (27-39)
Duration of infertility (years)	4.36 (2-13)
Average testis size (cm^3)	19.16 (16-24)
Grade of varicocele	1.96 (1-3)
Laterality of varicocele:	
Bilateral	21 (84%)
Unilateral	04 (16%)
Sperm count groups:	
Azoospermia	03 (12%)
Virtual azoospermia	14 (56%)
Severe oligospermia	08 (32%)
Testicular histopathology:	
Hypospermatogenesis	17 (68%)
Late maturation arrest	06 (24%)
Early maturation arrest	02 (8%)
Sertoli cell only syndrome	00

[Table/Fig-1]: Patient characteristics [mean (range or %)].

There was a significant overall improvement in both sperm count and progressive motility [Table/Fig-2]. Mean sperm count improved from 1.052 to 8.456 (million/mL) while mean progressive motility improved from 15.76% to 24.4%. Statistically significant improvement in sperm count was not seen in azoospermia group as opposed to the other two groups, although counts had increased in all the three azoospermic patients (maximum: 6 million/mL).

	Azoospermia	Virtual azoospermia	Severe oligospermia	p-value
Age (years)	30.66 (28-35)	30.07 (27-35)	31 (27-39)	0.917*
Duration of infertility (years)	4 (2-6)	4.57 (2-13)	4.125 (2-12)	0.861*
Average testicular size (cm^3)	17.66 (17-18)	19.28 (16-22)	19.5 (16-22)	0.443*
Grade of varicocele	2.33 (2-3)	1.85 (1-2)	2 (1-3)	0.38*

[Table/Fig-2]: Characteristics of patients having NOA, VA and SO.
*Kruskal-Wallis test

A total of 21 (84%) patients responded on follow-up [Table/Fig-3]. Improvement persisted for more than two years in eight out of ten (80%) patients who came for long term follow-up (maximum 3 year follow-up). Two (20%) of them had gradual decline in the parameters after first year. All four patients with unilateral varicocele responded. All the non-responders had grade 2 varicocele.

	Responders	Non responders	p-value
Number of patients	21 (84%)	4 (16%)	-
Age (years)	30.61 (27-35)	33 (28-39)	0.35*
Duration of infertility (years)	3.71 (2-10)	7.75 (2-13)	0.374*
Average testicular size (cm^3)	18.66 (16-23)	20.75 (20-24)	0.018*
Grade of varicocele	1.95 (1-3)	2 (in all patients)	0.888*
Testicular histopathology:			
Hypospermatogenesis	15 (88.2%)	02 (11.8%)	0.935'
Late maturation arrest	06 (100%)	00	0.934'
Early maturation arrest	00	02 (100%)	0.857'

[Table/Fig-3]: Characteristics of responders v/s non-responders.
*Mann-Whitney U-test; 'Fisher Exact test

The NOA, VA and SO groups had no statistically significant difference with respect to various patient parameters [Table/Fig-2]. The non-responders' group had two patients each from VA and SO groups.

Pregnancy was achieved in five patients (20%), with spontaneous pregnancy in two and IUI in three patients. Three and two patients in the pregnancy group had VA and SO respectively preoperatively. However, the postoperative sperm counts in this group ranged from 9-14 million/mL. Average age and duration of infertility of patients with successful pregnancy was 32.2 years and 4.6 years, respectively. Only the grade of varicocele was significantly higher in pregnancy group amongst various patient parameters. All patients with early maturation arrest were non-responders and had no pregnancy [Table/Fig-4,5].

There was no clinical recurrence of varicocele till maximum follow-up in any of the operated patients. One (4%) patient out of the total, operated had unilateral hydrocele as a complication on follow-up.

DISCUSSION

Benefit of varicocelectomy is proven in oligospermic men in multiple series till date [8,9]. Although the recent literature indicates benefit of varicocele treatment in cases of NOA and SO, there are no randomised controlled trials published to support this. Majority of the prospective studies have a limited sample size. Present study showed improvement in semen parameters in majority of patients. But the various patient factors and histopathology findings evaluated did not show any statistically significant difference favouring responders, due to small sample size, barring average testicular size. The same was true for pregnancy outcomes, barring grade of varicocele.

	Improvement in sperm count (million/mL)		Improvement in sperm motility (percent)	
	Mean (Range)	p-value	Mean (Range)	p-value
Overall	7.4 (-1 to 16)	<0.0001*	8.64 (-11 to 24)	<0.0001'
Responders	8.3 (0.7 to 16)	<0.0001*	11.66 (4 to 24)	<0.0001'
Non-responders	-3.78 (-0.2 to -12.9)	0.854*	-7.25 (-4 to -11)	0.0219'
Pregnancy	10.8 (5 to 13.6)	0.058*	7.2 (4 to 10)	0.0038'
No pregnancy	6.65 (-1 to 16)	0.0003*	9 (-11 to 24)	0.0005'
Azoospermia	4.66 (2 to 6)	0.174*	17 (14 to 22)	0.0005'
Virtual azoospermia	8.65 (-0.2 to 13.8)	0.001*	9.29 (-5 to 22)	0.0005'
Oligospermia	6.25 (-1 to 16)	0.042*	5.88 (-11 to 24)	0.1965'

[Table/Fig-4]: Changes in sperm counts and motility after surgery.
*Wilcoxon signed rank test; 'Paired t-test

	Pregnancy	No pregnancy	p-value
Number of patients	5 (20%)	20 (80%)	-
Age (years)	32.2 (29-34)	30.7 (27-39)	0.288*
Duration of infertility (years)	4.6 (2-10)	4.3 (2-13)	0.547*
Average testicular size (cm^3)	18.4 (18-19)	19.35 (16-24)	0.756*
Grade of varicocele	2.4 (2-3)	1.85 (1-3)	0.048*
Testicular histopathology:			
Hypospermatogenesis	04 (23.5%)	13 (76.5%)	0.961'
Late maturation arrest	01 (16.7%)	05 (83.3%)	0.98'
Early maturation arrest	00	02 (100%)	0.97'

[Table/Fig-5]: Fertility outcomes.
*Mann-Whitney U-test; 'Fisher Exact test

This study clearly shows that improvements can be obtained in all the sperm count groups, which was statistically significant in the majority. This contributed to the pregnancy outcomes which could be achieved either spontaneously or with the help of less costlier option of Assisted Reproductive Technology (ART), i.e., IUI. This benefited a fifth of our patients in a public hospital set-up, all of whom were from poor socio-economic background.

Youssef T et al., (n=79) introduced the term virtual azoospermia for pellet positive patients who had few sperms in the pellet and recommended varicocelectomy in NOA and VA groups with palpable varicocele [13]. Aboutaleb HA et al., (n=20) reported that the chance of improvement in semen parameters in patients of NOA was higher in cases of hypospematogenesis than maturation arrest or sertoli cell only syndrome [5]. They had recommended that testicular histology could be considered a prognostic indicator before offering varicocelectomy in NOA patients. The present study also showed most of the patients with hypospermatogenesis and late maturation arrest responding to treatment as compared to early maturation arrest patients, but could not achieve statistical significance due to small sample size. Kiraç M et al., (n=23) had reported the detection rate of motile sperms after varicocelectomy in NOA to the tune of 30.4% [14]. They also emphasised the importance of motile sperms in ejaculate as compared to motile sprems at TESE for pregnancy outcomes of ICSI. The index study also showed a mean improvement of 4.66 million/mL in sperm count in NOA patients. Matthews GJ et al., (n=78) also reported detection rate of 55% in 22 men with azoospermia after surgery [9]. Kadioglu A et al., (n=24) reported that pellet negative patients had 20.8% improvement whereas pellet positive patients had 85.7% improvement after surgery [15]. Present study findings align with the findings of the above mentioned studies. Pasqualotto FF et al., (n=15) reported that even patients having germ cell aplasia can have improvement in semen parameters after surgery [16]. Hence they recommended surgery in all patients irrespective of biopsy results as the biopsy sample represents only a focal portion of testis. This study did not have any patient with germ cell aplasia. The meta-analysis by Weedin JW et al., showed success of varicocelectomy to be significantly higher in maturation arrest (42.1%) and hypospermatogenesis (54.5%) over sertoli cell only syndrome (11.3%) [17]. Although present study did not have any patient with sertoli cell only syndrome, patients with hypospermatogenesis and late maturation arrest showed improvement as compared to early maturation arrest patients.

Pregnancy rates after varicocelectomy in patients with NOA and VA may vary from 12%-15% [18]. Inci K and Gunay LM, have summarised different studies and reported the rates of successful pregnancy to be around 15% (spontaneous or assisted pregnancy) [12]. Present study had similar pregnancy outcome rate of 20%. They have also quoted different studies reporting the loss of improvement in semen parameters of patients over longer follow-up. Hence they recommend cryopreservation of spermatozoa after initial improvement. The relapse rate varies from 29%-78% [15,18]. Esteves SC et al., have also mentioned in their meta-analysis that the forest plot for sperm retrieval rates, clinical pregnancy rates, live birth rates favours varicocelectomy in patients with NOA [19].

Limitation(s)

The study did not have a control group. Although all the patients could not afford IVF-ICSI, there were some who could afford IUI while others could not. Longer follow-up (>2 years) was done in less than half of the patients. All these factors can lead to multiple confounding parameters during statistical evaluation. The small sample size leads to under-powering of the study to detect statistically significant differences in parameters.

CONCLUSION(S)

Microsurgical subinguinal varicocelectomy can be offered as a management option in severe oligospermic men having varicocele, with increased chances of spontaneous or assisted pregnancy (IUI) in these couples. This is usually the only treatment option for patients with low socio-economic status and can culminate in pregnancy in a few, before proceeding to donor insemination or adoption. Hypospermatogenesis and late maturation arrest are favourable predictors of response after surgery.

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