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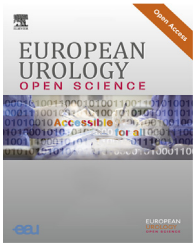

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Sexual Medicine

Unilateral Versus Bilateral Vasoepididymal Anastomosis for Idiopathic Obstructive Azoospermia: A Randomised Controlled Trial

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Abstract

Background: Men with idiopathic obstructive azoospermia (OA) are candidates for surgical reconstruction with a vasoepididymal anastomosis (VEA) performed on one or both testis. There are no randomised trials comparing the success of unilateral versus bilateral VEA.
Objective: We conducted a randomised trial to compare the two surgical options.
Design, setting, and participants: Between April 2017 and March 2022, men with infertility due to idiopathic OA were randomised to a unilateral (group 1) or bilateral (group 2) VEA in an ethics committee–approved clinical trial, registered with the Clinical Trials Registry.
Outcome measurements and statistical analysis: The primary outcome was successful surgery, defined as appearance of sperm in the ejaculate, evaluated at 3 mo intervals after surgery. Additional outcomes were pregnancy rates and complications between the two groups. Men with successful surgery were compared with those without patency to identify the predictors of success.
Results and limitations: Fifty-four men fulfilled the criteria and 52 who completed follow-up were included in the analysis. The overall patency rate was 36.5% (19/52 individuals). This was higher in men with bilateral surgery (12/26 patients, 46%) than in those with unilateral surgery (7/26 patients, 27%) but was not statistically significant ($p = 0.1$). The overall pregnancy rate with ejaculated sperm was significantly higher in the bilateral surgery group (4 vs 0, $p = 0.037$), while the spontaneous conception rate was higher but not statistically significant (3 vs 0, $p = 0.074$). The complication rates in the two groups were similar ($p = 0.7$), and all complications were Clavien-Dindo grade 1. Although bilateral surgery and presence of sperm in epididymal fluid were higher in men with patency, these were not statistically significant.
Conclusions: A bilateral VEA was associated with higher patency and spontaneous pregnancy rates than unilateral surgery, but the results were not statistically

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significant. However, the overall pregnancy rate with ejaculated sperm, spontaneous and assisted, was significantly higher in the bilateral surgery group.

Patient summary: In this study, we compared between unilateral and bilateral reconstructive surgery in azoospermic men and found better overall success with bilateral surgery. However, these results were not statistically significant.

1. Introduction

Infertility affects approximately 15% couples in the reproductive age group, and the male and female partners contribute in equal measure [1]. Among infertile men, azoospermia is identified as the causative abnormality in almost half of the affected individuals [2]. This is most often due to a previous vasectomy in populations where vasectomy is a preferred method of contraception [2,3]. However, in many men with azoospermia, the cause is indeterminate despite normal spermatogenesis on testicular histology and no history of previous vasal surgery. Such men are diagnosed to have idiopathic obstructive azoospermia (OA) [2,4].

While in vitro fertilisation (IVF) is an option for achieving fertility in most men with azoospermia, the subset with OA are also candidates for surgical reconstruction of the obstructed segment. When the obstruction is due to a prior vasectomy, success rates with reconstruction (vasectomy reversal) may be above 90% [5]. However, among men with idiopathic obstruction, success rates are much lower, at around 48% [6]. Among the men in whom reconstruction is unsuccessful, IVF using sperm extracted from the epididymis or testis remains an option for fertility.

Reconstruction for idiopathic obstruction requires a microsurgical vasoepididymal anastomosis (VEA) [2,3]. Since the obstruction must be bilateral in order to cause azoospermia unless it is in a solitary functioning testis, reconstruction can be performed on one or both sides and bilateral surgery may improve outcomes. It is expected that bilateral surgery would increase the costs, operative time, and risk of complications, while there is no clear evidence of benefit over unilateral surgery. Further, in our clinical experience, sperm retrieval for IVF using a percutaneous epididymal aspiration (PESA) is technically easier in men with a previously unoperated scrotum and epididymis since previous surgery leads to fibrosis and distortion of the anatomy. Considering the lower success rates of a VEA in idiopathic obstruction and our inability to perform cryopreservation of sperm during surgical exploration, many of our patients require a subsequent PESA, and therefore, we prefer to perform unilateral surgery and retain an unoperated side for PESA [6,7].

A post hoc subgroup analysis of our previous data on the outcomes of a VEA suggested that a bilateral VEA may be associated with higher success rates than unilateral surgery (80% vs 39%) [7]. Since there are no studies evaluating the outcomes of unilateral versus bilateral surgery, we conducted a randomised controlled trial to compare success rates after a unilateral versus bilateral VEA for idiopathic vasoepididymal junction obstruction. Additionally, we assessed factors that could predict successful surgery.

2. Patients and methods

2.1. Trial design

This randomised, controlled, parallel design trial with a 1:1 allocation ratio was conducted between April 2017 and March 2022 in a tertiary care centre with a dedicated andrology clinic and laboratory.

2.2. Ethics and registry

The trial was approved by the institutional ethics committee (approval letter number IECPG-415/28.09.02017/RT-13/16.10.2017) and was registered with the Clinical Trials Registry India (CTRI/2019/08/020934). All participants provided written, informed consent for inclusion. All raw data are available with the investigators.

2.3. Participants

Adult men presenting to our andrology clinic with infertility were evaluated and screened for inclusion in the study. Men were considered for inclusion if they were diagnosed to have idiopathic OA based on the following criteria:

1. Infertility of at least 1 yr duration
2. Normal testis size with palpable vas deferens on both sides
3. No prior history of vasectomy or inguinal, scrotal, or retroperitoneal surgery
4. At least two semen analysis reports analysed as per 2010 World Health Organization [8] standards with normal semen volume and azoospermia
5. Normal serum follicle stimulating hormone levels
6. Normal spermatogenesis using a fine-needle aspiration cytology of the testis [9]
7. No identifiable cause for azoospermia

Among the men considered for inclusion, those in whom reconstruction could not be performed due to dense epididymal fibrosis or absence of fluid within the epididymal tubule were excluded.

2.4. Intervention

All patients underwent a VEA as day care surgery. Surgery was performed under general anaesthesia with antibiotic prophylaxis. A VEA was performed using the two-suture longitudinal intussusception technique that has previously been described [6]. Briefly, after a scrotal incision, vasal patency was confirmed by infusing saline distally. The epididymis was examined under an operating microscope (Opmi Vario; Carl Zeiss, USA) to identify a site suitable for anastomosis. The surgery was abandoned if there was dense fibrosis or absence of fluid in the epididymal tubule, precluding an anastomosis. The vas deferens was anchored to the epididymal adventitia using two 8-0 polyamide sutures

(Ethicon, Ahmedabad, India). The epididymal tubule was kept in line with the vas deferens, and two double armed 10-0 polyamide sutures (Ethicon) were placed parallel to each other along the length of the tubule, which was then incised between the needles. The epididymal fluid was examined for the presence of sperm under a light microscope in the operating room, and the surgery was completed. Operative time was recorded from the time of skin incision to the time of placement of the last skin suture.

2.5. Outcome assessment

Patients were asked to maintain sexual abstinence for 6 wk. Semen analysis was obtained at 6 wk after surgery and subsequently at every 3-mo intervals for 12 mo or till sperm were seen in the ejaculate, whichever was earlier. Patients who were unable to complete the physical follow-up (due to closure of routine hospital services during the coronavirus disease 2019 [COVID-19] pandemic) were contacted by telephone for follow-up. Complications were recorded at each follow-up visit. The primary outcome was successful surgery (patent anastomosis), defined as the appearance of sperm in the ejaculate. The secondary outcomes were occurrence of spontaneous pregnancies and complications. Additional analyses were performed to assess the predictors of success by comparing the group with patent anastomosis versus the group without patency.

2.6. Sample size calculations

The sample size was calculated based on our previous study that showed that a bilateral VEA had 41% higher patency than unilateral surgery [7]. Keeping alpha and beta errors as 5% and 10%, respectively, the sample size required was 35 patients in each group (unilateral vs bilateral VEA). However, due to the COVID-19 pandemic outbreak, routine patient care was severely interrupted between March 2020 and January 2022, and patient recruitment could not be completed as planned. The study was closed prematurely when follow-up of 1 yr was completed among patients recruited till March 2021. The analysis was performed with the recruited patients.

2.7. Randomisation/allocation concealment/blinding

Randomisation was performed using the computer-generated random number technique. All patients fulfilling the inclusion criteria initially underwent unilateral surgery. On completion of the first side, randomisation was performed using sealed, coded envelopes. Two containers were used. One contained paper slips with serial numbers, while the second contained opaque envelopes marked with corresponding serial numbers, stating unilateral or bilateral surgery. After completion of surgery on one side, a paper slip was taken out of the first container followed by the retrieval of the envelope with the same number from the second container. If the patient was randomised to bilateral surgery, the contralateral surgery was performed similar to surgery on the first side. This ensured allocation concealment from the surgeon till the last possible moment (Fig. 1). The right side was explored first in all cases. If the right side was not reconstructable, the procedure was abandoned and no surgery was attempted on the left side. In no case was the VEA abandoned on the left side if the patient was randomised to bilateral surgery (after completing the right side surgery). The surgeon and the patient were not blinded, but the laboratory performing the postoperative semen analysis and statistician analysing the results were blinded to the surgical procedure. Since the primary outcome is objectively based on the semen analysis, it was not subject to an observer bias.

2.8. Statistical analysis

Patency, spontaneous pregnancy, and complication rates were compared between the two groups (unilateral vs bilateral surgery) using the chi-square test. The mean operative time was compared using the independent sample t test. Fischer exact test was applied for categorical variables to identify factors predicting the success of surgery.

3. Results

Seventy-five patients fulfilled the eligibility criteria, provided informed consent, and were considered for inclusion in the study. Among them, 21 were found to have dense fibrosis or no fluid in the epididymis during exploration, and were excluded from randomisation. The remaining 54 were included and underwent randomisation. Twenty-eight patients were randomised to unilateral surgery (group 1) and 26 to bilateral surgery (group 2). Two patients in group 1 did not complete 1 yr of follow-up and were excluded from the final analysis.

A total of 52 patients were included in the final analysis. Their mean age was 30.2 ± 3.5 yr (range 23–41 yr). Fifty patients had primary infertility, while two patients had secondary infertility. The mean duration of infertility was 5.6 ± 3.6 yr (range 2–20 yr). Their mean serum follicle stimulating hormone was 4.17 ± 2.01 mIU/ml (range 1.01–9.5 mIU/ml). Baseline details of the two groups are given in Table 1.

The overall patency rate was 36.5% (19/52 patients) and was higher in men with bilateral surgery, with 12 of 26 patients having sperm in the ejaculate (46%) compared with seven out of 26 patients in the unilateral surgery group (27%). However, the difference was not statistically significant (p = 0.1). The overall pregnancy rate with ejaculated sperm was significantly higher in the bilateral surgery group (4/26, 15.3%) than in the unilateral surgery group (0, p = 0.037). Three men achieved pregnancy with spontaneous conception and one with intrauterine insemination of ejaculated sperm. The spontaneous conception rate was also higher in the bilateral surgery group (3 vs 0, p = 0.074) but not statistically significant. Both groups had similar complication rates, and all complications were of Clavien-Dindo grade 1, with none requiring any intervention. The comparative data for the two groups are given in Table 1. A post hoc analysis revealed that the study had a power of 30% for assessing the patency rate as the primary outcome.

On comparing patients with a patent anastomosis versus those without patency, we could not identify any statistically significant predictor of success. The comparative data for the two groups are shown in Table 2. Bilateral surgery was more common in the group with a patent anastomosis, as was the presence of sperm in the epididymal fluid, but the difference did not reach statistical significance.

4. Discussion

We found a higher patency rate among men who underwent a bilateral VEA than in those who had unilateral surgery for idiopathic OA. Although the rate was nearly

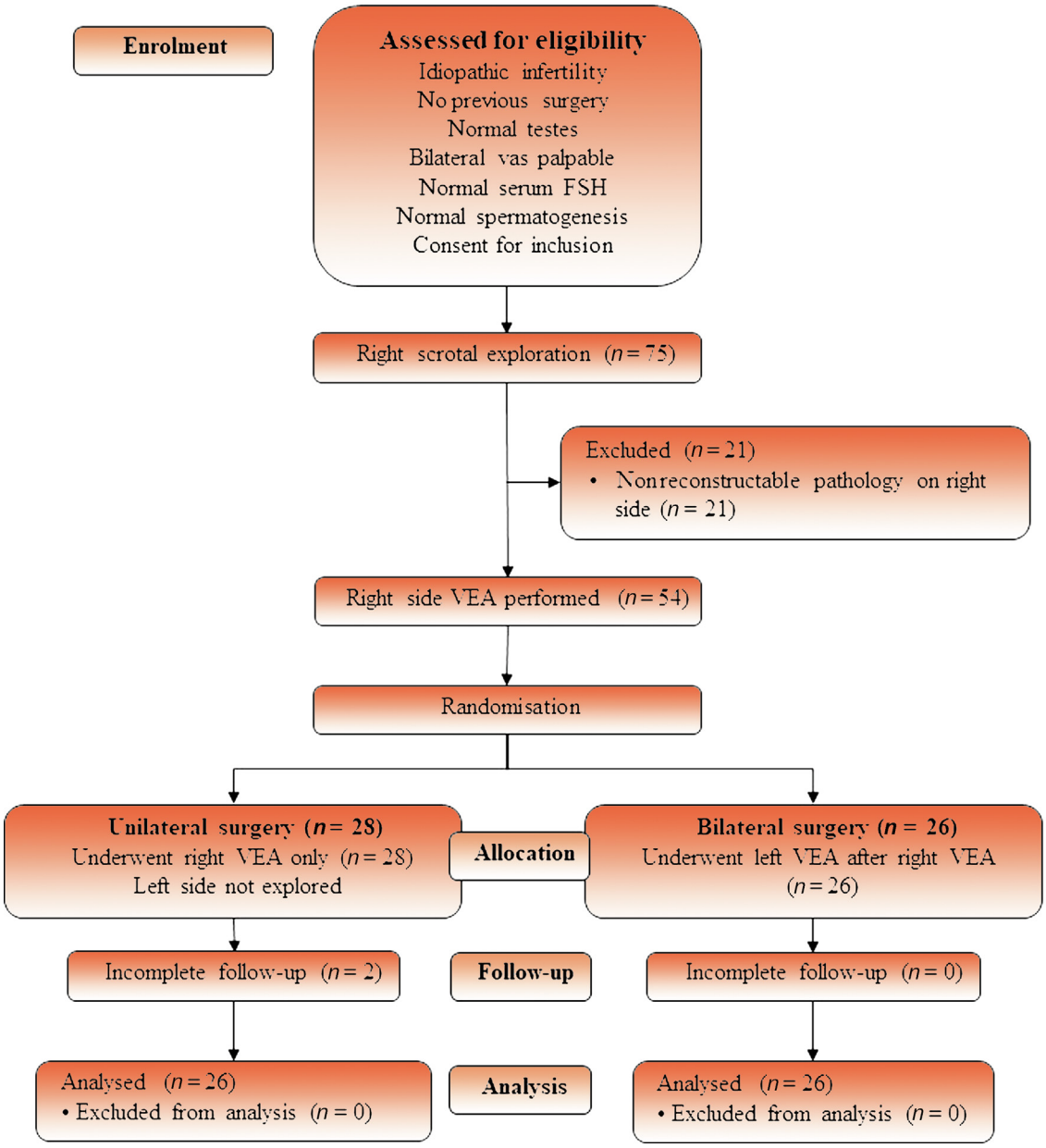

Fig. 1 – CONSORT flowchart of patient inclusion and randomisation. FSH = follicle stimulating hormone; VEA = vasoepididymal anastomosis.

double in the bilateral surgery group, this was not statistically significant, possibly due to inadequate power of the study because of to poor patient accrual. None of the operative findings could help predict a successful outcome.

Unlike countries where vasectomy is commonly performed for contraception, presumed infections and inflammation are frequent and often predominant causes of OA in many regions [10,11]. Despite advancements in assisted reproductive techniques (ARTs), reconstructive surgery has a significant role in management of OA as it offers a cost-effective, long-term solution in comparison with an ART [12]. Postreconstruction ejaculated sperm have similar pregnancy rates to ARTs with a possibility of natural conception [1]. Even if these patients require an ART, ejaculated sperm are easier to obtain than those acquired through surgical sperm retrieval and may also lower the level of the ART required.

However, microsurgical reconstruction is a difficult surgery with variable success rates. The rates are lower in men with idiopathic obstruction. The two-suture intussusception technique of a VEA was first described by Marmar [13] in 2000, and they reported a patency rate of 81.3% in 16 patients. Since then, many modifications have been described, with patency rates ranging from 48% to 81% [6,14–17]. In the present study, we found an overall patency rate of only 36.5%, with 46% patency in patients undergoing bilateral surgery. The higher patency with bilateral surgery would argue in favour of performing bilateral procedures routinely for such patients. The lack of statistical significance seems to be more due to the low power of the study

Table 1 – Comparative outcomes between groups

Parameter	Group 1 Unilateral	Group 2 Bilateral		*p* value
Number of patients	26	26		
Age (yr)	30.7 ± 3.8	29.6 ± 3.2		0.30
Duration of infertility (yr)	6.6 ± 3.8	4.6 ± 3.1		0.06
Prior pregnancy	1/26	1/26		
Testis size (ml)				
Right	19 ± 2.3	18.8 ± 1.8		0.85
Left	19 ± 2.1	19.1 ± 1.8		0.84
Serum follicle stimulating hormone (mIU/ml)	4.39 ± 2.14	3.9 ± 1.85		0.33
Side of surgery	Right	Right	Left	
Epididymal tubules dilated	17	18	17	0.76
Epididymal fluid colour				
White	17	10	8	0.08
Yellow	3	9	9	
Clear	6	7	6	
Haemorrhagic	0	0	3	
Sperm in epididymal fluid				
Not seen	10	2	2	0.01
Motile	15	20	20	
Nonmotile	1	4	4	
Site of anastomosis				
Head	22	23	21	0.76
Body	2	3	4	
Tail	2	0	1	
Operative time (min)	42.3 ± 4.0	76.3 ± 7.7		0.0001
Patency (sperm in ejaculate after surgery)	7 (27%)	12 (46%)		0.1
Pregnancy from ejaculated sperms	0	4		0.037
Spontaneous	0	3		0.074
Intrauterine insemination/patients attempted	0/2	1/3		
Pregnancy through epididymal or testicular sperm retrieval and intracytoplasmic injection/patients attempted	4/14	6/16		
Complications	10	9		0.77

Table 2 – Prediction of success of surgery

Characteristic	Patent (*N* = 19)	Nonpatent (*N* = 33)	*p* value
Bilateral surgery, *n* (%)	12 (63)	14 (42.4)	0.14
Sperm in epididymal fluid, *n* (%)	18 (94.7)	22 (66.6)	0.16
Dilated epididymal tubules, *n* (%)	14 (73.6)	21 (63.6)	0.45
Anastomosis at head of epididymis, *n* (%)	16 (84.2)	29 (87.87)	0.71

than a true lack of benefit. The low power itself is an unintended outcome of the COVID-19 pandemic that began in 2020. Patient accrual had been as expected till that time and would possibly have been completed had it not been affected by the hospital shutdowns that occurred after 2020. Despite the low patency rate, the overall rate of pregnancy using ejaculated sperm was significantly higher in the bilateral surgery group. Even though the spontaneous pregnancy rate was not significantly higher, the fact that ejaculated sperm could be used for intrauterine insemination is an important achievement for these couples, as it helps avoid the more extensive ARTs such as IVF and intracytoplasmic injection.

Some of the reasons for our lower patency rates are evident in the operative characteristics of our patients. The nature of epididymal fluid and presence of motile sperm have previously been reported to be predictors of patency [6]. Sperm motility is the result of effective epididymal function. In previously reported series of vasectomy reversal, the presence of clear epididymal fluid and motile sperm in intravasal samples translated into 34% higher patency rates than no sperm in samples (94% vs 60%) [18]. We found motile sperm in only 35/52 (67%) of our patients. The difference is possibly due to the aetiology and site of obstruction. In men with a prior vasectomy, OA is a definitive diagnosis, and these men have previously documented normal fertility. The level of obstruction is the vas deferens, and anastomosis is often done at the level of the distal epididymis where the tubular lumen is larger and the sperm potentially have a higher possibility of attaining maturity than the head of the epididymis. None of our patients had a previous vasectomy, and only two (4%) had previously documented fertility. We were able to perform anastomosis at the epididymal tail in only 4% of our patients. This would suggest that not only is the diagnosis of OA presumptive, but the sperm may also have inadequate maturity at the head of the epididymis and the anastomosis may not be technically as good as the one performed at the tail with a wider tubular lumen. These hypotheses seem reasonable as, even in our study, men with a patent anastomosis were more likely to have motile sperm in the epididymal fluid and have dilated tubules, even though these numbers were not statistically significant.

This is the first study to evaluate the patency of a bilateral VEA in a randomised controlled manner. Randomised trials of infrequent surgical procedures such as a VEA are

not common. Our evaluation of intraoperative parameters such as dilatation of tubules and presence of sperm as predictors of patency could help make decisions during the surgery on the value of proceeding with bilateral procedures. Although the complication rates were similar in both groups, bilateral surgeries took significantly longer operating times, and additional studies will be required to assess whether a VEA impacts sperm retrieval rates during PESA in such men. Sperm retrieval and cryopreservation can be done at the time of exploration for a VEA, and this would obviate the need for a subsequent PESA. However, this requires the availability of an embryologist or trained personnel for cryopreservation at the time of performing a VEA. This is not always possible, even at our tertiary care institution that has its own IVF facility.

Our study also emphasises the variability in outcomes due to aetiology of OA and the significant proportion of men who are deemed unsuitable for reconstruction. This is very important when counselling patients since the patency rate, as a function of all patients taken for surgery, becomes even smaller at 25% (19 out of 75 patients). While it could be argued that success also depends on surgeon expertise, we have been performing these procedures routinely for over 20 yr and have previously reported our results [1,6,7].

The principal limitation of the study is its low power due to our inability to accrue the requisite number of patients due to the COVID-19 pandemic. However, even at this lower power, the higher numerical values suggest that an appropriately powered study would only magnify this difference and thus the results of our study may be sufficient to recommend bilateral surgery. This is the sole randomised trial on this subject, and this would make the results useful and clinically significant even if not statistically significant.

5. Conclusions

We found that men who undergo a bilateral VEA for idiopathic OA may have higher patency and pregnancy rates than unilateral surgery, but the difference is not statistically significant, possibly due to the low power of our study. The presence of sperm in epididymal tubular fluid and distended tubules may help intraoperatively predict the outcome of surgery.

***Author contributions*:** Rajeev Kumar had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gurnani, Goel, M. Kumar, Dada, R. Kumar.
Acquisition of data: Gurnani, Goel, M. Kumar, Dada, R. Kumar.
Analysis and interpretation of data: Gurnani, Goel, M. Kumar, Dada, R. Kumar.
Drafting of the manuscript: Gurnani, Goel, R. Kumar.
Critical revision of the manuscript for important intellectual content: M. Kumar, Dada, R. Kumar.
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