ABSTRACT

INTRODUCTION: The objective was to compare the semen quality and hormonal levels of patients with varicocele receiving antegrade scrotal sclerotherapy (ASS) alone versus a combination of ASS and tamoxifen.

METHODS: The design was a cross-sectional investigation of 72 patients with varicocele that were surgically managed with ASS. The patients were admitted to the hospital urology department from January to June 2009 with different grades of varicocele and infertility. They were randomly divided into 2 groups: 37 patients underwent ASS only; 35 patients underwent ASS and received tamoxifen citrate 10 mg twice daily, starting immediately after ASS and continuing for 6 months. All patients were evaluated preoperatively and postoperatively by history, clinical examination, semen analysis, and Doppler ultrasound. Hormonal assay was indicated in cases of severe oligospermia. Outcome measures were semen parameters and hormonal levels. Operative time, length of hospital stay, length of time before return to normal activity, recurrence rate, and cost of each procedure were also recorded.

RESULTS: The mean (SD) ASS operative time was 20 (6.4) minutes for patients with unilateral varicocele and 28 (10.8) minutes for patients with bilateral varicocele. The hospital stay for patients with unilateral and bilateral surgery was < 24 hours and < 30 hours, respectively. Patients in both groups showed statistically significant improvement in semen count, motility, and abnormal forms 6 months after surgery ($P < .001$). Over 70% of the patients in both groups had improvement in all 3 measures and there were no significant group differences ($P > .05$). Eleven out of 35 patients in group 2 required hormonal assessment because they had severe oligozoospermia. There was a significant improvement in hormonal levels following treatment ($P < .01$). Over 80% of the patients in both groups had no recurrence. Persistent varicocele occurred in 10 patients (13.9%), scrotal hematoma in 5 patients, and postoperative scrotal pain in 1 patient.

CONCLUSION: ASS for varicocele in male infertility due to varicocele significantly improves semen parameters with or without tamoxifen. ASS is a rapid, effective, and low-cost procedure.

INTRODUCTION

Varicocele is dilatation of veins of the pampiniform plexus and the internal spermatic vein. It appears as a painless serpentine mass of dilated veins in the scrotum [1]. Varicocele occurs in 10-25% of the general male population and in 30-50% of infertile men. It represents the main cause of potentially correctable male infertility [3].

The main aim of treating a varicocele is to stop venous reflux into spermatic veins. If successful, there may be an improvement in semen quality in 40-60% of patients and recovery of fertility in 10-40% [3]. Antegrade scrotal sclerotherapy (ASS) is performed using local anesthesia because it is minimally invasive and requires patient cooperation to achieve increased abdominal pressure while the sclerosing substance is injected [4]. Transcatheter foam sclerotherapy (TCFS) for male varicocele is associated with a low recurrence rate, high pain resolution rate, and significant improvement in pretreatment sperm parameters [5].

Tamoxifen citrate is one of the antiestrogens that has been used extensively for the last 30 years for treatment of oligozoospermia, with an average dose of 20 mg/day [6]. Tamoxifen citrate inhibits hypothalamic estrogen receptors and causes stimulation of gonadotropin-releasing hormone (GnRH) secretion. As a result, gonadotropin levels increase to stimulate Leydig cells and seminiferous tubules [7].

The purpose of the present study was to compare the semen quality and hormonal levels of patients with varicocele receiving ASS alone versus a combination of ASS and tamoxifen.

METHODS

The study was a cross-sectional investigation of patients with varicocele that were surgically managed with ASS. They presented to the Urology Outpatient Clinic of Benha University Hospital between January and June, 2009. The protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Benha University. Written informed consent was obtained from all participants.

Participants

The participants were 72 patients with infertility due to varicocele. Their age range was 22-36 years. Exclusion criteria included patients with azoospermia, subclinical varicocele, cryptorchidism, unilateral orchidectomy, or known hypersensitivity to contrast media (urografin).

The patients were randomly assembled into 2 groups, with 37 patients in group 1 and 35 patients in group 2. The mean (standard deviation) ages were 27 (3.5) years for group 1 and 28.1 (3.2) years for group 2, with no statistically significant group difference. Table 1 contains the baseline type of infertility (primary or secondary), varicocele laterality,
and varicocele grade for both patient groups (the baseline semen parameters are provided as part of Table 4).

**Preoperative Evaluation**

All patients provided a full case history, including personal and fertility information. A physical examination was conducted. All patients had 2 seminal analyses and routine laboratory investigations. The patients also received power Doppler ultrasound imaging and duplex examination for the spermatic cord and testes. An example is provided in Figure 1. Hormonal assessment was completed when indicated; for example, in cases of severe oligospermia (sperm count < 5 million/mL) or evidence of impaired sexual function (eg, impotence or low libido). Tests of follicle-stimulating hormone (FSH), testosterone, and luteinizing hormone (LH) were done.

**Procedures**

Patients in group 1 underwent ASS only; patients in group 2 underwent ASS and received tamoxifen citrate 10 mg twice daily, starting immediately after ASS and continuing for 6 months. All patients were trained to perform a Valsalva maneuver.

All patients underwent ASS. The patient was placed supine in a slight anti-Trendelenburg position. Deep infiltration of local anesthesia (lidocaine 2%) was induced at the scrotal neck (inguinoscrotal area), by injecting 20 mL of a local anesthetic into the spermatic cord fascial layers and the surrounding area. The spermatic cord, along with the skin of the scrotum, was grasped between the index finger and the thumb. A 1-2 cm incision was made in the scrotal neck (Figure 2). A small clamp was drawn underneath the spermatic cord and a rubber band was pulled through it to prevent retrograde flow of sclerosant. A suitable vein (ie, large and easily dissectible) of the pampiniform plexus was selected from the dark yellow fat and exposed (Figure 3). A 24G thin-walled cannula was introduced into the selected vein in a proximal direction (Figure 4) and injected with a few milliliters of physiological saline. The direction of the flow of sclerosing agent (ethanolamine oleate 5%) was checked before sclerotherapy began by injecting 3-5 mL of contrast medium (urografin 76%) into the cannulated vein under fluoroscopic control (Figure 5). This medium was chosen because it was available and less expensive than alternatives. The sclerotherapy procedure then began using the air-block technique. The surgeon injected 1 mL of air followed by 3 mL of sclerosing agent, during which the patient was instructed to perform a Valsalva maneuver. The increased intraabdominal pressure opposes the upward flow of sclerosant into the spermatic vein system. Hence, there is a uniform and capillary diffusion into more collateral vessels. The cannula was then removed and the vein ligated proximally and distally using 3-0 vicryl sutures. Finally, the fascia and skin were closed in layers with 3-0 chromic cat gut sutures. The wound was dressed after 3-5 minutes of manual compression.

Patients were evaluated after 3 and 6 months by clinical examination, Doppler ultrasound, and semen analysis. Hormonal assay was completed in cases of severe oligospermia.

**Data Analysis**

The outcome measures were the semen parameters of count, motility, and abnormal forms. The pretreatment and posttreatment hormonal levels of FSH, LH, and testosterone were compared for patients with severe oligospermia. The operative time, length of hospital stay, length of time before return to normal activity, recurrence rate, and cost of each procedure were also recorded.
Figure 2. A 1 cm to 2 cm Incision Made in the Scrotal Neck.
doi: 10.3834/uij.1944-5784.2010.08.06f2

Figure 3. A Suitable Vein (ie, Large and Easily Dissectible) Selected From the Pampiniform Plexus.
doi: 10.3834/uij.1944-5784.2010.08.06f3

Figure 4. A 24G Thin-Walled Cannula Introduced Into the

Figure 5. Injection of 3-5 mL of Contrast Medium
Descriptive statistics of frequency, mean, and standard deviation were calculated. A microstat program was used to calculate Z scores. Group differences in the mean outcome measures were determined with the t test using the Statistical Package of Social Science version 11 (SPSS; Chicago, IL, USA). Statistical significance was set at \( P < .05 \).

**RESULTS**

No patient required general anesthesia during surgery; 14 patients required sedation in the form of 10 mg diazepam. The mean (SD) ASS operative time was 20 (6.4) minutes for patients with unilateral varicocele and 28 (10.8) minutes for patients with bilateral varicocele. The hospital stay for patients with unilateral and bilateral surgery was 6-24 hours and 8-30 hours, respectively. The patients were able to return to normal activity 3-5 days following unilateral surgery and 5-9 days following bilateral surgery, depending on the nature of their activities.

**Intragroup Treatment Comparisons**

The number of patients in both groups showing improvement from presurgery to 6 months postsurgery in semen count, motility, and abnormal forms is contained in Table 2. Patients in both groups showed statistically significant improvement in all 3 semen parameters when the presurgery means were compared with the 6-month postsurgery means \( (P < .001) \). Over 70% of the patients in both groups had improvement in all 3 measures.

There were no cases of severe oligozoospermia in group 1. Eleven out of 35 patients in group 2 required hormonal assessment because they had severe oligozoospermia (sperm count < 5 million/cc). Table 3 contains the results of the FSH, LH, and testosterone hormone tests before surgery and at the 6-month follow-up evaluation. There was a statistically significant improvement in all outcome measures following treatment \( (P < .01) \).

There was a significantly larger number of patients with no recurrence of the varicocele than with recurrence following treatment in both groups \( (P < .001) \). In group 1, 33 patients (89.2%) had no recurrence and 4 patients had recurrence; in group 2, 29 patients (83%) had no recurrence and 6 patients had recurrence.
**Intergroup Treatment Comparisons**

The mean semen parameters of count, motility, and abnormal forms measured for both groups at the preoperative, 3 month, and 6 month evaluations are contained in Table 4. There was no significant difference between the 2 groups on any of the parameters ($P > .05$). The $t$ values on the table are the result of the difference between the 2 means of 2 independent groups. The smaller the difference between the 2 means, the smaller the value of the $t$ and the larger the value of the probability, taking the SD into consideration because it is included in the $t$ test formula.

There was a difference in treatment cost between groups. The cost was $1000 (US) more for 6 months of treatment of each case in group 2 than for the same period of treatment for each case in group 1.

Table 2. Number of Patients in Both Groups Showing Various Improvement Levels From Presurgery to 6 Months Postsurgery in Semen Count, Motility, and Abnormal Forms (N = 72).

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Mean</th>
<th>SD</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (mIU/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>8.4</td>
<td>3.9</td>
<td>2.8</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>12.2</td>
<td>4.7</td>
<td></td>
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</tr>
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</table>

Table 3. Means, Standard Deviations, Z Scores, and $P$ Values of the Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), and Testosterone Tests Before Surgery and 6 Months After Surgery for Patients With Severe Oligospermia in Group 2 (n = 11).

doi: 10.3834/ujj.1944-5784.2010.08.0613

<table>
<thead>
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<th>Z</th>
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<tbody>
<tr>
<td>FSH (mIU/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>8.7</td>
<td>5.0</td>
<td>2.7</td>
<td>&lt; .01</td>
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<tr>
<td>Posttreatment</td>
<td>12.1</td>
<td>4.9</td>
<td></td>
<td></td>
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<table>
<thead>
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<th>SD</th>
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</thead>
<tbody>
<tr>
<td>Testosterone (pg/mL)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>4.8</td>
<td>2.8</td>
<td>2.4</td>
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<tr>
<td>Posttreatment</td>
<td>8.2</td>
<td>1.6</td>
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</table>

**Complications**
There were no intraoperative complications and no patient showed any allergy to the contrast or sclerosant. However, scrotal hematoma occurred in 5 patients (6.9%); 2 patients were in group 1 and 3 patients were in group 2. The hematoma was resolved by simple measures (ie, antibiotic and antiinflammatory medications) within 2 weeks. This complication occurred in early cases; afterward, careful handling of tissues and postoperative scrotal support decreased the incidence of scrotal hematoma. Six months after ASS, 10 patients (13.9%) had persistent varicocele (4 patients in group 1 and 3 patients in group 2 had clinical varicocele, and 3 patients in group 2 had persistent reflux that was consistent with a subclinical varicocele on color Doppler ultrasound). Finally, 1 patient in group 1 (1.4%) had scrotal pain that persisted for approximately 1 month.

There were some study limitations like the cost and patient compliance, but no patients were lost to follow-up.

**DISCUSSION**

Varicocele causes a progressive decline in testicular functions such as spermatogenesis and steroidogenesis over time. For couples desiring more than 1 child, the ability of varicocelectomy to prevent further deterioration may be even more important than the procedure’s early beneficial effects on semen quality. Furthermore, for couples who are unable to achieve spontaneous pregnancy following varicocelectomy and who require assistive techniques, the pregnancy rates for intrauterine insemination are improved following varicocelectomy [8].

**Surgical Issues**

Mazzoni et al [4], reported that mean (SD) operative time for varicocele was 30 (5) minutes and hospital stay was 6 hours. Ficarra et al [3] reported that the average hospital stay was < 12 hours, with return to work within 24-72 hours. Zaupa et al [9] reported that mean operative duration was 33.2 minutes and hospital stay was 2 days in their early cases; after that, all patients had 1-day surgical procedures. Zucchi et al [10] compared mean operative time and hospital stay for ASS with other modalities. They found that the operative time of bilateral inguinal varicocelectomy was 42 minutes (range, 36-60 minutes), whereas ASS required an average time of 25 minutes (range, 17-30 minutes). Most patients who underwent sclerotherapy returned to their normal activities the next day; patients with open surgery returned to normal activities after 3 to 4 days. The results of the present study showed similar operating times, hospital stays, and return to normal activities for patients with unilateral ASS. Patients with bilateral procedures remained in the hospital 8-30 hours and needed 5-9 days to return to normal activities. It should be noted that the definition of normal activities may vary across studies.

Technical failure during ASS is represented by an inability to catheterize a vein of the pampiniform plexus. It has been reported to occur in <1% of cases [11]. Zaupa et al [9] reported 1.14% conversion of ASS to Palomo repair because of technical failure. There were no technical failures in the present study.

No cases of epididymorchitis or contrast media allergy were reported in the present study. The same results were found by El-Shazly [12]. Tauber and Pfeiffer [13] reported epididymitis in 0.25% of their cases; May et al [14] stated that epididymorchitis occurred in 3.8% of their patients.

<table>
<thead>
<tr>
<th>Semen Parameters</th>
<th>Count (10^6/mL)</th>
<th>Motility (%)</th>
<th>Abnormal Forms (%)</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>t</td>
</tr>
<tr>
<td>Preoperative evaluation</td>
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<td></td>
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<tr>
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<td>18.2</td>
<td>6.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Group 2</td>
<td>17.0</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>6-month evaluation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>29.1</td>
<td>14.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Group 2</td>
<td>29.8</td>
<td>12.9</td>
<td></td>
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Sperm Parameters and Hormonal Levels

Results of the present study showed a statistically significant postoperative increase in sperm density, and sperm motility, and a statistically significant postoperative decrease in abnormal forms in both treatment groups. These results were in agreement with other studies using ASS to correct testicular varicocele that found a significant rise in sperm density, motility, and normal morphology following surgery [3, 10,15-17].

Results of the present study showed a statistically significant rise in FSH, LH, and testosterone levels in patients with severe oligospermia who were receiving tamoxifen citrate. These findings are close to the results of Kadioglu et al [7] and Adamopolous et al [18].

Complications

There were few complications in the present study. Scrotal hematoma represented the most common complication, occurring in 5 patients (6.9%) from among the early cases. Tauber and Pfeiffer [13] reported that scrotal hematoma occurred in 2% of their patients; Fette and Mayr [19] did not find this complication. In the present study, persistent scrotal pain occurred in 1 patient; this pain was relieved after 1 month by analgesics. Ficarra et al [3] reported that persistent scrotal pain occurred in 0.5% of their cases. The present study also had no cases of new testicular atrophy secondary to testicular artery injury. These results are identical to those of El-Shazly [12], but testicular atrophy secondary to a lesion of the testicular artery was reported in 0.6% of patients by Tauber and Johnsen [11]. Goll et al [20] reported a rare case of testicular atrophy arising from testicular infarction due to complete occlusion of the venous drainage. May et al [14] reported 1 case of testicular atrophy that required late surgical removal of the testis because of epididymorchitis.

Six months after ASS, 10 patients (14%) in the present study had persistent varicocele. Galfano et al [15] reported persistent reflux in 12.4% of their cases, Ficcarra et al [3] reported a persistence rate of 6%, and Mickevicius et al [1] reported the highest persistence rate of 21.9%.

CONCLUSION

ASS for varicocele in male infertility due to varicocele is a rapid, safe, and effective procedure that significantly improves semen parameters with or without tamoxifen.


