

A COMPARATIVE STUDY TO ASSESS THE EFFECT OF TESTICULAR VEIN LIGATION FOLLOWED BY SIX MONTHS COURSE OF CLOMIPHENE CITRATE AND TESTICULAR VEIN LIGATION ALONE IN PATIENTS PRESENTING WITH INFERTILITY AND VARICOCELE

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ABSTRACT

BACKGROUND

Infertility still remains a medical problem where a totally effective treatment remains distant. Approximately 8-12 % (60-80 million) of couples is infertile (WHO estimates).¹ Idiopathic male factor infertility accounts for 25% of these cases Male fertility is affected by a number of factors including varicocele, testicular failure, endocrine dysfunction, genital tract infection, testicular disturbances, testicular cancer, hormonal disturbances, retrograde ejaculation, prolonged exposure to heat, obesity, older age, smoking, alcohol, heavy metals, pesticides, oxidative stress, genetic factors and different environmental and nutritional factors. Varicocele causes 35% of primary and 75% of secondary male infertility and is the most common surgically correctable disorder of male infertility. Testicular vein ligation (TVL) is recommended in men with clinically evident varicocele and sub-fertile semen. TVL can improve semen quality and prevent testicular growth retardation. Apart from surgical correction, many medical management regimes are under trial. Clomiphene citrate is an orally active nonsteroidal agent related to diethylstilbestrol that has been tried independently, combined with other drugs and along with surgical correction, with varying outcomes. It significantly increases the motility percentage and normal morphology of sperms.

MATERIALS AND METHODS

In this study conducted at Govt. Medical College, Thiruvananthapuram, 45 patients were included during the period March 2016 to March 2017. Patients with male factor infertility, clear abnormalities in semen parameters (according to WHO criteria) and having clinical varicocele of varying grades were included in the study. Cases were randomized into two groups; one group (23 patients) underwent bilateral TVL (sub inguinal approach) alone; and second group (22 patients) b/l TVL plus a course of clomiphene citrate for a period of six months. Semen analysis was done after six months. The change in seminal parameters was compared and analyzed statistically.

RESULTS

In this study, we could observe no significant difference / improvement in seminal parameters by adding clomiphene citrate to TVL compared to TVL alone Observations were statistically not significant as the sample size was not adequate. The pregnancy rate in each arm could not be studied as the follow up was short. Pregnancy rate need not always correlate with seminal parameters. Further studies will be required to authenticate our observation.

CONCLUSION

There is no added advantage in adding clomiphene citrate to testicular vein ligation surgery in male infertility patients with varicocele.

KEYWORDS

Male Infertility, Varicocele, Testicular Vein Ligation, Clomiphene Citrate.

HOW TO CITE THIS ARTICLE: Haris CH, Kumar GS, Soni J, et al. A comparative study to assess the effect of testicular vein ligation followed by six months course of clomiphene citrate and testicular vein ligation alone in patients presenting with infertility and varicocele. J. Evid. Based Med. Healthc. 2017; 4(75), 4404-4407. DOI: 10.18410/jebmh/2017/877

Financial or Other, Competing Interest: None.

Submission 26-08-2017, Peer Review 30-08-2017,

Acceptance 13-09-2017, Published 15-09-2017.

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DOI: 10.18410/jebmh/2017/877



BACKGROUND

As per the WHO, in India, the overall prevalence of primary infertility ranges between 3.9% and 16.8%.² Nearly 50% of infertility is related to the reproductive anomalies or disorders in the male.³ Subnormal sperm count in the absence of recognizable testicular damage is frequently encountered in many of these patients. A common cause of male infertility is varicocele which is found to affect 4.4-22% of general population.⁴

Varicocele is an abnormal dilatation and tortuosity of veins that drain the pampiniform plexus of the testes. It was recognized as a medical problem by Ambrose Pare in 16th century. Barfield in 19th century first identified the relation between varicocele and infertility.

Varicoceles are seen predominantly on left side due to direct insertion into left renal vein, but it is now known that in patients with bilateral varicoceles the right testicular vein inserts aberrantly into the right renal vein. There is contralateral communication between the two venous systems, which is why varicocele of one side can affect the opposite testis too. A 2004 study by Gat et al suggested that up to 80% of men with a left clinical varicocele had bilateral varicoceles revealed by noninvasive radiologic testing.⁵ The entire venous system of the ipsilateral scrotum is dilated in the presence of a varicocele. Studies have shown that varicocele exerts a deleterious effect upon sperm motility, concentration, morphology, and testicular volume. Varicocele interferes with the counter current heat exchange system within the testes, elevating the intra testicular temperature. Under conditions of heat and hypoxic stress, the principal cells in the epididymis, the endothelial cells in the dilated pampiniform plexus and the testicular cells release reactive oxygen species in excess. This will lead to apoptosis, DNA fragmentation, and oxidative stress due to raised levels of reactive oxygen species and intracellular metabolic changes.⁶ TVL results in significant improvement in semen analysis in 60% to 80% of men. Reported pregnancy rates after testicular vein ligation vary from 20% to 60%.⁷

Surgery for Varicocele- Procedure.

Microsurgical ligation of testicular veins.

We approach the cord via the inguinal approach, under local anesthesia. A 2.5 cm. incision is made over the inguinal canal just lateral to the external inguinal ring. The incision is deepened through the superficial fascia and the external oblique is opened in the line of its fibers. The spermatic cord is identified and with careful dissection freed from the surrounding tissue, including the ilio-inguinal nerve. The cord is held with a Babcock forceps, and a right angled artery forceps is passed beneath to deliver it through the wound.

We use a Zeiss 4x 500 loupe for spermatic cord dissection. About 1 ml. papaverine is injected into the cord to dilate testicular/vasal artery and to aid its visualization. Using microsurgical instruments, the external and internal spermatic fascia are opened, and the vas deferens located. The vas is carefully dissected away; accompanying veins are ligated and divided only if they are more than 3 mm. size. As far as possible, at least one accompanying vein of the vas is preserved to prevent venous congestion.

Testicular veins reduce in the number of branches as it ascends. The veins lie in a mesh of lymphatics and nerves and the testicular artery lies within this mesh usually closely adherent to one of the larger veins. The artery is located by noting its pulsations and carefully dissected away from the accompanying vein. The vein is double ligated with 4-0 silk

and divided. All other veins are carefully separated from the mesh of lymphatics and divided.

The wound is closed in layers. The spermatic cord is closed with interrupted 3-0 Vicryl sutures and placed within the inguinal canal. The external oblique is closed with continuous 3-0 Vicryl suture. Superficial fascia and skin are sutured with 3-0 Monocryl sutures.

Medical Treatment for Varicocele

Many studies have reported medical treatment for infertile men with varicocele with varying results. Antiestrogens like clomiphene or tamoxifen, aromatase inhibitors like anastrozole, letrozole, and testolactone, selenium, zinc, L-carnitine, lycopenes etc. are some of the drugs tried.⁸ The rationale behind this might be that in infertile or subfertile men with clinical or subclinical varicocele, the sole reason for fertility issue may not be varicocele alone. The fact that surgical correction of varicocele fails to give 100% result substantiates the above finding. Many trials with clomiphene citrate alone show improvement in semen parameters.⁹ There are not many studies reported regarding the effectiveness of TVL followed by a course of clomiphene. The aim of this study is to look for any added advantage for post - TVL clomiphene treatment.

Clomiphene citrate is a selective estrogen receptor modulator that has been used employed in the treatment of unexplained infertility, oligo and asthenospermia, hypogonadism, and nonobstructive azoospermia. Clomiphene citrate can alter the function of the hypothalamic-pituitary-gonadal axis by blocking the negative feedback of estrogen on both the hypothalamus and pituitary, thereby increasing gonadotropin production, including LH, subsequently increasing testosterone production.¹⁰ The increase in endogenous testosterone, within the testes, stimulates spermatogenesis. Most adverse events associated with Clomiphene citrate are mild and dose related which include headache, dizziness, blurred vision, nausea, weight gain, vomiting, gynecomastia, and hypertension.

In the present prospective clinical trial, it was verified whether there is any advantage for combined TVL with clomiphene citrate over TVL alone, for treatment of men with primary infertility and evaluated in terms of improvements in seminal parameters in subjects with varicocele.

MATERIALS AND METHODS

This study was conducted at Department of Urology, Government Medical College Trivandrum, during the period March 2016 to March 2017. A total of 45 patients were included in this study.

Inclusion Criteria

1. Had varicocele diagnosed both clinically and through Doppler ultrasound
2. Had no other apparent historical or clinical factor affecting fertility lasting for a period more than 1 year
3. Had normal hormonal profile,

4. Had normal testicular size.
5. Had seminal values varying from oligoasthenospermia to normospermia
6. No pyospermia
7. Not on any empirical treatment with drugs in last three months.

Exclusion Criteria

1. Patients with urethral stricture,
2. Patients with obstructive azoospermia,
3. Patients with erectile dysfunction

After proper explanation and getting consent, patients were randomized into two groups. Every alternative case was included in either arm.

Group 1 (23 Patients)- Testicular vein ligation alone (by micro surgical technique).

Group 2 (22 Patients)- Testicular vein ligation followed by six month course of clomiphene citrate 25 mg daily.

Seminal parameter values evaluated were sperm density (million/mL), percent of motile sperm, and percent of sperm with normal morphology. Data was tabulated for each of the patient and then analyzed with statistical tests.

RESULTS

Mean ± SD age of the entire series was 32.7 ± 6.1 years. Mean ± SD age of group I was 32.2 ± 5.5 years and that of group II was 33.1 ± 6.7 years. The difference between mean ages of groups was not statistically important (p=0.680).

- However, in both groups only sperm density and percent of motile sperm values in the sixth month of varicocelectomy were statistically higher than those in the beginning of the study (group 1, P = 0.02 and P = 0.0001, group 2, P = 0.03 and P = 0.0001 respectively). In both groups, not much changes noted in morphology of sperms.

The change in all three parameters following treatment was almost same in both groups.

- However, no statistically important difference was found between groups I and II with regard to changes in seminal parameters observed following varicocelectomy and clomiphene treatment (Table 1).
- Clomiphene citrate was well tolerated and no serious side effects were reported.
- Clomiphene was given empirically without considering the serum testosterone value with the assumption that it will increase the intra testicular testosterone level.

Seminal Parameter	TVL Alone	TVL + Clomiphene	P value
1. Sperm Count			
Baseline	6.5 ± 4.1	8.5 ± 6.1	0.2311
Sixth month	17 ± 14.2	17.2 ± 15.2	0.9659
Change	10.5 ± 12.1	8.7 ± 10.1	0.6125
2. Sperm Motility			
Baseline	10.5 ± 8.1	10.2 ± 7.1	0.9015
Sixth month	32 ± 18.1	30 ± 18.2	0.7294
Change	21.5 ± 16.1	19.8 ± 15.1	0.7324
3. Sperm Morphology			
Baseline	69.1 ± 16.4	64.1 ± 15.4	0.3265
Sixth month	70.4 ± 12.4	70.4 ± 12.4	1.0000
Change	1.3 ± 18.6	6.3 ± 13.0	0.3333

Table 1. Changes in Seminal Parameters Observed following TVL Alone Compared to TVL Plus Clomiphene Treatment

There were some limitations-

1. Small study sample size.
2. Short duration of follow up.
3. Emphasis on seminal parameters rather on pregnancy outcomes.
4. Analysis not as per age (since semen quality decreases with age).
5. Grade of varicocele not taken into account during statistical analysis.
6. Blinding not done.
7. No proper randomization.

From this study, we could observe that there is no significant difference in effect of improvement in seminal parameters by adding clomiphene citrate to testicular vein ligation. Observations were statistically not significant as the sample size was not adequate. Long term effects of postoperative clomiphene citrate also not addressed here. The pregnancy rate in each arm could not be studied as the

follow up was short. Pregnancy rate need not always correlate with seminal parameters.

DISCUSSION

Testicular vein ligation is the major operative procedure for male infertility. About 60% of the operated men will show good improvement in semen parameters. Reports suggest that 32–41% of infertile men achieved pregnancy within one year after treatment.

Predicting Success of Surgery- Pre-operative semen parameters were important predictors of success of TVL. Significantly higher pregnancy rates (61% vs 8%) were observed in couples in whom the initial sperm concentration was greater than 5 million/mL.

Varicocele may cause deleterious alterations in early spermatid head differentiation during spermiogenesis and that varicocele patients with a high incidence of sperm acrosome and nucleus malformations are appropriate

candidates for varicocele correction.¹¹ Varicocele repair improves the morphologic abnormalities of the sperm and there is good correlation among sperm morphology, fertility index, and results from artificial reproductive techniques.

The results of varicocelectomy are also related to size of the varicocele. Large varicoceles are associated with greater preoperative impairment in semen quality than small varicoceles. Repair of large varicocele results in a significantly greater improvement in semen quality than repair of small varicocele.¹²

Clomiphene citrate is a drug commonly used successfully to treat female infertility, male subfertility and hypoandrogenic men in the reproductive age group. Several studies have demonstrated improved levels of testosterone after three months of therapy. In our small group of patients, the drug was well tolerated and no adverse effects were reported during the six months in our study. We had given clomiphene citrate empirically without considering the testosterone value, but not independently.

Genetic polymorphisms of cytochrome P450 D26 may be a biologic reason for variable responses of clomiphene. Cytochrome P450 D26 is an enzyme that metabolizes clomiphene citrate to its active forms (E)-4-hydroxyclophene and (E)-4-hydroxy-*N*-desethylclomiphene. Individuals with specific non-functional alleles for P450 D26 have 8- to 12-fold lower concentrations of these active metabolites.

Clomiphene citrate is a racemic mixture of two isomers: enclomiphene and zuclophene. The anti-oestrogen effect of clomiphene citrate is derived from enclomiphene, while zuclophene acts as an oestrogen agonist.¹³ Zuclophene stimulates oestrogen receptors and paradoxically may produce a decrease in testosterone levels. Hence this racemic mixture form of clomiphene citrate is not approved by the FDA.

CONCLUSION

Clomiphene citrate is a well-tolerated drug with antiestrogenic effect which may improve the semen parameters in infertile men. But in our study, when given to patients with varicocele who underwent TVL surgery, clomiphene citrate failed to demonstrate unequivocally any added advantage over varicocelectomy alone. Short duration of follow up, small dose of clomiphene, small sample size and non-consideration androgen levels for patients selected for the trial were shortcomings in the study. More studies need to be performed to investigate whether any additional treatment is needed in varicocele that are more non-invasive than surgery or more effective than surgery; and

regarding the duration of post testicular vein ligation dose of clomiphene or similar agents.

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