ORIGINAL ARTICLE

Minimally Invasive Intramedullary Fixation of Middle third clavicular Fractures Through the Medial Entry by Titanium Elastic Nailing System (TENS)

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Abstract

Background: ***Non-obstructive azoospermia (NOA) is a major clinical challenge, with spontaneous sperm recovery being rare and fertility treatment options remaining limited.***

Aim of the study: ***This study aims to explore the effectiveness of letrozole in improving sperm retrieval in NOA patients who have previously undergone unsuccessful testicular sperm extraction (TESE).***

Methodology: ***Thirty azoospermic patients with a history of previously failed TESE received 2.5 mg of letrozole daily for three months, followed by hormonal evaluation and semen analysis. Those who remained azoospermic underwent TESE.***

Results: ***Showed a significant increase in FSH, LH, and total testosterone (tT) levels, with a reduction in estradiol (E2) and an improved T/E2 ratio. The sperm retrieval rate (SRR) was 13.3%.***

Conclusion: ***The study suggests that letrozole could be considered for idiopathic NOA patients after failed TESE, potentially reducing the need for invasive surgical sperm retrieval.***

Keywords: Infertility; Letrozole; Aromatase inhibitors; Non-obstructive Azoospermia; TESE

1. Introduction

Non-obstructive azoospermia (NOA) is a severe form of male infertility, affecting 10-15% of infertile men .[1] The primary method for obtaining sperm in NOA patients is surgical retrieval, particularly microdissection testicular sperm extraction (TESE) .[2]

When TESE fails, alternative approaches such as hormonal therapies, including aromatase inhibitors, may be considered .[3] Letrozole; a potent aromatase inhibitor originally used in breast cancer treatment, has been explored for male infertility, particularly in cases of high estradiol (E2) or a low testosterone-to-estradiol (T/E2) ratio by inhibiting the aromatase enzyme, It prevents the conversion of testosterone to estrogen, thereby increasing intratesticular testosterone (ITT), which is crucial for sperm production .[4]

Letrozole has been used in other studies focusing on spermatogenesis and NOA, showing significant results in oligozoospermic patients, with variable outcomes in studies involving NOA patients .[5-6]

No interventional studies have specifically assessed the impact of letrozole on sperm retrieval rates (SRR) in patients with prior failed TESE.

This study aims to explore the effectiveness of letrozole in improving sperm retrieval in NOA patients who have previously undergone unsuccessful TESE.

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2. Patients and methods

A prospective interventional study was conducted on 30 azoospermic males with a documented history of unsuccessful previous TESE. These males were recruited from the Andrology outpatient clinic at the ART unit of the International Islamic Center for Population Studies and Research between December 2022 and May 2023. with exclusion criteria include: evidence of hypogonadotrophic hypogonadism, testicular atrophy, history of exposure to testicular toxins or cryptorchidism or mumps orchitis and any evidence of chromosomal abnormality. All participants provided informed consent before enrollment.

Each patient underwent a thorough medical history assessment and clinical examination, with a focus on signs of hypogonadism, testicular size, and body mass index (BMI) calculation. Baseline laboratory investigations included serum levels of FSH, LH, total testosterone, estradiol (E2), prolactin, and T/E2 ratio.

Patients received 2.5 mg of letrozole daily for three months, with follow-up visits every four weeks to monitor drug tolerance and complications. After three months, BMI measurements, hormonal profiling, and semen analysis were repeated. Patients who remained azoospermic subsequently underwent conventional TESE in an attempt to retrieve sperm.

3. Results

Selected patients age ranges from 20-44 years old. Data about BMI and hormonal profile of the studied patients shows a statistically significant (P= 0.037) decreased BMI after treatment, significantly increased serum FSH ($p < 0.001$) and LH levels ($p < 0.001$). Letrozole treatment significantly increased baseline tT levels ($p < 0.001$) as well as significant decreased E2 levels ($p < 0.001$). The T/E2 ratio was also increased significantly ($p < 0.001$).

Data shows successful sperm retrieval (SR) in 4 patients (statistically significant, p = 0.038) with SRR of 13.3% comparing to 0% before letrozole treatment.

Complications were developed in most of patients (86.7%) after letrozole treatment. loss of libido was the most common complaint which developed in 17 patients (65.4%). Other complications include bone aches, headache, fatigue and dry mouth. Despite these complications, all studied patients demonstrated 100% tolerance to letrozole.

Table (1): Description of age in all studied patients.

		All patients (n= 30)
Age	Mean ± SD	31.2 ± 6.04
	Min – max	20 – 44

This table shows:

- As regard age, the mean was (31.2 ± 6.04) years with range of (20 – 44) years in all studied patients.

Table (2): comparison of Sperm retrieval before and after treatment in all studied patients.

Sperm retrieval (semen + TESE)	Before treatment (n= 30)		After treatment (n= 30)		X^2	P-value
Yes	0	0.0%	4	13.3%	4.3	0.038 S
No	30	100.0%	26	86.7%		

X^2: chi-square test. S: P<0.05 is considered significant.

This table shows:

- A statistically significant increased number of patients with sperm retrieval after treatment (4 patients 13.3%) when compared with that before treatment (0 patients 0%).

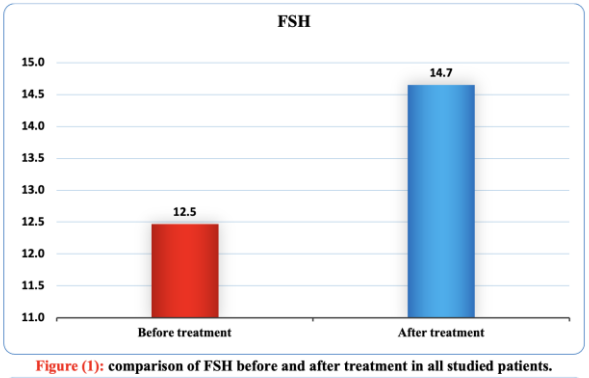

Figure (1): comparison of FSH before and after treatment in all studied patients.

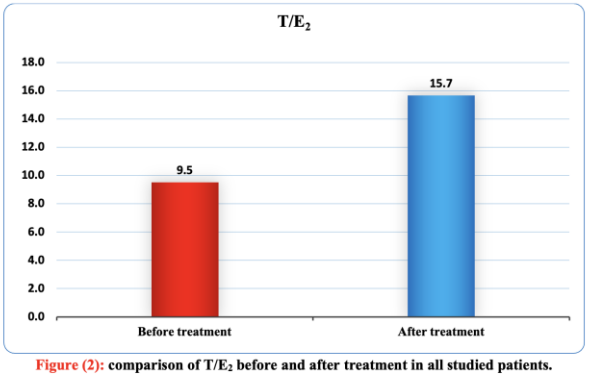

Figure (2): comparison of T/E_2 before and after treatment in all studied patients.

4. Discussion

Spermatogenesis relies on high androgen levels in the testis, while excessive E_2 inhibits FSH and LH through negative feedback, impairing sperm production .[4] A low T/E2 ratio (<10) is linked to male infertility, as men with impaired spermatogenesis often have excess aromatase activity, increasing estrogen conversion .[7]

Letrozole, an aromatase inhibitor, reduces estrogen, enhancing FSH and LH release, promoting spermatogenesis and testosterone production. It primarily increases testicular androgen concentration, as most aromatase activity occurs in the testis rather than peripheral fat .[8]

This study is a prospective interventional study that examined the effects of letrozole on sperm retrieval outcomes in men with NOA who

previously experienced unsuccessful TESE.

Our results showed a significant increase in FSH, LH, and total testosterone (tT) levels among patients treated with letrozole, while E2 levels decreased markedly. These findings align with previous research, which also reported a significant rise in serum tT, FSH, and LH levels in the letrozole group compared to the placebo group.[9]

The sperm retrieval rate (SRR) was 13.3%, which is statistically significant and consistent with the findings of Saylem et al., who reported an SRR of 23.5%. However, their study included a smaller group of NOA patients (n=17) and excluded those with a history of unsuccessful TESE 5. In contrast, a study by Cavallini et al. reported a higher success rate, finding spermatozoa in the ejaculate of all NOA patients treated with letrozole .[10]

On the other hand, a study by Zhao-Peng's team retrospectively analyzed 184 NOA patients and found no spermatozoa in semen or improvement in testicular pathology after treatment. Their regimen involved 2.5 mg of letrozole daily for 28 days, followed by a 2–3 day break, with treatment lasting 3 to 12 months. The intermittent dosing schedule may have led to fluctuations in blood drug concentrations, potentially reducing treatment effectiveness .[11]

Complications occurred in most patients (86.7%), but they were not life-threatening and resolved after treatment discontinuation. The most common issue was loss of libido (65.4%), likely due to estradiol's role in regulating libido in men with low testosterone. While estradiol enhances libido in such individuals, it tends to decrease libido in men with normal testosterone levels .[12]

4. Conclusion

This study suggests that clinicians may consider a trial of letrozole therapy for idiopathic NOA patients who remain azoospermic after initial TESE procedures, regardless of their BMI or T/E_2 ratios.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

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