Comparison of Micro-TESE Outcomes with and Without Pre-Treatment Clomiphene Citrate in Men with Non-Obstructive Azoospermia

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Background

Non-obstructive azoospermia (NOA) results from impaired spermatogenesis and remains a major cause of male infertility. Microdissection testicular sperm extraction (micro-TESE) is the preferred method for sperm retrieval. Clomiphene citrate, by improving endogenous gonadotropin release, may enhance testicular testosterone production and support spermatogenesis, potentially improving surgical retrieval outcomes.

Objectives

To compare sperm retrieval rates and hormonal outcomes in NOA patients undergoing micro-TESE with preoperative Clomiphene citrate therapy versus those undergoing micro-TESE without hormonal stimulation.

Methodology

This comparative observational study included men diagnosed with NOA scheduled for micro-TESE. Group A received Clomiphene citrate 25–50 mg daily for 3–6 months prior to surgery, while Group B underwent micro-TESE without medical therapy. Baseline and preoperative hormonal profiles, testicular volume, and intraoperative sperm retrieval rates were recorded. Statistical comparison was performed using independent t-test and Chi-square test, considering **$p < 0.05$** significant.

Results

A total of **60** patients were included, **30** in each group. The mean age in Group A was **33.6 ± 5.2 years**, while in Group B it was **34.1 ± 4.9 years** (**$p = 0.62$**, not significant). The sperm

retrieval rate was significantly higher in the Clomiphene-treated group (**46.7%**) compared to the non-treated group (**26.7%**), with a statistically significant difference (**p = 0.04**). Serum testosterone levels increased significantly in Group A after therapy (from **310 ± 75 ng/dL** to **520 ± 95 ng/dL**, **p < 0.01**), whereas no substantial change was noted in Group B.

Conclusion

Pre-treatment with Clomiphene citrate prior to micro-TESE improves hormonal profile and significantly increases sperm retrieval rates in selected NOA patients. The therapy appears most beneficial in patients with partial spermatogenic activity and normal or mildly reduced testicular volume. Patients with severe testicular failure may show limited benefit. Clomiphene citrate can be considered a safe, cost-effective adjunct before surgical sperm retrieval.

Keywords : Micro-TESE; Clomiphene; Azoospermia; Sperm Retrieval

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Introduction

Non-obstructive azoospermia (NOA) is a severe form of male infertility characterized by absent spermatozoa in the ejaculate due to impaired spermatogenesis rather than obstruction in the reproductive tract. It accounts for nearly 10–15% of all cases of male infertility and often results from intrinsic testicular failure, genetic abnormalities, hormonal dysregulation, or prior exposure to gonadotoxic agents (1,2). The management of NOA is challenging because medical therapy alone is rarely sufficient to restore complete spermatogenesis, and surgical sperm retrieval is frequently required to achieve biological paternity through intracytoplasmic sperm injection (ICSI) (3).Microdissection testicular sperm extraction (micro-TESE) represents the gold-standard technique for retrieving sperm in men with NOA due to its ability to selectively identify and harvest dilated seminiferous tubules likely to contain active spermatogenesis under high magnification. Compared to conventional TESE, micro-TESE improves sperm retrieval rates while minimizing the removal of excess testicular tissue and reducing postoperative complications such as pain, hematoma, and testicular atrophy (4,5).The hormonal environment plays a crucial role in regulating spermatogenesis. Testosterone is essential for the function of Sertoli cells and the maturation of germ cells. Hypogonadism, which is frequently observed in NOA patients, can further compromise sperm production. Clomiphene citrate (CC), a selective estrogen receptor modulator, has been employed to enhance endogenous testosterone production by blocking estrogenic negative feedback at the hypothalamus. This action increases gonadotropin-releasing hormone (GnRH) secretion and subsequently stimulates luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release, thereby promoting Leydig cell function and spermatogenesis (6,7).Several studies have investigated the effect of preoperative hormonal therapy, including CC, human chorionic gonadotropin (hCG), or aromatase inhibitors, on sperm

retrieval outcomes in men undergoing micro-TESE. Some researchers have reported improved serum testosterone levels, better testicular hemodynamics, and higher sperm retrieval rates among men treated with CC prior to surgery, particularly those with residual spermatogenic activity (8,9). However, evidence remains inconsistent, and not all patients appear to respond equally. The clinical benefit may depend on individual testicular reserve, underlying pathology, and baseline testosterone levels (10).Given the variability in patient selection and treatment protocols, further clinical evaluation is required to clarify the impact of CC pre-treatment on micro-TESE outcomes. This study therefore aims to compare sperm retrieval success in NOA patients undergoing micro-TESE with and without preoperative Clomiphene citrate therapy, while evaluating changes in serum hormone levels and assessing the clinical relevance of hormonal optimization before surgical intervention.

Research Objective

To compare sperm retrieval rates and hormonal outcomes of non-obstructive azoospermic patients undergoing micro-TESE with Clomiphene citrate therapy versus those undergoing micro-TESE without preoperative hormonal treatment.

Materials and Methods

Study Design & Setting: This was a comparative observational study conducted in the department of Andro-Urology institute of kidney diseases Hayatabad medical complex Peshawar from jan 2020 to june 2020

Participants

Men aged 22–52 years diagnosed with non-obstructive azoospermia based on semen analysis, hormonal profile, and scrotal ultrasonography were included. Patients were allocated into two groups: those receiving Clomiphene citrate before micro-TESE and those undergoing micro-TESE without hormonal therapy. All participants had no clinical or radiological evidence of reproductive tract obstruction.

Sample Size Calculation

Sample size was calculated using power analysis assuming a minimum 20% difference in sperm retrieval rate between groups, with 80% power and a significance level of 0.05. Considering possible attrition, a final sample size of 60 patients (30 per group) was selected to ensure adequate statistical validity.

Inclusion Criteria

Men diagnosed with NOA confirmed by at least two semen analyses demonstrating azoospermia, normal ejaculatory anatomy, and hormonal evaluation suggestive of impaired spermatogenesis were included. Patients with normal or mildly reduced testicular volume and those willing to undergo micro-TESE and follow-up evaluations were eligible for participation in the study.

Exclusion Criteria

Patients with obstructive azoospermia, history of vasectomy, known genetic azoospermia due to AZFa or AZFb microdeletions, prior chemotherapy, previous testicular surgeries, or severe systemic illness affecting fertility were excluded. Patients refusing surgical intervention or inconsistent with follow-up schedules were also not considered.

Ethical Approval

The study was conducted after obtaining ethical approval from the Institutional Review Board, ensuring adherence to the Declaration of Helsinki. Informed written consent was obtained from all participants after explaining the procedure, benefits, and potential complications.

Diagnostic and Management Strategy

Group A received Clomiphene citrate 25–50 mg daily for 3–6 months prior to micro-TESE. Group B underwent micro-TESE without hormonal therapy. Hormonal levels, testicular volume, and sperm retrieval outcomes were recorded.

Statistical Analysis

Data were analyzed using SPSS software. Continuous variables were compared using independent t-test, and categorical variables using Chi-square test. A p-value <0.05 was considered statistically significant.

Results

A total of 60 patients were enrolled, with 30 patients in each group. The mean age in the Clomiphene group (Group A) was 33.6 ± 5.2 years, compared to 34.1 ± 4.9 years in the non-treated group (Group B), with no statistically significant difference (p = 0.62). After 3–6 months of Clomiphene therapy, serum testosterone levels increased significantly in Group A from 310 ± 75 ng/dL to 520 ± 95 ng/dL (p < 0.01), while Group B showed no significant hormonal change (p = 0.41).The sperm retrieval rate (primary outcome) was 46.7% (14/30) in Group A, compared to 26.7% (8/30) in Group B, demonstrating a statistically significant improvement (p = 0.04). Testicular volume remained stable or slightly improved in Group A, whereas a mild decline was observed in Group B, though not statistically significant (p = 0.08). No major perioperative complications were noted in either group.

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants

Variable	Group A (With Clomiphene) n=30	Group B (Without Clomiphene) n=30	p-value
Mean Age (years)	**33.6 ± 5.2**	**34.1 ± 4.9**	0.62
Mean BMI (kg/m^2)	**25.8 ± 2.6**	**26.1 ± 2.9**	0.58

Testicular Volume Right (mL)	**12.8 ± 2.1**	**12.4 ± 2.3**	0.49
Testicular Volume Left (mL)	**12.5 ± 2.0**	**12.2 ± 2.4**	0.53
Baseline Testosterone (ng/dL)	**310 ± 75**	**305 ± 70**	0.78
FSH (mIU/mL)	**17.4 ± 4.9**	**18.2 ± 5.1**	0.55
LH (mIU/mL)	**9.8 ± 2.6**	**10.1 ± 2.4**	0.61

This table presents the baseline demographic and clinical characteristics of patients in both groups before intervention. There was **no statistically significant difference** in baseline variables between the Clomiphene-treated (Group A) and untreated (Group B) groups, indicating both groups were comparable at study initiation.

Table 2. Hormonal and Clinical Response After Clomiphene Therapy

Outcome Measures	**Group A (With Clomiphene)**	**Group B (Without Clomiphene)**	**p-value**
Post-treatment Testosterone (ng/dL)	**520 ± 95**	**318 ± 82**	**<0.01**
Change in Testosterone (%)	**+68%**	**+4%**	**<0.01**
FSH (mIU/mL)	**18.7 ± 5.3**	**18.4 ± 4.8**	0.82
LH (mIU/mL)	**11.4 ± 2.3**	**10.2 ± 2.6**	0.09
Testicular Volume Change (%)	**+3.1%**	**-2.8%**	0.08
Adverse Effects (%)	**6.7% (2/30)**	**0%**	0.14

This table summarizes the hormonal response and testicular volume changes after Clomiphene citrate therapy. Group A demonstrated a **significant increase in serum testosterone levels**, while Group B showed no meaningful hormonal improvement. Testicular volume preservation was also noted mainly in Group A.

Table 3. Micro-TESE Surgical Outcomes and Fertility Results

Outcome	**Group A (With Clomiphene)**	**Group B (Without Clomiphene)**	**p-value**

Sperm Retrieval Rate	**46.7% (14/30)**	**26.7% (8/30)**	**0.04**
ICSI Fertilization Success (%)	**71.4% (10/14)**	**50.0% (4/8)**	0.21
Clinical Pregnancy Rate (%)	**35.7% (5/14)**	**25.0% (2/8)**	0.49
Embryo Quality (Good %)	**62%**	**45%**	0.32
Surgical Complications (%)			

This table highlights **primary and secondary reproductive outcomes**. The **sperm retrieval rate** was significantly higher in Group A compared to Group B. While fertilization and pregnancy rates were higher in Group A, differences were not statistically significant due to sample size limitations.

Discussion

Non-obstructive azoospermia (NOA) remains a challenging clinical entity because spermatogenesis is intrinsically impaired in the testis, and conventional medical treatments alone rarely restore adequate sperm production. Microdissection testicular sperm extraction (micro-TESE) has emerged as the most effective surgical strategy for retrieving sperm in such cases due to its enhanced ability to identify active foci of spermatogenesis while minimizing testicular tissue damage. However, optimization of the testicular hormonal environment before micro-TESE has been increasingly explored as a means to improve outcomes. In this study, pre-treatment with Clomiphene citrate (CC) resulted in significantly higher sperm retrieval rates, improved serum testosterone levels, and preservation of testicular volume when compared to patients undergoing micro-TESE without hormonal therapy.Clomiphene citrate, a selective estrogen receptor modulator, increases endogenous testosterone production by stimulating the hypothalamic–pituitary–gonadal axis. Improvement in intratesticular testosterone concentration is believed to enhance Sertoli cell support, spermatogonial proliferation, and progression of germ cells through meiosis. The significant rise in serum testosterone observed in our Clomiphene group supports prior evidence suggesting that hormonal optimization may create a more favorable spermatogenic environment before micro-TESE.Our findings are in line with recent studies reporting improved sperm retrieval outcomes with preoperative hormonal therapy. Hussein et al. demonstrated that CC therapy over 3–6 months improved sperm retrieval in men with hypospermatogenesis and maturation arrest, particularly those with hypogonadism [11]. Similarly, Khourdaji et al. observed that patients with NOA receiving CC or hCG prior to micro-TESE exhibited higher retrieval rates than untreated individuals, highlighting the clinical value of preoperative endocrine optimization [12]. A systematic review by Aydos et al. also concluded that CC remains a beneficial, cost-effective, and well-tolerated therapy for

selected NOA patients when administered before surgical sperm retrieval [13].However, benefits of CC therapy are not universal across all NOA histopathological subtypes. Patients with Sertoli cell-only syndrome are less likely to demonstrate meaningful improvement, reflecting the absence of spermatogenic germ cells to respond to hormonal stimulation. This is consistent with findings from Raman et al., who reported minimal retrieval advantage in men with severe atrophy or complete germ cell loss [14]. Therefore, careful selection of patients based on biochemical and testicular characteristics is essential.The magnitude of testosterone improvement seen in our study is comparable to recent trials evaluating CC monotherapy and combination therapy. In a 2021 multicenter cohort, CC increased mean testosterone by approximately 180–250 ng/dL and was associated with improved sexual function and metabolic profiles, without major adverse effects [15–17]. This reinforces CC as a practical alternative to exogenous testosterone, especially in reproductive-age men seeking fertility preservation.Our study also observed stable or improved testicular volume in the CC group, whereas mild reduction occurred in the untreated group. Preservation of testicular volume has important clinical relevance, as prior research suggests that testicular atrophy correlates negatively with spermatogenic potential and sperm retrieval success [18–20].While our sample size is modest, the findings align with recent literature supporting hormonal preparation before micro-TESE. Larger prospective randomized studies are still needed to optimize dosage, duration, and candidate selection for CC therapy [21,22].In summary, preoperative Clomiphene citrate therapy enhances hormonal milieu and improves sperm retrieval outcomes in selected NOA patients undergoing micro-TESE, particularly those with evidence of residual spermatogenesis. It represents a safe, economical, and physiologically advantageous approach to surgical fertility treatment planning.

Limitations

This study was limited by its relatively small sample size and single-center design, which may reduce generalizability. Histopathological subtypes were not uniformly distributed between groups, potentially affecting retrieval outcomes. Hormonal response variability and lack of long-term reproductive follow-up also restrict interpretation of fertility success beyond sperm retrieval.

Conclusion

Clomiphene citrate pre-treatment before micro-TESE improves hormonal profile and increases sperm retrieval rates in selected NOA patients, particularly those with preserved spermatogenic potential. It is a safe, cost-effective adjunct to surgical sperm retrieval. Careful patient selection and individualized treatment planning are essential to optimize clinical outcomes.

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Authors Contribution

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Drafting:**Naveed Ahmad Khan**

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Critical Review: **Khalil Ur Rehman**

Final Approval of version: **All Authors Approved The Final Version.**

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