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A PROSPECTIVE COMPARATIVE STUDY TO ANALYSE THE EFFECT OF A SINGLE DOSE OF ORAL SILDENAFIL CITRATE (50MG) ON SPERM CONCENTRATION, VOLUME AND MOTILITY

Obstetrics & Gynaecology

Dr. Sonam Simpatwar	M.D., D.N.B., D.G.O., Clinical Assistant, Diploma in Reproductive Medicine & IVF, Kiel, Germany
Dr. Priyanka Vora	D.G.O., D.F.P., FCPS, BIMIE, MICOG, FCCS-OBS Consultant, Masters in Reproductive Medicine, (UK), Diploma in Reproductive Medicine & IVF, Kiel, Germany
Ms. Mansi More	B. VOC. MLT., Embryologist
Dr. Rana A. Choudhary	Consultant, Masters in Reproductive Medicine, Kiel, Germany, Diploma in Reproductive Medicine & IVF, (UK)
Dr Manju Ganla	M.R.C.O.G., D.N.B, Associate Consultant
Dr. Kedar Ganla	M.D., D.N.B., F.C.P.S., D.G.O., D.F.P., FICOG, Director and consultant, Ankoor Fertility Clinic, Mumbai

ABSTRACT

Background: Sildenafil Citrate, a widely recognized treatment for erectile dysfunction, has shown potential effects on various sperm parameters. This prospective comparative study aims to analyse the impact of a single oral dose of Sildenafil Citrate (50mg) on sperm volume and motility. **Methods:** The study enrolled infertile men between the ages of 21-50 years, diagnosed with oligoasthenospermia. Participants received a single oral dose of tablet Sildenafil Citrate (50mg). Semen samples were collected and analysed both before and after the administration of the medication. Average of two samples were used before and after sildenafil administration. Sperm volume and motility were assessed using standard laboratory procedures. **Results:** Following the administration of a single tablet of sildenafil, a notable rise in the concentration of sperm was observed. After tablet intake, both the total progressive motility and rapid progressive motility showed a considerable increase. The volume of semen did not significantly change following the administration of sildenafil. **Conclusion:** To summarize, an oral dose of Sildenafil can enhance sperm motility and concentration in individuals who are oligoasthenozoospermic, and this could serve as a substitute approach in assisted reproductive treatments. It can provide a substitute one-time approach before any planned assisted reproductive technology viz planned relation, IUI and IVF. To validate these findings, large-scale prospective randomized controlled trials are needed.

KEYWORDS

INTRODUCTION

Male infertility is currently a major issue in reproductive medicine. We now understand that anomalies in the male are the sole cause of infertility in approximately 20% of infertile couples and have a substantial role in another 20-40% of couples with reproductive failure.[1] The assessment of semen parameters including volume, concentration, motility, and morphology – is fundamental in diagnosing male infertility. Normal semen volume ranges between 1.3-1. 5 ml per ejaculation as per World Health Organization (2021)[2]. Volumes outside this range may indicate various pathological conditions, such as ejaculatory duct obstruction or hormonal imbalances. Sperm concentration is defined as the number of spermatozoa per millilitre of ejaculate. The WHO (2021) considers a concentration of 16 million sperm/ml as the lower threshold of normal.[2] Conditions like oligozoospermia can be linked to genetic factors, lifestyle influences, or environmental exposures[3]. Sperm motility, categorized into progressive, non-progressive, and immotile, is critical for fertilization. Asthenozoospermia can be caused by lifestyle factors, varicocele, or even idiopathic reasons[4].

Understanding semen parameters is vital for the assessment and management of male infertility. This area of reproductive medicine requires continuous research for better diagnostic and therapeutic approaches. Collaboration between gynaecologists, urologists, and fertility specialists is essential for comprehensive care.

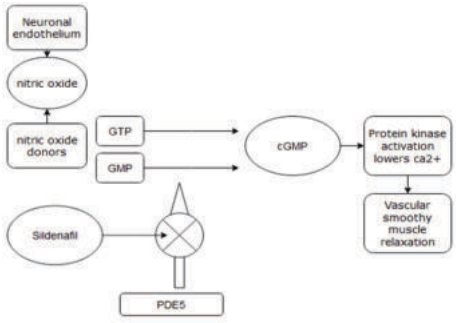
Sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, is primarily recognized for its role in treating erectile dysfunction (ED). However, emerging research suggests its potential implications in male infertility, a subject of increasing interest in gynaecological and reproductive medicine. PDE5 is an enzyme found primarily in the smooth muscle cells of the corpus cavernosum in the penis. Here's a simplified description of the molecular mechanism:

1. Normal Physiological State:
- In the absence of sexual stimulation, the corpus cavernosum does not emit nitric oxide (NO).
- Guanylate cyclase is an enzyme that converts GTP to cGMP, maintaining a low amount of the latter.

2. Initiation of Sexual Stimulation:
- During sexual stimulation, the corpus cavernosum releases NO from nerve terminals and endothelial cells.
- NO activates guanylate cyclase, leading to increased synthesis of cGMP.

3. Effect of Sildenafil:
- Sildenafil inhibits PDE5, preventing the breakdown of cGMP.
- Higher levels of cGMP promote smooth muscle relaxation and improve blood flow to the penis. This increased blood flow causes an erection because the higher pressure traps blood in the erectile tissues.

4. Termination of Action:
- Once sexual stimulation ceases, the release of nitric oxide stops.
- Without continuous stimulation, cGMP levels decrease naturally as PDE5 resumes its activity, and the smooth muscle returns to its normal state.
- The proposed mechanism by which sildenafil could selectively potentiate the physiological response for penile erection provides a theoretical rationale for using this drug in erectile dysfunction.



cGMP: cyclic guanosine monophosphate, GMP: guanosine monophosphate, GTP: guanosine triphosphate, NO: nitric oxide, PDE-5: phosphodiesterase 5

Fig 1. Schematic Representation Of Mechanism Of Action Of Sildenafil[5]

In addition to enhancing prostatic secretory function, this medication promotes leydig cell secretory activity. Additionally, it raises citrate and cholesterol levels in the semen, which may protect the sperm's normal shape against osmotic shock and environmental stress.[6]

Studies have investigated sildenafil's impact on various sperm characteristics and noted improvements in sperm motility post-sildenafil administration, suggesting its utility beyond ED treatment[7].

The clinical application of sildenafil in male infertility requires careful consideration. While there is evidence of improved sperm parameters, the effect on actual fertility outcomes, such as pregnancy rates, remains under-researched. Gynaecologists and reproductive specialists should weigh these findings with the understanding that male infertility is multifactorial, and sildenafil's role may be adjunctive rather than primary[8]. Several studies have been done with other pharmacological agents such as pentoxifylline, avanafil, a phosphodiesterase inhibitor, and clomiphene citrate. This antiestrogenic chemical raises endogenous serum follicle-stimulating hormone, luteinizing hormone, and testosterone levels, all of which have been linked to increased sperm motility. While sildenafil shows promise, there are concerns. The drug's cardiovascular effects necessitate caution, especially in patients with underlying heart conditions[10]. Additionally, its impact on hormone levels and long-term reproductive health needs further exploration. Further longitudinal studies are needed to assess the long-term effects of sildenafil on male fertility, including randomized controlled trials to understand its impact on pregnancy rates and offspring health. This study may provide valuable insights into the potential role of Sildenafil Citrate in improving sperm motility.

METHODOLOGY

Aims

The aim of this study is to assess the effect of Sildenafil Citrate 50mg on volume and sperm motility in infertile men between ages of 21-50 years. Specifically, the study aims to compare the parameters before and after giving sildenafil citrate as a single dose of 50mg.

Objectives

- To evaluate the change in sperm motility and volume before and after administration of single dose of Sildenafil Citrate 50mg.
- To assess the potential adverse effect associated with the use of Sildenafil Citrate in this context.

Inclusion Criteria:

- Infertile men aged 21-50 years diagnosed with oligoasthenospermia (sperm concentration <16 million/ml, total motility <42%, progressive motility <30%, volume <1.4ml)[1].

Exclusion Criteria:

- Known hypersensitivity or contraindication to Sildenafil Citrate.
- History of severe cardiovascular, hepatic or renal disorders.
- Recent history of priapism or retinal disorders.
- Use of nitrate medications or alpha-blockers.
- History of recent fever
- Any malignancy
- Azoospermia (no sperm detected)
- Hypertension
- Addictions

The study was conducted at private fertility clinic over a duration of 6 months. Eligible participants were recruited from the outpatient department. For each participant, two semen samples were collected six weeks apart after valid written consent and ethical clearance. Subsequently two semen samples were collected after single dose of sildenafil citrate two hours prior to collection and assessed by embryologist. Average of two samples were used before and after sildenafil administration. Semen samples were evaluated using standard procedures to determine sperm motility parameters including sperm count, volume, progressive motility and total motile sperm count. The collected data was analysed using appropriate statistical tests to compare the sperm motility parameters before and after Sildenafil therapy.

The average of all parameters of two semen samples was used before and after sildenafil administration. The results were reported as mean plus or minus standard deviation of the mean (SD). The Student's T-test was employed to make statistical comparisons. The statistical study was carried out with Windows' GraphPad Prism version 4.00. A p-value of <0.05 was judged statistically significant.

Variables to be Studied:

- Independent Variable: Administration of a single dose of Sildenafil Citrate 50mg.
- Dependent Variables: Volume, sperm concentration, rapid progressive motility and total progressive motility.
- Covariates: Age, baseline semen parameters, and relevant medical history.
- All participants, and confidentiality of the collected data will be ensured.

OBSERVATIONS & RESULTS:

96 Indian infertile men aged 21 to 50 years participated in the study. The demographic parameters is given in table 1.

Table 1. General Features Of Participants

General features of participants	
Parameter	Value
Patients (number)	96
Age (in years)	34
Adverse side effects (%)	14.58

Table 2. Adverse Effects Of Sildenafil On Study Patients

Adverse effect	No. of patients	Percentage
Flushing	6	6.25
Headache	5	5.20
Dizziness	3	3.12
Abnormal vision	0	0

Following the delivery of sildenafil, fourteen patients (14.58%) reported side effects that may have been attributable to the medication. The side effects that were mentioned the most were flushing headache and dizziness. They were of mild severity and were self-limited and did not require any treatment. No serious side effect of sildenafil was noted.

Table 3. Changes In Semen Parameters Before And After Sildenafil Administration.

Parameters	Normal	Before Sildenafil (X +/- SD)	After Sildenafil (X +/- SD)	P
Volume (Ml)	1.4	1.241 +/-1.162	1.325 +/- 0.998	NS
Concentration(*10 6/Ml)	16	8.32 +/-7.6	12.005 +/- 9.02	S
Motility A (%)	42	1.7 +/- 2.28	3.26 +/- 3.83	S
Motility A + B (%)	30	11.31 +/- 8.2	14.43 +/- 10.61	S

(x +/- SD) Mean +/- standard deviation. Samples were compared using student's t test.
S- Significant
NS- not significant *p<0.050 with statistical significance

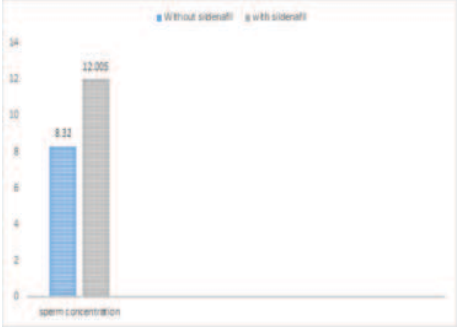


Fig 1. Changes In Sperm Concentration (*10 6/ml)

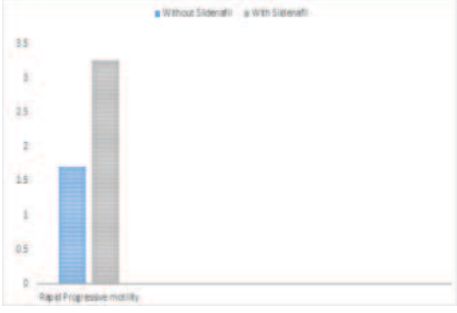


Fig 2. Changes In Rapid Progressive Motility (%)

Fig. 3 Changes In Total Progressive Motility (%)

Fig. 3 Changes In Semen Volume (ml)

Following the administration of a single dose of sildenafil, a notable rise in the concentration of sperm was observed. After taking sildenafil, both total progressive motility and rapid progressive motility showed a considerable increase. The volume of semen did not significantly change following the administration of sildenafil.

DISCUSSIONS

There are various studies conducted regarding the effect of sildenafil on sperm parameters. The present study shows improvement in sperm concentration and motility of the respective parameter after administration of sildenafil.

Dong L's systematic review and meta-analysis of the effect of phosphodiesterase-5 inhibitors in the treatment of male infertility, which included nine studies with 1121 participants, revealed that patients treated with PDE5, as opposed to those who received placebo therapy, had statistically significant improvements in sperm parameters such as semen volume, sperm concentration, and straight progressive motility (%) grade A, sperm motility, and sperm morphology.[11]

David R et al. studied 57 men after sildenafil citrate administration and discovered a significant increase in the quantity of progressively motile sperms between 15 and 135 minutes, as well as their velocity. Furthermore, the samples demonstrated that these effects are consistent in both the 90% and 45% populations of sperm.[12]

Tan P et al. (2017) discovered that oral PDE5 inhibitors increased the fraction of motile spermatozoa, total progressive motility, and rapid progressive motility. It only revealed these changes in patients with oligoasthenospermia[13].

A study conducted by Martínez FAM et al. in 2021 found no statistically significant variations between the samples taken before and after the drug administration. Nonetheless, in patients with asthenozoospermia, a single oral dose of 100 mg of sildenafil increases the proportion of motile sperm retrieved following density gradient centrifugation8.

Mostafa T. et al. found that using sildenafil citrate solution in vitro had a concentration-dependent stimulatory effect on ejaculated sperm motility[14].

According to research by Aversa A. et al., acute sildenafil therapy has a beneficial effect on the return of erections after ejaculation in the presence of a continuous sexual stimulation and does not alter the features of semen in normal persons[7]. Research indicates that sildenafil may influence the seminal fluid composition. The increased local cGMP concentrations could affect the secretory activity of the prostate and seminal vesicles, potentially altering the seminal fluid composition, which is crucial for sperm viability and function[15].

On the other hand, Song SH found in 2021 that all three groups showed a pattern of reduction. Still, the average sperm motility declined over time non-significantly in the control, sildenafil, and tadalafil groups. It also postulated that PDE-5 inhibitors, when taken on-demand, are safe and valuable for the male partner of an infertile couple. Daily usage of PDE-5 inhibitors, however, needs further studies.[18]

A comparative study was done to determine the short-term effects of sildenafil and tadalafil on seminal parameters in young infertile persons. When sildenafil was used to treat sperm progressive motility, there was a considerable increase (median value, 37.0% vs. 28.5%) compared to the baseline; however, tadalafil treatment resulted in a significant decline. These preliminary findings suggest that in young, infertile patients, a single dose of sildenafil and tadalafil, which have opposite effects (stimulatory for the former and inhibitory for the latter), may have an immediate influence on sperm motility.[19]

On the contrary, a study showed that although sildenafil increases the motility of human sperm, it hinders mouse fertilization and embryo cleavage and causes early acrosome reactions in humans. The utilization of this study in assisted reproduction raises serious questions.[20]

CONCLUSION

To summarize, an oral dose of Sildenafil can enhance sperm motility and concentration in individuals who are oligoasthenospermic, and this could serve as an alternative approach in assisted reproductive treatments. Long-term administration may provide superior results, however this is still up for debate. To validate these findings, large-scale prospective randomized controlled trials are needed. This study will provide valuable insights into the potential effects of Sildenafil Citrate on sperm motility, contributing to the understanding of its role in male fertility.

Limitations

The study duration may limit the evaluation of long-term effects. The sample size may impact the generalizability of the findings. Individual variations in response to Sildenafil Citrate may influence the results.

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