Effectiveness and Safety of Silodosin in Treatment of Premature Ejaculation: Placebo Double Blind Control Study

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ABSTRACT

Background: Premature ejaculation (PE) is a common sexual problem, many epidemiological reports have shown that approximately 20–30% of men have complaints of PE.

Objective: The aim of this study was to evaluate the effectiveness of silodosin 4mg in treatment of premature ejaculation.

Patients and methods: This study was conducted on 160 subjects with premature ejaculation. The patients were recruited from Dermatology and Andrology Outpatient Clinics in Al-Azhar University Hospitals .

Results: According to our results, there is highly statistically significant difference (p-value < 0.001) between patient group (559.3 ± 159.9) and control group (248.4 ± 83.7) as regard intravaginal ejaculatory latency time (IVELT) post-treatment (p-value < 0.001). Also, we found highly statistically significant difference (p-value < 0.001) between premature ejaculation profile questionnaire (PEPQ) pre- and post-treatment in patients' group. As silodosin caused improvement of control over ejaculation, satisfaction with sexual intercourse, personal distress related to ejaculation and interpersonal difficulty. At the end of the study only 11 (13.75%) patients reported that they had a decreased semen volume as a side effect of silodosin, which disappeared completely after discontinuation of the drug.

Conclusion: we found that, silodosin 4 mg is a promising idea in treatment of premature ejaculation, as it is effective, cheap, safe and available in Egyptian market. We recommend administration silodosin 4mg 2 hours before sexual intercourse for treatment of premature ejaculation.

Keywords: Silodosin, Premature Ejaculation.

INTRODUCTION

Premature ejaculation is defined as a deviation from the normal length of intravaginal ejaculatory latency time (IVELT), which is the time taken from vaginal penetration to ejaculation. Control over the moment of ejaculation and sexual satisfaction of the man and woman are possible components and are included in the standard classification systems and guidelines of large urological organizations [(1)]. Premature ejaculation was classified as lifelong (primary) or acquired (secondary). Lifelong PE is characterized by its onset from the first sexual experience and remains a problem throughout life. Ejaculation occurs too quickly, either before vaginal penetration or < 1-2 min afterwards. Acquired PE is characterized by its gradual or sudden onset, with ejaculation being normal before onset of the problem. Time to ejaculation is short but not usually as fast as in lifelong PE [(2)].

Waldinger and Schweitzer [(3)] identified a disparity in the prevalence of objectively measured PE i.e., IVELTs of <1 minute in the general population (~2.5%) and the subjective self-reporting of men with PE with IVELT greater than 1 minute in other studies being much higher. As a consequence of this, they attempted to rationalize this difference by adding two new subtypes on top of the pre-existing lifelong and acquired PE: variable PE and subjective PE.

Treatment for PE has included oral medication, such as SSRI, topical agents and behavioral and cognitive therapy. Recently, dapoxetine, a novel fast acting SSRI, was approved for the on-demand treatment of PE in several countries. However, SSRI have possible SSRI-related adverse effects. Although, the safety and efficacy of some treatments for PE have been reported, safer and more effective treatment options are still required [(4)].

The prostate and the seminal vesicles play a vital role in the physiology of ejaculation and the smooth muscle of both of these organs contains alpha-1 receptors. Considered the gold standard for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia, alpha-1 blockers have been reported to cause ejaculatory dysfunction [(5)]. Although this ejaculatory dysfunction was originally thought to be caused by retrograde ejaculation, studies have shown that it is caused by contraction failure of the seminal vesicles, resulting in emission reduction [(6)]. The most common alpha-1 blockers used in the treatment of PE include tamsulosin, silodosin, terazosin and alfuzosin, with all showing a statistically significant increase in IVELT [(7)].

Silodosin showed 85.7% success rate in treatment of PE in a study done by **Akin *et al.*** [(8)]. Other studies had been highlighted that a therapy

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with "on demand" silodosin 3 hours before sexual intercourse determined a lengthening of the IVELT, positive impact on PEP, global impression of change and also improvement of sexual satisfaction [9].

AIM OF THE WORK

The aim of this study was to evaluate the effectiveness of silodosin 4 mg in treatment of premature ejaculation.

PATIENTS AND METHODS

Study population: This study was conducted on 160 subjects with premature ejaculation. The patients were recruited from Dermatology and Andrology Outpatient Clinics in Al-Azhar University Hospitals.

Ethical consideration: An informed consent was taken from all subjects before enrollment in the study **after approval of the Medical Research Ethics Committee.**

Inclusion criteria:

1- Premature Ejaculation (PE) diagnosed by Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria.
2- Stable heterosexual, monogamous relationships more than 3 months.
3- Age of 20 years or older.

Exclusion criteria:

1- Age below 20 years.
2- Patients who received any medication for premature ejaculation during the last 4 weeks.
3- Patients on sex hormones supplementation.
4- Erectile dysfunction.
5- History of physical or psychological disorder (patient or partner).
6- Antidepressant therapy, local anesthetic spray, intracavernosal injection or psychotherapy within 4 weeks.
7- History of alcohol or drug abuse.
8- Hypotensive patients.

Methods:

The 160 subjects were divided into 2 groups:

- **Group 1**: 80 male patients with premature ejaculation (on demand) silodosin.
- **Group 2**: 80 male patients with premature ejaculation on (placebo) as a starch capsule.

All members of the study were subjected to the following:

(A) History taking:

Demographic data such as age, course, duration of the disease, medical history and history of drugs that may interact with silodosin.

(*B*) Procedure:

- **Group 1**: were informed to administrate 4 mg of silodosin 2 hours before intercourse for 6 times/month at least, for 2 months.
- **Group 2**: were informed to administrate a starch capsule as (placebo) before intercourse for 6 times/month at least, for 2 months.

***(C)* Measurements:**

1- All patient in this study were evaluated according to IVELT in seconds by stopwatch by patients themselves pre- and post-treatment to determine the exact effect of the drug in this study either silodosin 4 mg in case group or placebo in control group.
2- All patients in this study were evaluated pre and after treatment according to premature ejaculation profile questionnaire (PEPQ) as mentioned in table **(1)** to determine the exact effect of the drugs in this study either silodosin 4 mg in case group or placebo in control group.

This questionnaire, developed by **Patrick *et al.*** [10] assesses four domains of PE;

- Perceived control over ejaculation.
- Personal distress related to ejaculation.
- Interpersonal difficulty related to ejaculation.
- Satisfaction with sexual intercourse.

Each domain is assessed by using a single question, and the response is rated on a five-point scale from 0–5; higher scores indicate better functioning.

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 15.0. Quantitative data were expressed as mean ± standard deviation (SD), median and IQR, which is the measure of statistical dispersion, being equal to the difference between 75^{th} and 25^{th} percentile. Qualitative data were expressed as frequency and percentage.

The following tests were done:

Independent-samples t-test of significance: was used when comparing between two means.

Chi-square test: was used when comparing between non-parametric data.

Probability (P-value)

- P-value < 0.05 was considered significant.
- P-value < 0.001 was considered as highly significant.
- P-value > 0.05 was considered insignificant.

RESULTS

Age of the patients:

Table (1): Comparison between patients and control groups as regard age

Variables \ Groups		Patients (N = 80)	Control (N = 80)	P-value
Age (years)	**Mean ± SD**	29.39 ± 7.6	30.91 ± 7.5	0.203 NS
	Median – IQR	28 – 10.5	30 – 12	

NS: p-value > 0.05 is considered non-significant.

There was no statistically significant difference between patients and control groups as regard age as shown in table (1).

Type of PE:

Table (2): Comparison between patients and control groups as regard PE type

Variables \ Groups		Patients (N = 80)		Control (N = 80)		P-value
PE type	**Acquired**	71	88.75%	76	95%	0.148 NS
	Life long	9	11.25%	4	5%	

NS: p-value > 0.05 is considered non-significant.

There was no statically significant difference between patient group (71 acquired PE\9 lifelong PE) and control group (76 acquired PE\4 lifelong PE) as shown in table (2).

IVELT:

Table (3): Comparison between patients and control groups as regard IVELT

Variables \ Groups		Patients (N = 80)	Control (N = 80)	P-value
IVELT (pre) (sec)	**Mean ± SD**	225.3 ± 69.1	238.1 ± 60.2	0.231 NS
	Median – IQR	240 – 110	240 – 120	
IVELT (post) (sec)	**Mean ± SD**	559.3 ± 159.9	248.4 ± 83.7	**< 0.001 HS**
	Median – IQR	600 – 120	240 - 120	
p-value		**< 0.001 (HS)**	0.372 (NS)	

S: p-value < 0.05 is considered significant.

NS: p-value > 0.05 is considered non-significant.

HS: p-value < 0.001 is considered highly significant.

This table showed:

- No statistically significant difference **(p-value > 0.05)** between patients and control groups as regard IVELT **(pre-treatment, p-value = 0.231).**
- Highly Statistically significant difference **(p-value < 0.001)** between patient group (559.3 ± 159.9) and control group (248.4 ± 83.7) as regard IVELT **(post-treatment p-value < 0.001).**
- Highly Statistically significant difference **(p-value < 0.001)** between IVELT (pre and post-treatment) in patient group **(p-value < 0.001).**
- No Statistically significant difference **(p-value > 0.05)** between IVELT (pre and post-treatment) in control group **(p-value = 0.372)** as shown in table (3).

Side effects:

As regards post-treatment side effects, we found that 11 patients (13.75%) of all patients group complained of decreased semen volume, but there were no any side effects on control group (0%). There was statistically significant difference (p-value < 0.05) between patients and control groups regarding side effects as shown in table (4).

Table (4): Comparison between patients and control groups as regard side effects

Variables / Groups		Patients (N = 80)		Control (N = 80)		P-value
Side effects	**No side effects**	69	86.25%	80	100%	**0.001 S**
	↓ semen volume	11	13.75%	0	0%	

S: p-value < 0.05 is considered significant.

❖ **Premature ejaculation profile questionnaire (PEPQ):**

Table (5): Comparison between PEPQ pre- and post-treatment in patients' group

PEFQ / Patients group		Pre (N = 80)		Post (N = 80)		P-value
Perceived control over ejaculation	**Very poor**	42	52.5%	4	5%	**< 0.001 HS**
	Poor	38	47.5%	2	2.5%	
	Fair	0	0%	0	0%	
	Good	0	0%	50	62.5%	
	Very good	0	0%	24	30%	
Satisfaction with sexual intercourse	**Very poor**	23	28.8%	4	5%	**< 0.001 HS**
	Poor	22	27.5%	1	1.3%	
	Fair	35	43.8%	20	25%	
	Good	0	0%	36	45%	
	Very good	0	0%	19	23.8%	
Personal distress with sexual intercourse	**Extremely**	26	32.5%	4	5%	**< 0.001 HS**
	Quite a bit	29	36.3%	1	1.3%	
	Moderately	25	31.3%	18	22.5%	
	A little bit	0	0%	57	71.3%	
	Not at all	0	0%	0	0%	
Interpersonal difficulty related to ejaculation	**Extremely**	9	11.3%	3	3.8%	**< 0.001 HS**
	Quite a bit	19	23.8%	2	2.5%	
	Moderately	34	42.5%	5	6.3%	
	A little bit	18	22.5%	42	52.5%	
	Not at all	0	0%	28	35%	

HS: p-value < 0.001 is considered highly significant.

a) Perceived control over ejaculation;

As shown in table (5), we found that 42 patients (52.5**%**) with very poor control and 38 patients (47.5%) with poor control pretreatment but post-treatment results were completely different 4 patients (5%) with very poor control, 2 patients (2.5%) with poor control, 50 patients (62.5%) with good control and 24 patients (30%) with very good control over ejaculation, with highly statistical significant difference pre- and post-treatment concerning control over ejaculation (P-value < 0.001).

b) Satisfaction with sexual intercourse;

As shown in table (5), we found that 23 patients (28.8%) with very poor satisfaction, 22 patients (27.5%) with poor satisfaction and 35 patients (43.8%) with fair level of satisfaction pretreatment but, post-treatment results were completely different 4 patients (5%) with very poor satisfaction, 1 patients (1.3%) with poor satisfaction, 20 patients (25%) with fair level of satisfaction, 36 patients (45%) with good level of satisfaction and 19 patients (23.8%) with very good satisfaction level with highly statistical significant difference pre- and post-treatment regarding satisfaction with sexual intercourse (P-value < 0.001).

c) Personal distress with sexual intercourse;

As shown in table (5), we found that 26 patients (32.5%) with an extreme level of personal distress, 29 patients (36.3%) with a quite level of personal distress and 25 patients (31.3%) with a moderate level of personal distress pretreatment, but post treatment results were completely different 4 patients (5%) with extreme level of personal distress, 1 patients (1.3%) with a quite level of personal distress, 18 patients (22.5%) with a moderate level of personal distress and 57 patients (71.3%) with a little level of personal distress with highly statistical significant difference pre and post treatment as

regard Personal distress with sexual intercourse (P-value < 0.001).

d) Interpersonal difficulty related to ejaculation;

As shown in table (5), we found that 9 patients (11.3%) with extreme level of interpersonal difficulty, 19 patients (23.8%) with a quite level of interpersonal difficulty, 34 patients (42.5%) with moderate level of interpersonal difficulty and 18 patients (22.5%) with a little level of interpersonal difficulty pretreatment, but post-treatment results were completely different 3 patients (3.8%) with extreme level of interpersonal difficulty, 2 patients (2.5%) with a quite level of interpersonal difficulty, 5 patients (6.3%) with moderate level of interpersonal difficulty, 42 patients (52.5%) with a little level of interpersonal difficulty and 28 patients (35%) with no any level of interpersonal difficulty with highly statistical significant difference pre- and post-treatment as regards Interpersonal difficulty related to ejaculation (P-value < 0.001).

DISCUSSION

PE is a common sexual problem. Many epidemiological reports showed that approximately 20–30% of men have complaints of PE. Its prevalence varies widely depending on definitions of PE and the manner in which the prevalence data was gathered. PE is significantly related to high levels of distress, low satisfaction with sexual intercourse and reduced sexual self-confidence and overall quality of life. For female partners, PE is a significant cause of distress**.** There are various versions in its definition, classification and treatment **(4).**

Treatment for PE included oral medication, such as SSRI, topical agents and behavioral and cognitive therapy. SSRI have possible SSRI-related adverse effects. Although, the safety and efficacy of some treatments for PE have been reported, safer and more effective treatment options are still required **(4).**

The prostate and the seminal vesicles play a vital role in the physiology of ejaculation, and the smooth muscle of both of these organs contains alpha-1 receptors. Considered the gold standard for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia, alpha-1 blockers have been reported to cause ejaculatory dysfunction **(5).** Although this ejaculatory dysfunction was originally thought to be caused by retrograde ejaculation, studies have shown that it is caused by contraction failure of the seminal vesicles, resulting in emission reduction **(6).**

This study was conducted on 160 married sexually active male patients (2 times per week at least), complaining of premature ejaculation either lifelong or acquired type, most of them were acquired type, all of them not suffering from erectile dysfunction or any systemic diseases. The patients were divided into 2 equal groups, patients' group (80) patients on silodosin 4 mg 2 hours pre-coitus and control group (80) patients on placebo effect 2 hours pre-coitus.

In this study, IVELT pretreatment of both patients and control groups were almost equal with no statistically significant difference (p-value > 0.05) (pre-treatment, p-value = 0.231). We found that, there was highly statistically significant difference between IVELT pre- and post-treatment with silodosin 4 mg on demand in patients' group (p-value < 0.001), as silodosin prolonged IVELT from 225.3 ± 69.1 sec pretreatment to 559.3 ± 159.9 sec post-treatment because silodosin has a strong suppressive action on seminal emission through its high α1A selectivity. Therefore, suppression or delay of seminal emission might prolong ejaculation latency. These results are similar to a study conducted by **Sato *et al.*** **(9)** as he mentioned that the mean average of IVELT was significantly prolonged (from 3.4 ± 2.2 min to 10.1 ± 4.7 min) post-treatment by silodosin 4 mg on demand when taken 2 h before planed sexual intercourse.

We found that no statistically significant difference in IVELT post-treatment with placebo effect compared to pretreatment in control group.

We found highly statistically significant difference (p-value < 0.001) between PEPQ pre- and post-treatment in patients' group because silodosin 4 mg on demand caused much improvement in patients perceived control over ejaculation from (52.5% with very poor control and 47.5% with poor control) before treatment to became (30% with very good control, 62.5% with good control, 2.5% with poor control and only 5% with very poor control) after treatment.

Also, we found highly statistically significant difference (p-value < 0.001) between satisfaction with sexual intercourse pretreatment from 28.8% with very poor, 27.5% with poor and 43.8% with fair level of satisfaction to become 23.8% with very good, 45% with good, 25% with fair, 1.3% with poor and 5% with very poor level of satisfaction post treatment with silodosin 4 mg on demand.

Also, we found highly statistically significant difference (p-value < 0.001) between level of personal distress with sexual intercourse pretreatment from 32.5% with extreme, 36.3% with quite a bit and 31.3% with moderate level of personal distress to become 71.3% with little a bit, 22.5% with moderate, 1.3% with quite a bit and only 5% with extreme level of personal distress.

Also, we found highly statistically significant difference (p-value < 0.001) between level of interpersonal difficulty related to ejaculation

pretreatment from 11.3% with extreme, 23.8% with quite a bit, 42.5% with moderate and 22.5% with a little bit level of interpersonal difficulty to become 35% with no, 52.5% with little a bite, 6.3% with moderate, 2.5% with quite a bite and only 3.8% with extreme level of interpersonal difficulty. These results are similar to a study reported by **Akin *et al.*** [8] **and Sato *et al.*** [9] as they mentioned that, silodosin 4 mg on demand caused improvement of perceived control over ejaculation, satisfaction with sexual intercourse, personal distress related to ejaculation and interpersonal difficulty in patients of PE.

In this study, the side effect that was reported by participants received silodosin 4 mg on demand in patients' group was only decreased semen volume in 11 patients (13.75%). And no any side effects reported in control group (placebo) effects. This side effect was reported before by **Sato *et al.*** [4] but in larger percentage (37.5% with decreased semen volume). A weak point of silodosin treatment was its reversible reduction of semen volume. A new trial to overcome this adverse effect by reducing the dose of silodosin to 2 mg on demand, which has a magnificent result of restored semen volume with a good satisfaction for sexual intercourse.

CONCLUSION

Finally, we have found that, silodosin 4mg is a promising idea in treatment of premature ejaculation, as it is effective, cheap, safe and available in Egyptian market. We recommend administration silodosin 4 mg 2 houres before sexual intercourse for treatment of premature ejaculation.

RECOMMENDATION

1) Silodosin 4mg is a promising effective drug for treatment of premature ejaculation.
2) We need more studies on silodosin with larger numbers of patients for more evaluation of silodosin efficacy and safety.
3) We suggest new trial with smaller dose than 4 mg to imitate reported adverse effects as much as we can.

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