Al-Azhar International Medical Journal

Volume 4 | Issue 5 Article 27

2023
Section: Urology

Does the Hypothetical Aetiology Affect the Response to Serotonin Reuptake Inhibitors and Local Anesthetics Therapies in Patients with Primary Premature Ejaculation? A Prospective, Placebo-Controlled, Crossover Study

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How to Cite This Article

Shahat, AbdulHakeem Bayomy AbdulNaeem; Mohammed, Hasan Ismail; and Hindawy, Mohammed Abdallah (2023) "Does the Hypothetical Aetiology Affect the Response to Serotonin Reuptake Inhibitors and Local Anesthetics Therapies in Patients with Primary Premature Ejaculation? A Prospective, Placebo-Controlled, Crossover Study," *Al-Azhar International Medical Journal*: Vol. 4: Iss. 5, Article 27.
DOI: https://doi.org/10.58675/2682-339X.1809

ORIGINAL ARTICLE

Does the Hypothetical Aetiology Affect the Response to Serotonin Reuptake Inhibitors and Local Anesthetics Therapies in Patients with Primary Premature Ejaculation? A Prospective, Placebo-controlled, Crossover Study

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Abstract

Introduction: **Premature ejaculation (PE), which has a 30% prevalence rate among the population, is one of the most prevalent male sexual dysfunctions.**

Aim of work: **To evaluate the effectiveness of Selective Serotonin Re-uptake Inhibitors (SSRI) and local anesthetics treatments in patients with primary life-long PE induced by tactile stimulation and those induced by non-tactile stimuli.**

Patients and methods: **Fifty patients who were presented to Al-Hussein and Sayed Galal, Al-Azhar University Hospitals, Cairo, Egypt, were enrolled in a prospective, interventional, cross-over study in Dec 2021, randomized into double-blinded groups. The first group involved 25 patients with premature ejaculation not evoked by tactile stimulation, received local anesthesia cream and placebo SSRI for 8 weeks then 1 week washout, then received local cream as placebo and SSRI for another 8 weeks, While the second group involved 25 patients with premature ejaculation evoked by tactile stimulation, received local cream placebo and SSRI for 8 weeks then one-week washout then received local anesthesia cream and placebo SSRI for 8 weeks.**

Results: **There was statistically significant difference as regard Intra-vaginal Ejaculatory Latency Time (IELT) and sex satisfaction score after both phases ($P = 0.001$), with predominant significant improvement after phase two.**

Conclusion: **In non-tactile stimulation-induced premature ejaculation, selective serotonin reuptake inhibitors (SSRI) are efficient, while local anesthetic creams are effective in tactile stimulation-induced premature ejaculation. More research should be done to compare different SSRI doses and the results of abrupt discontinuation of such treatment.**

Keywords: Premature ejaculation, SSRI, IELT

1. Introduction

In 2014, the International Society of Sexual Medicine (ISSM) defined premature ejaculation (PE) as "ejaculation that always or almost always happens before or within around 1 min of vaginal entry from sexual experience (lifelong PE) or a clinically significant decrease in delay time to 3 min or less" (acquired PE).[1]

With a 30% prevalence rate in the population, it represents one of the most common male sexual dysfunctions. PE is linked to anomalies of the central nervous system, such as reduced serotonin levels and hypersensitivity of the glans penis.[2]

Treatment of PE includes systemic drugs as oral serotonin reuptake inhibitors (SSRIs) (long-acting or on-demand short-acting SSRIs), tramadol,

Accepted 29 November 2022.
Available online 2 January 2024

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https://doi.org/10.58675/2682-339X.1809

phosphodiesterase type-5 inhibitors, and locally acting topical anesthetics like neuromodulation.[3]

Due to a lack of understanding about the condition's etiology and treatment options, it is still undertreated. The currently available pharmaceutical therapies have demonstrated various degrees of efficacy and tolerability.[4]

We hypothesize that the etiology of PE could affect the response to therapy. Serotonin reuptake inhibitors may be beneficial in patients who suffer from PE induced by nontactile stimuli, while local anesthetics may be beneficial in patients provoked by tactile stimuli.

The purpose of this study is to evaluate the effectiveness of SSRI and local anesthetic treatments in patients with primary life-long PE induced by tactile stimulation and those induced by non-tactile stimuli.

2. Patients and method

Fifty patients were presented to Al-Hussein and Sayed Galal, Al-Azhar University Hospitals, Cairo, Egypt., in Dec 2021, were enrolled in Prospective, interventional, cross-over study, their selection criteria included being adults patients, married, sexually active (at least two sexual intercourses/week), with primary PE. Exclusion criteria included erectile dysfunction, loss of libido, mental retardation, alcohol and drug abuse, Diabetes mellitus, neuropathy, ischemic heart disease and other medical comorbidities preclude the use of study medications, previous use of study medications.

Those patients had been randomly assigned to two groups: Group 1 (PE evoked by tactile stimulation, received an everyday dosage of fluoxetine 20 mg tab and applied local gel placebo 5 min before sexual intercourse), while Group 2 (PE evoked by non-tactile stimulation, applied a local Lidocaine gel 5 min before sexual intercourse and an everyday dosage of fluoxetine 20 mg placebo). Both groups continued their treatment for 8 weeks, and after a period of one week, Group 1 applied a local Lidocaine gel 5 min before sexual intercourse and an everyday dosage of fluoxetine 20 mg placebo, while Group 2 received an everyday dosage of fluoxetine 20 mg tab and applied a local lidocaine gel placebo 5 min before sexual intercourse for another 8 weeks, Fig. 1.

Patients and outcome assessors were blinded to the study (using a double-dummy placebo), evaluation was done by complete medical history, sexual history included ejaculatory latency time (IELT), Provocative stimuli, sexual satisfaction (using the Sexual satisfaction scale questionnaire), Table 1.

2.1. Post-treatment evaluation

Patients were encouraged for sexual intercourse, asked not to used condoms, sex-enhancing medication, or topical penile anesthetic creams, gels or sprays and after each treatment cycle, all patients were subjected to complete medical history taking, including 'IELT, sexual satisfaction score, Compliance with the medications, Side effects of the medications'. The primary endpoint was Change in the IELT, while the Secondary endpoints were change in the sexual satisfaction score, side effect of study medications and the discontinuation rate of study medications.

2.2. Statistical analysis

The SPSS program was used to conduct the statistical analysis. The Shapiro–Wilk and One-Sample Kolmogorov–Smirnov tests revealed that the data was normally distributed. As a result, when applicable, data were reported as mean ± SD and/or number (%). The paired *t*-test was used to compare variables within every group before and following therapy. The study groups were compared following therapy using a one-way ANOVA test. Statistical significance has been defined as a *P*-value of ≤ 0.05.

3. Results

Patients that were enrolled had a mean age of 37.9 years (SD = 3.8), ranging from 30 to 46 years. Nonsmoker patients were 30/50 (60%), while smoker patients were 20/50 (40%). The mean number of active sex years was 8.1 years (SD = 2.8), ranging from 2 to 20 years (Table 2).

All of the enrolled 50 patients, completed the study and no one was missing. Mean IELT was 36 s at baseline for non-tactile stimulation induced PE group, while was 35.7 s, for tactile stimulation induced PE group. PE was improved in 12/50 patients (24%) after phase I.

The mean baseline IELT for both groups was 35.8 s (SD = 8.09), improved after phase I and became 46.1 s by paired sample T test (*P Value = 0.001)*. The PE was improved in five patients (20%) of the non-tactile stimulation induced PE group who received lidocaine and placebo, while improved in 7/25 patients (28%) in the tactile stimulation induced PE group who received SSRI + placebo, with no statistically significant differences in IELT between the two groups *(P-Value = 0.9)*.

After Phase II, PE was successfully treated in 38/50 patients (76%), as the outcome after phase II seemed

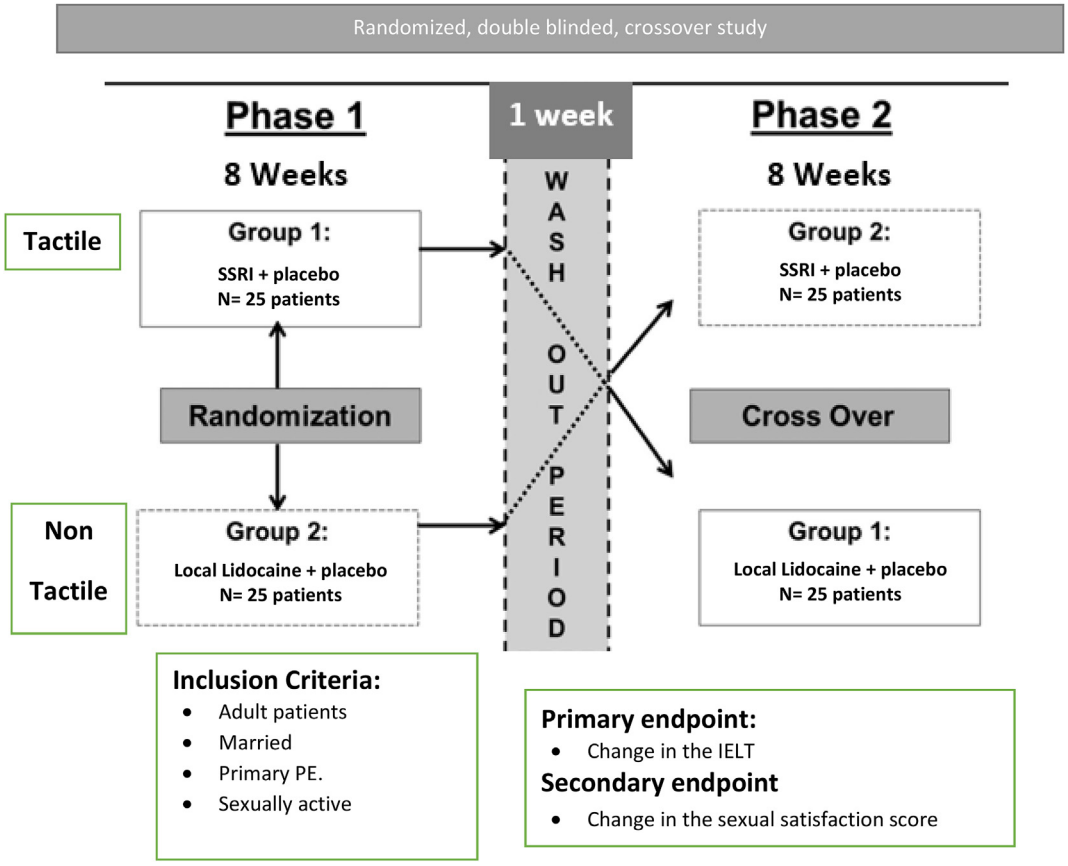

Fig. 1. Study design.

to be higher and more effective in comparison to the outcome after phase I. There were statistically significant differences between the outcomes of phase I and phase II *(P value = 0.002).* 18/25 patients (72%) in the non-tactile stimulation induced PE group who received SSRI and placebo improved, while 20/25 patients (80%) in the tactile stimulation induced PE group who received local lidocaine + placebo improved, with no statistically significant differences between the two groups as regard to IELT *(P Value = 0.3).*

As regard to the sex satisfaction score, the mean sex satisfaction score was 11.8 at baseline for the non-tactile stimulation induced PE group, while it was 10.9 for the tactile stimulation induced PE group. The satisfaction score was improved in all treated patients after phase I *(P Value = 0.001),* with no statistically significant differences between the two groups as regard to satisfaction (*P Value = 0.9).* By using the Anova test, after Phase II, the satisfaction score was also improved in all treated patients after phase I *(P value = 0.02).* With statistically significant differences between the two groups as regard to satisfaction *(P Value = 0.01)* Fig. 2, Table 3.

Table 1. Sexual satisfaction scale questionnaire to assess sex satisfaction among the studied patients (Rosen et al., *2004).*

Sexual satisfaction scale questionnaire
Satisfaction with the sexual relationship as a whole
Satisfaction with the quality of the sex life
Satisfaction with the number of times having
Satisfaction with the way of showing affection during sex
Satisfaction with the way of communication about sex with partner.
Satisfaction with other aspects of the relationship with the partner.
The maximum score for every item is 5, giving the questionnaire a total score of 30.
The level of satisfaction was graded into:
Extremely satisfied (item scores = 5)
Moderately satisfied (item scores = 4)
Neither satisfied nor unsatisfied (item scores = 3)
Moderately unsatisfied (item scores = 2)
Extremely unsatisfied (item scores = 1)

4. Discussion

Premature ejaculation (PE) is among the most common male sexual dysfunctions since it can affect the quality of life directly. Despite wide research interest, this problem is still underestimated due to low rates of therapy seeking brought on by shame or

Table 2. Patient demographic Data between variant groups before and after treatment, using CHI square test to detect significant correlation. NS= Non significant, S = significant, SD: standard deviation.

	Non-Tactile (*N* = 25)	tactile (*N* = 25)	*P* value	HR (95%CI)	Sig
Age					
Below 35 years	2 (8%)	12 (48%)	0.004	0.09 (0.01,0.4)	S
Above 35 years	23 (92%)	13 (52%)			
Mean (SD)	36.2 (3.4)	39.7 (3.5)			
Median (range)	37.5 (30,46)				
Base line IELT					
Mean (SD)	35.7 (8.8)	36 (7.5)			
IELT after phase one					
Mean (SD)	43 (17.26)	49.2 (18.12)	0.9	1 (0.2, 4.2)	NS
IELT after phase two					
Mean (SD)	69.8 (18.2)	61 (14.3)	0.3	1.7 (0.5, 5.6)	NS
Base line Sex satisfaction					
Mean (SD)	10.9 (1.9)	11.8 (2.5)	0.1	0.6 (0.4, 1)	NS
sex satisfaction score after phase one					
Mean (SD)	16.4 (4.6)	16.56 (4.6)	0.9	1 (0.8, 1.2)	NS
sex satisfaction score after phase two					
Mean (SD)	23.2 (3.4)	25.4 (2.7)	0.01	1.3 (1, 1.8)	S
active sex years					
Above 10 years	10 (40%)	5 (20%)	0.1	0.3 (0.1, 1.3)	NS
Less than 10 years	15 (60%)	20 (80%)			
Mean (SD)	8 (2.9)	11.2 (4)			
Median (range)	10 (2,20)				
Smoking					
Yes	11 (44%)	9 (36%)	0.5	0.7 (0.2, 2.2)	NS
No	14 (56%)	16 (64%)			

embarrassment.[5] We can follow up the improvement in PE by using 2 parameters, intravaginal ejaculation latency time (IELT) and sex satisfaction index.[6] About 30% of adult men between the ages of 18 and 59 reported experiencing issues with premature ejaculation, although some studies estimate the rate as high as 75%.[4]

From multiple modalities to treat PE, such as surgical, medical with tramadol, SSRI, local anesthesia … etc., we chose to compare between local anesthesia and SSRI in cross sectional study, to recognize the efficacy of both modalities.

We hypothesize that local treatment is effective for tactile stimulus induced PE, while systemic treatment is effective for nontactile stimulus induced PE, so patients with tactile stimulus induced PE were exposed to systemic treatment + local placebo, then Local treatment + oral placebo, while patients with non-tactile stimulus induced PE were exposed to local treatment + oral placebo then systemic treatment + local placebo.

Particularly when penile hypersensitivity is considered to be the reason, using lidocaine cream for 30–60 days significantly increased the mean IELT. The main adverse impacts of topical anesthesia were delayed ejaculation of more than 30 min, diminished penile sensitivity, irritation of the penis, and reduced vaginal sensitivity.[7]

In phase-2 and phase-3 clinical studies, Dapoxetine has demonstrated effectiveness in managing all aspects of premature ejaculation in people suffering lifelong PE.[8] This included significantly raising IELT, raising the perception of control over ejaculation, and lowering the negative personal effects, such as distress, associated with PE. The findings of the clinical trials have been supported by dapoxetine's subsequent clinical study evidence.[9]

Our results showed that PE was successfully treated in 12/50 patients (24%) after phase I. This explains that either local anesthesia or SSRI are effective in treating PE, since the mean baseline IELT for both groups was 35.8 s (SD = 8.09), improved after phase I and became 46.1 s, and this is considered statistically significant employing a paired sample T test (*P Value = 0.001).*

After phase I, we didn't find significant difference between both modalities as regards IELT, since there was an improvement in five patients (20%) of non-tactile stimulation induced PE group who received lidocaine and placebo, while in 7/25 patients (28%) in tactile stimulation induced PE group who received SSRI + placebo, *(P-Value = 0.2)* by using one-way Anova Test.

We have used fluoxetine 20 mg as SSRI, which resembles Paroxetine. Safarinegad trial have used paroxetine to study the efficacy of increased dose or cumulative effect on PE. They found that increasing the dosage resulted in an additional increase in ejaculation latency. In comparison to patients who started on-demand dosage using 20 mg paroxetine,

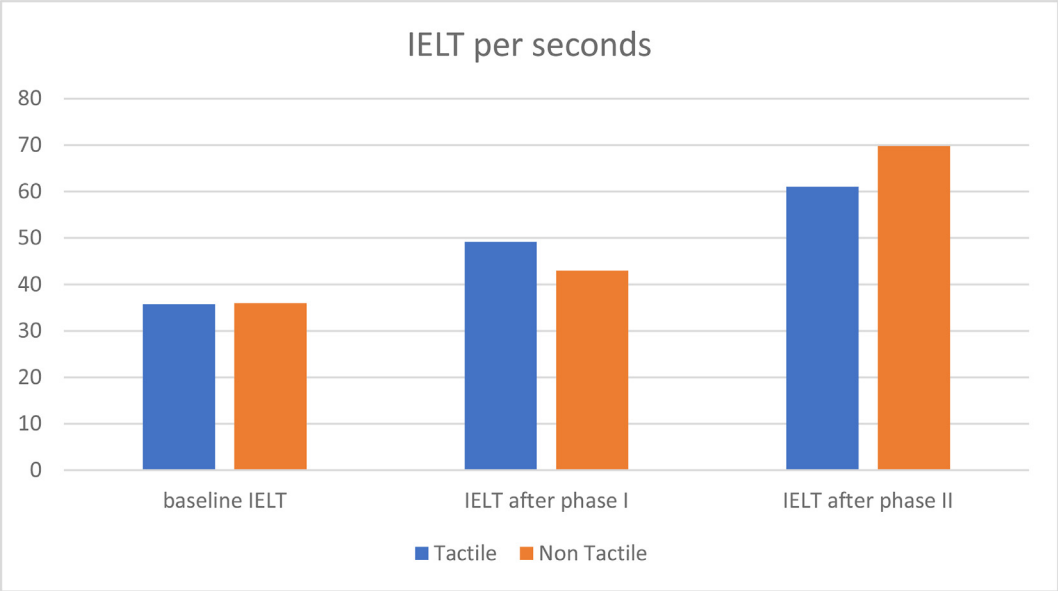

Fig. 2. Success rate of premature ejaculation treatment as regard to IELT per seconds, among studied patients.

the impact of paroxetine on the lengthening of the IELT following 6 weeks of therapy was much superior if patients were managed first using 20 mg paroxetine every day for 2 weeks, accompanied by 4 weeks of on-demand dosage.[10]

Our results emphasized the efficacy of local treatment in tactile stimulus induced PE and systemic treatment in non-tactile stimulus induced PE, since after Phase II, PE was successfully treated in 38/50 patients (76%), *(P -value = 0.002)* compared to (24%) of patients after phase I, using IELT parameter.

Studying the difference between local treatment and SSRI as regard to IELT, we didn't find statistically significant difference between both types of modalities, since improvement was seen in 18/25 patients (72%) of nontactile stimulation induced PE group who received SSRI and placebo, while in 20/25 patients (80%) of tactile stimulation induced PE group who received Local lidocaine + placebo, *(P-Value = 0.06)*.

Table 3. Efficacy of treatment after phase one and phase two, using paired sample test.

Paired Samples test			
After phase one	*P* value	(95%CI)	Sig
IELT			
IELT base line	0.001	(0.08,0.31)	S
IELT after phase one			
Sex satisfaction score			
Base line sex satisfaction score	0.001	(4,6.1)	S
sex satisfaction score after phase one			
After phase Two			
P-value	(95%CI)	Sig	
IELT			
IELT after phase one	0.002	(12.5,26)	S
IELT after phase two			
Sex satisfaction score			
sex satisfaction score after phase one	0.02	(6.4,9.1)	S
sex satisfaction score after phase two			

NS, Non significant; S, significant.

The sex satisfaction score also significantly improved after phase I *(P-Value=0.01)* with no statistically significant differences between the two groups *(P-Value=0.9)* by using the Anova test, and the cumulative effect was significantly noted after phase *II (P -value = 0.02)*, but using local anesthesia showed a better cumulative effect as regards sex satisfaction score than SSRI (*P-Value=0.01)*.

All patients who were enrolled this study completed and continued the treatment schedule, with no significant side effects related to any arm of treatment. Gillman trial showed that the peripheral actions of SSRI such as dapoxetine were minimal.[8]

4.1. Conclusion

In non-tactile stimulation-induced premature ejaculation, selective serotonin re-uptake inhibitors (SSRI) are efficient, while local anesthetic creams are effective in tactile stimulation-induced premature ejaculation. More research should be done to compare different SSRI doses and the results of abrupt discontinuation of such treatment.

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.

Conflicts of interest

The authors declared that there were no conflicts of Interest.

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