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# A randomized single-center study to compare the efficacy and tolerability of tadalafil once daily plus lidocaine anesthetic spray on premature ejaculation

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**Abstract. – OBJECTIVE: The use of topical local anesthetics in the form of creams, gel or spray is the oldest method of retarding ejaculation. However, several studies have suggested that phosphodiesterase type 5 inhibitors (5-PDEiS) show a potential therapeutic use in the treatment of premature ejaculation (PE).**

**The aim of this study was to compare the efficacy and tolerability of tadalafil-only, tadalafil plus local anesthetic spray (lidocaine), and topical lidocaine spray-only before intercourse on the intravaginal ejaculatory latency time (IELT) of patients with lifelong PE.**

**PATIENTS AND METHODS: The study included 78 men in stable heterosexual, monogamous relationships (of ≥3 months) who were diagnosed with lifelong PE. The patients were divided into three groups: G1: 25 patients who received lidocaine spray 10 g/100 ml at 5 min before intercourse; G2: 27 patients who received tadalafil 5 mg once daily; G3: 26 patients who treated with tadalafil once daily plus lidocaine spray before planned sexual activity. The treatments were continued for up to three months in all groups. Moreover, the quality of their sexual attempts was rated on a 5-point scale. Follow-up was made at 1-month and 3-month.**

**RESULTS: Not statistically significant differences emerged between the three groups at baseline. Mean ejaculatory latency time at the 3-month follow-up in G1, G2 and G3 was 3.7±1.3, 3.4±1.5, 5.6±1.7 ($p$<0.001). Mean satisfaction score was at the 3-month follow-up in G1: 2.8±1.4, in G2: 2.9±1.8, and G3: 3.7±1.5 ($p$<0.002). None of the patients withdrew from the study because of these adverse events.**

**CONCLUSIONS: This study demonstrates that tadalafil used daily has a role on treatment in lifelong PE. This action is valid when combined strategically to the synergistic action of lidocaine spray applied before intercourse increasing significantly the mean IELT.**

Key Words
Premature ejaculation, Lidocaine, Local anesthetics, Spray anesthetics, Phosphodiesterase type 5 inhibitors, Tadalafil.

## Introduction

The prevalence rates of premature ejaculation (PE) is 20-30% in the male population according to several epidemiological studies[1]. This sexual condition is poorly defined and linked with negative personal and interpersonal psychological consequences[2]. According to the International Society for Sexual Medicine, lifelong PE is "an ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and the inability to delay ejaculation on all, or nearly all vaginal penetrations, along with negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy"[3]. The use of local anesthetics is one of the oldest treatments for PE[4]. Topical therapy reduces the sensitivity of the glands penis improving intravaginal ejaculatory latency time (IELT). Topical creams may, however, be associated with penile hypoanesthesia, and condom must be used to avoid transvaginal absorption[5]. Anesthetics spray are a topical agent for treating PE and consist of a metered-dose aerosol formulation of lidocaine dissolved in a non-chlorofluorocarbon propellant. The spray covers different regions of the glans penis. It is faster to penetrate intact keratinized skin and as such is not likely to anaesthetise the female partners[6]. Phosphodiesterase type 5 inhibitors (PDE5is) represent the gold standard first-line treatment for erectile dysfunction (ED). PDE5is have shown efficacy in increasing IELT when used in association with the pause-squeeze technique or as monotherapy[7]. However, the therapeutic role of PDE5is is not yet fully determined[4]. In this study, we compared the efficacy and tolerability of tadalafil-only, tadalafil plus local anesthetic spray (lidocaine), and topical lidocaine spray-only before intercourse on the IELT of patients with lifelong PE.



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## Patients and Methods

The study included 78 men in stable heterosexual, monogamous relationships (of ≥3 months) who were diagnosed with lifelong PE according to the ISSM definition. For homogenization of results, patients with ED [defined as a score from 5-item version of the International Index of Erectile Function (IIEF-5) of ≤ 21], significant organic abnormalities or metabolic disorders (such as prostatitis, active urinary tract infection, diabetes mellitus, acute or chronic renal failure, and thyroid disease), use of tricyclic antidepressants, monoamine oxidase inhibitors (SSRIs), use of any treatment for PE, use of anti-arrhythmic drugs, a current history of alcohol or drug abuse, pregnancy of partner, and incomplete clinical data were excluded from our study. The patients were informed about the efficacy and tolerability of the drugs; they were randomized into three groups, using a computer-generated random tabulation list. Group 1 (G1) included 25 patients who received Lidocaine spray 10 g/100 ml (Ecocain spray®, Molteni, Milan, Italy) and instructed to apply three sprays (one dose) to cover different regions of the glans penis (after retracting any foreskin), at 5 min before intercourse. Group 2 (G2) included 27 patients who received tadalafil 5 mg (Cialis®, Eli Lilly Italia SpA, Florence, Italy) once daily. Group 3 (G3) included 26 patients who treated with tadalafil 5 mg once daily plus Lidocaine spray before planned sexual activity. The patients did not use a condom during sexual acts. The treatments were continued for up to three months in all groups. After a least one-month, we rated the quality of their sexual attempts on a 5-point scale: "no change", "poor", "satisfactory", "good", "excellent". Therefore, our primary outcome was IELT and secondary was intercourse satisfaction in patients and drugs side effects. Follow-up was made at 1-month and 3-month after beginning therapy to assess primary and secondary outcomes.

### Statistical Analysis

Demographic and clinic-pathologic variables were analysed using a Fisher's exact test and *chi-square* analysis to determine statistical differences between the three groups. All statistical analyses were conducted on Microsoft Excel 2010 platform version 10.1. A $p < 0.05$ was considered to indicate statistical significance.

## Results

Not statistically significant differences emerged between the three groups at baseline. The mean age of patients in the three groups was respectively: 31.6±9.5 in G1, 32.5±9.7 in G2, and 33.1±9.3 in G3 ($p$ =0.364); in each treatment group, the number of intercourses per week was in G1, G2 and G3: 1.09±0.6, 1.13±0.5 and 1.16±0.7 respectively ($p$ =0.625). The clinical responses are given for each group in Table I. None of the patients experienced a decrease in IELT. Mean ejaculatory latency time at the 3-month follow-up in G1, G2 and G3 was 3.7±1.3, 3.4±1.5, 5.6±1.7 ($p$ <0.001). Mean satisfaction score was at the 3-month follow-up in G1: 2.8±1.4, in G2: 2.9±1.8, and G3: 3.7±1.5 ($p$ <0.002). The difference between G1 and G2 at the 1-month and 3-month was not significant ($p$ =0.48). None of the adverse events reported by patients were rated as "severe" and none of the patients withdrew from the study because of these adverse events (Table II).

## Discussion

PE is known to be a multifactorial sexual dysfunction. Various reasons of premature ejaculation have been supposed: genetics, physiological causes, psychosocial contributions and neurobiological involvements[8]. In 1943, Schapiro[9] recognized two types of PE, type A and B, which later have been renamed to lifelong and acquired PE. In lifelong PE, the man suffers from early ejaculations since puberty and/or adolescence at each coitus or with each female partner. In contrast, in acquired PE the early ejaculation begins later in life after a period of normal ejaculatory performance[6,9]. Sometimes the most efficacious treatments are medication combined with non-medication treatments. An increase in IELT is the main goal of PE therapy. There are different behaviour therapies, such as squeezing and start-stop techniques, but many couples find these uneasy. Pharmacologic therapy includes: selective serotonin reuptake inhibitor (SSRI) therapy (citalopram, sertraline, fluoxetine, dapoxetine or paroxetine), PDE5is (tadalafil, sildenafil or vardenafil), local anesthetics (lidocaine or prilocaine) and other agents (tramadol)[10]. Paroxetine is better than clomipramine, sertraline and fluoxetine in the treatment of PE. A few days after SSRI intake, ejaculation delay may occur, but 2 weeks later, the effect is more obvious because

**Table I.** Patient characteristics and clinical responses in three groups of the study.

| Mean ± SD | Group 1 (No. 25) | Group 2 (No. 27) | Group 3 (No. 26) | *p*-value |
|---|---|---|---|---|
| Age (years) | 31.6±9.5 | 32.5±9.7 | 33.1±9.3 | NS |
| Body Mass Index (kg/m$^2$) | 26.7±4.6 | 25.2±3.9 | 26.5±4.1 | NS |
| Intercourses per weeks, n. | 1.09±0.6 | 1.13±0.5 | 1.16±0.7 | NS |
| IELT baseline (minutes), n. | 1.1±0.3 | 1.08±0.6 | 1.05±0.9 | NS |
| IELT 1-month (minutes), n. | 2.1±0.6 | 2.2±0.9 | 3.3±0.3 | <0.001 |
| IELT 3-month (minutes), n. | 3.7±1.3 | 3.4±1.5 | 5.6±1.7 | <0.001 |
| Satisfaction score, n. | 2.8±1.4 | 2.9±1.8 | 3.7±1.5 | <0.002 |

SD = standard deviation; IELT = intravaginal ejaculatory latency time; NS = not significant.

the receptor desensitization takes time[11]. Fatigue, nausea, vomiting, diarrhea, dry mouth and drowsiness are the common side effects of SSRIs[12]. The use of topical local anesthetics, such as lidocaine or prilocaine, in the form of creams, gel or spray is now well established as a moderately effective method of retarding ejaculation. The theory being that reducing the sensitivity of the glans penis with a desensitizing agent might improve IELT whilst maintaining the sensations associated with orgasm and ejaculation[13]. The problems in using topical anesthetics are significant penile hypoesthesia, vaginal numbness and female anorgasmia. The formulation of the anesthetics spray can be easily removed prior to vaginal penetration, circumventing the need for a condom that most patients find undesirable[14]. Dinsmore and Wyllie[5] have investigated the efficacy of PSD502, a metered-dose aerosol spray containing a eutectic mixture of lidocaine (7.5 mg) and prilocaine (2.5 mg). The study was a 3-month, multicenter, randomized, double-blind, placebo-controlled trial of 300 heterosexual men with lifelong PE. At 12 weeks the authors reported, for PSD502 and placebo, respectively, a 6.3-fold and 1.7-fold increase in mean IELT. Treatment was well tolerated, and no systemic adverse events were showed. Being introduced in 1970, lidocaine spray (STUD 100-7.7 mg) is the oldest topical anesthetic which is still on the market as delaying ejaculation. The recommended dosage is three or more metered sprays. The spray has to be applied to the glans penis 5-10 min before intercourse[15]. The absence of reliable clinical trials data means that the validity of the claims cannot be assessed. In our study the lidocaine-treated patients increased markedly IELT on the first measurement after initiation of treatment during the first month. Medications that inhibit PDE5, sildenafil, vardenafil, and tadalafil are effective treatments for erectile dysfunction (DE). However, several recent studies[16,17] have investigated the therapeutic role of PDE5is in PE. The possible mechanisms underlying the effect of PDE5is on primary PE could be explained by the inhibition of the contractile response of the vas deferens, seminal vesicle, prostate and urethra, inducing a state of peripheral analgesia, augmenting the duration of erection and thus lessening the central sympathetic output[18]. PDE5is may maintain a higher activation of the cyclic guanosine monophosphate pathway and promoting a prolonged nitric oxide effect on seminal emission. The mechanism of action of this treatment is thought to be linked to its capacity to reduce performance anxiety by improving erections[19]. However, many of the actions that are involved remain notional, and the role of these drugs in the treatment of PE is not yet well established[20]. A systematic review[21] of 14 studies on the PDE5is treatment of PE failed to provide any strong evidence to encourage a role of these medications in the treatment of PE with the exception of patients with PE and ED associated. Chen et al[22] showed the efficacy of

**Table I.** Treatment-related side effects reported by patients after starting treatment for premature ejaculation.

| Side Effects | Group 1 (No. 25) | Group 2 (No. 27) | Group 3 (No. 26) |
|---|---|---|---|
| Headache | 0 | 1 | 1 |
| Flushing | 0 | 1 | 0 |
| Nasal congestion | 0 | 2 | 2 |
| Dyspepsia | 0 | 1 | 0 |
| Genital burning sensation | 1 | 0 | 1 |
| Genital erythema | 1 | 0 | 1 |
| Hypoesthesia of genital male | 2 | 0 | 2 |

sildenafil as adjuvant therapy with paroxetine in potent patients with PE. In this study, 97% of patients who received adjuvant sildenafil were satisfied compared with 42% who were satisfied with paroxetine alone and 28% who were satisfied with topical lidocaine. In an other prospective, randomized study, Wang et al[23] assessed efficacy and safety of sildenafil alone in the treatment of 180 potent men with PE. Sildenafil showed significant differences in all the parameters compared with paroxetine and the pause-squeeze technique. Recent small study[24] in patients with lifelong PE compared vardenafil or sertraline in a randomized, prospective, cross-over design and reported an increase in IELT ($p$ <0.001). Other PDE5is such as tadalafil have limited data on their effect in PE. A controlled study[25] involving effect of tadalafil (20 mg) alone and in combination with fluoxetine (90 mg) in lifelong PE men demonstrated that the increase in IELT was greater in patients who received combined treatment with fluoxetine taken once a week and tadalafil taken before sexual acts when compared with placebo, fluoxetine, or tadalafil alone. In a recent study, Moudi et al[11] reported on 100 men affected by PE and without any clear organic disease that tadalafil 10 mg on-demand could increase the mean IELT alone and in association with paroxetine at 3-month of follow-up.

The current work is the first in literature that analyzed the efficacy and tolerability of the PDE5is drugs taken once-daily (tadalafil 5 mg) alone and in combination with local anesthetics (lidocaine spray) for the treatment of PE. However, several limitations need to be acknowledged. A first limitation, we had no data available regarding the ethnic background of the patients. This detail could be of special interest, there are few data on the impact of birth country, religion or culture on the prevalence of PE[26]. An increased susceptibility to premature ejaculation in men from the Indian subcontinent has been reported. Richardson et al[27] observed that Asian men have shorter times to ejaculation than Caucasians, who in turn have shorter times to ejaculation than Afro-Caribbeans, has been interpreted to suggest that some races are more "sexually restrained" than others. However, although we did not expressly document race, the majority of the patients in our study cohort were white and Italian population. Thus, the number of Asian and black patients was very small and surely did not exceed 1% of the entire cohort. Second, in our study, we don't know whether female anorgasmia happened during intercourses because the partners were not evaluated after treatments. Third, this is a single-center study with a limited number of patients in all analyzed groups. The limitation of these data includes the lack of a double-blind, and absence of consistent objective physiological measures or sensitive, validated outcome assessment instruments as study endpoints.

## Conclusions

This study demonstrates an interesting therapeutic signal in which tadalafil used daily has a role on treatment in lifelong PE. This action is valid when combined to the synergistic action of lidocaine spray applied directly to the glans penis before intercourse. The evaluation of how PE affects the unconscious minds of men who are affected by this dysfunction and the implementation of placebo-controlled, randomized, cross-over studies with long follow-up periods should be mandatory for future investigations.

### Conflict of Interest

The Authors declare that there are no conflicts of interest.

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