

# Practical and Effective Treatment of Premature Ejaculation (PE) with a Lidocaine-Prilocaine Spray

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## Abstract

### INTRODUCTION AND OBJECTIVE:

Premature Ejaculation is thought to be the most common sexual dysfunction in men. Many patients exhibit abnormally heightened autonomic reflex pathways involving ejaculation (lower penile vibratory threshold, shorter bulbocavernosus latency time and higher bulbocavernosus evoked potentials). Lowering these sensitivities with local anaesthetics represents a potential therapeutic intervention point. A topical local anaesthetic cream (EMLA®), when applied in a condom to the glans and shaft of the penis for 30 minutes before intercourse, 89 has been shown to be effective but has significant drawbacks. We describe here a new spray formulation of lidocaine plus prilocaine.

### METHODS:

The local anaesthetic is provided as a combination of lidocaine and prilocaine base (7.5 and 2.5mg per actuation) that is dissolved in a non-CFC propellant and dispensed by a metered-dose aerosol device. The spray forms a clear, slightly oily, odourless solution that remains adherent to the application site, but is easily wiped off before penetration. Fourteen heterosexual men with PE were enrolled in this open label pilot study. Using a stopwatch, patients timed their intravaginal ejaculation latency time (IELT) without treatment (baseline). For the next five consecutive encounters they applied the spray to the glans 10 to 30 minutes before intercourse and again timed their IELT. Both partners rated their level of satisfaction with each encounter, using a scale of -1 being worse, 0 the same, +1 better and +2 much better than the baseline encounter. Any local or systemic effects felt by either patient or partner were recorded.

### RESULTS:

The available results for eight patients that have completed the study show an increase in IELT from a mean baseline of 1 min 44 sec (range: 12 sec to 4 min 13 sec) to 13 min 2 sec (range: 1 min 4 sec to 18 min). No patients deteriorated. The average satisfaction score was +1.3 for patients and +1.1 for their partners.

### CONCLUSIONS:

Topical lidocaine plus prilocaine spray applied to the glans penis 15 to 30 minutes before intercourse prolongs ejaculation time and improves sexual satisfaction of both men with PE and their partners. Any glandular numbness did not adversely affect the quality of the orgasm and no other significant adverse effects were reported.

Source of funding: None

## Introduction

Premature ejaculation (PE) is a common condition affecting over 30% of the general male population<sup>1</sup>. Incidence is thought to be higher than that of erectile dysfunction (ED)<sup>2</sup>. In contrast to ED, however, no effective pharmacological therapy has been approved for the treatment of PE.

In men with PE, the autonomic reflex pathways involved in ejaculation are often abnormally heightened. They may therefore exhibit lower penile vibratory threshold, shorter bulbocavernosus latency time and higher bulbocavernosus evoked potentials<sup>3</sup>.

Such exaggerated penile responses provide a therapeutic rationale for lowering sensitivity levels using local anaesthetic (LA). The fact that the neural pathways responsible for orgasm are different to those related to PE suggests that quality of orgasm may be unaffected by such an approach.

Previous research involving application of a cream-based LA to the entire penis showed promising results, but had a number of significant drawbacks relating to the mode of application and time to onset<sup>4</sup>.

## Objective

A new LA formulation has been developed as a spray, designed to be applied only to the glans of the penis prior to intercourse.

The aim of this study was to determine the efficacy of this spray treatment in men with PE, in terms of intravaginal ejaculation latency time (IELT), satisfaction among both patients and their partners and overall safety.

## Mode of Action

Based on the law of mass action, fewer LA molecules penetrate the mucous membrane with cream-based formulations compared to spray formulations, where a mono-filament layer is produced. (Figure 1)

Following application of the LA, un-ionised molecules penetrate the mucous membrane of the glans penis and, subsequently, the axonal membrane. Within the cytoplasm of the axon, due to the change in pH of the environment, the molecules become ionised and bind to the inside of the sodium channels, thereby inactivating them. As the pKa of the LA is close to physiological pH, the majority of molecules in close proximity to the axonal membrane are un-ionised; penetration of the membrane is therefore enhanced and onset of action is reduced.

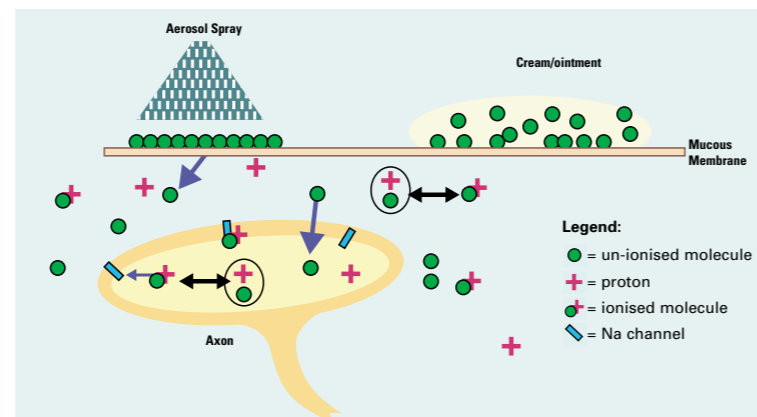


Figure 1: A layer of LA at a pKa close to physiological pH is delivered directly to the glans penis. Absorption is facilitated compared to cream-based formulations.

## Materials and Methods

TEMPE (Topical Eutectic Mixture for Premature Ejaculation) is a novel formulation comprising a pure lidocaine-prilocaine base dissolved in a non-CFC propellant (hydrofluorocarbon 134a). It is dispensed by metered-dose aerosol and delivers 7.5mg lidocaine and 2.5mg prilocaine per actuation.

The spray forms a clear, slightly oily, odourless solution that is deposited in a dose-controlled manner on the glans penis, and can penetrate the glans within 5 minutes.

Fourteen heterosexual men with PE, aged 23 to 70, all of whom were in stable relationships, took part in the trial. Exclusion criteria included the use of condoms as contraception and allergy of either partner to amide LAs.

Participants recorded their baseline, treatment-free IELT using a stopwatch during one sexual encounter. For the next five consecutive encounters at least three doses of the test spray were applied to the glans around 15 minutes before intercourse. The glans was wiped with a warm cloth prior to penetration and subjects again used a stopwatch to time their IELT.

Both patients and partners rated their levels of satisfaction relative to baseline according to a scale (-1 = worse than baseline, 0 = the same, +1 = better and +2 = much better). Local and systemic effects were also recorded.

## Results

A total of eight men had completed the trial at the time of abstract submission. A further three participants have since completed the trial.

The improvement in IELT following treatment is expressed in the graph below (Figure 2). For the completed patients, the average baseline IELT increased from 1:24 minutes (SD = 1.07) to 11:21 minutes (SD = 10.43), representing at least an eight-fold increase over baseline (range, 1.4–18). Deterioration in IELT was not observed in any patient.

Analysable data from six patients showed that the response on repeat administration of TEMPE was durable with little evidence of tachyphylaxis or tolerance to treatment (Figure 3).

The average satisfaction scores were +1 for patients (range, 0 to 2) and +1 (range, -0.5 to 2) for their partners (Figure 4).

No serious adverse events were reported. One man experienced a transient burning sensation just after the first application and five reported episodes of difficulty maintaining an erection while waiting for the drug to take effect. In addition, one patient did not ejaculate on four of the five encounters (while reporting an average IELT of 11 minutes and satisfaction score of +1) and two partners noted vaginal numbness on one occasion.

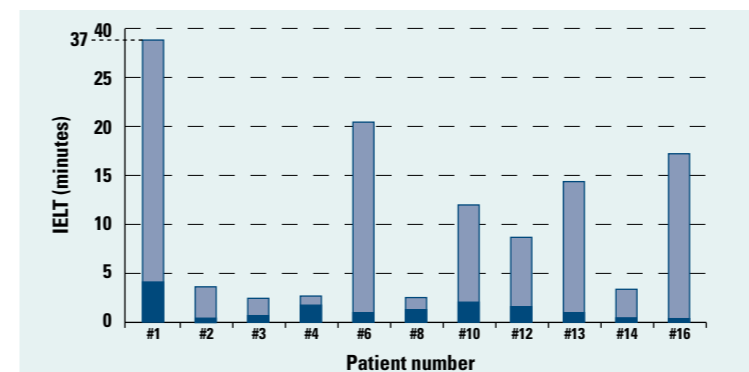


Figure 2: Degree of improvement in IELT following treatment with TEMPE from baseline

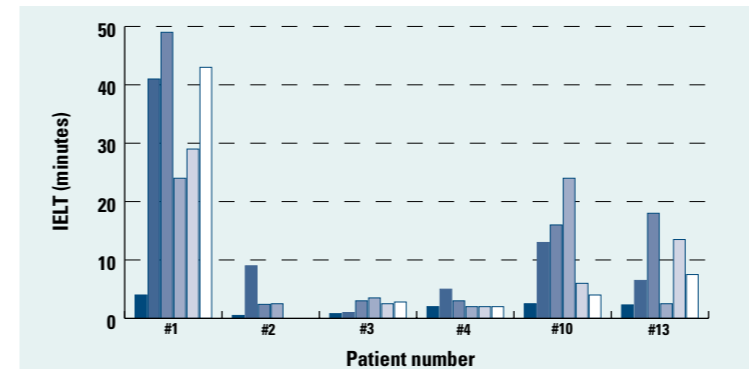


Figure 3: The effect of TEMPE on repeated administration from analysable data for six patients.

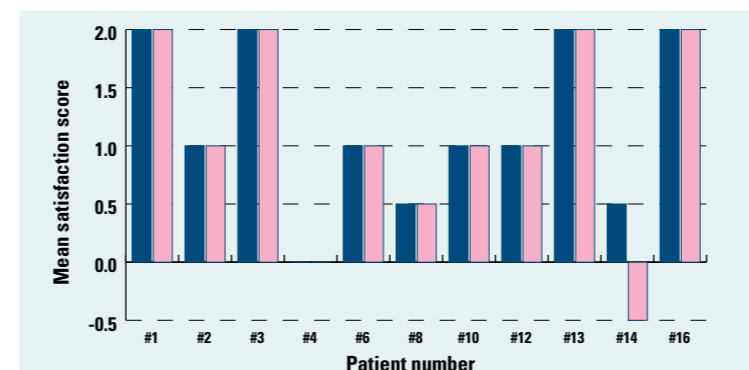


Figure 4: Satisfaction results for 11 couples on a range of -1 = worse, 0 = no change, +1 = better, +2 = much better.

## Discussion

PE is a distressing condition which occurs across all age groups and affects a similar number of men as ED. The lack of approved therapies for PE means that most men remain untreated.

Previous research involving an LA cream (EMLA®) provided encouraging results, which suggested that topical treatments could offer hope for men with PE. Significant drawbacks are associated with this treatment, however. The method of administration (cream is applied to the glans and shaft of the penis in a condom) and time to onset (around 30 minutes) are likely to limit patient compliance. EMLA® was also found to anaesthetise the entire penis and diminish pleasurable sensation<sup>4</sup>.

The development of the novel LA spray formulation described here avoids several of the negative aspects associated with cream formulations. It is easily and cleanly applied, has a reduced period of onset and is easily removed before intercourse.

Delivery of pure base drug at a pH close to the pKa of the drug (the pH at which half of the drug is ionised and half is in the base form) optimises uptake of the molecules through the nerve sheath and axon membrane. Keratinised skin, such as that of the shaft of the penis or hands, is not affected.

Treatment is therefore not associated with numbing of the whole penis and the quality of the orgasm is not adversely affected by glandular numbness. Increased difficulty maintaining an erection for the required onset time was reported by some participants in this trial, however.

Partner-reported side-effects are also limited. Vaginal numbness noted in two cases probably arose as a result of incomplete removal of the anaesthetic from the glans before penetration.

The increase in time to ejaculation in men with PE significantly increased their satisfaction and that of their partners with the sexual experience, indicating important quality of life benefits in this patient group.

## Conclusions and Future Directions

Topical lidocaine-prilocaine spray applied to the glans penis 15 minutes before intercourse prolonged ejaculation time and improved sexual satisfaction in both men and their partners with minimal local and no systemic adverse effects.

A double-blind, placebo-controlled, crossover trial of TEMPE is currently underway. Participants with an IELT of less than 2 minutes will be randomised to receive either placebo or TEMPE for four sexual encounters followed by the alternative regimen for a further four encounters.

If the results of this Phase II trial mirror those described here, it is possible that TEMPE may represent a suitable first-line therapy for this underserved area of sexual dysfunction.

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