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Penile Vibratory Threshold Changes with Various Doses of SS-cream in Patients with Primary Premature Ejaculation

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Abstract

SS-cream made with extracts from natural products is a topical agent for treating premature ejaculation (PE). In order to elucidate the penile vibratory threshold changes and clinical effects of various doses of SS-cream, 53 patients with primary PE were investigated in a double-blind randomized placebo-controlled study. The mean age was 37.3±6.4 years and mean ejaculatory latency was 1.37±0.52 minutes. Neither the patients nor their sexual partners were satisfied with their sexual lives. Vibratory threshold at the glans penis, penile shaft, scrotum and index finger were measured using a biothesiometer twice during the screening period and three times one hour after the application of respective creams (SS-cream 0.05, 0.10. 0.15, 0.20 gm and placebo 0.10 gm) on the glans penis according to the order of the allocation table in a randomized fashion. The efficacy of SS-cream was defined as when the vibration threshold increased by more than 4 microns compared to the value tested during the screening period. The vibratory thresholds at the glans penis increased significantly in a dose-dependent manner after the application of various doses (0.05, 0.10. 0.15, 0.20 gm) of SS-cream ($p<0.001$), and the efficacy of SS-cream on the penile vibration threshold increased according to the increased dosage (penile shaft: 48.4, 51.6, 54.8, 64.5%, glans penis: 58.1, 67.7, 77.4, 83.9%, respectively). With these results, we concluded that SS-cream increased the penile sensory threshold dose dependently, and therefore it is clinically effective for treating the heightened penile sensory response in patients with PE.

Key Words: Premature ejaculation, vibration threshold, SS-cream

INTRODUCTION

Epidemiological studies suggest that premature ejaculation (PE) is the most common male sexual dysfunction, with a prevalence rate between 20 and 40% of the male general population.[1-4] It is defined as persistent or recurrent ejaculation prior to, at, or shortly after, vaginal penetration due to the absence of any voluntary control of ejaculatory reflex.[2,3,5] The causes of PE are thought to be psychologic disorder and the traditional therapies of PE are "squeezing technique", "stop/start technique" or behavioral therapy.[6] Despite a reported initial success rates of nearly 90%,[2,6] other authors have rarely been able to achieve this level of success in their clinical practice, and recidivism rates were high.[7] Medical therapies recently published for the treatment of PE have included the use of intracavernous injection therapy, sympathetic alpha blockers, topical anesthetics along with clomipramine, and the more recent selective serotonin reuptake inhibitors (SSRI's).[7-9] However, these forms of therapy have been reported to be effective in 50% of patients, and unfortunately the frequency of side effects makes them difficult to use.[8,10]

Recent studies with penile biothesiometry, sympathetic skin potential levels and penile somatosensory evoked potential (SEP) have demonstrated that the lack of voluntary control in ejaculation may have a more fundamental neurologic explanation.[11,12] In our studies of penile biothesiometry and penile SEP in patients with PE showed that the vibration threshold was significantly lower than that of normal men and that the latency of SEP was reduced and the amplitude of SEP was increased compared to

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normal men.[13-15] Some studies on the penile vibration threshold in patients with PE showed that there was no significant statistical difference between patients with PE and normal control men.[4,16] But these studies were limited by a small sample size.[17] Patients suffering from PE appeared to have a heightened sensory response to stimulation of their genitalia, as well as an inability to maintain the sympathetic dampening of the sympathetic nerve system (as occurs in normal subjects) when they had an erect penis.[13,14,18,19] Penile hypersesitivity and/or hyperexcitability may be the organic basis of PE. Therefore, we hypothesized that decreasing penile hypersensitivity would be an effective treatment against PE.

SS-cream is a topical agent made from extracts of 9 natural products for treatment of PE. Animal studies showed that SS-cream inhibited a pin-prick-induced corneal reflex dose dependently and prolonged latency and reduced amplitude of SEP of rabbits in a dose-dependent fashion.[15,20-22]

We investigated the effects of various doses of SS-cream on the penile vibration threshold to elucidate the action mechanism of SS-cream on patients with PE.

MATERIALS AND METHODS

Fifty-three patients with primary PE visiting the Department of Urology, Yongdong Severance Hospital from July 1997 to May 1998, agreed to participate in this study and signed an explanatory consent form. PE was classified as primary if it was life long and the patient had never experienced a satisfactory sexual performance. It was considered secondary if acquired after a period of normal ejaculation. Our subjects were all patients with primary PE, all married, heterosexual men in stable relationships of at least more than 6 months. Their mean age was 37.3 ± 6.4 years, while each had an ejaculatory time of less than 3 minutes and a self-reported satisfaction rate of less than 50%. Exclusion criteria included patients with secondary PE, or if PE was combined with erectile dysfunction, genitourinary infection (such as prostatitis, urethritis, epididymitis) and neurological disorders. As well, patients with obvious psychological problems requiring psychiatric support and administration of antidepressants that might alter sexual activities were excluded. Physical examination including the genitalia, as well as complete blood profile, liver and renal function, and testosterone were normal in all patients.

SS-cream (0.05, 0.10, 0.15, 0.20 gm) and placebo (identical with SS-cream but not containing active ingredients) were packaged the same and labeled according to an allocation table (supplied by Cheil Jedang Company, Seoul, Korea).

We investigated the vibratory thresholds of the penis with internal checks of the technique by also doing vibratory thresholds on the index finger and scrotum using a biothesiometer (model PVD, Bio-Medical Instruments Company, Newbury, Ohio, USA) twice in the screening period and three times during the treatment phase one hour after applying of each cream on the glans penis by an examiner according to the order of the allocation table in a randomized fashion. Each test was performed by the same examiner, with both the examiner and the patient blinded as to which cream was being used. The information about the test drug was kept by a controller and provided at the time of data analysis. The efficacy of SS-cream in vibration threshold was defined as an increase of more than 0.04 microns after application.

A mixed model analysis was used for analyzing repeated measures on vibratory threshold from the pretreatment for each patient. Cochran-Armitage trend test was used for analysis of the efficacy of SS-cream according to the dosage. Values represented as mean $\pm$ standard error and p-value less than 0.05 were considered to be statistically significant.

RESULTS

Fifty-three patients completed penile biothesiometry twice during the screening test and three times (159 tests) after the application of each test drug according to the order of the allocation table. However, 2 cases (6 tests) were omitted due to an incorrect allocation code. The mean age was 37.3 ± 6.4 years and the mean ejaculatory latency in the screening phase was 1.45 ± 0.57 minutes. The mean sexual satisfaction rate of the patients and their partners was 16.2% when enrolled in this study. Vibratory thresholds at the index finger, penile shaft, glans penis and scrotum assessed in the screening period were 0.057 ± 0.003, 0.073 ± 0.003, $0.086 \pm$

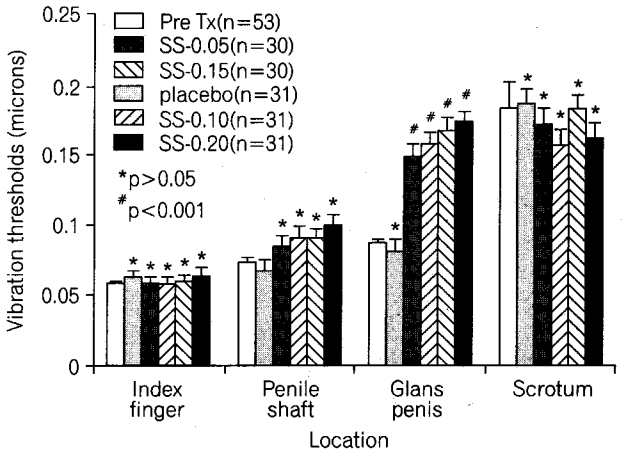

Fig. 1. Vibration threshold at the index finger, penile shaft, glans penis and scrotum after the application of various doses of SS-cream on the glans penis. Vibration thresholds at the glans penis were significantly increased as the dose increased ($p<0.001$), but vibration thresholds at the index finger, penile shaft and scrotum were not significantly different from the mixed model analysis ($p>0.05$).

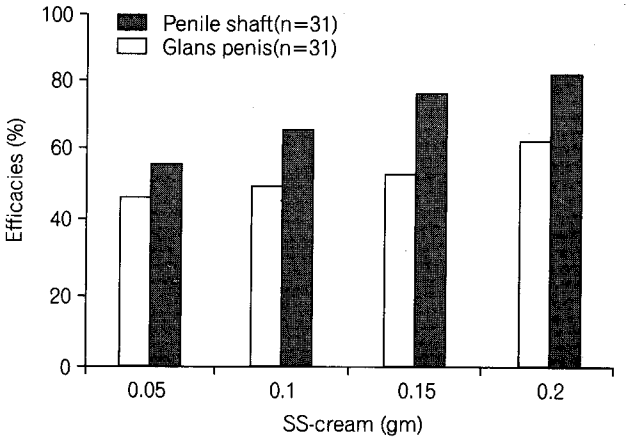

Fig. 2. Clinical efficacy evaluated by vibratory threshold at the penile shaft and glans penis after application of various doses of SS-cream on the glans penis in patients with primary PE. The clinical efficacy increased as the dose increased from the Cochran-Armitage trend test ($p<0.001$). The clinical efficacy evaluated by vibratory threshold was defined as vibratory threshold increased by more than 0.04 microns compared to the pre-treatment period.

0.003 and 0.184±0.019 microns, respectively.

From the results of 153 tests with various doses of SS-cream (0.05=30, 0.10=31, 0.15=30, 0.20 gm=31 tests) and placebo (31 tests), we observed that the mean vibratory thresholds of the glans penis were significantly increased from the pre-treatment as the dose increased ($p<0.001$), while that of the index finger, penile shaft and scrotum were not significantly changed ($p>0.05$) using the mixed model analysis. However, the mean vibratory thresholds of the penile shaft, glans penis, index finger and scrotum after the application of placebo were not significantly increased ($p>0.05$) (Fig. 1). The efficacy of SS-cream on the vibration threshold at the penile shaft and glans penis (as defined previously) increased according to the increased dose (48.4, 51.6, 54.8, 64.5% at the penile shaft and 58.1, 67.7, 77.4, 83.9% at the glans penis, respectively) from the Cochran-Armitage trend test ($p<0.001$) (Fig. 2).

DISCUSSION

Human sexual dysfunction includes disorders of sexual libido, penile erection, ejaculation and orgasm. Ejaculation requires a complex process of erection, emission, ejaculation, and orgasm.[5] Erection is signified by penile tumescence and rigidity primarily under the control of parasympathetic nerves from the sacral plexus and pelvic splanchnic nerves, or nervi erigentes. Emission refers to the collection and transport of semen into the posterior urethra before ejaculation. After closure of the bladder neck and distal urethral sphincter, the posterior urethra becomes filled with semen. This induces the ejaculation process. Ejaculation is the rhythmic expulsion of semen through the urethra, and the perineal skeletal muscles play an essential role. Orgasm is a usually enjoyable cerebral event and is closely related to ejaculation.[23,24] The neurophysiology of ejaculation is only partly understood. Ejaculation is related to an immediate sequential reflex mechanism and one of the apparent functions of the afferent fibers of penile innervation is to provide the cerebral sensory cortex with appropriate information to promote efferent stimulation of the pelvic-cavernous pathway.[12,25]

PE is the most common type of male sexual dysfunction and its prevalence is 20−40% of the general male population.[1-3] Until the 1980s, the etiology of PE was thought to be purely psychogenic, and thus psychotherapy and various behavior modifications claimed clinical success.[2,6,19] These therapies are intended to extend the pre-ejaculatory period, and require the active participation of both partners. However, recent investigations on the pharmacological aspects of ejaculation have shed new light on the mechanisms of ejaculation. Thus, the traditional

belief of sex therapists that PE is caused by psychological derangement and that it is easily treated with behavioral therapy is being questioned. In addition, long-term follow-up of behavioral treatments for PE has revealed that it is not effective as previously reported. The techniques are time consuming and difficult to follow, and in our experience they produce poor results. Recent pharmacological treatment has been attempted, using neuroleptics, antidepressants, alpha blockers, lorazepam and clomipramine, as well as the selective serotonin reuptake inhibitors (SSRI's).[7-9] However, they have not been entirely successful and are associated with various adverse effects. Other treatments such as local anesthetic spray or jelly have also been reported. Again however, in our experience, the use of a topical lidocaine spray (9.6%) was clinically effective in less than 50% of cases and it caused penile numbness which often resulted in erectile dysfunction and failure to achieve orgasm. If not used correctly it had the problem of affecting the partner's genital tract. Thus, for the treatment of PE, the currently available methods seem to have their limitations. The ideal management of PE must be effective in controlling the ejaculatory reflex and should be simple with minimal untoward effect upon penile erection and orgasm, as well as not to interfere with the sexual experience of the partner.

SS-cream is a topical agent made from extracts of nine natural products. Among the active components of SS-cream are euganol from Cryophylli Flos, bufosteroid from Bufonis Veneum, methyl leugenol from Asiasari Radix, and sanshol from Zanthoxylli Fructus, which all have excellent local desensitizing effects, as well as smooth muscle relaxation effects.[21,26] Animal studies with rabbits have shown that SS-cream inhibited a pin-prick-induced corneal reflex in a dose-dependent manner, and its pharmacological period of action was longer than that of lidocaine cream. In terms of adverse effects, SS-cream had almost no toxicity (LD_{50}=9.3 gm./Kg) and no histological changes after the long-term topical application of SS-cream on the glans penis, cornea and skin of rabbits and rats.[15] SS-cream also prolongs the latency and reduces the amplitude of SEP stimulation of the glans penis in rabbits.[15,21] The results of pilot clinical studies showed that SS-cream was effective for the treatment of PE either along with or in combination with mild erectile dysfunction.[22] The clinical efficacy of SS-cream evaluated ejaculatory latency (defined as an ejaculation latency period prolonged more than 2 minutes) in patients with primary PE were 84.0% and 18.8% for placebo, respectively. SS-cream works naturally and completely restores the sense of physical well being in patients with PE. In the results of this study, the response of the penile vibratory threshold for patients with primary PE treated with various doses of SS-cream was increased significantly compared to that of a placebo. In the results of our previous study investigating penile vibration threshold in patients with primary PE and normal controls, the mean vibration threshold of the glans penis and penile shaft in patients with primary PE were 0.058 ± 0.026 and 0.055 ± 0.023 respectively, while in normal controls they were 0.222 ± 0.133 and 0.124 ± 0.046 respectively.[13] So, in this study, the clinical efficacy of SS-cream on penile vibration threshold was defined as when the vibration threshold increased more than 0.04 microns compared to the value of the previous test, and we believed this value can nearly reach the level of normal controls. The efficacy of various doses of SS-cream evaluated by the penile vibratory threshold at the penile shaft and glans penis were significantly increased according to dose increases from the Cochran-Armitage trend test (penile shaft; 48.4, 51.6, 54.8, 64.5% and glans penis; 58.1, 67.7, 77.4, 83.9% respectively).

In consideration of these results, we concluded that SS-cream can increase penile sensory threshold for treating heightened penile sensory response for patients with PE.

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