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Safety and efficacy study with various doses of SS-cream in patients with premature ejaculation in a double-blind, randomized, placebo controlled clinical study

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Objectives: SS-cream is a topical agent made from the extracts of natural products for treating premature ejaculation (PE). To determine the optimal clinical dosage of SS-cream on PE, we investigated the safety and efficacy of SS-cream with various doses. A double blind, randomized placebo controlled clinical study was performed.
Methods: Fifty patients completed the study. Mean age of the patients was 37.1 ± 1.0 y and mean ejaculatory latency was 1.35 ± 0.07 min. Sexual satisfaction rate of both the partner and patient was 16.2%. Each patient was instructed to apply the different cream (placebo, SS-cream 0.05, 0.10, 0.15, 0.20 g) on glans penis 1 h before sexual intercourse in random fashion. The ejaculatory latency was measured by stop watch and the satisfaction rate of both partner and patient was also recorded two times in the screening period and after the application of each test drugs. Clinical efficacy was considered if ejaculatory latency was prolonged more than 2 min and sexual satisfaction rate increased more than 20% than that of pretest values.
Results: The mean ejaculatory latencies were significantly prolonged after using various test drugs (placebo 2.27 ± 0.32, SS-cream 0.05 g 4.47 ± 0.81, 0.10 g 5.34 ± 0.79, 0.15 g 6.22 ± 0.87, 0.20 g 11.06 ± 1.17 min, respectively). Clinical efficacies evaluated by ejaculatory latency were placebo 18%, SS-cream 0.05 g 30%, 0.10 g 60%, 0.15 g 54%, 0.20 g 84%, respectively. The satisfaction rate was also significantly increased dose-dependently (placebo 26%, SS-cream 0.05 g 60%, 0.10 g 70%, 0.15 g 78%, 0.20 g 90%, respectively). A side effect such as local mild burning sensation was noted in 35/250 times (14%) and no adverse effect on sexual function and no systemic side effects were observed. From the result of logistic regression analysis on clinical efficacy, the ED_{50} of SS-cream was obtained as 0.10 g. SS-cream 0.20 g was effective in 84% without any serious systemic side effects.
Conclusion: From the above results, our conclusions are that SS-cream is effective on the treatment of PE with a few local side effects and that clinical optimal dose of SS-cream is 0.20 g.

Keywords: premature ejaculation; SS-cream; ejaculatory latency

Introduction

Premature ejaculation (PE) is the most common type of male sexual dysfunction and defined as the absence of voluntary control over the ejaculation resulting ejaculation either precedes vaginal entry or occurs immediately upon vaginal entry.[1,2] The cause of PE has been thought to be psychological in the majority of patients and little is known about its organic basis.[3–5] Therefore, the management of PE rests primarily on sex therapy and counseling. The expanded 'squeeze technique' and 'stop-start technique' is also attempted to increase the pre-ejaculatory period. However, these therapies require the active participation of both partners and is hard for the patients to follow the techniques. In our experience such therapies have been dismal in successfully treating the male patient with PE. Other treatments and approaches have been tried and suggested. Pharmacological treatment has been attempted with neuroleptics, antidepressants, α-blockers, lorazepam, clomipramine but this approach is not entirely successful and is associated with various adverse effects.[6–10] Other treatments for PE, such as topical application, neurotomy, and intracavernosal medication have been reported.[11–13] As for the treatment of PE, every currently available method has its limitations and side effects.

Our studies of penile biothesiometry and penile somatosensory evoked potential (SEP) in patients with PE showed the vibration threshold in patients with primary PE was significantly lower than that of normal men and the latency SEP was reduced and

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amplitude of SEP was increased those of normal men.[14–16] It can be suggested that the penile hypersensitivity and/or hyperexcitability may be the organic basis of PE. Therefore, we hypothesized that decreasing the penile hypersensitivity will be an effective treatment against PE.

SS-cream is a topical agent for treatment of PE which was made with carefully selected extracts of nine natural products (Ginseng Radix alba, Angelicae gigantis Radix, Cistanchis Herba, Torilidis Semen, Caryophylli Flos, Cinnamoni Cortex, Zanthoxyli Fructus, Asiasari Radix and Bufonis Veneum), which is based on the traditional herb remedy and the action mechanisms of SS-cream are believed to have local desensitizing effects and enhancing capabilities of the local blood flow and was effective in the treatment of PE in the pilot, clinical studies.[18,19] The composition of the cream is: 70% extract of Bufonis Veneum, 10 mg; Ginseng Radix Alba fructose, 100 mg; extract of Asiasari Radix, Carophylli Flos, Cinnamoni Cortex, 10 mg. In order to evaluate clinical efficacy and safety of SS-cream to determine clinical optimal dose of SS-cream, a double blind, randomized, placebo controlled clinical study was performed with various doses of SS-cream.

Materials and methods

Seventy-three patients with primary PE visiting the Department of Urology, Yongdong Severance Hospital who agreed to participate in the clinical study and signed an informed consent enrolled in our study from January 1997 to June 1997. Subjects included patients with primary PE only who complained of PE from their beginning of their sexual life and married and heterosexual with stable partner. The ejaculatory latencies of patients were less than 3 min and/or sexual satisfaction rate were less than 50%. In all patients, physical examinations, including genitalia were normal and complete blood profile, liver and renal function test, testosterone, and prolactin were also without abnormalities. Patients with secondary PE and PE combined with erectile dysfunction, genitourinary tract infection such as prostatitis, urethritis and epididymitis, neurological disorders, and obvious psychological problems requiring psychiatric support and administration of any anti-depressants that might alter sexual activities were excluded. Patients where the ejaculatory latency time was longer than 3 min and/or sexual satisfaction rate was more than 50% were excluded from study.

Test drugs included SS-cream 0.05 g, 0.10 g 0.15 g, 0.20 g and placebo which was made with cream base of the same color and smell of SS-cream. Each test drug packaged and labelled in the same manner. They were given a code randomly according to allocation table and the information about the test drug was kept by the controller and provided at the time of data analysis.

All subjects were instructed to apply the cream on the glans penis 1 h before sexual intercourse and wash it off before sexual intercourse and asked to measure the ejaculatory latency from vaginal intromission to ejaculation with a stop-watch. The degree of satisfaction of both the patient and their partners were recorded and they were asked to complete the report form that included the occurrence of side effects.

Clinical efficacies were interpreted as if ejaculatory latency was prolonged more than 2 min and the sexual satisfaction rate was increased more than 20% over the screening period.

Statistical analysis was performed using paired Student's *t*-test, ANOVA and multiple comparison test, and χ^2-test for differences between test drugs. The logistic regression analysis was used to find the dose relation of SS-cream. Values represented in mean ± standard error and *P*-value less than 0.05 was regarded as having statistical significance.

Results

Seventy-three patients were enrolled in this study and 50 completed the entire study and mean age of patients was 37.1 ± 0.96 y and mean ejaculatory latency time was 1.35 ± 0.07 min and sexual satisfaction rate of both the partner and patient was 16.2%. Twenty-three patients dropped out (lost during follow up 18, incorrect code recording 3, marital/partner problem 2).

After the application of each test drugs ejaculatory latencies were significantly prolonged (placebo 2.27 ± 0.32, SS-cream 0.05 g 4.47 ± 0.81, SS-cream 0.10 g 5.34 ± 0.79, SS-cream 0.15 g 6.22 ± 0.87, SS-cream 0.2 g 11.06 ± 1.17 min) (Figure 1).

Clinical efficacies evaluated by ejaculatory latency were placebo 18%, SS-cream 0.05 g 30%, SS-cream

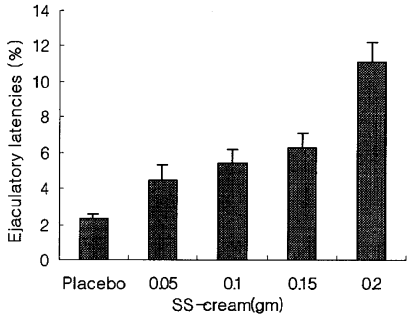

Figure 1 Ejaculatory latencies of before and after application of different doses of SS-cream on the glans penis in patients with primary premature ejaculation. The ejaculatory latencies were significantly prolonged as dose increased ($P < 0.001$).

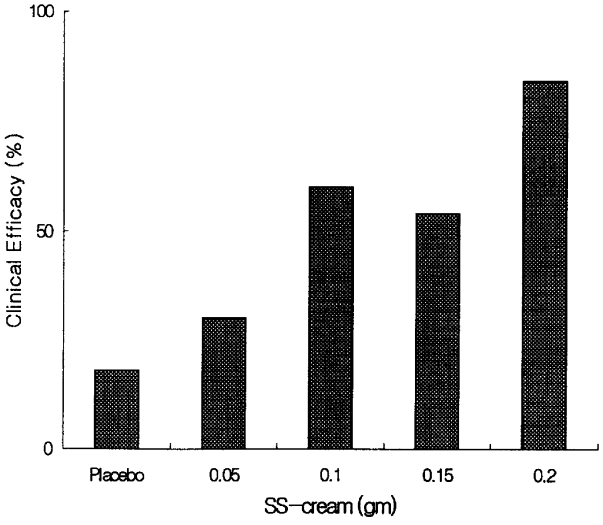

Figure 2 Clinical efficacies according to different doses of SS-cream in patients with primary premature ejaculation. The clinical efficacies were 18% in placebo, 30% in 0.05 g, 60% in 0.10 g, 54% in 0.15 g and 84% in 0.20 g of SS-cream. **Clinical efficacies were calculated by the ejaculatory latency prolonged more than 2 min after the application of the cream on glans penis.

0.10 g 60%, SS-cream 0.15 g 54%, SS-cream 0.20 g 84%, respectively (Figure 2).

Satisfaction rate before treatment was $16.2 \pm 13.5\%$ and after the application of different test drugs were: placebo 26%, SS-cream 0.05 g 60%, SS-cream 0.10 g 70%, SS-cream 0.15 g 78%, SS-cream 0.20 g 90%, respectively (Figure 3).

Thirty-seven of 250 (14.8%) test trials of SS-cream have been associated with mild local burning sensations (placebo 4, SS-cream 0.05 g 7, 0.10 g 9, 0.15 g 7, 0.20 g 10 respectively) and one (0.04%) complained of mild penile pain. The occurrence of side effects tended to increase according to increase in dosage, but no statistical importance was observed. Systemic or other local minor side effects

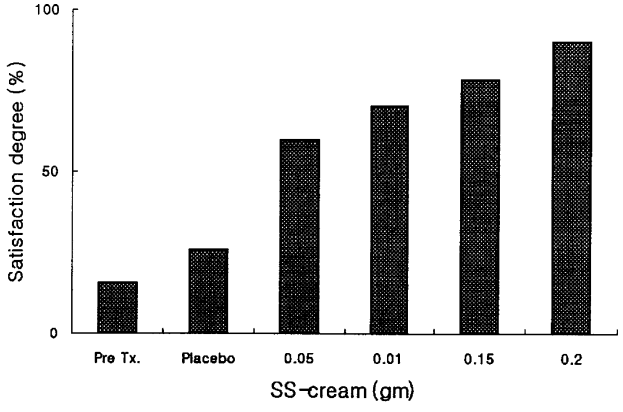

Figure 3 Satisfaction degree according to different doses of SS-cream and placebo in patients with primary premature ejaculation. The satisfaction degrees were significantly increased as doses of SS-cream were increased ($P < 0.001$).

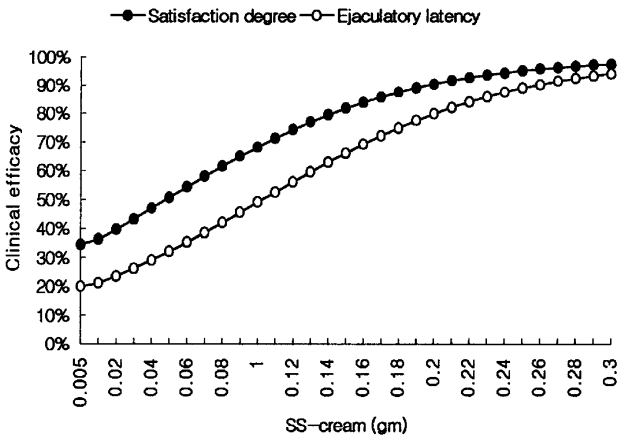

Figure 4 Dose–response curve of the clinical efficacy of SS-cream evaluated by the ejaculatory latency and the satisfaction degree. The clinical efficacy of SS-cream increased as dose increased ($P < 0.001$).

were not noted and no adverse effects on sexual function and on partners were observed.

According to the result of logistic regression analysis, ED_{50} of SS-cream was 0.10 g. In the result of clinical optimal dose (0.2 g) of SS-cream showed efficacy of 84%, and no significant increase in side effect was noted compared to ED_{50} (0.10 g) (Figure 4).

Discussion

Human sexual function includes sexual libido, penile erection, ejaculation and orgasm. Ejaculation is related to immediate sequential reflex mechanisms. One of the apparent functions of the afferent fibers of penile innervation is to provide the cerebral sensory cortex with appropriate information to promote the efferent stimulation of the pelvic-cavernous pathway. Premature ejaculation is the most common type of sexual dysfunction of uncontrolled ejaculatory reflex. Causes of PE may be a psychologic disorder and somatic basis of penile hypersensitivity and/or hyperexcitability.

Patients with PE can be divided into primary and secondary PE. Primary PE patients were those who had suffered chronically since the beginning of their sexual lives and secondary PE patients were those who suffered from PE after years of normal sexual functioning. In our study we evaluated only patients with primary PE because other conditions, which have been implicated with PE but not clearly proven to be etiologic, were excluded.

In this study we investigated ejaculatory latency from vaginal entry of penis to ejaculation and investigated satisfaction and clinical efficacy considered as ejaculatory latency prolonged more than 2 min and satisfaction rate increased more than 20%

over that of screening period. Even so, the clinical efficacy of SS-cream showed dose dependently increased to 84% evaluated by ejaculatory latency and 90% evaluated by satisfaction rate.

The ideal management modality of PE should be simple with maximal effects with little side effects. A topical agent that desensitizes the penile hypersensitivity, restores the normal ejaculatory reflex and also enhances the penile erection, with no adverse effects on the individual's orgasm or upon the partners, can be the ideal drug.

SS-cream is a topical agent for treatment of PE which was made with carefully selected extracts of nine natural products (Ginseng Radix alba, Angelicae gigantis Radix, Cistanchis Herba, Torilidis Semen, Caryophylli Flos, Cinnamoni Cortex, Zanthoxyli Fructus, Asiasari Radix and Bufonis Veneum) and is taken as mixture for a particular ailment so the interaction or synergy is far more significant than the specific reaction of each individual drug. Therefore SS-cream may work naturally and completely to restore physical well being for treating PE.

An animal study showed that SS-cream had almost no toxicity ($LD_{50} = 9.3$ g/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. SS-cream inhibited pin-prick induced corneal reflex of rabbit dose dependently and prolonged the latency of SEP and reduced amplitude of SEP stimulated glans penis of rabbit. Some components of SS-cream, such as eugenol from Caryophylli Flos, bufotalin from Bufonis Veneum and methyl leugenol from Asiasari Radix, have local desensitizing effects. SS-cream also showed the relaxation effect on rabbit corpus cavernosal muscles in a dose dependent manner.[18] The main pharmacological action of SS-cream on the treatment of PE is believed to be in decreasing the penile hypersensitivity to a normal level for restoring the ejaculatory reflex arc and in enhancing the penile blood flow due to combined activity of vasoactive principles.

In this study the side effect of SS-cream was mild local burning sensation in 39 of 250 trials (14.8%: placebo 7, SS-cream 0.05 g 8, 0.10 g 9, 0.15 g 12, 0.20 g 10) and mild pain 0.04%. The occurrence of side effects tended to increase according to the increase of dosage, but no statistical importance was observed. Systemic or other local minor side effects were not noted and no adverse effect on sexual function and on partner was observed.

Conclusions

With these results, we can conclude that SS-cream is effective and safe in the treatment of PE. In the result of logistic regression analysis on clinical efficacy, the ED_{50} of SS-cream was 0.10 g. As the clinical efficacy of SS-cream ranged from 0.05 g to 0.20 g with no significant increase in side effects compared to ED_{50} (SS-cream 0.10 g), SS-cream 0.20 g was determined as the clinical optimal dose.

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