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Efficacy of a Topical Agent SS-cream in the Treatment of Premature Ejaculation: Preliminary Clinical Studies

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SS-cream is a topical agent for treating premature ejaculation (PE) which is made with extracts from 9 natural products. We evaluated the efficacy of SS-cream in the treatment of PE. An open pilot study was performed in 186 patients with PE. The mean ejaculatory latency from intromission to ejaculation was 1.5 minutes. Sixty-four of the 186 patients (34.4%) were combined with mild erectile dysfunction in whom penile rigidity was not sufficient to be satisfied in sexual activity. Patients were instructed to apply 0.1 gm. of SS-cream on the glans penis 1 hour before sexual contact and to wash out the cream before sexual intromission. Patients were asked to complete a report form including ejaculatory latency, the degree of satisfaction in the sexual lives of both themselves and their partners, and any adverse effects after each application. One hundred and sixty-six out of 186 patients (89.2%) reported they were satisfied with the application of the SS-cream and the mean ejaculatory latency was significantly prolonged to 10.89± 5.60 minutes. The mean ejaculatory latency was 9.85±3.58 minutes in 52 out of 64 patients (81.2%) with mild erectile dysfunction. There was no significant difference in the changes of ejaculatory latencies between patients with pure PE and patients with mild erectile dysfunction. Twenty patients (10.8%) claimed to have no changes of ejaculatory latencies after the application of SS-cream. Adverse effects were noted in 11 patients (5.9%), which were mild local irritation symptoms in 7 patients, and delayed ejaculation of more than 30 minutes in 4 patients, the symptoms subsided spontaneously within 4 hours. These results indicate SS-cream is effective in the treatment of PE and also PE combined with mild erectile dysfunction with a few side effects. Further studies on the action mechanisms of SS-cream and a double blind placebo-controlled trial are needed.

Key Words: Premature ejaculation, penis, erection, topical agent

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Premature ejaculation (PE) is the most common type of male sexual dysfunction. It is defined as the absence of voluntary control over ejaculation with the result that ejaculation either precedes vaginal intromission or occurs immediately upon vaginal entry. As a result, the partner's sexual satisfaction is less than 50% in their sexual encounters(Kaplan, 1989; Strassberg *et al.* 1990; Seong *et al.* 1994). The

cause of PE has been thought to be psychological in the majority of patients and little is known about its organic basis(Levine, 1976; Murphy and Lipshultz, 1987; Bush, 1994). Therefore, the management of PE rests primarily with sex therapy and psychological counselling. The expanded "squeeze technique" and "stop-start technique" are also recommended to increase the pre-ejaculatory period. However, these therapies require the active participation of both partners and it is difficult for patients to follow these techniques. In our experience such therapy has had poor results in treating the male patient with PE. Other treatments and approaches have been suggested and tried. Pharmacological treatment has been attempted with neuroleptics, antidepressants, α -blockers, lorazepam and clomipramine, but this approach has not been entirely successful and is associated with various adverse effects(Shilon *et al.* 1984; Segraves *et al.* 1993). Other treatments for PE, such as topical application, neurectomy, intracavernous medication, *et al.* have been reported (Boneff, *1972;* Fein, 1990; Tullii *et al.* 1994; Berkovitch *et al.* 1995). As for the treatment of PE, every currently available method seems to have its limitations and side effects.

In our studies of penile biothesiometry, patients with PE had a penile hypersensitivity and/or hyperexcitability (Xin *et al.* 1995c, 1996d). Therefore, we hypothesized that decreasing penile hypersensitivity and/or hyperexcitability would help treat PE. To decrease penile hypersensitivity in patients with PE, we developed a topical cream based on the traditional Chinese Royal Herb Remedy, which is named SS-cream (Xin *et al.* 1996a). SS-cream is made with extracts of 9 kinds of natural products (Table 1). The action mechanisms of SS-cream are believed to have local desensitizing effects and enhancing capabilities on the local blood flow (Han, 1988; Xin *et al.* 1995c; Choi *et al.* 1996; Xin *et al.* 1996a,b,c). We report the results of a pilot test of the clinical efficacy of SS-cream in patients with PE.

MATERIALS AND METHODS

We investigated 186 patients with long-standing histories of PE visiting the Severance Institute of Andrology, They agreed to participate in this clinical study and signed an informed consent from Jan. 1995 to Dec. 1995. The subjects included patients with primary PE who complained of PE from the beginning of their sexual life and whose ejaculatory latency was less than 3 minutes. The degree of satisfaction of the partner and patient was also less than 50% in their sexual encounters. Subjects also included patients with PE combined with mild erectile dysfunction in whom penile rigidity was not sufficient to be satisfied in sexual activity but was within normal limits in an erectile function test(such as nocturnal penile tumescence, rigiscan, or penile duplex doppler sonography). We excluded patients with organic erectile dysfunction, genitourinary tract infection such as prostatitis, urethritis and epididymitis or neurological disorders and obvious psychological problems requiring psychiatric support or continuous drug administration that might alter sexual activities. In all patients, physical examinations including genitalia were normal and a complete blood profile, liver function test, testosterone and prolactin were also without abnormalities. The mean age was 42.3 years (range 21 to 63), the mean duration suffering from PE was 14.3 years (range 1 to 40). A total of 148 patients (79.6%) with PE were married. Patients were divided into primary and secondary PE. One hundred and thirty-two patients (70.9%) were primary PE who had suffered from PE since the beginning of their sex lives, and 54 patients (29.0%) were secondary PE who had suffered from PE after previously maintaining normal ejaculation. Sixty-four patients (34.4%) with PE exhibited a concomitant mild erectile dysfunction. The mean ejaculatory latency from intromission to ejaculation was 1.5 ± 0.58 minutes (immediately after intromission in 21 patients; within 30 seconds in 34; within 1 minute in 69; within 2 minutes in 43; and within 3 minutes in 19. The partner's satisfaction was less than 30% in their sexual encounters.

SS-cream (0.1 gm. in each package) was provided to participating patients. Each patient was instructed to apply 0.1 gm SS-cream on the glans penis and to wash off the cream before sexual intromission. Sexual intercourse was performed 1 hour after the application of the SS-cream. Patients were asked to measure the ejaculatory latency from intromission to ejaculation with a watch or clock and to estimate the

degree of satisfaction for both their partners and themselves. Adverse effects were reviewed.

Statistical analysis was performed using the paired Student's t test for the effect of SS-cream and unpaired Student's t test for the difference between patients with PE only and patients with PE combined with mild erectile dysfunction. Values represented mean±standard error and p-value less than 0.05 were regarded as having statistical significance.

RESULTS

There was a significant improvement of symptoms in patients with PE. A total of 166 patients out of 186 patients (89.2%) were satisfied with the topical application of SS-cream on the glans penis. The ejaculatory latency was significantly prolonged from 1.5±0.48 to 10.89±5.60 minutes after the application of SS-cream($p<0.001$); prolonged for 3-5 minutes in 31 patients (19%), 5-10 minutes in 59 patients (36%), 10-15 minutes in 29 patients (17%), 15-20 minutes in 24 patients (14%) and 20-30 minutes in 23 patients (14%).

SS-cream was also effective in 52 out of 64 patients (81.2%) with PE combined with mild erectile dysfunction, as the mean ejaculatory latency was prolonged for 9.85±3.58 minutes. There was no significant difference in the effect of SS-cream between patients with primary PE only(mean ejaculatory latency prolonged from 1.45±0.52 to 11.52±4.05 minutes) and PE combined with mild erectile dysfunction (mean ejaculatory latency prolonged from 1.5±0.45 to 9.85±3.58 minutes) after the application of SS-cream ($p>0.05$, Fig. 1). Forty-two (65.6%) out of 64 patients combined with mild erectile dysfunction reported a potentiating effect on their erectile capacity after the topical application of SS-cream on the glans penis.

Twenty patients (10.8%) were not satisfied with the application of SS-cream and claimed to have no change compared to ejaculation before using of SS-cream. Adverse effects were noted in 11 of these patients (5.9%), which included mild local irritation symptoms such as a mild burning sensation and discomfort in 7 patients, and delayed ejaculation of more than 30 minutes in 4 patients. These side

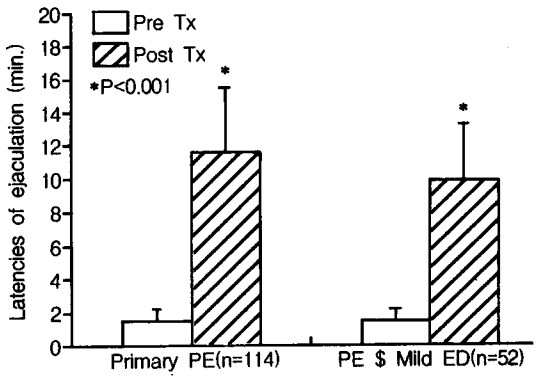

Fig. 1. Ejaculatory latencies before and after the application of SS-cream in patients with primary PE only and PE combined with mild erectile dysfunction(ED). The mean ejaculatory latencies were significantly prolonged after the application of SS-cream($p<0.001$ by paired Student's t test). However, the differences between two groups showed no significance($p>0.05$). Values represented mean±standard error.

effects subsided spontaneously within 4 hours. No adverse effects on the penile erection and the orgasm of the patients and sexual senses of the partners were noted.

DISCUSSION

Premature ejaculation is an uncontrolled ejaculatory reflex. Generally it has been said to be persistent or recurrent ejaculation with minimal sexual stimulation before, upon, or shortly after intromission, and before the person wishes it(Kaplan, 1989). The cause of PE has been thought to be psychological in the majority of patients and its cause is still unknown in most cases. Little is known about the organic basis of PE and a few organic conditions, such as urinary tract infection, diabetes mellitus, multiple sclerosis *et al.* have been suggested (Murphy and Lipshultz, 1987; Bush, 1994). However, our's and others studies have found differences in the penile sensitivity between patients with primary PE and normally potent men(David *et al.* 1993; Rebello and Romero, 1994). In our studies of penile biothesiometry, patients with PE had a penile

hypersensitivity which suggested a neurologic basis for PE(Xin *et al.* 1995c, 1996d). Various approaches to decrease the sensitivity of the penis for the treatment of PE have been attempted. Use of topical anesthesia with ethyl amino benzoate, lidocaine and/or prilocaine have been reported but with different degrees of success(Berkovitch *et al.* 1995). A surgical procedure for some kinds of organic PE (neurectomy) has been done in some reports(Tullii *et al.* 1994), but these methods were limited and have the potential of serious side effects.

The ideal management of PE must be effective control over the ejaculatory reflex and the method should be simple and effective with little adverse effect on penile erection, orgasm and the sexual sensitivity of partners.

We hypothesized that decreasing penile hypersensitivity with topical cream could treat patients with PE. We developed a new topical cream (SS-cream) which is made with extracts of 9 natural products (Table 1). An animal study showed that SS-cream had almost no toxicity (LD_{50}=9.3 gm./kg) and no histological changes after its application on the glans penis and cornea of rabbits(Xin *et al.* 1995b, 1996c). With the various active components of SS-cream, the action mechanisms of SS-cream are believed to have a local desensitizing effect and enhancing capabilities on local blood flow. Some components of SS-cream, such as ginsenoside from Ginseng Radix Alba, eugenol from Caryophylli Flos, bufosteroid from Bufonis Veneum and methyl leugenol from Asiasari Radix, have the local desensitizing effects and/or smooth muscle relaxation effects(Han, 1988; Choi *et al.* 1996). The main pharmacological action of SS-cream on the treatment of PE is believed to be in decreasing penile hypersensitivity and/or hyperexcitability to a normal level, and in restoring the ejaculatory reflex arc and enhancing the penile blood flow due to its combined activity of vasoactive principles(Xin *et al.* 1996a, b,c).

Clinically, 20~40% of patients with PE were combined with mild erectile dysfunction(Seong *et al.* 1994). SS-cream has been effective in most patients with PE without erectile dysfunction and it was also effective in the treatment of PE combined with mild erectile dysfunction. Our studies in the isolated rabbit corpus cavernosal muscle showed SS-cream had the dose-dependent relaxation effect on cavernosal muscle strips precontracted with phenylephrine (Xin *et al.* 1996a) and SS-cream increased the temperature on the penis which was measured by penile DITI (digital infrared thermography imaging) (Xin *et al.* 1995a). Thus, the potentiating effect on erectile capacity after the topical application of SS-cream was suggested to be due to the vasodilating effect on penile cavernosal smooth muscle.

Table 1. Ingredients & active compositions of SS-cream

Ingredients	Active compositions
Bufonis Venenum	*Bufosteroid*
Ginseng radix Alba	*Ginsenoside Rb*
Angelicae Gigantic Radix	*Decursin*
Cinnamoni Cortex	*Cinnamic aldehyde*
Caryophylli Flos	*Euganol*
Asiasari Radix	*Methyleuganol*
Cistanchis Herba	*Alkaloids*
Torilidis Semen	*Pinene, Camphene*
Zanthoxylli Fructus	*Sanshool*

Twenty out of 186 patients (10.8%) were refractory to continuous use of SS-cream. Based with these findings, penile hypersensitivity is not the sole basis for the cause of PE. So other implications for the pathophysiologic basis of PE should be considered.

SS-cream showed mild adverse effects in 11 patients (5.9%), which were mild local irritating symptoms and delayed ejaculation for more than 30 minutes. But these effects were transient. Long-term follow up study is needed.

With these results, SS-cream was effective in the treatment of PE and also PE combined with mild erectile dysfunction with few side effects. Further studies for an organic basis of PE, action mechanisms of SS-cream, and a double blind placebo-controlled trial are required.

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