A Pilot Study of a Topical Intervention for Treatment of Female Sexual Dysfunction

Adel Abdel-Wadood Gomaa, PhD, Nermeen M. Abdel Aziz, PhD,† Romany H. Thabet, PhD,* Howieda A. Fouly, PhD,‡ Sara H. Altellawy, PhD,§ and Ghada A. Gomaa, MSc||*

Abstract:

Purpose/Background: Many investigators reported that pharmacological treatment of female sexual dysfunction (FSD) has been a promising field yet to be explored. The purpose of this pilot study was to investigate the efficacy and safety of a topical cream containing small concentrations of three vasodilators with different mechanisms of action in treating FSD.

Methods: In this randomized, controlled pilot trial, premenopausal (n = 30) and postmenopausal (n = 30) cases of 21- to 62-year age range with FSD were allocated randomly into 15 given placebo or 15 given active cream in each group. The women included had FSD for more than a 6-month duration and a total score of Female Sexual Distress Scale-Revised of at least 15. Assessing sexual function by measuring female sexual function index (FSFI) during five clinic visits, one at the end of baseline week and at the end of each week of the 4-week treatment period. The primary end point was changed from baseline FSFI total scores to week 4 treatment. Secondary end point included the changes from baseline arousal, desire, orgasm, and satisfaction scores to week 4 treatment.

Findings/Results: The sexual problem reported by patients was orgasmic or/and arousal disorders. In premenopausal cases, active cream led to a high significant increase in mean change FSFI total score from the baseline to week 4 compared with placebo (1.7 ± 1.886 vs 13.35 ± 4.646, respectively; $P < 0.0001$). Greater improvement of mean change of orgasm and arousal domain score was also observed (0.3 ± 0.45 and 0.35 ± 0.39 vs. 2.66 ± 0.63 and 1.87 ± 0.168, respectively; $P < 0.0001$). In postmenopausal cases, there were significantly greater improvements with active cream in all sexual functions compared with placebo cream ($P < 0.0001$). In triple cream, mean change of FSFI total score, orgasm domain score, and arousal score domain were 14.85 ± 6.33, 1.87 ± 0.168 and 2.66 ± 1.182, whereas in the placebo cream, they were 1.54 ± 2.1,0.7 ± 0.76 and 0.22 ± 0.44, respectively. Meanwhile, orgasm scores increased significantly after the use of placebo cream. No serious adverse effects were reported during treatment.

Implications/Conclusions: The results of the pilot trial suggest that topical cream containing small concentrations of three vasodilators may act synergistically, and was effective in improving arousal, orgasmic, and satisfaction disorder with a safer profile for premenopausal and postmenopausal women with FSD. Further studies are recommended to be conducted using a large number of nondepressive and depressive patients.

Key Words: female sexual dysfunction, orgasm, arousal, vasodilators, topical

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From the *Department of Medical Pharmacology, Faculty of Medicine, †Department of Gerontology, Faculty of Nursing, ‡Department of Obstetrics and Gynecology, Faculty of Nursing, and §Department of Psychology, Faculty of Arts, Assiut University, Egypt; and ||Department of Dermatology, University Hospital, Assiut University, Egypt.

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Reprints: Adel Abdel-Wadood Gomaa, PhD, Faculty of Medicine, Assiut University, Assiut, Egypt (e-mail: a.gomma@aun.edu.eg; adelgomaa15@yahoo.com).

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Problems with sexual function, such as difficulties with desire, arousal, or orgasm, are highly prevalent. Between 15% and 30% of men and 34% to 40% of women in the United States and Europe report some form of sexual dysfunction.[1,2] In Egypt, the prevalence of female sexual dysfunction (FSD) is higher than that reported in the United States and Europe owing to circumcision status (female genital mutilation).[3] Symptoms of FSD, when associated with distress, have been shown to negatively affect the quality of life.[1] Sexual dysfunction is also frequently reported by people with untreated depression,[4] and these rates increase in patients receiving antidepressant therapy.[5,6] Improving sexual function among those affected can reduce distress and enhance antidepressant treatment outcomes.[7]

Flibanserin was approved by the Food and Drug Administration as first pharmacological therapy for hypoactive sexual desire disorder in August 2015. Unlike sildenafil, which is only taken before sexual activity by men, flibanserin is intended to be taken on a daily basis for longer periods. In general, Jaspers et al[8] and Yoon and Park[9] suggested that the benefits of flibanserin treatment are marginal, particularly when taking into account the concurrent occurrence of adverse reactions. Thus, there seemed to be a weak signal, suggesting that flibanserin carries benefits for sexual functioning in women with or without depression due to controversial outcomes of published trials.[10] Many other pharmacological treatments have been considered for FSD mainly focusing on the use of hormones (androgen or estrogens). However, controversies still remain regarding hormonal therapies for FSD; these therapies still require more reliable safety and efficacy.

Recently, Yoon and Park[9] and Farmer et al[11] reported that pharmacological treatment of FSD has been a promising field yet to be explored. Therefore, we undertook this study to investigate the efficacy and safety of a topical cream containing small concentrations of three vasodilator agents acting in different mechanisms as a treatment for FSD. Isosorbide dinitrate, nitric oxide donor, increases the production of cyclic guanosine monophosphate (GMP), whereas theophylline, a phosphodiesterase inhibitor, decreases the breakdown of cyclic GMP. Co–dergocrine mesylate, an alpha 1 blocker, stimulates the central dopamine receptor.[12] A small concentration of each agent was used to avoid the adverse effects of each. This cream has been used successfully for the treatment of some types of erectile dysfunction.[12] It also has been used successfully for enhancing female orgasm and sexual satisfaction by a case reported by Bartlike et al.[13] It has been approved for use by Drug Committee of Egyptian Ministry of Health for male erectile dysfunction since 1999 (Reg. No. 20391/99). It may produce smooth muscle relaxation and vasodilatation in the genital area, coupled with an increase of blood flow to the genital area and enhancement of genital sensation. Owing to the presence of co-dergocrine, which stimulates central dopamine receptor, the triple cream may facilitate the central sexual-related reflexes and enhance sexual response. It is postulated that triple cream would be useful in overcoming symptoms of female sexual disorders. Therefore, in this pilot study, we examined the feasibility, preliminary effectiveness, and safety of this cream. A pilot

study is a smaller version of the main study used to test whether the components of the main study can all work together. It resembles the main study in many respects, including an assessment of the primary outcome.[14]

METHODS

Study Design

The present work represented a randomized, prospective, double-blinded, placebo-controlled pilot trial that included a 1-week baseline period followed by a 4-week treatment period. This pilot study was approved by the local ethical committee of the Faculty of Medicine, Assiut University, Egypt, complying with international standards of clinical trials. Before participation in the study, all patients signed a written informed consent. In all the selected patients, FSD was diagnosed by a clinical psychologist who was unaware of the type of the intervention given to the patient. Female Sexual Distress Scale-Revised (FSDS-R) was used to present study for diagnosis of FSD in addition to female sexual function index (FSFI). The concept of sexually related personal distress is currently central to the diagnosis of all FSDs. The FSDS-R is a 13-item self-administered questionnaire that assesses sexual distress. All 13 items are rated on a five-point scale from zero (never) to 4 (always), so the total score can range from 0 to 52, with lower scores indicating less distress.[15,16]

The present 5-week study included five clinic visits, one at the end of baseline week and the end of each week of the 4-week treatment period. During each visit, a 19- item questionnaire of six domains to FSFI was filled by the patient, that is, self- questionnaire, aided by a female therapist who helped the patient in reading questions loudly, clarifying any queries, and completing the questionnaire.

Subjects

This pilot study included 60 patients with FSD divided into 30 premenopausal and 30 postmenopausal women. By the procedure of permuted-block randomization, premenopausal patients were allocated randomly into 15 given placebo and 15 given an active cream. In addition, postmenopausal patients were randomized into 15 and were given placebo and 15 were given the active cream. Women with a diagnosis of FSD for more than a 6-month duration were included in this study. Patients selected had to have a total FSDS-R score of at least 15 and a total FSFI total score 28 or less.[15,16] Selected women should be heterosexual in a stable monogamous relationship for at least 1 year with their sexually functional partners. Exclusion criteria included the following: women with any psychiatric disorders that may impair sexual function, for example, women with depression within the previous 6 months; women with any ongoing serious clinical disorder, for example, women with spinal cord damage, uncontrolled diabetes; serious cardiovascular disorders, for example, arrhythmias, heart attacks and heart failure; women abusing drugs in the past year; women using antiarrhythmics, beta blockers, nitrates, anticoagulants, central nervous system stimulants, dopamine agonists, muscle relaxants, benzodiazepines, hypnotics, antidepressants, antipsychotics, mood stabilizers, antiepileptics, metoclopramide, triptans, sex hormones other than contraceptives or any other drugs or herbs that may affect sexual function within the previous 4 weeks; women with a history of suicidal attempt, women with major life stress, for example, loss of income, death of a family member, family conflicts; women receiving any psychotherapeutic therapy, for example, marital counseling, sex therapy; pregnant or breastfeeding women (during the study or in previous 6 months; women with pelvic inflammatory diseases, urinary tract or vaginal infections, vaginal atrophy, interstitial cystitis, cervicitis; and women whose sexual partner had inadequately treated sexual erectile dysfunction.

Randomization of Selected Patients and Blinding

The present pilot trial study used permuted-block approach for randomizations, that is, a "block size" and "allocation ratio" (the number of subjects in one group versus the other group) were specified, and patients were allocated randomly within each block.[17] For example, a block size of 6 and an allocation ratio of 2:1 would lead to the random assignment of four subjects to one group and two to the other. Randomization was carried out by one of the investigators who did not have any role in the treatment of the participants. After randomization, all participating patients were given either the placebo or the test drug.

Study Medication

The study medication was a white cream containing theophylline, 2%, isosorbide dinitrate, 0.3%, and co-dergocrine mesylate, 0.065%. The placebo cream and active cream have similar physical characteristics and appearance. Each premeasured dose was double blinded and individually packaged and labeled in a plastic dispenser. The patient was instructed to apply 2 grams of

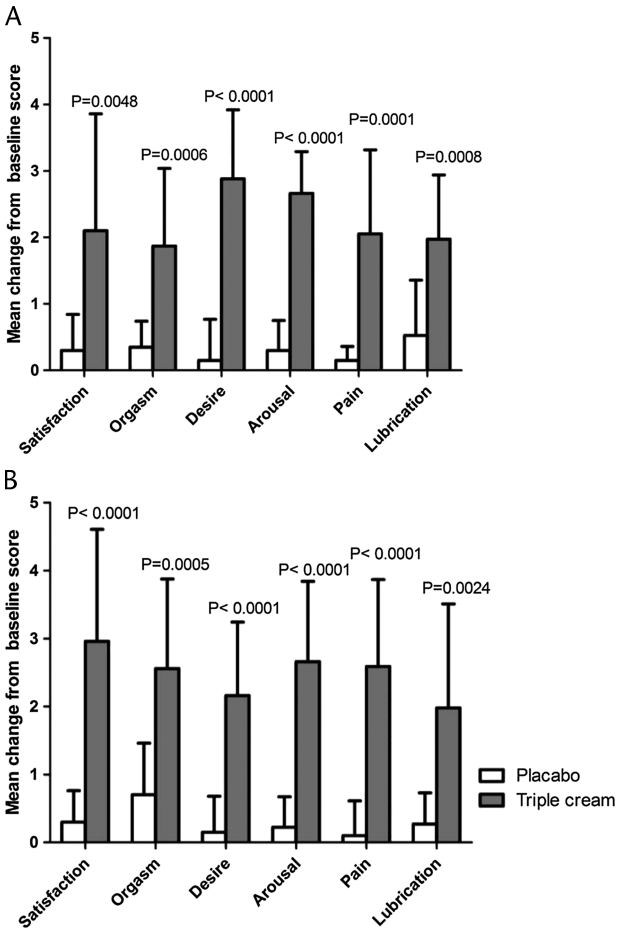

FIGURE 1. Improvement of sexual functions from baseline in premenopausal (A) and postmenopausal women (B) with FSD treated with placebo or active (triple) cream. Mean change from baseline scores before treatment to week 4 scores at the end of study.

the study cream on the dorsum of hand 1 hour before the sexual intercourse for systemic effects. For systemic and local effects, another dose should be applied on the external genital area (vestibule, clitoris, and vulva) approximately 15 to 30 minutes before sexual activity, with a gentle massage for seconds to enhance the absorption. After the second application of the cream, the patient was instructed to engage in foreplay to facilitate the action of the medication.

Assessment of Efficacy Outcome

The primary end point was changed from baseline FSFI total scores to week 4 treatments. Secondary end point included the changes from baseline arousal and orgasm scores to week 4 treatment. The FSFI is a self-report measure widely used for the assessment of sexual function in women. The FSFI, which contains 19 items, considers all sexual subscales, which include desire (two questions), arousal (four questions), lubrication (four questions), orgasm (three questions), satisfaction (three questions), and pain (three questions).[18] Lower scores of any of the six domains or of the total FSFI indicate worse sexual function.[18] Scores 28 or less were considered as sexual dysfunction. The total score is calculated by adding the six domain scores, and a score of zero means that no sexual activity was reported during the past month. The domain scores and a total score can be derived by the following formula. For individual domain scores, items that comprise the domain are added. Then, the sum is multiplied by the domain factor (ranging from 0.3 to 0.6). The total score is the sum of six domains scores, which range from 2 to 36.[19,20]

Safety Assessment

Throughout the total 4-week treatment period of the study, women given the triple or placebo cream were asked about any adverse events and report any observation in the questionnaire. Physical examinations (included vital signs and electrocardiogram) were performed during every patient's visit. Adverse events were reported as serious or nonserious

Statistical Analysis

Data were presented as mean ± standard deviation (SD). Paired *t* tests were used to test the difference in each domain score and total FSFI between baseline and at the end of the treatment period. Unpaired *t* tests were performed to compare FSFI for patients given the active drug versus those given placebo. The two-tail value of $P < 0.05$ was considered statistically significant. Data analysis was conducted using Prism 5 GraphPad Software. Demographic and baseline characteristics for selected cases regarding their age, weight, education, marital status, testosterone level, history of sexual activity, duration of FSD, FSDS-R score, FSFI score smoking history and comorbid diseases were characterized using frequency distribution.

RESULTS

In this pilot study, 60 women with FSD were studied. Half of the patients were premenopausal. Their mean age was 37.25 ± 5.44 years (range, 22–45 years). The mean duration of the heterosexual relationship was 10 years, and the mean duration of FSD was approximately 5 years. The sexual problems reported by those patients were orgasmic and/or arousal disorders. There were no significant differences between women who received placebo or those who received active cream in their baseline characteristics. There were no significant differences between the two groups in age, weight, medical history, and frequency of sexual activities. Comparing the two groups with regard to the primary mean baseline of the total scores of sexual function (FSFI) and FSDS-R scores showed similarities at the beginning of the study ($P = 0.8051$). Mean FSFI total score and FSDS-R for patients who received placebo cream were 21.63 ± 3.12 and 31.27 ± 8.19, respectively, whereas these were 18.27 ± 3.62 and 32.23 ± 8.27, respectively, for patients who received active cream.

TABLE 1. Comparison of the Mean ± SD FSFI Total Scores of Premenopausal and Postmenopausal Women With FSD Received Placebo or Active Cream

Menopausal Status	Time	Placebo Cream	Triple Cream
Premenopausal	Before treatment	21.63 ± 3.12	18.27 ± 3.62
	1 wk after treatment	22.7 ± 2.73	28.25 ± 3.77
	2 wks after treatment	22.6 ± 2.47	30.91 ± 2.77
	3 wks after treatment	22.23 ± 2.8	31.85 ± 3.79
	4 wks after treatment	23.33 ± 2.16	31.62 ± 3.58
	Change from baseline to wk 4	1.7 ± 1.886	13.35 ± 4.646
	Entire treatment period	22.71 ± 2.46	30.66 ± 3.71*
	P value vs before treatment	NS 0.2981	* <0.0001
Postmenopausal	Before treatment	15.54 ± 2.76	12.09 ± 4.1
	1 wk after treatment	17.3 ± 3.59	26.51 ± 5.13
	2 wks after treatment	15.85 ± 2.76	27.44 ± 3.92
	3 wks after treatment	17.7 ± 3.42	27.55 ± 3.61
	4 wks after treatment	17.1 ± 3.03	26.95 ± 2.77
	Change from baseline to wk 4	1.54 ± 2.1	14.85 ± 6.33
	Entire treatment period	16.97 ± 3.14	27.11 ± 3.87*
	P value vs before treatment	NS 0.2448	* <0.0001

The data represent mean ± SD.

*$P < 0.0001$ for triple cream vs placebo cream, with regard to the total treatment period.

The mean age of the postmenopausal patients was 57 ± 3.58 years (range, 49–62 years old). The mean duration of heterosexual relationship was 30 years, and the mean duration of FSD was approximately 12 years. Orgasmic and/or arousal disorders were the sexual problems reported by those cases. By comparing the two groups (placebo and active cream) with regard to demographic characteristics of age, weight, education, medical history, and frequency of sexual activities, no significant difference was observed and both groups were relatively similar. Comparing the two groups with regard to baseline FSFI total score and FSDS-R showed similarities at the beginning of the study ($P = 0.8051$). Mean baseline FSFI total score and FSDS-R for the postmenopausal patients who received active cream were 12.09 ± 4.1 and 33.07 ± 9.36, respectively, whereas they were 15.54 ± 2.76 and 31.07 ± 8.16, respectively in patients who received placebo cream.

Efficacy End Point in Premenopausal and Postmenopausal Women

The results of this study revealed nonsignificant increases concerning all of the FSFI domains between the mean scores before the intervention (baseline) and scores of all domains after the use of placebo cream in premenopausal and postmenopausal women except there was a significant increase in orgasm domain of postmenopausal women ($P = 0.0283$). However, there were significant increases in all sexual domains scores after the use of active cream compared to the baseline. Improvement in both orgasmic and arousal scores in addition to FSFI total scores of the entire period was observed by testing cream group versus the placebo group in premenopausal and postmenopausal women (Fig. 1)

In premenopausal women, compared with placebo, active cream led to highly significant increases in FSFI total score changes from the baseline (1.7 ± 1.886 vs 13.35 ± 4.646, respectively; $P < 0.0001$; Table 1) and in orgasmic and arousal score changes from the baseline (0.3 ± 0.45 and 0.35 ± 0.39 vs. 2.66 ± 0.63 and 1.87 ± 0.168, respectively; $P < 0.0001$; Fig. 1). The improvement of orgasmic and arousal sexual domain was demonstrated in the group that used the active cream starting from the first week of use. The mean scores of arousal and orgasmic sexual domain increased significantly from 2.72 ± 0.56 and 3.28 ± 0.51, the baseline score, to 4.84 ± 1.00 and 4.53 ± 0.63, respectively, at the end of the first week of treatment. In addition,

TABLE 2. Comparison of Satisfaction and Orgasm Mean Scores of Premenopausal and Postmenopausal Women With FSD Who Received Placebo or Active Cream

Sexual Domain	Menopausal Status	Time	Placebo Cream	Triple Cream
Satisfaction	Premenopausal	Before treatment	2.8 ± 0.71	3.41 ± 1.53
		1 wk after treatment	3.1 ± 0.59	5.01 ± 0.58
		2 wks after treatment	3.05 ± 0.42	5.63 ± 0.44
		3 wks after treatment	2.9 ± 0.67	5.57 ± 0.63
		4 wks after treatment	3.1 ± 0.73	5.467 ± 0.7
		Entire treatment period	3.04 ± 0.59	5.42 ± 0.63*
		P value versus before treatment	NS 0.3345	* <0.0001
	Postmenopausal	Before treatment	1.45 ± 0.47	1.84 ± 0.93
		1 wk after treatment	1.9 ± 0.85	4.21 ± 0.85
		2 wks after treatment	1.55 ± 0.45	4.45 ± 0.64
		3 wks after treatment	2.1 ± 0.91	4.72 ± 0.66
		4 wks after treatment	1.75 ± 0.52	4.75 ± 0.85
		Entire treatment period	1.82 ± 0.7	4.53 ± 0.77*
		P value vs before treatment	NS 0.1698	* <0.0001
Orgasm	Premenopausal	Before treatment	3.05 ± 0.6	3.28 ± 0.51
		1 wk after treatment	3.25 ± 0.54	4.53 ± 0.63
		2wks after treatment	3.15 ± 0.33	5.1 ± 0.68
		3wks after treatment	3.15 ± 0.54	5.12 ± 0.87
		4wks after treatment	3.4 ± 0.43	5.15 ± 0.85
		Entire treatment period	3.24 ± 0.46	4.97 ± 0.79*
		P value vs before treatment	NS 0.3373	* <0.0001
	Postmenopausal	Before treatment	1.5 ± 0.55	2.1 ± 1.1
		1 wk after treatment	2.15 ± 0.74	4.45 ± 0.96
		2 wks after treatment	1.8 ± 0.6	4.77 ± 0.91
		3 wks after treatment	2.2 ± 0.71	4.7 ± 1.06
		4 wks after treatment	2.2 ± 0.68	4.64 ± 0.42
		Entire treatment period	2.08 ± 0.67	4.64 ± 0.86*
		P value vs before treatment	NS 0.0283	* <0.0001

The data represent mean ± SD.

*$P < 0.0001$ for triple cream vs placebo cream, with regard to the entire treatment period.

TABLE 3. Comparison of Desire and Arousal Mean Scores of Premenopausal and Postmenopausal Women With FSD Who Received Placebo or Active Cream

Sexual Domain	Menopausal Status	Time	Placebo Cream	Triple Cream
Desire	Premenopausal	Before treatment	3 ± 0.55	2.52 ± 0.76
		1 wk after treatment	3.15 ± 0.53	4.320 ± 0.72
		2 wks after treatment	3 ± 0.45	5.16 ± 0.55
		3 wks after treatment	2.92 ± 0.59	5.48 ± 0.71
		4 wks after treatment	3.15 ± 0.53	5.4 ± 0.75
		Entire treatment period	3.06 ± 0.51	5.1 ± 0.81*
		P value vs before treatment	NS 0.7865	* <0.0001
	Postmenopausal	Before treatment	2.17 ± 0.64	2.16 ± 0.67
		1 wk after treatment	2.47 ± 0.81	4 ± 1.1
		2 wks after treatment	2.17 ± 0.55	4.36 ± 1.19
		3 wks after treatment	2.47 ± 0.67	4.52 ± 0.71
		4 wks after treatment	2.32 ± 0.67	4.32 ± 0.69
		Entire treatment period	2.36 ± 0.66	4.3* ± 0.94
		P value vs before treatment	NS 0.4756	* <0.0001
Arousal	Premenopausal	Before treatment	2.85 ± 0.51	2.72 ± 0.56
		1 wk after treatment	3.1 ± 0.57	4.84 ± 1.00
		2 wks after treatment	3.2 ± 0.53	5.3 ± 0.54
		3 wks after treatment	3.04 ± 0.44	5.4 ± 0.73
		4 wks after treatment	3.15 ± 0.42	5.38 ± 0.56
		Entire treatment period	3.11 ± 0.47	5.23 ± 0.75*
		P value vs before treatment	NS 0.1751	* <0.0001
	Postmenopausal	Before treatment	2.14 ± 0.52	1.88 ± 0.52
		1 wk after treatment	2.36 ± 0.71	4.5 ± 1.06
		2 wks after treatment	2.17 ± 0.47	4.42 ± 0.97
		3 wks after treatment	2.51 ± 0.59	4.7 ± 1.04
		4 wks after treatment	2.36 ± 0.56	4.54 ± 1.194
		Entire treatment period	2.35 ± 0.57	4.54 ± 0.96*
		P value vs before treatment	NS 0.3410	* <0.0001

The data represent mean ± SD.

*$P < 0.0001$ for triple cream vs placebo cream, with regard to the entire treatment period.

at the end of the second week, both scores increased significantly to 5.3 ± 0.54 and 5.1 ± 0.68, respectively ($P < 0.001$; Tables 2 and 3). Similarly, the improvement in sexual arousal and orgasmic sexual domain were more marked in postmenopausal women. Their mean scores increased from 1.88 ± 0.52 and 2.1 ± 1.1, the baseline score, to 4.5 ± 1.06 and 4.45 ± 0.96, respectively, after 1 week on the use of active cream. These scores became 4.42 ± 0.97 and 4.77 ± 0.91, respectively, at the end of the second week ($P < 0.0001$). In comparison with postmenopausal women who received the placebo cream, highly significant increase in arousal and orgasm scores were observed in postmenopausal women who received the active cream (Tables 2 and 3).

The finding of the current pilot study indicated a significant increase in scores of desire and satisfaction domains compared to the baseline scores in premenopausal and postmenopausal patients who received the active cream. In premenopausal cases, mean ± SD scores of desire and satisfaction increased significantly from 2.52 ± 0.76 and 3.41 ± 1.53, baseline scores, to 5.1 ± 0.81 and 5.42 ± 0.63, respectively, at the end of the study ($P < 0.0001$; Tables 2 and 3). In postmenopausal cases, they increased significantly from 2.16 ± 0.67 and 1.84 ± 0.93 to 4.3 ± 0.96 and 4.75 ± 0.96, respectively ($P < 0.0001$; Tables 2 and 3). In the present study, the active cream showed greater improvement of patients' desire and satisfaction compared to the placebo cream in premenopausal and postmenopausal patients (Tables 2 and 3).

The differences between placebo and the tested drug, with regard to the pain and lubrication domain scores for the entire period were nonsignificant in the premenopausal patients (5.1 ± 0.75 and 5.16 ± 0.62 vs 4.950 ± 0.72 and 4.77 ± 1.1, respectively), whereas there was marked improvement in lubrication in postmenopausal women who received active cream compared to placebo scores (4.68 ± 0.57 vs 3.88 ± 0.72; $P < 0.001$; Table 4). The mean change of pain and lubrication scores from baseline to week 4 showed highly significant differences between the active cream and placebo (Fig. 1).

Safety

The active cream was well tolerated by the premenopausal and postmenopausal women. No serious events were reported during the use of the testing cream or the placebo cream. There were

TABLE 4. Comparison of Pain and Lubrication Mean Scores of Premenopausal and Postmenopausal Women With FSD Who Received Placebo or Active Cream

Sexual Domain	Menopausal Status	Time	Placebo Cream	Triple Cream
Pain	Premenopausal	Before treatment	5.2 ± 0.52	3.1 ± 1.47
		1wk after treatment	5.1 ± 0.7	4.13 ± 1.01
		2wks after treatment	5.05 ± 0.71	4.67 ± 1.01
		3wks after treatment	5.15 ± 0.66	5.12 ± 1.04
		4wks after treatment	5.35 ± 0.47	5.15 ± 1.1
		Entire treatment period	5.16 ± 0.62	Ns (P = 0.0621) 4.77 ± 1.1
		P value versus before treatment	NS 0.8761	* <0.0001
	Postmenopausal	Before treatment	4.75 ± 0.54	1.65 ± 0.74
		1wk after treatment	4.4 ± 0.68	4.56 ± 1.16
		2wks after treatment	4.4 ± 0.71	4.69 ± 0.95
		3wks after treatment	4.55 ± 0.74	4.53 ± 0.97
		4wks after treatment	4.65 ± 0.6	4.24 ± 0.92
		Entire treatment period	4.5 ± 0.66	4.51 ± 0.99 Ns P = 0.9728
		P value versus before treatment	NS 0.3283	* P < 0.0001
Lubrication	Premenopausal	Before treatment	4.65 ± 0.78	3.24 ± 0.41
		1wk after treatment	5.02 ± 0.78	4.48 ± 0.66
		2wks after treatment	5.14 ± 0.85	5.1 ± 0.64
		3wks after treatment	5.02 ± 0.86	5.16 ± 0.74
		4wks after treatment	5.17 ± 0.64	5.1 ± 0.7
		Entire treatment period	5.1 ± 0.75	Ns (P = 0.3834) 4.950 ± 0.72
		P value versus before treatment	NS 0.1499	* <0.0001
	Postmenopausal	Before treatment	3.52 ± 0.71	2.48 ± 1.19
		1 wk after treatment	3.97 ± 0.92	4.78 ± 0.65
		2 wks after treatment	3.75 ± 0.68	4.9 ± 0.43
		3 wks after treatment	4.01 ± 0.69	4.6 ± 0.55
		4 wks after treatment	3.79 ± 0.68	4.46 ± 0.58
		Entire treatment period	3.88 ± 0.72	4.68 ± 0.57*
		P value vs before treatment	NS 0.2188	* <0.0001

The data represent mean ± SD.

*P < 0.0001 for triple cream vs placebo cream, with regard to the entire treatment period.

no discontinuation cases due to the use of placebo or the tested cream. No incidence of urogenital events except burning and itching in 2 patients The other reported adverse events with the use of active cream was a headache in 2 patients and mild hypotension in one patient.

DISCUSSION

Female sexual dysfunction is a complex, persistent, and recurrent problems with sexual response, desire, orgasm, or pain that may cause marked distress and interpersonal difficulty. Compared with the extensive research and treatment of male sexual dysfunction, research on FSD is less significant and received little attention. Except for psychological therapy, pharmacotherapy of FSD is greatly limited.[21]

In the present randomized, placebo-controlled pilot trial in 60 women with FSD, 4 weeks' treatment of premenopausal and postmenopausal women with the active cream significantly caused improvement in FSFI total scores, the primary end point, which was described by Rosen et al[18] as the successful published instrument validated on a sample of women with clinically diagnosed FSD. It has also demonstrated the marked improvement of orgasmic and arousal sexual domains, the secondary end point, in premenopausal and postmenopausal women who received active cream compared with that received placebo cream. Unlike with flibanserin, the improvement in orgasmic and arousal sexual domains with overall sexual life was obtained with the active cream as early as the first week of use.

The baseline FSDS-R total score of the premenopausal (32.27 ± 8.19) and postmenopausal (33.07 ± 9.36) women in this trial were broadly similar to those of the premenopausal (32.8 ± 9.0)[22] and postmenopausal (31.2 ± 9.2) women who participated in a recent hypoactive sexual desire disorder registry.[23] In addition, the mean baseline FSFI total score in our trial was 19.9 ± 3.37 in the premenopausal women, which were similar to scores in the premenopausal women (19.0 ± 6.1) who participated in the recent registry.[22] However, baseline measures of the FSFI total score were lower in the postmenopausal women in our trial (13.81 ± 3.38) than in studies of flibanserin in postmenopausal women (15.9 ± 6.6).[23] The magnitude of improvement in FSFI-total scores with triple cream was higher than with flibanserin trials in the premenopausal and postmenopausal women, with

FSFI total score improvements of 4.1 to 5.3 points in the DAISY, VIOLET, and BEGONIA trials[22,23] versus 13.35 ± 4.646 and 14.85 ± 6.33 points in the premenopausal and postmenopausal women, respectively, in our trial. However, the changes from baseline of FSFI total score in women who received placebo cream and the active cream were smaller in this trial than that in studies of alprostadil cream published by Liao et al.[24] The changes of FSFI total score points in our trial were 1.7 ± 1.886, 13.35 ± 4.646, and 14.85 ± 6.33 in the placebo-treated premenopausal and postmenopausal groups, respectively. In alprostadil cream trial, the FSFI total score change points were 14.68, and 22.89 for placebo and treated groups, respectively. The high FSFI total score change points of alprostadil cream trial may due to the high value of FSFI score change points of their placebo group.

The combination of theophylline, a phosphodiesterase inhibitor, and isosorbide dinitrate, nitric oxide donor in the triple cream, will augment the production of cyclic GMP with high vasodilation action.[12] The active cream can produce smooth muscle relaxation in the genital area, an action which leads to reduced sexually related distress. In addition, topical application of triple cream leads to clitoral, vulval, vestibular, and vaginal vasodilatation. Therefore, it is postulated that the triple cream acts on the genital chemoreceptors and facilitates sexually related nerve reflexes, where the sensitivity of sensory receptor will be augmented.

Many investigators suggested that nitric oxide can be used as a dilator of vascular smooth muscle in the cavernous body of the clitoris and have vaginal muscle relaxant effects and, by a mechanism similar to that seen in men with erectile dysfunction, it also may prove effective in the treatment of women suffering from sexual dysfunction.[25] Liao et al[24] also demonstrated that the application of topical alprostadil, applied to the clitoris and the G-spot in the vagina before vaginal intercourse, significantly improved FSFI scores and sexual arousal rates relative to baseline scores. Dirim et al[26] reported that genital blood flow plays an important role in female sexual function. They observed that topical misoprostol can significantly increase clitoral blood flow. They concluded that increased genital blood flow may be a therapeutic approach for female sexual dysfunction.

Recently, Pelekanos et al[27] demonstrated the positive effect of the new topical vasodilating cream (NTVC) for enhanced lubrication, genital sensation, intercourse, and overall sexual experience. They suggested that the positive subjective trends combined with a significant and substantial increase in clitoral blood flow may result in enhanced female sexual satisfaction. Moreover, Goldstein et al[28] suggested that the vasodilating effect of topical alprostadil induced significant sustained increases in genital temperature of vestibule, clitoris, and vulva within 20 minutes, an action that leads to enhancement of sexual functions.

The active cream also contains co-dergocrine that increases cerebral blood flow and stimulates the central dopamine receptor, whereas dopamine and norepinephrine putatively increase sexual desire and arousal.[12] Previous work has highlighted the importance of cerebral activation in sexual arousal.[29] Lee et al[24] found that alprostadil affects patterns of cerebral activation at functional magnetic resonance imaging and postulated that, when applied to the genitals, the drug might not act only on local vascular dilation but also on local chemoreceptors, which could facilitate sexually related nerve reflexes. The central effect of triple cream may be behind the higher efficacy of triple cream in improving the orgasmic and arousal disorders in premenopausal and postmenopausal women more than other vasoactive drugs.

In this pilot study, there are a number of important limitations. This study had a small sample size from a single community. Only one dose of the cream was tested. The duration of study was short. There was no serum drug monitoring for the active ingredients of triple cream. The relation between topical application of the cream on the dorsum of hand or genital area and central nervous system actions was not studied. In addition, the assessment of genital blood flow changes in women using the triple cream was not demonstrated. Further investigations with a large number of patients are warranted to verify the current results.

In conclusion, the present randomized pilot trial suggests a potential novel therapeutic approach for FSD by topical cream containing three vasodilators in small concentrations may act synergistically, with a safer profile for premenopausal and postmenopausal women with FSD. The active cream mostly exerts its beneficial effects via increased cGMP and central effects that ultimately result in enhancing most of the sexual functions. Further studies are recommended to be conducted using a large number of patients and different doses of triple cream.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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