Effect of Red Clover Vaginal Cream on Dyspareunia and Sexual Satisfaction in Postmenopausal Women: A Triple-Blinded Clinical Trial

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ABSTRACT

Introduction: One of the common complaints in postmenopausal women is the decreased sexual activity, desire, and satisfaction due to the reduction of estrogen and androgen hormones. This study aimed to investigate the effect of red clover vaginal cream (RCVC) on dyspareunia and sexual satisfaction in postmenopausal women. Method: This study was performed as a triple-blinded clinical trial on 76 postmenopausal women referred to Health Center No. 1 in Ahvaz during 2018. The women were divided randomly in two groups of A and B. Group A received RCVC 2% and Group B used a placebo applicator every night for eight weeks. It should be noted that the severity of dyspareunia was assessed with a checklist and sexual satisfaction by Larson questionnaire. Data were analyzed using paired t-test, Chi-square, Mann-Whitney, independent t, and Friedman tests along with SPSS software (Version 22) at a significance level of $p < 0.05$. Results: Mean post-intervention score of sexual satisfaction in RCVC group was significantly higher than the placebo group ($p < 0.001$). In the subjects who used RCVC, there was a significant improvement in pain during intercourse ($p < 0.001$). Conclusion: Based on the findings of this study, the use of RCVC for 8 weeks could increase the libido, and reduce the pain during intercourse. More studies are needed to prove the effect and safety of this herbal drug.

Key Words: *Red clover, Postmenopausal women, Sexual satisfaction, Painful intercourse.*

eIJPPR 2019; 9(4):23-29

HOW TO CITE THIS ARTICLE: Khayatan J, Iravani M, Moghimipour E, Haghighizade M.H., Jelodarian J, (2019). Effect of red clover vaginal cream on dyspareunia and sexual satisfaction in postmenopausal women: A triple-blinded clinical trial, Int. j. pharm. phytopharm. res. 9 (4), pp.23-9.

INTRODUCTION

Women's health provision is of paramount importance as they are the pillar of the family and society [1]. Researchers believe that menopause is the last natural event in the physical and sexual life of any woman, which begins with the cessation of menstruation resulted from the ceased ovarian function due to the dropped estrogen levels, disrupting female sexual function and reducing her sexual activity [2]. The age of menopause in women is naturally in the range of 42-58 years with an average of

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest .
Received: 11 March 2019; **Revised:** 18 July 2018; **Accepted:** 23 July 2019

51.4 years [3]. This stage of life for women is associated with several problems such as physical, anatomical, and clinical changes [4]. According to existing statistics, there are currently 470 million women over 50 years worldwide [5]. Since 1970, the number of elderly people has observed an increase compared to the number of young people. It is predicted that there will be one elderly per five people by 2050, of which women are expected to encounter with injuries and complications due to the presentation of menopause symptoms [6]. Reductions in estrogen and androgen hormones during menopause lead to the appearance of menopausal symptoms. Early symptoms include atrophic changes in the urinary tract, breast shrinkage and pain, axillary and pubis hair loss, phalacrosis, hand and feet tingling, headache, dizziness, tinnitus, syncope, dyspnea, weakness, anorexia, constipation, diarrhea, arthralgia, cognitive impairments, myalgia [7], burning and itchy skin, fatigue, hot flashes, nausea and vomiting, genitalia atrophy with discharge, burning, itching, infection, bleeding, pain when urinating, frequent urination, suprapubic pain [8], decreased sexual desire and response, painful intercourse, and sleep disorders [9]. Late symptoms include the increased risk of cardiovascular diseases, hypertension [7], and osteoporosis [9]. Vaginal atrophy leads to the increased vaginal dryness, dyspareunia, and decreased sexual pleasure during menopause. Pain and spotting during sexual intercourse are resulted from the vaginal mucosal vulnerability, with likely occurrence of frequent and urgent urination without infection [10]. As it has been predicted, vaginal dryness occurs in more than 50% of postmenopausal women, which exacerbates with rising age [11]. As far as possible, such women should avoid sexual activity due to the painful intercourse caused by vaginal dryness. Under such conditions, sexual quality and satisfaction decrease resulting in the appearance and intensification of vaginal atrophy symptoms. In other words, many women believe that aging expose them to symptoms of menopause. Some of such women have also been observed to be unaware of their own therapies, and of changing their lifestyles to cope with menopause and its symptoms [12]. Sexual satisfaction has many dimensions, including physiological and emotional dimensions of sexual relation. It brings physical pleasure and also influences all the emotions remaining after negative and positive dimensions of sexual relation [13]. As such, people with high sexual satisfaction declare a better quality of life than those without sexual satisfaction [14].

Because there is an inverse relationship between sexual satisfaction and menopause, experts have proposed two types of treatments for quality development and improvement of sexual satisfaction during menopause. The first category consists of hormone therapy, and the second is the complementary therapies [15]. One of the ways for developing sexuality during menopause and resolving the related disorders is the treatment with estrogen usage. However, it should be noted that only less than 20% of postmenopausal women receive estrogen. A study conducted in 2001 in Iran determined that 8.57% of postmenopausal women used hormone replacement therapy indicating that some women were likely inclined to use a standard hormone replacement therapy [16]. The results of the study showed that estrogen therapy, both topically and systemically, increased the tissue thickness and collagen levels. Treatment with synthetic estrogen has not been accepted by many women yet, due to the concerns about its complications [17, 18]. It raises the risk of cardiovascular, thromboembolic, endometrial hyperplasia, and breast cancer, rendering women to show more tendencies to alternative therapies for improving menopausal symptoms than estrogen therapy [19]. The second group is phytotherapy, which is nowadays increasingly used in women. Researchers have stated that some herbs contain effective substances that can be used to treat menopausal disorders [20]. Among the alternative treatments, phytoestrogens (estrogen-containing plants) have been more appropriate [21, 22]. They are structurally similar to 17 beta-estradiol and act similar to estrogen in the body [23, 24]. Herbal sources contain phytoestrogens which include fenugreek, soybean, licorice, and red clover [25, 26]. Red clover (*Trifolium pratense*) is one of the phytoestrogens that has been studied in other countries, and it has been anticipated to be able to show acceptable effects on the relief of menopause symptoms [27]. Lipovac et al. (2011) studied the effect of red clover supplement on improving the health of skin, hair, mood, libido, and fatigue in postmenopausal women, and proposed the use of red clover due to its phytoestrogenic property in controlling menopausal symptoms [28]. Also, another study by Thorup et al. (2015) demonstrated that the oral supplementation of red clover had beneficial effects on bone health in postmenopausal women [29]. Since many attempts have been done to prevent and treat menopausal complications, sexual relation problems in this period have still been highly underestimated. So far, no studies have been conducted in the country on the effect of red clover on sexual satisfaction and dyspareunia in postmenopausal women. This research, therefore, sought to investigate the effect of RCVC on sexual satisfaction and dyspareunia in postmenopausal women. In case of the proved effectiveness of this drug, an effective step can be taken in promoting the health of postmenopausal women.

METHOD

This triple-blinded clinical trial aimed to investigate the effect of RCVC on dyspareunia severity and sexual satisfaction in postmenopausal women referred to Health Center No. 1 in Ahvaz, Iran, during 2018. Sampling was carried out after obtaining permission from the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.REC.1396.728) registered as (IRCT20171224038036N2) at the Clinical Trial Center. In this study, sampling was done randomly using computer numbers. A sample size of 32 per group was determined according to the sample size estimation through the comparison of mean values in two independent populations with a power of 90%, and a confidence coefficient of 90%. With a sample drop probability of 20%, 38 subjects were considered for each group. Inclusion criteria were dyspareunia, age range of 45-65, women with menstrual cessation for one year or having a hormonal test with a FSH level of over 40 IU, and monogamous women with sexual intercourse. Exclusion criteria included vaginal bleeding with unknown cause, consumption of isoflavones in the diet, vaginal infection, hormone therapy, or sex hormone use 8 weeks before the study, and smoker and alcoholic women. In order to select the samples, the researcher first referred to the selected health center on all weekdays. Among the referring individuals, 76 eligible volunteer women with postmenopausal status were explained about the goals and the procedure of this study. It is worth mentioning that a written consent and the trust of individuals in the confidentiality of their information were received in advance. Demographic information was completed in the personal profile questionnaire by the participants. Before and after the treatment, dyspareunia severity was self-reported at 4 degrees (0 = no, 1 = mild, 2 = moderate, and 3 = severe) by the participants using a checklist. Sexual satisfaction level was determined using Larson sexual satisfaction questionnaire with 25 questions. The responses were scored based on 5-point Likert scale, with 1 and 5 points for the answers from “never” to “always”; respectively. In questions 1, 2, 3, 10, 12, 13, 16, 17, 19, 21, 22, and 23, the responses were scored as never = 1 to always = 5 points. In questions 4, 6, 5, 6, 7, 8, 9, 11, 14, 15, 18, 20, 24, and 25, the responses were scored in reverse so that never = 5 and always = 1. The points of 25-50 showed sexual dissatisfaction, 51-75 low sexual satisfaction, 76-100 moderate sexual satisfaction, and 101-125 high sexual satisfaction [30, 31]. In this research, the validity of the questionnaires was determined using the content validity method. To this end, the questionnaires were first prepared by the researcher with necessary examinations, and then scrutinized by 10 faculty members from the Faculty of Nursing and Midwifery at Ahvaz Medical Sciences University. A final version was drafted after making necessary changes and amendments. It should be noted that the reliability coefficient of 83% was reported for Larson questionnaire by Pazandeh et al. [32].

RCVC was prepared in the laboratory of the Faculty of Pharmacy, Ahvaz University of Medical Sciences. Each participant was given an applicator and six 50 g tubes for nightly use within 8 weeks. The way of drug use was described to the subjects both personally and verbally, and the questionnaires were completed by them before and after the intervention. They were also asked to use no other herbal or hormonal remedies during this period. The envelopes were packed by an uninformed individual in collecting and analyzing data so that the user, prescriber, and data analyzer were not aware of the applied intervention. At the end of the 8th week, the completed questionnaires were collected from the subjects, and all data were analyzed by SPSS 22 statistical software. Paired t-test, Mann-Whitney, Chi-square, independent t, and Friedman tests were used for data analysis with a significance level of $P < 0.05$.

FINDINGS

In this study, there were no statistically significant differences in demographic data between the two groups ($P < 0.22$). According to Table 1, mean ages of RCVC and placebo groups were 56.18 ± 3.55 years and 56.0 7 ± 3.63 years; respectively. Mean menopausal ages in RCVC and placebo groups were 49.60 ± 3.04 years and 50.26 ± 1.34 years; respectively. BMI averaged 29.75 ± 3.46 and 29.20 ± 2.71 kg/m^2 in RCVC and placebo groups; respectively. The highest frequency of sexual activity was once a week, with 68.4% and 60.5% in RCVC and placebo groups; respectively.

Table 1. The demographic information of individuals of the research units

Group / Demographics	RCVC n = 38	Placebo n=38	p-value
	Mean ± SD		
Age (year)	56·18 ± 3/55	56·07 ± 3·63	0.89
Menopausal age (year)	49·60± 3·04	50·26 ± 1·34	0.22
Menarcheal age (year)	12·21± 0·52	12·39± 0·75	0.22
BMI	29·75± 3·46	29·20± 2·71	0.44
	Number (%)		

Education	Illiterate	0(0%)	2(5·3%)	0.10
	Under diploma	21(55·3%)	23(60·5%)	
	Diploma	13(34·2%)	13(34·2%)	
	Academic	4(10·5%)	0(%0)	
Occupation	Housewife	33(86·8%)	37(97·4%)	0.10
	Retired	5(13·2%)	1(2·6%)	
Economic status	Weak	0(0%)	0(0%)	0.43
	Medium	20(52·6%)	17(44·7%)	
	Good	17(44·7%)	21(55·3%)	
	Excellent	1(2·6%)	0(0%)	
Intercourse per week	0	0(%0)	0(0%)	0.63
	1	26(68·4%)	23(60·5%)	
	2	10(26·3%)	11(28·9%)	
	3	(5·3%) 2	4(10·5%)	
	4	0(%0)	0(0%)	

In terms of the economic status, 20 (52.6%) and 20 (55.3%) of the subjects in RCVC and placebo groups were in the middle and good classes; respectively. With respect to the employment status, 33 (86.8%) and 37 (97.4%) were housewives in RCVC and placebo groups, respectively. According to Table 2, Friedman test showed a significant difference in dyspareunia severity before and after the treatment in RCVC group compared to placebo treatment ($p < 0.001$). In the first visit, 26 (68.4%), 9 (23.7%), 2 (5.3%), and 1 (6.2%) of the subjects in RCVC group had severe, moderate, mild, and no dyspareunia; respectively. In the second visit, mild, moderate, severe, and no dyspareunia were observed in 25 (65.8%), 3 (7.9%), 2 (5.3%), and 8 (21.1%) of the participants with significant differences ($p < 0.001$). After 8 weeks of intervention, 34 (89.5%), 2 (3.5%), 1 (6.2%), and only 1 (2.6%) of the subjects presented zero, moderate, mild, and severe dyspareunia suggesting a positive effect of RCVC. The treatment of dyspareunia between the two groups of RCVC and placebo at follow-up periods (every 2 weeks) was compared by the Mann-Whitney test. There was a significant difference between the two groups in the treatment of dyspareunia severity ($p < 0.001$).

Table 2. Comparison of dyspareunia severity before the intervention and after 2, 4, and 8 weeks of treatment in the two groups of the research subjects

Group / Time / Dyspareunia		RCVC n=38	Placebo n=38	p-value
		Number (%)		
Pre-treatment	Not present	1(2·63%)	0(0%)	0.29
	Mild	2(5·3%)	2(5·26%)	
	Medium	9(23·7%)	6(15·8%)	
	Severe	26(68·4%)	30(78·9%)	
Week 2	Not present	1(2·6%)	0(0%)	<0.001
	Mild	5(13·2%)	2(5·3%)	
	Medium	28(73·7%)	19(50%)	
	Severe	4(10·5%)	17(44·7%)	
Week 4	Not present	8(21·1%)	1(2·6%)	<0.001
	Mild	25(65·8%)	16(42·1%)	
	Medium	3(7·9%)	6(15·8%)	
	Severe	2(5·3%)	15(39·5%)	
Week 8	Not present	34(89·5%)	2(5·3%)	<0.001
	Mild	1(2·6%)	15(39·5%)	
	Medium	2(5·3%)	6(15·7%)	
	Severe	1(2·6%)	15(39·5%)	
p-value		<0.001	<0.001	

Table 3. Comparison of mean sexual satisfaction scores between the groups receiving RCVC and placebo treatments

Group / Sexual satisfaction scores	RCVC n=38	Placebo n=38	p-value
	Mean ± SD		
Pre-intervention	58·81± 7·82	58·65± 7·24	0.92
Post-intervention	77·92± 6·00	62·47± 7·86	<0.001

According to Table 3, the mean score of sexual satisfaction was 58.81 ± 7.82 before the intervention in RCVC group, which significantly rose to 77.92 ± 6.00 after the intervention ($P < 0.001$).

DISCUSSION

The present study aimed to investigate the effect of RCVC on sexual satisfaction and dyspareunia in postmenopausal women. The results showed that the use of RCVC for 8 weeks resulted in greater sexual

satisfaction and lower dyspareunia in postmenopausal women than placebo users. Nowadays, the administration of synthetic estrogen is common in the treatment of menopausal disorders and complications [21]. Over the past ten years, however, women were mostly inclined to use natural replacement therapy to eliminate menopausal complications. Therefore, complementary therapies were increased as compared to the estrogen therapy [33]. Lipovac et al. (2009) launched a research on the use of isoflavones (red clover extract) to improve the symptoms of anxiety and depression in postmenopausal women. They found that the use of this extract could both reduce the symptoms of anxiety and depression, and increase the sexual satisfaction in postmenopausal women [27]. Some researchers detected a significant positive relationship between libido and depression. They believed that mental and emotional distress and interpersonal distress can be resulted from the ailments of dropped libido, ultimately leading to the decreased general health status [34]. Salehi et al. (2012) also reported the effect of red clover on hot flashes in postmenopausal women. They used red clover extract for 8 weeks to treat hot flashes in postmenopausal women, and concluded that red clover could be suggested as a treatment for hot flashes in postmenopausal women [35]. Hidalgo et al. used 80 mg of isoflavone (red clover) in postmenopausal women for 90 days, and reported a total score of 27.2 ± 7.7 for menopausal symptoms at the treatment onset, which then reached 5.9 ± 3.9 based on the Kupperman index showing a significant decrease [36]. An increase in elasticity, mucosal enhancement, and blood flow occurred as a result of estrogen hormone. This hormone also reduced the sensory threshold of the vulvovaginal area, irritation, and itching, and stimulates sexual arousal and pleasure [37, 38]. In addition, Rosa lima et al. (2013) studied the effect of soybean isoflavone vaginal gel on vaginal atrophy symptoms in postmenopausal women for the severity of dyspareunia, and noticed the improvements in the soybean group after 12 weeks ($P < 0.001$) [33], which was in line with the present research. Yaralizadeh et al. (2016) examined the effect of fennel vaginal cream on sexual satisfaction and dyspareunia in postmenopausal women and showed that the use of this cream for 8 weeks had significant effects on decreasing dyspareunia and increasing sexual satisfaction compared to placebo group ($P < 0.001$), which was consistent with the results of this study [39]. Mazaalzadeh et al. (2018) investigated the effect of fenugreek vaginal cream on sexual satisfaction and dyspareunia in postmenopausal women. After 8 weeks, the results showed a significant increase in sexual satisfaction score and a decrease in dyspareunia ($P < 0.001$) [40] as was also found in this study. In a study entitled "the effect of red clover isoflavin extract on menopausal symptoms and vaginal cytology in postmenopausal women, Tedeschi et al. (2012) concluded that red clover could be used for dyspareunia treatment and sexual satisfaction rise [41]. Del Giorno et al. also investigated the effect of red clover extract on the physical and sexual characteristics of postmenopausal women. They recommended oral use of 40 mg isoflavone capsules to postmenopausal women for 12 months, which resulted in some reductions in menopausal symptoms, though, there were no improvements in their sexual satisfaction [42]. The ineffectiveness of isoflavones has been seen in one fifth of the population with no specific justifications [43] suggesting that some previous studies on the impacts of isoflavones have not yielded satisfying therapeutic outcomes.

Many medicinal plants have been tested to confirm their phytoestrogenic properties. Moreover, the use of phytoestrogens for the relief and reduction of menopausal symptom severity has lesser complications than chemical drugs. It may, therefore, be hoped that confirming the effect of RCVC on the sexual satisfaction and dyspareunia of postmenopausal women can be an effective step towards improving the health of postmenopausal women.

CONCLUSION

Based on the findings of this study, the use of RCVC for 8 weeks seemed to increase the libido and reduce pain during intercourse. More studies are needed to prove the effect and safety of this herbal drug.

ACKNOWLEDGEMENTS

This research was a part of a master's thesis by Jamileh Khayatan with the ethics code of IR.AJUMS.REC.728 dated 30.08.2017, registered as IRCT20171224038036N2 at Clinical Trial Registration Center. The research group hereby would like to appreciate all the participated women and the Health Center No. 1 in eastern Ahvaz.

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ISSN (Online) 2249-6084 (Print) 2250-1029

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