The effect of oxytocin vaginal gel on vaginal atrophy in postmenopausal women: a randomized controlled trial

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Abstract

Background: Around 90% of postmenopausal women are suffering from vaginal atrophy. This study aimed to evaluate the effect of oxytocin vaginal gel on vaginal atrophy among postmenopausal women. Methods: This was a randomized controlled trial that was conducted on 96 postmenopausal women who suffered from vaginal atrophy. The inclusion criteria were: literate women, age 40-60, at least one year passed from their last menstrual period or the level of FSH>40IU, monogamous women with the sexual relationship. Women in the intervention group, requested to use one applicator of 400 IU oxytocin gel per night and women in the placebo group used placebo each night. The subjective symptoms of vaginal atrophy, vaginal PH, maturation index were measured before and after the intervention. Results: The number of superficial cells was increased significantly in the oxytocin group compared to placebo (38.7±7.18 vs. 3.69±2.76, p=0.0001), while the number of parabasal cells was decreased significantly in the oxytocin compared to placebo after the intervention. The improvement of the maturation index was more dominant in the oxytocin group (increased from 7.76±4.68 to 52.48±7.54) in comparison to the placebo group (increased from 8.58±4.35 to 13.25±5.06). The PH of the vagina decreased significantly in the oxytocin group in comparison to the placebo group (p=0.0001). After eight weeks, 88.6% and 7.1% of women in the oxytocin and placebo groups did not show the severe symptoms of vaginal atrophy (p=0.001) Conclusion: The results of this study showed that eight week intervention with oxytocin vaginal gel (400 IU) could significantly improve the vaginal maturation index, subjective symptoms of vaginal atrophy and reduce the PH of the vagina. Using this medication in women who have a contraindication for hormone therapy is recommended.

Background

Vulvovaginal atrophy (VVA) is a phenomenon that happens mostly after menopause and affects around 90% of postmenopausal women [1]. Only a quarter of women with VVA seek treatment [2]. Women with VVA may experience symptoms such as dryness, irritation, itching, burning and dyspareunia [3]. The VVA is often due to the estrogen deficiency after menopause and may negatively affect the quality of life [1]. The low level of estrogen decreases the blood flow to the vulvovagina and making the tissue of vagina to be thinner and prone to bleeding and infection. On the other hand, the low level of estrogen may decrease the number of lactobacilli and causing increased PH of vagina [4].

The first line treatment of VVA is continuous sexual relationship, using non-hormonal over the counter vaginal lubricant and lifestyle change [5]. Women can use vaginal lubricants before each sexual relationship or vaginal lubricant with long-term impact in which they should use regularly (two or three times a week) [6].

The systemic and local estrogen is recommended for treatment of VVA in postmenopausal women, in which low dose local vaginal cream preferred [7]. According to the US Department of Health and Human Services, Food and Drug Administration, estrogen is recommended for treatment of vasomotor symptoms and volvovaginal atrophy in postmenopausal women [8]. Although hormone therapy may alleviate the

short-term and long term complications of menopause such as hot flashes, night sweats, mood swings and osteoporosis, it may increase the risk of breast and endometrial cancer [9].

Because of adverse effects of HRT, some women prefer not to use this method for alleviating of vaginal atrophy, and they tend to use non-hormonal medication for this matter [10]. Studies showed that some herbs and vitamins such as fennel [11], vitamin E [12], vitamin D [13], could reduce vaginal atrophy in postmenopausal women. Oxytocin is a hormone and a neurotransmitter of the brain and its main role is flow of milk from the breasts [14]. Oxytocin also promotes positive social behavior, stress regulation, [15] and female sexual arousal [16]. The role of oxytocin on vaginal atrophy was examined first by Al-Saqi et al, and they found that oxytocin is a useful means for reducing vaginal atrophy in postmenopausal women [17]. Recently another study examined the effect of oxytocin vaginal gel on vaginal atrophy and the results showed that oxytocin could significantly reduce the vaginal atrophy after 30 days of intervention [18]. There are only few studies that evaluated the impact of vaginal gel of oxytocin on vaginal atrophy that one of they followed participants for four weeks and the other for seven weeks. As using non-hormonal methods for vaginal atrophy needs more investigation, therefore, we intended to evaluate the effect of intra-vaginal oxytocin gel on vaginal atrophy in postmenopausal women in a longer period.

Methods

This was a randomized controlled trial that was conducted on 96 postmenopausal women who suffered from vaginal atrophy in two health centers in Ahvaz, Iran. The inception date of this study was in April 2018 and the completion date was September 2018. The protocol of this study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ref No: IR.AJUMS.REC.1396.720). This study was registered in the Iranian Registry for Clinical Trials (Ref No: IRCT20160602028220N2). This study adheres to CONSORT guidelines for randomized controlled trial (CONSORT checklist, supplementary material). The inclusion criteria were as follow: literate women, age 40–60, at least one year passed from their last menstrual period or the level of FSH>40IU, monogamous women with sexual relationship. Women with following criteria were excluded from the study: vaginal infection, women who used hormone replacement therapy, any undiagnosed genitalia diseases, smoker's women, the body mass index more than 30kg/m^2, vaginal bleeding or spotting, any breast diseases with unknown cause, using vaginal lubricant at least 15 days before the intervention.

Sample size calculation

We used the following formula with considering Al-Saqi et al's study, [17] $\beta = 0.9$, $\alpha = 0.01$, and considering 20% attrition the total sample size for each group was calculated to be 48.

[Due to technical limitations, this equation is only available as a download in the supplemental files section.]

Drug preparation

For the vaginal gel preparation, at first the 2% sodium carboxymethyl cellulose was added to the 20% propinyl glycol gradually when it was stirring. Then the boiled water containing 0.2% methyl paraben was added and stirred until it was cool. Then 2gr oxytocin powder in the distilled water residue (39%) was added and stirred to form the oxytocin gel. The same steps were taken to make placebo, except the oxytocin powder was not added. Oxytocin gel and placebo were placed in similar tubes and the pharmacist assigned codes to these tubes. The researcher and the participants were no aware of content of each tube.

Recruitment

Eligible women were placed in the lithotomy position and vagina was assessed regarding infection and any abnormal discharge. Women who did not have any of these symptoms were considered for intervention. Then women were evaluated regarding vaginal signs and symptoms of vaginal atrophy such as dryness, pallor, dyspareunia, redness, inflammation, and vulvovaginal erosion. The subjective symptoms of vaginal atrophy were assessed using the self- reported scale of burning, itching, feeling of dryness and dyspareunia. The severity of each symptom was determined by the patient and then an appropriate score was applied as follows: absence of any symptoms received zero, mild symptoms received 1, moderate and intense symptoms received 2 and 3 respectively. The sum of scores was calculated for each woman.

For measuring vaginal PH, a disposable speculum (Bekr brand) was inserted into vagina and a sample from the posterior fornix was taken using a cotton swab (Wooden Ajer) and placed in the lamella and fixed with fixator (Patofix) and sent to a reference laboratory for vaginal maturation index evaluation (VMI). The vaginal PH was measured using PH gauge paper (Macherey Nagel, Germany). The paper tape was contacted to the vaginal wall and kept for one minute and the corresponding strip was compared to the PH bar and the number recorded in the checklist. If the vaginal atrophy (signs and subjective symptoms) was confirmed, women were recruited for the intervention.

Randomization

Eligible women were randomly assigned in two groups of vaginal gel of oxytocin or placebo using block randomization with a block size of 4 and ratio of 1:1. For allocation concealment, each woman received a code and all codes were kept in opaque envelope until the time of intervention. The researcher and the participant were not aware of groups and the intervention that they received. The oxytocin and placebo were placed in similar tubes and coded by pharmacist. None of the researcher or participants was aware of real treatment.

Measurement

The following forms were used for data collection. A demographic questionnaire was used for recording characteristics such as age, education level, and economic situation. A checklist was used for recording signs and symptoms of vaginal atrophy and PH. Also, a checklist was used for recording the subjective symptoms of vaginal atrophy. Except for the demographic questionnaire that completed at baseline, other checklists were completed at baseline, two and eight weeks after intervention. The validity and reliability of all questionnaire and checklist was assessed using content validity. The body mass index of was calculated by weight (kg)/height (m^2) and self-reported by participants.

Intervention

Women in the intervention group requested to use oxytocin gel (400IU) and women in the placebo group used placebo vaginal gel for eight weeks. An applicator contains 4 gr and participants requested to filled-up one quarter of each applicator per night and continue to use for eight consecutive weeks.

Statistics

All data entered SPSS version 22. The normal distribution of data was assessed using Shapiro–Wilk test. The continuous data was analyzed using independent t-test, while the categorical data was analyzed using chi-square test. For variable with more than two measurement, the GEE was used. The $p<0.05$ was considered significant.

Results

A total number of 98 women were recruited in this study; however, four women in the placebo and five women in the oxytocin group withdrew the study. The reasons for drop-out are listed in Figure 1. Table 1 shows the socio-demographic characteristics of participants in two groups of oxytocin and placebo. The mean age of women was 54.18 and 54.1 in the oxytocin and placebo groups. Most women in two group experienced menopause around age of 50 and most of women were overweight. The frequency of coitus was low and in both groups was around three per month. Most of women had primary education and were categorized in the moderate level regarding to economic situation.

Table 2 shows the mean of superficial, intermediate and para basal, maturation index and PH of vagina before and after intervention. The number of superficial cells was increased significantly in the oxytocin group compared to placebo (38.7±7.18 vs. 3.69±2.76, $p = 0.0001$). The number of intermediate cell increased, while the number of para basal cells was decreased significantly in the oxytocin compared to placebo after intervention. The improvement of maturation index was more dominant in the oxytocin group (increased from 7.76±4.68 to 52.48±7.54) in compare to placebo group (increased from 8.58±4.35

to 13.25±5.06). The PH of vagina decreased significantly in the oxytocin group in compare to placebo group after eight weeks treatment (p = 0.0001).

Table 3 shows the subjective symptoms of vaginal atrophy before and after intervention. As evident from this table, at baseline most women in two groups had severe symptoms. Two weeks after intervention, 20.5% and 4.8% in the oxytocin and placebo groups were free of severe subjective symptoms of vaginal atrophy (p = 0.001). After eight weeks intervention, 88.6% and 7.1% of women in the oxytocin and placebo groups did not show the severe symptoms of vaginal atrophy (p = 0.001).

Table 4 demonstrates the mean of subjective symptoms score in two groups of oxytocin and placebo. The scores of subjective symptoms was decreased significantly in the oxytocin group (from 6.2±2.67 to 0.38±0.96) compared to placebo group (from 6.54±2.82 to 4.9±2.9) (p = 0.0001).

No adverse effect was reported by any of participant in the oxytocin or placebo groups.

Discussion

This study was designed to evaluate the effect of oxytocin vaginal gel on vaginal atrophy in postmenopausal women. Our results revealed that oxytocin vaginal gel could significantly increase the superficial cells after two months intervention, and also the vaginal maturation index improved significantly in the oxytocin compared to the placebo groups. Oxytocin is a hormone that has many receptors in the endometrium and these receptors can be stimulated for onset of labor [19]. Although we could not find a study that shows the effect of oxytocin on cell maturation, we rely on results of some studies that evaluated the effect of oxytocin on endometrial cells. Roshangar et al, found that oxytocin has a stimulating effect on endometrium cells in mice [20]. Also, Al-Eknah et al, in their study found that oxytocin injected to goats could significantly reduce the level of progesterone in the plasma and also could change the content of protein, acid and alkaline phosphatase in the cervical mucus [21].

In the present study all of subjective symptoms of vaginal atrophy significantly improved in the oxytocin group compared to the placebo. The effect of oxytocin on vaginal atrophy in postmenopausal women also was investigated by Jonasson et al (2011) and the results showed that oxytocin could significantly reduce the symptoms of vaginal atrophy such as vaginal dryness, pain, itching, discomfort and dyspareunia after one week intervention. The level of circulating estrogen was remained unchanged in compare to the baseline. The authors concluded that this study should be repeated with a larger sample size [22]. These results are in line with our study.

Our results showed that PH of vagina was decreased significantly after eight weeks intervention in the oxytocin group compared to the placebo. A study assessed the effect of prostaglandin F2α and oxytocin on vaginal micro flora in awassi sheep ewes and concluded that while prostaglandin F2α decreased the amount of vaginal micro flora, the micro flora remained unchanged in the oxytocin [23].

Al-Saqi et al (2015) conducted a study on 64 postmenopausal women and assessed the effect of oxytocin vaginal gel (400 IU, 100 IU or placebo) on vaginal atrophy. Their results showed that after seven weeks intervention the cytology of vagina improved and number of superficial cells was increased and PH of vagina decreased. The thickness of endometrium did not change [17]. Torky et al, conducted a study on 140 women (70 in the oxytocin and 70 in the placebo groups) and used 600 IU oxytocin gel or placebo to relief the vaginal atrophy and followed patients for one month. Their results showed that all subjective and objective symptoms of vaginal atrophy decreased significantly in the oxytocin group [18]. These results are similar to what we found in our study.

Strengths and limitations of the study

This was a double blind randomized controlled trial with the eight weeks intense follow-up. All measurements and follow-ups were conducted by one researcher. One of the limitations of this study is; we did not assess the level of blood estrogen of participants. However, other studies showed that oxytocin did not affect the blood estrogen level [18]. In this study because of financial constraints, we were not able to prepare disposable applicator and used one applicator to transfer oxytocin gel or placebo into vagina. Participants were taught to fill a quarter of applicator to reach the level of 1gr. This may cause errors and affected the results.

Conclusion

The results of this study showed that eight weeks intervention with oxytocin vaginal gel (400 IU) could significantly improve the vaginal maturation index, subjective symptoms of vaginal atrophy and reduce the PH of vagina. Using this medication in women who have contraindication for hormone therapy is recommended.

Abbreviation

VVA: Vulvovaginal atrophy

VMI: Vaginal Maturation Index

Declarations

Ethics approval and consent to participate: The protocol of this study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ref No: IR.AJUMS.REC.1396.720). This study was registered in the Iranian Registry for Clinical Trials (Ref No: IRCT20160602028220N2). All participants provide written informed consent prior to the data collection.

Consent for publication: N/A

Availability of data and materials: Data of this study will be available upon the request from the corresponding author.

Competing interests: Parvin Abedi is an associate editor of BMC Pregnancy and Childbirth and other than this; the authors declare that they have no competing interests.

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Authors' contribution: IZ, PA and SA were contributed to the conception of this study. IZ collected the data. EM was responsible for data analyzing and interpretation. NS was responsible for drug and placebo preparation. PA was responsible to writing and finalizing the manuscript in English. All authors are in agreement with the content of the manuscript.

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Tables

Table 1: Socio-demographic characteristics of participants in the oxytocin and placebo groups

Variables	Oxytocin n=44	Placebo n=42	P value
	Mean ± SD		
Age(y)	54.18±3.31	54.1±3.68	0.98
Age of menopause (y)	50±2.16	50.38±2.59	0.51
Body mass index(kg/m^2)	28.5±1.54	28.8±1.49	0.26
Coitus per month	2.75±1.34	2.38±0.88	0.27
	N(%)		
Education			
Primary	20(45.5)	14(33.3)	0.46
Secondary	13(29.5)	17(40.5)	
Diploma and higher	11(25)	11(26.2)	
Economic situation			
Weak	17(38.5)	16(38.1)	0.92
Moderate	21(47.7)	19(45.2)	
Good	6(13.6)	7(16.7)	
Job			
Housewife	2(4.5)	1(2.4)	0.58
Employee	42(95.5)	41(97.6)	

Table 2: The maturation index and vaginal PH before and after intervention in two groups of oxytocin and placebo

Variables		Oxytocin N=44	Placebo N=42	P value between groups
			Mean ± SD	
Superficial cells	Before	0.59±1.38	0.35±0.79	0.34
	After	38.7±7.18	3.69±2.76	0.0001
P value within group		0.0001	0.0001	
Intermediate cells	Before	14.54±8.53	16.6±8.59	0.26
	After	27.56±5.77	19.07±8.56	0.0001
P value within group		0.0001	0.0001	
Para basal cells	Before	84.8±9.18	83.02±8.57	0.35
	After	33.95±9.17	77.23±8.97	0.0001
P value within group		0.0001	0.0001	
Vaginal maturation index	Before	7.76±4.68	8.58±4.35	0.4
	After	52.48±7.54	13.25±5.06	0.0001
P value within group		0.0001	0.0001	
Vaginal PH	Before	6.01±0.75	6.19±0.79	0.28
	After	4.51±0.51	6.07±0.73	0.0001
P value within group		0.0001	0.13	

Table 3: The subjective symptoms of vaginal atrophy and dyspareunia before and after intervention in the oxytocin and placebo groups

Variables	Dyspareunia	Oxytocin n=44	Placebo n=42	P value using t- test	P value using GEE
		N(%)			
Before intervention	Negative	2(4.5)	2(4.8)	0.6	
	Mild	13(9.5)	12(28.6)		
	Moderate	14(31.8)	9(21.4)		
	Severe	15(34.1)	19(45.2)		
Two weeks after intervention	Negative	9(20.5)	2(4.8)	0.001	0.0001
	Mild	19(43.2)	13(31)		
	Moderate	13(29.5)	9(21.4)		
	Severe	3(6.8)	18(42.9)		
Eight weeks after intervention	Negative	39(88.6)	3(7.1)	0.001	
	Mild	5(11.4)	19(45.2)		
	Moderate	0	13(31)		
	Severe	0	7(16.7)		

Table 4: Comparison of scores of subjective symptoms of vaginal atrophy in two groups of oxytocin and placebo

Variables	Oxytocin n=44	Placebo n=42	P value
	Mean ±SD		
Before intervention	6.2±2.67	6.54±2.82	0.56
After intervention	0.38±0.96	4.9±2.9	0.0001
P value	0.0001	0.0001	

Figures

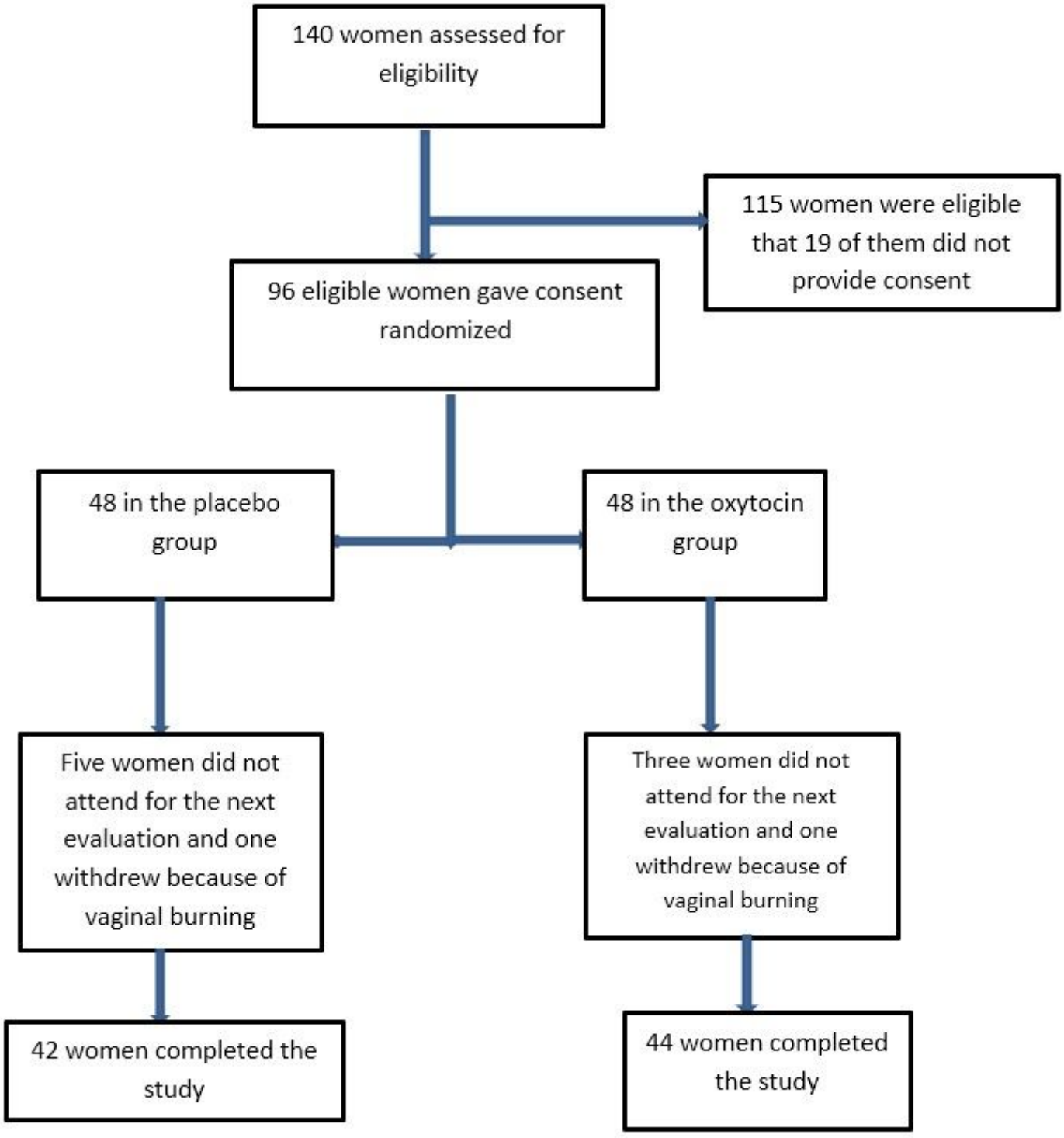

Figure 1

Flow diagram of recruitment and retention of participants in the study

Supplementary Files

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