ORIGINAL RESEARCH—WOMEN'S SEXUAL HEALTH

Efficacy of Vaginally Applied Estrogen, Testosterone, or Polyacrylic Acid on Sexual Function in Postmenopausal Women: A Randomized Controlled Trial

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ABSTRACT

Introduction. Female libido is multifactorial and complex. Declining estrogen levels in postmenopausal women affects vaginal function.

Aim. The aim of this study was to evaluate female sexual function after using topical estrogen, testosterone, or polyacrylic acid as vaginal lubricants with K-Y jelly as a placebo lubricant.

Methods. This was a randomized controlled clinical trial on 80 postmenopausal women between 40 and 70 years of age with follow-up at the Menopause Clinic of the CAISM Unicamp. The women were randomized to treatment with topical vaginal estrogen, testosterone, polyacrylic acid, or oil lubricant alone, three times a week for a period of 12 weeks from November 2011 to January 2013.

Main Outcome Measure. We used the Female Sexual Function Index (FSFI) to assess changes in sexual response at baseline, and after 6 and 12 weeks.

Results. After 12 weeks of treatment, polyacrylic acid and topical testosterone produced improvements in the FSFI domains of sexual desire, lubrication, satisfaction, reduced pain during intercourse, and total score compared with lubricant alone. Treatment with topical estrogen in comparison with lubricant alone showed an improvement in the FSFI field of desire. The intragroup analysis over the time of the treatment showed improvements in the fields of desire, lubrication, and reduced pain for polyacrylic acid, testosterone, and estrogen. Furthermore, women who used testosterone showed improvements over time in the fields of arousal, orgasm, and satisfaction.

Conclusions. Treatment of postmenopausal women with symptoms of vaginal atrophy with polyacrylic acid, testosterone, and estrogen for 12 weeks produced improvements in self-reported female sexual function when compared with a placebo lubricant. **Fernandes T, Costa-Paiva LH, and Pinto-Neto AM. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on sexual function in postmenopausal women: A randomized controlled trial. J Sex Med 2014;11:1262–1270.**

Key Words. Vaginal Atrophy; Sexuality; Hormones

Introduction

Female libido is multifactorial and complex. It is negatively affected by organic diseases, psychological factors, and relationship difficulties with a partner. Declining estrogen levels in postmenopausal women affects vaginal function and often leads women to complain of dryness, itching, burning, dyspareunia, and urinary dysfunction [1,2]. Such changes are often related to coital discomfort and pain, with a consequent negative influence on female sexual function [3,4]. A study involving 3,046 postmenopausal women in the United States with symptomatic vaginal atrophy showed that 59% of women felt that this impaired their level of sexual satisfaction [5]. Therefore, it is believed that the complex interaction of factors that affect sexual dysfunction in women after

menopause might be associated with progressive vaginal atrophy [6]. For women who need treatment for their urogenital symptoms, several clinical research studies have consistently documented the effectiveness of estrogen therapy administered orally and vaginally; moreover, topical application is more effective and faster [7–9]. Furthermore, the use of topical estrogen provides better sexual satisfaction and reduces pain during intercourse [10]. Although intravaginal formulations have been developed to decrease systemic exposure, it is known that topical use can also increase the serum level of estrogens [11]. Given the known risks of estrogen therapy, many postmenopausal women do not want to use this method or have a contraindication to it.

Testosterone has been investigated in the treatment of menopausal symptoms, especially for women complaining of decreased libido and sexual desire. Recent studies using subcutaneous injections of testosterone for 3 months showed improved physiological and psychological symptoms of menopause, including improvements in vaginal atrophy and sexual function [12–14]. Other studies showed that the use of topical testosterone and vaginal estrogen either alone or in combination showed improvements in vaginal trofism associated with an improvement in sexuality [15,16].

Alternatively, one nonhormonal therapy used by women for the treatment of vaginal atrophy is the topical moisturizer, polyacrylic acid [17]. This is a calcium salt of divinyl glycol that can absorb 60 times its weight in water. This remarkable absorption capacity is the basis of its therapeutic effect and provides vaginal lubrication and hydration. Its efficacy in improving symptoms of vaginal atrophy is similar to that of topical estrogen [17–19]. Such water-based lubricants, although widely used, do not improve vaginal trofism per se but partially improve some symptoms such as dryness and pain during intercourse [20].

Given that topical testosterone and polyacrylic acid provide good alternative treatments to estrogens for relieving the symptoms of vaginal atrophy and improving sexuality, it is necessary to compare the results for such agents with those obtained with topical estrogen. This could help in the development of other treatment options for improving sexual function in postmenopausal women. The present study aimed to evaluate sexual function in postmenopausal women during treatment for 12 weeks with topical estrogen, testosterone, polyacrylic acid, or lubricant alone using the Female Sexual Function Index (FSFI) [21,22].

Methods

Study Participants

Out of a cohort of 1,112 postmenopausal women interviewed in the Menopause Clinic CAISM Unicamp, the first 80 women who met the inclusion and exclusion criteria of the study were invited to participate in a randomized controlled trial involving 12 weeks of topical treatment with an assessment of sexual function.

Inclusion criteria were women aged 40–70 years with physiological menopause and a history of amenorrhea for >3 years with a follicle-stimulating hormone level of >30 mIU/mL.

They had not taken hormonal treatment for menopausal symptoms in the past 6 months, had shown normal Pap smears and mammograms for the past 12 months, and had complaints compatible with the symptoms of vaginal atrophy (vaginal dryness, vulvovaginal irritation/itching, and pain at sexual activity 6 months ago). Exclusion criteria consisted of women who were expected to undergo an oophorectomy or hysterectomy and those with a body mass index <18.5 kg/m^2 or >30 kg/m^2. We excluded those women with a contraindication for the use of estrogen or testosterone, namely those with a history of myocardial infarction, severe hypertension, diabetes mellitus, thromboembolic disease, liver failure, ulcerative colitis, Crohn's disease, breast or endometrial cancer, fibrocystic breast disease with atypical hyperplasia, genital bleeding of unknown origin, a family history of breast cancer, endometrial hyperplasia, or positive serology for human immunodeficiency virus, hepatitis B, or C. Finally, women were excluded if they had a vaginal infection at the time of their gynecological examination.

This study was conducted between November 2011 and January 2013. The protocol was approved by the Ethics Committee of the Faculty of Medical Sciences—Unicamp number 990/2011. CONSORT guidelines were observed and cataloged in the Brazilian Registry of Clinical Trials (Rebec): UTN identifier U1111–11255434. All participants signed an informed consent form prior to the baseline evaluation.

Randomization

After the initial screening, 80 women were assigned to the 4 treatments, with 20 women in

each group. All participants were given a number (1–80) according to their order of inclusion in the study and the corresponding allocation of topical treatment with polyacrylic acid, testosterone, estrogen, or placebo lubricant. The randomized sequence was compiled in Microsoft Excel for Windows 2007 (Microsoft Corporation, Redmond, WA, USA) and its order was unknown to the investigator. Dispensation of the topical agent was done by a gynecologist who was not part of the selection/interview team. The drug was supplied in a sufficient dose for the 12 weeks of treatment.

Intervention

The women were randomly assigned to one of four treatment groups for vaginal application three times a week for 12 weeks as follows:

- Vaginal cream with polyacrylic acid (Vagidrat®, Myralis Pharma Ltd, Aguai, Sao Paulo, Brazil) (n = 20): one vaginal applicator with 3 g cream per application.
- Vaginal cream with testosterone propionate (n = 20): one vaginal applicator with 1 g of cream per application containing 300 μg testosterone propionate prepared using testosterone micronized powder in an emollient cream with silicone to keep the cream iso-osmolar [23].
- Vaginal cream with conjugated estrogens (Premarin®, Wyeth Pharmaceuticals, Itapevi, São Paulo, Brazil) (n = 20): one vaginal applicator with 1 g of cream per application containing 0.625 mg conjugated estrogens.
- Lubricant with glycerin gel (K-Y jelly®, Johnson & Johnson, São José dos Campos, São José dos Campos, Brazil) (n = 20): 3 g in one applicator per application adjusted to maintain similarity with the polyacrylic acid application. This group was used as a control for the three other treatment groups.

Main Outcome Measures

Measurements

In the first interview, the women answered a standardized questionnaire with information on demographic characteristics including age, time since menopause, skin color, education level attained, smoking habit, parity, and socioeconomic classification. They underwent interviews and completed the Sexuality FSFI questionnaire validated in Brazil by Thiel et al. [22] on admission and at weeks 6 and 12 of treatment. The FSFI is a brief, multidimensional questionnaire used to assess key dimensions of sexual function in women. It consists of 19 questions that inform on 6 domains of sexual response: desire (questions 1 and 2), arousal (questions 3–6), lubrication (questions 7–10), orgasm (questions 11–13), satisfaction (questions 14–16), and sexual pain or discomfort (questions 17–19). Individual scores are obtained by summing the items that comprise each domain (simple scores) and are multiplied by the weighting factor for that domain to provide the weighted score. The total score is obtained by summing the weighted scores and ranges from 2 to 36 points. Any side effects were analyzed in accordance with the appearance of symptoms during treatment.

Compliance

Compliance was assessed by self-reporting on the proper use of medication.

Statistical Analysis

Data were analyzed according to intention to treat, including all participants in each group. Data from epidemiological and clinical characteristics were analyzed using chi-squared, Fisher's exact, nonparametric Kruskal–Wallis, and Snedecor's F-tests and analysis of variance. The mean score of each domain and the total FSFI score of each group were analyzed. Comparisons of the mean for each treatment group compared with the group using placebo lubricant were done using the Mann–Whitney nonparametric U-test. Comparisons of each treatment over time were performed using the nonparametric Friedman's test. $P < 0.05$ was assumed significant. The software used was SPSS for Windows, version 20.0 (SPSS, Inc., Armonk, NY, USA).

Sample Size

As we did not know of any studies comparing the use of topical testosterone with a lubricant, we chose to use an article comparing the androgenic hormone dehydroepiandrosterone (DHEA) as a topical lubricant [24]. Therefore, the sample size was based on the difference found in that study between DHEA and placebo groups for improving dyspareunia (1.5 ± 0.14). Considering a test power of 80% and aiming at $P < 0.05$ using Student's t-test, the sample size was calculated for $n = 4$ groups to meet the probable loss of follow-up. Accordingly, the sample size was increased to 20 in each group.

Results

The most frequent reasons for noninclusion in the study were a history of breast cancer or because the woman had been hysterectomized. This is because the menopause clinic is in a tertiary hospital with patients showing multiple morbidities.

Of the 80 women analyzed, 4 discontinued the study before 12 weeks. One woman using estrogen developed allergic vaginitis in week 4, and the treatment was suspended immediately. Another three women discontinued the study spontaneously (Figure 1). No other adverse effects were reported. Women who used topical testosterone did not show androgenic side effects such as acne, increased hair growth, and clitoral hypertrophy.

Table 1 shows the characteristics of the studied population according to treatment. We observed significant differences in the duration of education between the treatment groups compared with the placebo lubricant group. There were no significant differences between groups in terms of age, time after menopause, skin color, smoking habits, numbers of pregnancies, or socioeconomic status. After 12 weeks of follow-up, women treated with polyacrylic acid and topical testosterone showed significant improvements in scores of the domains of sexual desire, lubrication, satisfaction, pain during intercourse, and total score compared with the group treated with the placebo lubricant (Table 2). The group of women who used topical estrogen showed an improvement in the field of desire compared with the placebo lubricant group (Table 2).

None treatment groups showed improvements in arousal and orgasm compared with the placebo lubricant group. Analysis of the average intragroup scores over time showed that the use of polyacrylic acid and estrogen for 12 weeks improved the domains of desire, lubrication, and pain during intercourse. Treatment with testosterone for 12 weeks showed significant improvements in all the areas assessed by the FSFI questionnaire: desire ($P < 0.001$), arousal ($P < 0.001$), lubrication ($P <$

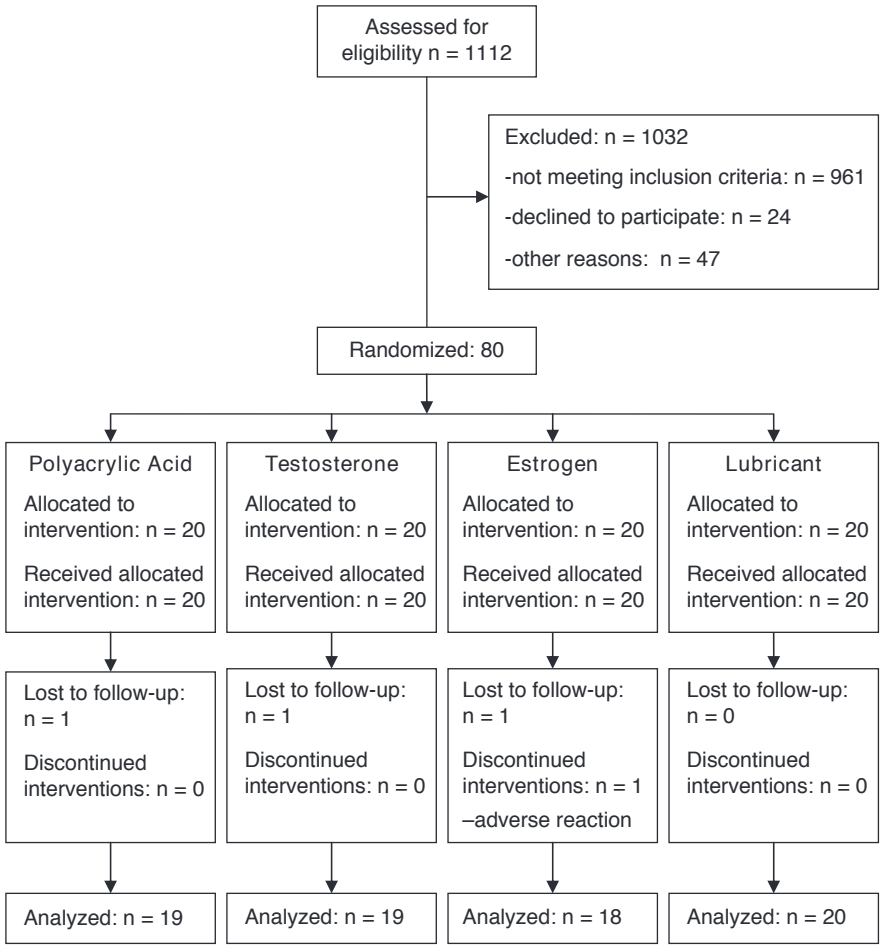

Figure 1 CONSORT flow of women participating in the study.

Table 1 Characteristics of the women according to study group (n = 80)

Characteristics	Group				P
	Acid polyacrylic	Testosterone	Estrogen	Lubricant	
Mean age (years SD)	57.0 (5.4)	56.2 (5.3)	56.4 (4.8)	57.7 (4.7)	0.796*
Mean time since menopause (years SD)	8.9 (4.8)	10.3 (4.0)	8.1 (4.5)	9.3 (4.1)	0.365†
Skin color (%)					§
White	95	80	70	65	
Nonwhite	5	20	30	35	
Education (%)					<0.001‡
≤8 years	20	40	25	80	
>8 years	80	60	75	20	
Smoking habits (%)					0.214‡
Current smoker/ex-smoker	20	50	45	35	
Never-smoker	80	50	55	65	
Parity (%)					0.144‡
≤2	55	55	55	25	
>2	45	45	45	75	
Social status (%)					§
Classes A/B	85	90	85	50	
Classes C/D	15	10	15	50	

*ANOVA test
†Kruskal–Wallis nonparametric test
‡Pearson's chi-square test
§Chi-square test inapplicable
ANOVA = analysis of variance; SD = standard deviation

0.002), orgasm (P < 0.001), satisfaction (P < 0.001), and reduced pain (P < 0.001) (Table 2). The group of women who used the placebo lubricant for 12 weeks showed improvements in the arousal and lubrication domains (P = 0.032 and P = 0.011, respectively). Finally, evaluation of the total intragroup scores for 12 weeks showed improved sexual function following topical treatments with polyacrylic acid, testosterone, and placebo lubricant (Figure 2).

Discussion

The objective of this trial was to compare the use of vaginal creams containing polyacrylic acid, testosterone, or conjugated estrogens with placebo lubricant on self-reported sexual function in postmenopausal women complaining of vaginal atrophy. In agreement with other studies, this study found that, compared with the placebo lubricant, topical treatments with estrogen, testosterone, and polyacrylic acid improved sexual function in postmenopausal women [9,16,17,25]. To our knowledge, this is the first randomized controlled clinical trial literature comparing these treatments in relation to sexual response. Furthermore, we observed that the topical use of testosterone cream improved sexual function from the start of treatment. This showed the best response to therapy compared with other treatments, with improved scores in all domains of the FSFI over 12 weeks of treatment. The findings of an increase in sexual desire, improved lubrication, and sexual satisfaction, in addition to decreased dyspareunia, were similar to other studies evaluating testosterone therapy in postmenopausal women [12,15,26].

The influence of androgens on the vaginal wall has been the subject of research aimed at understanding their roles in vaginal pathophysiology. Recent studies, particularly in experimental animals, suggest that testosterone might have a direct effect on the structure and function of the vagina in an estrogen-independent manner [27]. The androgenic effects on collagen formation might explain the positive effect of testosterone, reducing vaginal atrophy and consequently decreasing the symptoms of discomfort [28]. Another study showed a decrease in androgen receptors in the vaginal mucosa of postmenopausal women [29]. This decline in androgen receptors must make the vagina of such women even more insensitive to lower circulating levels of testosterone, which would explain the impaired vaginal sexual response, even with hormone replacement therapy. However, the use of testosterone for the exclusive treatment of low sexual desire is questionable and requires caution in prescribing because its efficacy and long-term safety still need to be demonstrated [30].

The effects of a cream with conjugated estrogens on sexual function were evident after 6 weeks of treatment. Although not significant after 12

Table 2 Mean overall Female Sexual Function Index and domains at baseline and 6 and 12 weeks of treatment

FSFI	Baseline Mean (SD)	6 weeks mean (SD)	12 weeks mean (SD)	P * value intergroup differences	P † value intragroup differences
Desire					
Acid polyacrylic	3.1 (1.3)	3.4 (1.1)	3.6 (0.9)	0.002	0.039
Testosterone	2.1 (0.8)	3.8 (1.5)	4.7 (1.0)	<0.001	<0.001
Estrogen	3.4 (1.2)	3.7 (1.2)	4.1 (1.0)	<0.001	0.005
Lubricant	2.4 (1.2)	2.5 (1.2)	2.5 (1.2)		0.116
Excitation					
Acid polyacrylic	3.0 (2.1)	3.0 (2.3)	3.4 (2.1)	0.066	0.387
Testosterone	1.7 (1.58)	2.5 (2.3)	3.3 (2.4)	0.099	<0.001
Estrogen	1.7 (2.1)	1.6 (2.3)	2.3 (2.5)	0.761	0.122
Lubricant	2.0 (2.0)	2.0 (2.0)	2.2 (1.9)		0.032
Lubrication					
Acid polyacrylic	2.9 (2.2)	3.7 (2.6)	4.4 (2.4)	0.002	0.014
Testosterone	1.6 (1.6)	2.8 (2.6)	3.9 (2.7)	0.032	<0.002
Estrogen	1.5 (2.0)	2.1 (2.8)	2.8 (2.9)	0.513	0.04
Lubricant	1.9 (1.6)	2.6 (2.2)	2.88 (2.2)		0.011
Orgasm					
Acid polyacrylic	2.7 (2.3)	2.9 (2.4)	3.1 (2.1)	0.058	0.36
Testosterone	1.1 (1.3)	2.2 (2.3)	3.3 (2.4)	0.053	<0.001
Estrogen	1.6 (2.2)	1.7 (2.4)	2.2 (2.4)	0.692	0.25
Lubricant	1.7 (1.7)	1.7 (1.8)	1.8 (1.7)		0.337
Satisfaction					
Acid polyacrylic	3.9 (1.5)	4.2 (1.5)	4.4 (1.3)	0.003	0.219
Testosterone	2.6 (1.0)	3.6 (1.4)	4.5 (1.7)	0.022	<0.001
Estrogen	3.0 (1.5)	3.4 (1.5)	3.7 (1.8)	0.894	0.656
Lubricant	2.8 (1.1)	2.9 (1.3)	3.1 (1.0)		0.052
Pain					
Acid polyacrylic	2.6 (2.1)	3.7 (2.6)	4.3 (2.6)	0.033	0.006
Testosterone	1.5 (1.6)	3.1 (2.7)	4.3 (2.6)	0.013	<0.001
Estrogen	1.3 (2.0)	2.1 (2.9)	3.0 (2.9)	0.583	0.022
Lubricant	2.1 (2.1)	2.8 (2.5)	3.1 (2.4)		0.127
General score					
Acid polyacrylic	18.5 (10.5)	21.2 (12.0)	23.4 (10.3)	0.007	0.029
Testosterone	9.9 (6.8)	17.6 (11.8)	24.9 (12.0)	0.003	<0.001
Estrogen	12.7 (10.1)	14.9 (12.5)	18.2 (13.0)	0.225	0.138
Lubricant	13.1 (9.0)	14.7 (10.4)	15.8 (10.0)		0.011

*Nonparametric Mann–Whitney U test for comparison of the specific group treatment with lubricant for 12 weeks
†Nonparametric Friedman's test for evaluation over time of treatment
FSFI = Female Sexual Function Index; SD = standard deviation

weeks of treatment compared with the placebo lubricant, we observed a trend toward improved sexual function. Therefore, we suppose that if the evaluation time of this study were longer, topical estrogen treatment might also have produced a significant improvement in sexual response. Our protocol of applying low-dose topical estrogen only three times a week was supported by the report of Freedman et al. [31], who showed improved trofism of the vagina after 4 weeks of treatment following application of 0.625 mg/g conjugated estrogen twice a week. Improved vaginal tropism with topical estrogen was associated with improved sexual function in another study on postmenopausal American women, who reported reduced pain and more satisfying sex [32]. The highly vascularized nature of the vagina means that there is good absorption of topical estrogen and testosterone; this circumvents the enterohepatic circulation, which is associated with fewer adverse effects [33]. However, the use of this vaginal route for drug administration is still little explored.

The use of topical polyacrylic acid produced significant improvements within the first 6 weeks of use compared with the placebo lubricant. Polyacrylic acid is used to replace the normal vaginal secretions, while the K-Y jelly lubricant is designed to reduce friction associated with sexual activity [34]. Compared with the placebo lubricant, the use of polyacrylic acid also showed improvements in the sexual function domains of desire, lubrication, sexual satisfaction, and total pain score, suggesting that this treatment might have benefits for the quality of sex life of women with contraindications for hormone use.

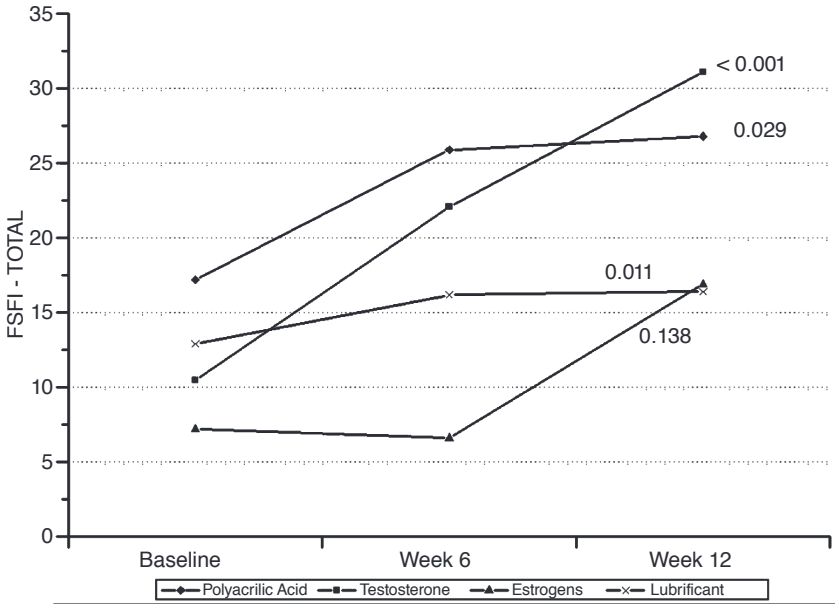

Figure 2 Mean total FSFI scores for study groups. FSFI = Female Sexual Function Index

None of the treatments used here were significantly better in the field of orgasm compared with the placebo lubricant, showing that this domain must be multifactorial.

This clinical, randomized controlled trial was not truly double blind because the color and consistency of the products differed: the polyacrylic acid cream was transparent, the creams with estrogen and testosterone were white, and the testosterone cream had a more pasty consistency. In addition, the therapeutic dosages and the treatment were obvious from the packaging leaflet for the women.

We've chosen to manipulate the testosterone propionate with silicone because as a iso-osmolar emollient, it does not change [23] the vaginal environment. It is believed that improvements in sexual function shown by the topical treatment of testosterone cream was due by the active product and not the silicone. Unfortunately, lubricants that are commercially silicone based are not present in our country and therefore our control is a water-based lubricant (K-Y)—hyperosmolar [35].

Although these subjective assessments were based on a small group of women, the beneficial effects of topical treatments regarding sexuality can be considered sufficient to justify further studies. The results observed with the use of topical testosterone with the sole purpose of improved sexual function in postmenopausal women are preliminary and require confirmation in other studies with larger samples, longer observation times, and extended follow-up to monitor possible adverse effects before we could recommend clinical routine use. However, the significant improvements in sexual function in these postmenopausal women suggest that health professionals, particularly gynecologists, should be informed of the possibilities of therapeutic interventions for these women, with accuracy in the clinical laboratory and especially with the need for individualized treatment.

Conclusion

Postmenopausal women complaining of vaginal atrophy used topical vaginal applications of testosterone, estrogen, and polyacrylic acid for 12 weeks. When compared with the placebo lubricant alone, they showed improvements in all fields and in the total score of the FSFI questionnaire, indicating enhanced sexual function.

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