ORIGINAL RESEARCH

Efficacy of Polycarbophil Moisturizing Gel in Women with Genitourinary Syndrome of Menopause: A Randomized Control Trial

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Abstract

Introduction: Menopausal symptoms have defected the quality of life of elderly women. Several studies have examined a nonhormonal bioadhesive moisturizer gel, such as polycarbophil, for genitourinary syndrome of menopause (GSM) therapy. However, there was no such study in Indonesia. Thus, this study aims to compare the efficacy of polycarbophil moisturizer gel and placebo for women with GSM.

Materials and methods: A randomized clinical trial with a total of 40 subjects was enrolled in Cipto Mangunkusumo General Hospital, Jakarta from April to December 2019. Subjects were divided into polycarbophil group (n = 21) and the placebo group (n = 19). Polycarbophil and placebo were given two times per week for 3 weeks. Genitourinary syndrome of menopause symptoms (vaginal dryness, itching, dyspareunia, dysuria, and burning sensation) and vaginal health index scores (VHIS), including vaginal elasticity, fluid volume, pH, epithelial integrity, and vaginal moisture, were assessed before and after the intervention.

Results: Most of the GSM symptoms, especially vaginal dryness and dyspareunia, improved in week 2 for both interventions. Related to VHIS, polycarbophil gel improved the vaginal fluid volume, pH, and moisture, while placebo improved epithelial integrity. The polycarbophil gel was found to significantly (p <0.001) raise the vaginal pH compared with placebo. Overall, there were 18 subjects (85.7%) from the polycarbophil group who felt an improvement of symptoms after therapy, while only 11 subjects (57.9%) from the control group felt it.

Conclusion: Polycarbophil gel may raise vaginal pH in postmenopausal women with GSM. The overall VHIS efficacy between polycarbophil and placebo was relatively the same.

Keywords: Genitourinary syndrome of menopause, Polycarbophil, Vaginal health index score, Vaginal moisturizer.

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Introduction

Genitourinary syndrome of menopause is the newest terminology for vulvovaginal atrophy symptoms. This is a group of symptoms happening due to the continuing loss of estrogen level, which causes a decrease in vaginal secretion, thinning of urethral mucosa, or even inflammation. Genitourinary syndrome of menopause is the most common condition associated with the genital, sexual, and lower urinary tract, where postmenopausal women may feel vaginal dryness, itching, dysuria and dyspareunia.[1,2] Surveys and clinical studies have shown that among all symptoms, vaginal dryness and dyspareunia are the most common complaints by postmenopausal women.[3]

A study has shown that the average age of menopausal women in Asia was 51.1 years old.[4] In Indonesia, a previous study also showed that the average age of menopausal women is between 50 and 55 years old.[5,6] On the other hand, the level of women's life expectancy continues to rise every year. In 2020, women in Indonesia were expected to live up to 71 years old, which was higher than previous years. This condition results in the longer duration of women to experience the menopausal symptoms. A study by Mirhaghjou et al. also showed that vaginal dryness affects the quality of life of 16.8% of subjects.[7] Therefore, GSM symptoms, including vaginal dryness, should be seriously managed.

The first-line therapy for GSM is nonhormonal vaginal lubricants or moisturizers. Most of the vaginal lubricants do not have long-term effects as they cannot be absorbed by the skin. Another therapy is vaginal moisturizer using bioadhesive gel, which contains polycarbophil. This moisturizer adheres to epithelial cells and vaginal mucus, thus able to maintain vaginal hydration. Studies have shown that polycarbophil moisturizing gel has superior efficacy compared with other lubricants, including water-based lubricants. As a result, there will be vaginal fluid volume correction and improvement of vaginal elasticity without changing the cytology compositions of vaginal mucus.[8,9] With all these positive effects of polycarbophil, it is still important to confirm the efficacy and safety of polycarbophil moisturizing gel for GSM symptom treatment in Indonesian menopausal women.

Since there has been no study about the efficacy of polycarbophil moisturizing gel to treat GSM in Indonesia, this study aims to

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explore the effectiveness of the gel compared with placebo in GSM women using subjective symptom evaluation, including vaginal dryness, itching and irritation, dyspareunia, dysuria and burning sensation, as well as objective parameters using VHIS.[10]

Materials and Methods

Study Design and Sample Recruitment

This randomized controlled trial study was conducted in Obstetrics and Gynecology Clinic of Cipto Mangunkusumo General Hospital from April to December 2019. This study was restricted to sexually active postmenopausal women who had at least one of these following symptoms: vaginal dryness, itching, dyspareunia, dysuria, and burning sensation. Women who underwent systemic or local hormone replacement therapy in the last 3 months before admission, had genital or urinary tract infection, abnormal Pap smears, or pelvic organ prolapse, were excluded.

The sample size was calculated based on comparative–numeric analysis for two groups, with effect size 1, thus the minimum sample required was 19 for each group. A total of 22 subjects for the intervention group and 21 subjects for the control group were obtained. One subject from the intervention group and 2 subjects from control group were dropped out because subjects refused to undergo reevaluation after interventions, resulting in a total of 21 subjects from the intervention group and 19 subjects from the control group being analyzed.

This study has been approved by The Ethical Committee for Research in Humans from The Faculty of Medicine, Universitas Indonesia (KET-627/UN2.F1/ETIK/PPM.00.02/2019). All of the participants agreed to participate and signed the informed consent prior to the study.

Intervention

The randomization was done by researchers, with simple randomization (1:1) and no restriction, using computer. The intervention group will be given polycarbophil bioadhesive gel (Ragelle), and the control group will be given placebo gel. Polycarbophil gel (Ragelle) contains polycarbophil, glycerol, mineral oil, hydrogenated palm oil glycerides, carbopol 974P, and sorbic acid. Whereas the placebo gel had 13800 centipoise and pH 4.5. The gel that was given in either intervention or control was transferred to the same appearance tubes placed in plain brown boxes. There were 22 boxes of intervention gel and 22 boxes of control gel given.

Patients were instructed how to use the lubricants inside their vagina, and were advised to use them two times per week for 3 weeks. Patients were assessed before they started the treatments, and follow-up each week up to week 3. Both of the patients and the examiners' team were blinded throughout the study.

Clinical Examination

The overall satisfaction level with the treatment procedure and outcome was recorded during initial subjects' recruitment and followed up each week, up to 3 weeks, while using the therapy. The improvement or each symptoms, including vaginal dryness, itching and irritation, dyspareunia, dysuria, and burning sensation, was assessed. The improvement of symptoms was evaluated using a questionnaire related to the presence of the symptoms, with closed or polar question (yes–no question).

Using VHIS tool, five parameters were evaluated, including vaginal elasticity, fluid volume, moisture, pH, and epithelial integrity. These will allow prediction of genitourinary tract atrophy. The VHIS was calculated with minimum score = 1 and maximum score = 5 for each parameter. The total score ranges from 5 to 25, with higher scores associated with lesser urogenital atrophy.[10] The vaginal elasticity was evaluated with digital palpation and speculum examination using VAS for acute pain measurement. The vaginal fluid volume was evaluated using cotton tip to evaluate the posterior wall of vaginal fluid quantity. Vaginal moisture was visually evaluated related to vaginal fluid secretion and inflammation signs. Vaginal pH measurement was evaluated using litmus paper. Epithelial vagina integrity was evaluated by determination of color, fold, and friability using a speculum showing thinning vaginal walls and missing vaginal rugae in cases of loss of integrity. The score of each parameter was calculated in accordance with VHIS tool.[10] This clinical measurement was calculated before treatment and after week 3 of treatment. Both participants and healthcare personnel were blinded throughout the assessment.

The presence of side effects of the therapy was also recorded, including vaginal itching, an increase in vaginal secretion, vulvovaginal bleeding, and burning sensation.

Statistical Analysis

The data were analyzed using statistical program SPSS 21 (Service Product for Statistical Solution 21). Paired samples *t*-test was used for normal data distribution or Wilcoxon signed-rank test for abnormal data distribution to analyze the differences before and after treatment in each therapy. Following that, the efficacy of both intervention and placebo was compared using unpaired *t*-test or Mann–Whitney test. The *p*-value <0.05 was considered to be statistically significant.

Results

Demographic Characteristics

The demographic characteristics of both groups were considered similar, with age 54–56 years old, an obese body mass index (BMI), about 4–5 years of menopausal duration, and 3 times parity. The demographic data of subjects from both groups are presented in mean ± SD if normally distributed or median (minimum–maximum) if abnormally distributed, and can be seen in Table 1.

GSM Symptoms Improvement

Complaints related to vulvovaginal atrophy were vaginal dryness, itching and irritation, difficulty holding urination, and burning sensation during urination, in which each of them were assessed separately. The improvement of these complaints was divided into three categories, improvement at week 1, week 2, and week 3.

Majority of vaginal dryness symptoms were improved in week 2, with 66.7% subjects from polycarbophil group and 81.3% of subjects from control group. Itching and irritation were only experienced by 10% of subjects from the intervention group, in

Table 1: Demographic data of menopausal women with vaginal dryness

Characteristics	*Polycarbophil (n = 21)*	*Placebo (n = 19)*
Age (years)	56.57 ± 5.94	54.22 ± 4.54
BMI (kg/m^2)	25.8 (19.6–35.6)	25.6 (19.4–36.7)
Menopause duration (years)	5 (2–17)	4 (1–10)
Parity	3 (0–5)	3 (1–5)

Data presented as mean ± SD or median (min–max)

Table 2: Etiological distribution of AUB as per PALM-COEIN in various age groups

	Before treatment (n)		*Improvement n (%)*		
Complaints	*No complaint of symptoms*	*Complaint of symptoms*	*Week 1*	*Week 2*	*Week 3*
Vaginal dryness					
Polycarbophil ($n = 21$)	6	15	4 (26.6)	10 (66.7)	1 (6.7)
Placebo ($n = 19$)	3	16	2 (12.5)	13 (81.3)	1 (6.2)
Itching and irritation					
Polycarbophil ($n = 21$)	19	2	2 (100)	0	0
Placebo ($n = 19$)	17	2	1 (50)	0	1 (50)
Dyspareunia					
Polycarbophil ($n = 21$)	8	13	2 (15.4)	8 (61.5)	3 (23.1)
Placebo ($n = 19$)	8	11	1 (9.1)	8 (72.7)	2 (18.2)
Dysuria					
Polycarbophil ($n = 21$)	16	5	2 (40)	1 (20)	2 (40)
Placebo ($n = 19$)	16	3	0	1 (33.3)	2 (66.7)
Burning sensation					
Polycarbophil ($n = 21$)	21	0	0	0	0
Placebo ($n = 19$)	19	0	0	0	0

which all of them claimed to feel improvement after the first week of therapy. While 2 subjects who experienced itching and irritation from control group, improved after week 1 and week 3 of therapy. Dyspareunia was improved mostly at week 2 of therapy in both the intervention group (61.5%) and control group (72.7%). Dysuria was only experienced by a few subjects in both groups. Subjects who experienced this complaint showed improvement at week 3 in both groups. Finally, no subject claimed to have burning sensation during urination. The improvement of complaints related to vulvovaginal atrophy is shown in Table 2.

In addition, the duration of moisturizing effect by subjects while using the polycarbophil gel was also assessed. However, only 15 out of 30 subjects from the intervention group give the report. Among 15 subjects, 5 subjects claimed the effect lasted up to 8 hours, while 5 others felt the effect up to 10 hours. Four subjects said the effect could last until 12 hours. Meanwhile, 1 subject felt that the moisturizing effect could last up to a whole day.

Overall, there were 18 subjects (85.7%) from the intervention group who mentioned that there was an improvement of symptoms and were satisfied after therapy, while in the control group, only 11 subjects (57.9%) felt the improvement. This result was considered statistically significant with $p = 0.049$. Subjects from both groups also mentioned that there was no side effect, including the presence of itching, irritation, or burning sensation.

Efficacy of the Interventions

The efficacy of therapy was assessed using VHIS. This tool was used to evaluate the clinical symptoms of vulvovaginal atrophy, which represent changes in the morphology of vagina. Parameters in VHIS include elasticity, fluid volume, pH, epithelial integrity, and moisture, in which each parameter will be rated from 1 (very poor) to 5 (excellent), so that the maximum total score will be 20. Analysis was done to see changes in each parameter of VHIS in intervention and control groups. Almost all parameters showed statistically significant changes between baseline and end of therapy at week 3 in both groups. We also analyzed VHIS total score to see changes between baseline and week 3. In the intervention group, the average total score was 14.14 ± 2.49 at baseline and 15.47 ± 2.06 at week 3. Meanwhile, in the control group, the average total score was 11.53 ± 2.79 at baseline and 12.36 ± 2.36 at week 3. The differences of total scores between baseline and week 3 in both groups were considered statistically significant. Analysis of VHIS parameters is shown in Table 3.

The efficacy of polycarbophil gel compared with placebo based on VHIS was analyzed on each parameter with results as shown in Table 4. Among all parameters, vaginal pH differences were the only parameter found to be statistically significant, with $p = 0.001$.

Discussion

Menopause is defined as the permanent cessation of menstruation due to natural loss of ovarian follicle activity related to aging, characterized by the absence of a menstrual period for 12 consecutive months. In this study, the mean age of participants ranged from 54 to 56 years old, with the mean of menopause duration being about 4–5 years. These data were similar to previous study, which stated that the average age of menopause is 50–52 years old in industrialized countries, where developing countries such as Indonesia, Latin America, and Pakistan had a few years earlier of natural menopausal age compared with developed countries.[11]

The improvement of complaints related to vaginal dryness, itching, and dyspareunia was observed in both groups. Subjects showed improvement in those complaints at various durations of treatment, except for burning sensation, as no subject complained of it from the first place. In addition, both groups also showed a significant improvement of VHIS total score, with only about 1 point of increase (polycarbophil gel from 14.14 ± 2.49 to 15.47 ± 2.06 and placebo gel from 11.53 ± 2.79 to 12.36 ± 2.36). Particularly for polycarbophil gel, it only showed a significant improvement of VHIS

Table 3: Vaginal health index score changes prior and after intervention

Vaginal health index score	*Baseline*	*Week 3*	*p-value*
Elasticity			
Polycarbophil	4 (2–5)	4 (3–5)	0.317[a]
Placebo	3 (2–4)	3 (2–4)	0.317[a]
Fluid volume			
Polycarbophil	2 (1–4)	3 (2–4)	0.005[a]
Placebo	2 (1–3)	2 (2–3)	0.014[a]
pH			
Polycarbophil	2 (1–2)	2 (2–3)	0.002[a]
Placebo	1 (1–2)	1 (1–2)	>0.999[a]
Epithelial integrity			
Polycarbophil	4 (1–5)	4 (2–5)	0.564[a]
Placebo	3 (1–4)	3 (1–4)	0.014[a]
Moisture			
Polycarbophil	3 (2–4)	3 (2–5)	0.008[a]
Placebo	2 (1–4)	3 (1–4)	0.008[a]
Total score			
Polycarbophil	14.14 ± 2.49	15.47 ± 2.06	<0.001[b]
Placebo	11.53 ± 2.79	12.36 ± 2.36	0.001[b]

Data presented as mean ± SD or median (min–max), Statistical analysis; [a]Wilcoxon test, [b]Paired *t*-test

Table 4: Vaginal health index score changes prior and after intervention

ΔVaginal health index score	*Polycarbophil*	*Placebo*	*p-value*
Elasticity	0 (0–1)	0 (–1–1)	0.571
Fluid volume	0 (0–1)	0 (0–1)	0.433
pH	0 (0–2)	0 (0–0)	0.001
Epithelial integrity	0 (0–1)	0 (0–1)	0.917
Moisture	0 (0–1)	0 (0–1)	0.819
Total score	1 (0–4)	1 (–1–3)	0.230

Data presented as median (min–max), Statistical analysis: Mann–Whitney test

score for vaginal pH compared with placebo, with no improvement of vaginal elasticity and epithelial integrity.

Previous study has shown that polycarbophil has improved vaginal moisturizer level, fluid volume, and vaginal epithelial integrity.[12] The dissimilarity may also be caused by different durations of the treatment. Our study only gave treatment for 3 weeks, while treatment duration in that study was 12 weeks.[12] Better vaginal acidity in our study was also different from another study using polycarbophil gel with different brands (Hidrafemme).[12] This was owing to the fact of different pH baselines of study populations, where our population had slightly lower values than the previous study. Since polycarbophil gel had almost similar pH with natural vaginal secretions, it could balance the osmolality and pH of vaginal secretions.[13] Vaginal acidity is one of the protective mechanisms of the vagina. The acidity of vaginal pH level was influenced by estrogen, glycogen, and microorganisms, such as *Lactobacillus*.[14] When the level of estrogen is at the highest state, homeostasis will occur. This condition triggers maturation and proliferation of vaginal epithelial cells, resulting in the accumulation of glycogen in those epithels. Glycogen acts as a medium for microorganisms to proliferate, such as *Lactobacillus*. In the normal vagina, acidity was achieved by the high level of lactic acid produced by those microorganisms through metabolism of glycogen. Previous studies stated that the low pH of the vagina will significantly increase the adherence ability of *Lactobacillus* to vaginal epithelial cells and reduce enzymatic activity of pathogens, such as *Gardnella*, which produced sialidase enzyme.[14,15] Polycarbophil is a bioadhesive polymer that could lower pH to the normal level. Polycarbophil itself is a weak poly-acid with big molecules that are immunogenic and cannot be absorbed. The high amount of carboxyl in polycarbophil makes it able to bind with vaginal epithelial cells and sustain vaginal pH into the acidity state (pH ≤4.5).[15–17]

Overall, our study suggested that polycarbophil gel has improved GSM symptoms and VHIS after 3 weeks of intervention, but was not significantly different compared with placebo. This result was consistent with another study by Mitchell et al.,[18] which compared the efficacy of low-dose estradiol, polycarbophil gel (Replens), and placebo gel in 302 postmenopausal women. The treatments were given for 12 weeks, with most subjects complaining of dyspareunia (60%), dryness (21%), itching (7%), irritation (6%), and pain (5%). Although all the symptoms were improved, the study found that there were no significant differences of complaint improvement between those 3 groups among baseline, week 4, and week 12 of therapy. The placebo gel has been suggested not to alter vaginal microbiota or inflammation.[19] Since our placebo gel has shown to effectively relieve GSM symptoms as well as VHIS improvement, it may suggest that mucoadhesive properties from certain manufacturers may not be that necessary for certain GSM symptoms' correction.

Nevertheless, our study found that 80.9% felt satisfied of the use of polycarbophil moisturizing gel, while 19.1% felt less satisfied. Previous study also stated that in the group receiving polycarbophil gel, about 59.5% felt very satisfied, 37.8% satisfied, and 2.7% felt indifferent.[12] Another study also showed that most of the patients using polycarbophil moisturizing gel feel satisfied. A prospective cohort study in Thailand has shown that polycarbophil-based cream was effective to improve lower urinary tract and sexual symptoms after 12 weeks of treatment, thus improving patient's quality of life.[20] These data supported the recommendation by The North American Menopause Society that nonhormonal therapy is still the first-line therapy for GSM treatment, apart from lifestyle modification such as prohibition of smoking, as it could enhance estrogen metabolism, thus enhancing vaginal atrophy.[9,21] However, this polycarbophil gel is only symptomatic and could not replace intravaginal estrogen therapy as the gold standard for more chronic and persistent cases of GSM.[2,3]

To the best of our knowledge, this was the first study to identify the effectiveness of polycarbophil gel compared with placebo in Indonesia. However, there were certain limitations that should be considered to interpret our study. First, the GSM symptoms and VHIS assessments were subjective, thus different personnel may have different interpretations. This study was also conducted in a limited number of subjects, restricted to one place of study, and short duration of treatment. Therefore, further study is required to have better understanding related to the efficacy of polycarbophil gel for GSM in longer duration and larger population, such as using Likert scale for patients' satisfaction and Female Sexual Function Index (FSFI) for sexual function assessment.

Conclusion

In conclusion, polycarbophil gel had improved vaginal dryness, dyspareunia, and dysuria within 2 weeks of treatment. In comparison with placebo, polycarbophil gel has only had better outcome in raising vaginal pH level by using VHIS assessment. However, the satisfaction rate for the therapy was found to be higher in subjects who used polycarbophil gel compared with placebo gel. Thus, the use of polycarbophil gel for postmenopausal women in Indonesia was recommended in order to increase their quality of life.

Authors' Contributions

JI designed study, RPP conducted the research, performed the analysis, and interpretation of data, RPP and RI wrote the paper, JI validated the data, revised the paper, and had primary responsibility for the final content. All authors agreed to the published version of the paper.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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