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Combination therapy with Baofukang suppositories and promestriene cream for postmenopausal atrophic vaginitis: A randomized controlled trial

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Abstract: Postmenopausal atrophic vaginitis is a prevalent condition that significantly impacts the quality of life. This study aimed to evaluate the efficacy and safety of combining Baofukang suppositories with Promestriene cream in treating this condition, with a particular focus on clinical outcomes and endometrial thickness. Sixty-eight patients underwent random allocation into either the control group (Baofukang suppositories) or the observational group (Baofukang suppositories and Promestriene cream). Endometrial thickness was measured using transvaginal ultrasound, and clinical indicators, including symptom resolution time, vaginal cleanliness, and adverse reactions, were assessed. The observational group showed a higher effective rate (97.06% vs. 79.41%, $P<0.05$) and faster symptom relief ($P<0.05$), with significant improvements in vaginal cleanliness and symptom scores ($P<0.05$). No significant differences in endometrial thickness or adverse reactions were observed ($P>0.05$). Combining Baofukang suppositories with Promestriene cream offers an effective and safe therapeutic option for postmenopausal atrophic vaginitis, promoting superior symptom recovery without compromising endometrial safety.

Keywords: Baofukang suppositories, promestriene cream, perimenopause, atrophic vaginitis, endometrial thickness.

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INTRODUCTION

Menopause is diagnosed when a woman over 40 has been without menstruation for a year, excluding pregnancy and other causes of amenorrhea. Women typically spend a third of their lives in menopause, experiencing predictable symptoms due to declining sex hormone levels and aging (National Institute for Health and Care Excellence: Clinical Guidelines 2024; Panay *et al*., 2024). The menopausal transition, marked by irregular cycles and symptoms like hot flashes and night sweats, precedes menopause by several years (Paciuc 2020; Talaulikar 2022).

Atrophic vaginitis, a common gynecological issue in postmenopausal women, is becoming increasingly prevalent as the global population ages (Benini *et al*., 2022; Bleibel and Nguyen 2023). Key symptoms include abnormal vaginal discharge and vulvar itching, which in severe cases can lead to vaginal stenosis. Some patients also experience urinary symptoms, impacting their quality of life (Mesbahi *et al*., 2022).

These symptoms are primarily caused by estrogen deficiency and can be effectively managed with hormone therapy (Xu *et al*., 2024). Promestriene, a topical hormone, has shown efficacy in alleviating symptoms and improving lab markers of vaginal atrophy (Ilhan *et al*., 2021). Baofukang suppositories, a traditional Chinese medicinal product, support immune function and enhance recovery by promoting phagocytic cell activity (Maffei and Guiducci 2022).

Although studies have shown that Baofukang suppositories and Promestriene cream individually are effective in treating atrophic vaginitis (Sun *et al*., 2009; Wang *et al*., 2010), there is a lack of research evaluating the combined efficacy of these treatments. This research investigated the combined use of Baofukang suppositories and Promestriene cream to provide insights for clinical practice.

MATERIALS AND METHODS

Study design

This randomized controlled trial (RCT) with an open-label, parallel-group design was conducted at Beijing Longfu hospital from January 2022 to December 2022. A total of 68 postmenopausal patients diagnosed with atrophic vaginitis were enrolled and randomly assigned to either the observation group or the control group using a computer-generated random number table (n=34 per group). Randomization was performed using a computer-generated random number table by an independent researcher, ensuring allocation concealment. The sample size was determined using G*Power software, with a power of 0.90 and a significance level of $\alpha=0.05$, to ensure adequate statistical power.

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The inclusion criteria included: (1) diagnosed with vaginal atrophy presenting with discomfort, itching, discharge, or thin/purulent secretions; (2) vaginal mucosal atrophy with congestion observed via colposcopy; (3) no hormonal treatment in the past 3 months and (4) normal cognitive function, able to cooperate with treatment. The exclusion criteria were as follows: (1) unexplained vaginal bleeding; (2) pathogenic bacterial infection; (3) known drug allergies; (4) severe organic diseases; (5) malignancies or fungal, Candida, or Trichomonas infections; (6) uncontrolled diabetes and (7) existing cervical lesions.

Intervention

The control group received Baofukang suppositories (Hainan Bikai Pharmaceutical Co., Ltd., National Medical Drug Approval No. Z46020058; 1.74g) administered vaginally. Patients were instructed to insert one suppository nightly, increasing to two suppositories per night if symptoms were severe. Treatment continued for one month and adverse reactions were closely monitored.

The observational group received Baofukang suppositories as described above, combined with Promestriene cream (Jiangxi Decheng Pharmaceutical Co., Ltd., China Drug Approval No. H20046587; 0.5-1.0 g) administered vaginally using an applicator. The cream was applied 1-2 times daily, depending on symptom severity for 30 consecutive days.

Observational Indicators

The primary outcomes evaluated were clinical efficacy, symptom resolution time and adverse reactions, while secondary outcomes included clinical symptom scores, vaginal cleanliness, endometrial thickness (Palacios *et al*., 2023).

Clinical efficacy was assessed at the end of treatment and classified into complete recovery, marked response, improvement, or failure, with an overall effective rate calculated (He *et al*., 2022). Symptom resolution times for vaginal congestion, discharge and itching were recorded to measure the speed of therapeutic response.

Clinical symptom scores comprehensively evaluate vaginal health and vaginal symptoms. Vaginal health parameters included vaginal moisture, mucosal status, secretion, and elasticity, while vaginal symptom severity was assessed by evaluating pain, discharge, burning, and itching. Higher scores indicated better vaginal health and reduced symptom severity (Le *et al*., 2022).

Vaginal cleanliness was assessed using a standard clinical grading system based on the microscopic examination of vaginal secretions collected during gynecological evaluations (Alexiades 2021). Cleanliness was classified into four grades: Grade I (optimal cleanliness, with lactobacilli predominating and no inflammatory cells), Grade II (moderate cleanliness, with decreased lactobacilli and increased mixed flora), Grade III (poor cleanliness, with a significant increase in mixed flora and the presence of inflammatory cells), and Grade IV (very poor cleanliness, with pathogenic microorganisms predominating and significant inflammation). This assessment was conducted by experienced clinicians following standardized criteria to ensure consistency and reliability.

Endometrial thickness was measured pre- and post-treatment via transvaginal ultrasound (Philips IU22). Three measurements were taken for each patient and the average value was recorded to ensure accuracy.

Adverse reactions, including fever, chills and allergic reactions, were documented throughout treatment period. Allergic reactions were identified based on patient-reported symptoms and confirmed through clinical examination. The severity of adverse reactions was categorized as mild, moderate, or severe according to standard clinical criteria.

Ethical approval

The study was approved by the Ethics Committee of Beijing Longfu Hospital (Approval No. KY-BTLF2023081). Written informed consent was obtained from all participants before enrollment. The study adhered to the ethical principles outlined in the Declaration of Helsinki and followed relevant guidelines for human clinical research.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS 25.0 software (IBM, Armonk, NY, USA). Categorica data, were analyzed using the chi-square test and expressed as n (%). Continuous variables were expressed as mean ± SD and analyzed using homogeneity of variance and t-tests. $P<0.05$ represented the statistical significance threshold.

RESULTS

General characteristics

As presented in table 1, the baseline characteristics of the observation and control groups were comparable. The mean age was 54.90±2.95 years and 54.46±2.80 years for the observation and control groups, respectively, with similar ranges ($P>0.05$). Menopause duration and disease duration were also not significantly different between the groups ($P>0.05$). The distribution of educational levels showed no significant differences, with proportions of primary education or below, junior high, and high school or above being similar in both groups ($P>0.05$). These findings confirm the groups' comparability at baseline, ensuring that observed treatment differences are not due to confounding demographic factors.

Clinical efficacy

The total effective rate was significantly higher in the observation group compared to the control group (97.06% vs. 79.41%) (P<0.05, table 2). Specifically, the observation group demonstrated a higher proportion of patients achieving complete recovery or marked improvement, suggesting combining Baofukang suppositories with Promestriene cream provided enhanced therapeutic benefits.

Symptom resolution time

In comparison with the control group, the observation group experienced faster resolution of vaginal congestion, abnormal vaginal discharge and itching (P<0.05, table 3). This indicated that combining Baofukang suppositories with Promestriene cream could promote symptom resolution in patients with postmenopausal atrophic vaginitis.

Clinical symptom scores

As outlined in table 4, pre-treatment vaginal health and symptom scores in both groups showed no significant notably different (P>0.05). However, post-treatment, the observation group demonstrated significantly higher vaginal health scores (16.34±2.15 vs. 12.76±2.04, P< 0.05) and lower vaginal symptom scores (4.52±0.60 vs. 6.70±0.78) (P<0.05) compared to the control group. These findings demonstrated that the combination therapy not only significantly improved vaginal health parameters, such as moisture, secretion, and elasticity, but also effectively alleviated symptoms like pain, itching, and discharge severity. The superior efficacy of the combination therapy highlights its potential as a more effective treatment option for postmenopausal atrophic vaginitis.

Vaginal cleanliness

As shown in table 5, pre-treatment vaginal cleanliness grades were similar between the two groups (P > 0.05). Post-treatment, the observation group displayed a significantly higher proportion of patients with optimal cleanliness (I or II grade) compared to the control group (P<0.05). These results suggested that the combination therapy effectively restored the vaginal microenvironment, which is critical for overall vaginal health.

Endometrial thickness

Table 6 illustrated that endometrial thickness did not change significantly in either groups following treatment (P>0.05). This indicated that the combination therapy did not affect endometrial thickness, supporting its safety for postmenopausal atrophic vaginitis patients.

Adverse reactions

Adverse reactions, including transient fever, chills, and allergic reactions, were rare and not significantly different between the two groups (5.88% vs. 2.94%) (P>0.05). In the observation group, one patient reported a mild allergic reaction characterized by local redness and itching, while another experienced chills (5.88%). In the control group, one patient experienced transient fever (2.94%). All adverse events were classified as mild, resolved spontaneously within a few days, and did not require additional interventions. These findings indicated that the combination therapy was well-tolerated and has an excellent safety profile.

DISCUSSION

Atrophic vaginitis, a common gynecological condition in postmenopausal women, is primarily caused by estrogen deficiency, which weakens vaginal defenses, promotes bacterial overgrowth and triggers inflammation (Karlson *et al*., 2023). The condition significantly impacts quality of life, especially as its prevalence rises with the aging population (Wierzbicka *et al*., 2021). Effective treatment options are therefore crucial. Previous research, such as Rioux J E *et al*. (Rioux *et al*., 2018), has shown that combining estrogen cream with Baofukang suppositories achieves a higher effectiveness rate (98.15%) compared to either treatment alone (79.63%) (P<0.05). This study supports those findings, with the observation group achieving a 97.06% effectiveness rate, significantly higher than the 79.41% rate in the control group.

The improvement outcomes observed in the observation group may be attributed to the complementary mechanisms of the two treatments. Baofukang suppositories, a traditional Chinese medicine formulation, exhibit antimicrobial and anti-inflammatory effects. Key components, such as borneol, have been reported to promote blood circulation, clear heat, resolve stasis, relieve pain, and support vitality (Langella 2023). Curcuma oil, another active ingredient, provides estrogen-like effects, promotes mucosal restoration, and inhibits vaginal pathogens (de Oliveira *et al*., 2021). Promestriene cream, a topical estrogen, enhances vaginal epithelial cell growth, glycogen synthesis, and lactobacilli regeneration, creating an acidic environment that deters pathogens and supports symptom resolution (Segal *et al*., 2011; de Oliveira *et al*., 2021). Together, these mechanisms may explain the superior efficacy of the combination therapy.

In this study, the observation group demonstrated faster symptom relief, higher vaginal health scores, and better cleanliness compared to the control group. Promestriene's ability to promote epithelial cell differentiation, glycogen synthesis and lactobacilli regeneration aligns with findings from Sanchez-Borrego *et al*. (Sanchez-Borrego *et al*., 2014), where estrogen therapy improved vaginal cleanliness in patients with atrophic vaginitis. Furthermore, the observation group achieved these benefits without significant differences in endometrial thickness or adverse reactions compared to the control group, underscoring the safety of this combination therapy.

Table 1: Comparison of general characteristics in both groups

Groups	Number of Cases	Age (years)	Disease Duration (days)	Menopausal Duration (years)	Education Level		
					Primary school or below	junior high school	High school or above
Observation Group	34	54.90±2.95	4.37±1.15	5.58±1.46	16 (47.06)	12 (35.29)	6 (17.65)
Control Group	34	54.46±2.80	4.33±1.20	5.45±1.10	15 (44.12)	11 (32.35)	8 (23.53)
χ^2/t		0.631	0.140	0.415	0.128		
P		0.530	0.889	0.680	0.938		

Note: Data were expressed as mean ± SD or n (%).

Table 2: Comparison of clinical efficacy in both groups

Groups	N	Healing	Remarkably Improvement	Improvement	No Improvement	Total Effective Rate
Observation Group	34	16 (47.06)	10 (29.41)	7 (20.59)	1 (2.94)	33 (97.06)
Control Group	34	12 (35.29)	9 (26.47)	6 (17.65)	7 (20.59)	27 (79.41)
χ^2						5.100
P						0.024

Note: Data were expressed as n (%).

Table 3: Comparison of symptom resolution time in both groups

Groups	N	Vaginal Congestion Symptom Resolution Time	Abnormal Vaginal Discharge Symptom Resolution Time	Vulvar Itching Symptom Resolution Time
Observation Group	34	11.45±1.08	6.38±0.85	7.06±1.25
Control Group	34	15.78±2.56	10.52±1.74	12.32±2.94
t		9.087	12.466	9.601
P		0.001	0.001	0.001

Note: Data were expressed as mean ± SD.

Table 4: Comparison of clinical symptom scores pre- and post-treatment in both groups

Groups	N	Vaginal Health Score		Vaginal Symptom Score	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation Group	34	9.24±1.10	16.34±2.15	9.26±1.74	4.52±0.60
Control Group	34	8.95±1.22	12.76±2.04	9.35±1.86	6.70±0.78
t		1.029	7.043	0.206	12.917
P		0.307	0.001	0.837	0.001

Note: Data were expressed as mean ± SD.

Table 5: Comparison of vaginal cleanliness pre- and post-treatment in both groups

Groups	N	Before Treatment				After Treatment			
		I Degree	II Degree	III Degree	IV Degree	I Degree	II Degree	III Degree	IV Degree
Observation Group	34	0 (0.00)	1 (2.94)	12 (35.29)	21 (61.76)	15 (44.12)	10 (29.41)	8 (23.53)	1 (2.94)
Control Group	34	0 (0.00)	2 (5.88)	13 (38.24)	19 (55.88)	7 (20.59)	5 (14.71)	15 (44.12)	7 (20.59)
χ^2		0.473				15.206			
P		0.789				0.011			

Note: Data were expressed as n (%).

Table 6: Comparison of endometrial thickness pre- and post-treatment in both groups

Group	Number	Endometrial Thickness (mm)	
		Before	After
Observation Group	34	3.30±0.52	3.52±0.58
Control Group	34	3.24±0.55	3.46±0.56
t		0.462	0.434
P		0.645	0.666

Note: Data were expressed as mean ± SD.

This aligns with previous findings by Sarmento ACA *et al*. (Sarmento *et al*., 2021), which reported that Promestriene cream does not lead to endometrial hyperplasia, supporting its favorable safety profile. The absence of changes in endometrial thickness in this study likely reflects Promestriene's local action and minimal systemic absorption (Ilhan *et al*., 2021; Donders and Donders 2023), making it suitable for postmenopausal women concerned about endometrial and systemic safety. However, it should be noted that the treatment duration of one month may not be sufficient to assess long-term endometrial safety, including risks such as hyperplasia. Longer-term studies are needed to evaluate these outcomes comprehensively.

Adverse reactions in this study were infrequent and mild, with no significant differences between groups. Reported events included transient fever, chills, and mild allergic reactions, all of which resolved without intervention. No cumulative or long-term effects were observed during the treatment period, consistent with Promestriene's safety profile. However, a longer follow-up period is necessary to monitor delayed adverse effects or symptom recurrence, particularly in the context of extended or repeated therapy.

Despite its promising findings, this study has limitations. The relatively small sample size and the short treatment duration may restrict the generalizability of the results to broader populations. Additionally, the study population was relatively homogeneous in terms of age and menopausal duration, and stratification based on factors such as the severity of atrophic vaginitis was not conducted due to the limited sample size. Future research should include larger, more diverse populations and incorporate stratified analyses to better understand the efficacy and safety of this combination therapy across different subgroups. Moreover, extended treatment durations and post-treatment follow-up periods are essential to assess long-term efficacy, safety and the potential for symptom recurrence.

CONCLUSION

Overall, combining Baofukang suppositories with Promestriene cream demonstrates both efficacy and safety in treating postmenopausal atrophic vaginitis, promoting symptom recovery, improving vaginal cleanliness, and maintaining endometrial safety. While the findings of this study are encouraging, further research with larger sample size, longer treatment durations, and extended follow-up is recommended to confirm and expand upon these results, ultimately optimizing clinical application.

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