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Original Article

A Randomized Trial Comparing the Effect of Unani Formulation with Metronidazole in Bacterial Vaginosis

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ABSTRACT

Background and objectives: Bacterial vaginosis (BV) is recognized as the most prevalent type of vaginal infection, impacting approximately 19-24% of women in their reproductive years. The recurrence rate of BV is significant, negatively impacting the well-being of affected women. This study aimed to compare the therapeutic effects of a polyherbal Unani formulation and metronidazole in treating bacterial vaginosis.

Methodology: In this prospective patient blinded standard controlled trial, a total of 40 individuals with a clinical diagnosis of bacterial vaginosis were randomly assigned to receive either an active control treatment (n = 20) or a test drug (n = 20). In the test drug combination of *Acacia catechu, Azadirachta indica* and *Quercus infectoria* in tablet (1g) form in the dose of 2 tablets orally twice daily with water was administered for 3 weeks. In the active control standard drug, metronidazole 400 mg tablet, orally twice daily was given for one week. The primary outcome measure was clinical cure; H. negative Amsel's criteria and a reduction in subjective symptoms, while the secondary outcome measure was an improvement in SF-36 quality of life (QOL).

Results and conclusion: Both the experimental treatment and the metronidazole demonstrated a significant clinical cure for bacterial vaginosis as well as an increase in health-related quality of life. Based on these findings, it appears that the test medication is a potent Unani formulation for the treatment of bacterial vaginosis. A well conducted trial with a bigger sample size is required to corroborate these findings.

Key words: bacterial vaginosis; polyherbal; quality of life; Unani medicine

INTRODUCTION

Bacterial vaginosis is a syndrome characterized by a decrease in the normally abundant lactobacilli that produce hydrogen peroxide(H2O2), along with an overgrowth of other bacteria such as *Gardnerella vaginalis*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, and anaerobes.[1-3] Among women of reproductive age, BV is recognized as the most prevalent form of vaginal infection, affecting approximately 19-24% of them.[4] The Centers for Disease Control and Prevention (CDC) has recently classified bacterial vaginosis as an emerging infectious disease.[5] Women with BV face a heightened risk of contracting human papillomavirus, herpes simplex virus type 2 (HSV-2), *Trichomonas vaginalis, Neisseria gonorrhoeae*, and HIV.[2,6] Additionally, BV is frequently associated with postpartum endometritis, increased susceptibility to surgical infections, pelvic inflammatory

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diseases, spontaneous abortions, preterm rupture of membranes and delivery, as well as an elevated risk of sexually transmitted infections.[7-9] In women undergoing in vitro fertilization, bacterial vaginosis can reduce the success rate of embryo implantation and contribute to early pregnancy loss[10]. BV often presents as a chronic or recurrent condition, and the underlying cause of these recurrences remains poorly understood. The high recurrence rate of BV significantly impairs the quality of life for affected women.[12]

WHO noted that more than 80% of the global population relies on plants to provide for their basic medical needs.[13] Various religious documents such as Quran and Bible also supported the role of the herb in health care and prevention[14]. *Unani* literature says that in *Sayalān al-Raḥim* there is continuous discharge from the vagina and the cause behind this is weakness of Quwwat ghādhiya of the *rehm*.[15] Also it has been claimed by Unani scholars that vaginal discharge occurs due to weakness of *Q*uwwat māsika.[16] Renowned Unani physicians have described the use of drugs having astringent, anti-inflammatory and antiseptic properties to treat vaginal discharge.[15,17] Unani literature refers to several medications for the treatment of vaginal discharge; however, their efficacy has not been scientifically validated.[15,18,19] *Habb Mufeed Sailan* (a polyherbal Unani formulation) is one among them which is a compound formulation of *Post Darakhte Neem* (*Azadirachta indica*), *Kath Safaid* (*Acacia catechu*) and *Mazu* (*Quercus infectoria*).[18] *Azadirachta indica* is found to be active against microorganisms in several in vivo and in vitro studies.[20-23] Besides it also showed anti-inflammatory activity in experimental studies.[24,25] A herbal formulation containing *Azadirachta indica* showed a significant reduction in the symptoms of Trichomonal vaginitis[25]. Similarly, *Acacia catechu*[27,28] and *Quercus infectoria*[29-31] was also found active against microorganisms as well as showed anti-inflammatory activity in animal studies.[32-34] As a result, clinical research was started to determine whether a polyherbal formulation was successful in treating bacterial vaginosis. The study's goal was to conduct a rigorous investigation on the polyherbal remedy known as (*Hab Mufeed Sailan*) effectiveness in treating bacterial vaginosis.

Materials and methods

Study Design: From November 2016 to April 2018, this prospective, randomized, controlled trial was conducted out at the Luqman Unani Medical College Hospital and Research Centre in Vijaypur, Karnataka, in the department of Ilmul Qabalat wa Amraze Niswan. The Institutional Ethics Committee granted approval for the protocol under IEC No. LUMC/IEC/2015-16/01/ANQ/01, and it was carried out in accordance with the principles of the Declaration of Helsinki. The trial was registered at www.ctri.gov.in with trial registration no. CTRI/2017/10/010172

Participants: Patients complaining of vaginal discharge were interrogated thoroughly for detailed history, particularly about the duration of discharge, presence or absence of foul smell, vulval itching, dysuria, low backache and dyspareunia. Married women in the age group of 18-45 years with positive Amsel's criteria were included in the study. Pregnant and lactating women, recent h/o topical or systemic use of antibiotics (within 1 month), women using OCPs and IUCDs and concomitantly having organic pelvic pathology, sexually transmitted diseases and systemic illnesses were excluded from the study. Patients who met the above specified inclusion criteria were provided with an information sheet containing comprehensive details about the study. Adequate time and opportunity were given to the patients to review the study information presented in the sheet and to ask any questions they had. They were fully entitled to decline their consent or withdraw from the study at any point, without having to provide a reason. Once their willingness was obtained, they were invited to participate in the study and

requested to sign the informed consent form. A comprehensive medical history was collected, and a thorough physical examination, including a pelvic examination, was conducted. Each patient underwent a systemic examination of the central nervous system (CNS), cardiovascular system (CVS), respiratory system (RS), and abdominal region. All relevant information was documented in the designated case record form created specifically for the study. The socioeconomic status of the patients was assessed using Kuppuswamy's scale. The assessment of Mizāj, a concept related to temperament, was performed based on the provided temperament chart within the case record form. Prior to the examination and sample collection, verbal consent was obtained from all participants. Patients were advised to empty their bladders. During the pelvic examination, the patient assumed a lithotomy position. The vulva and perineum were examined for any signs of discharge, redness, irritation, or swelling. Genital cleaning was done using a 10% savlon solution, and a Cusco's speculum was gently inserted to observe the cervical texture, external os, presence of hypertrophy or erosion, and any discharge. A manual examination was conducted to assess the position (anteverted or retroverted), mobility, size, and texture of the uterus. Using Ranbaxy pH indicator paper, the pH of the vagina was tested, and the colour shift was contrasted with the given standard colour chart and pH range. It was carefully avoided that cervical fluid would contaminate the paper. The vaginal discharge was tested using a 10% KOH solution, and the presence of a fishy odor indicated a positive result for the whiff test. Additionally, the discharge was examined under a microscope at the LUMC laboratory within 10 minutes of preparation for clue cells and flagellar movements of trichomonas using the saline mount technique. The pathologist responsible for this examination was unaware of the patient groups, ensuring blinding. Furthermore, the patients underwent various tests such as Hb% (hemoglobin level), random blood sugar measurement, complete urine examination, liver function test, kidney function test, DRL (routine blood count), HIV I & II screening, Pap smear, and pelvic scan.

Intervention: In the test group *Hab Mufeed Sailan* containing *Post Darakht Neem* (bark of *Azadirachta indica*), *Mazu* (*Quericus infectoria* galls) and *Kath Safaid* (extract of *Acacia catechu*) was selected as test drugs for the trial. All three drugs in equal quantity were cleaned and powdered. *Hab* (tablet) of 1g was made by using water. 2 tablets BD daily were given for 3 weeks with water after food. In the control group tablet of metronidazole 400 mg BD daily for one week was given. Every time a follow-up visit was made, the medication packets that were given out at the prior session were examined in order to gauge compliance.

Outcome Measures: Primary outcome was the negative Amsel's criteria and the reduction in the subjective symptoms. According to Amsel's criteria, BV can be identified by the presence of at least three of the four parameters: an elevated vaginal pH, homogenous vaginal discharge, the presence of clue cells and an amine odour after the addition of potassium hydroxide to the discharge. The quality of life (QOL), which was measured using the SF-36 (short form questionnaire 36), was the secondary outcome. This instrument was used in the study to measure the QOL of both the general population and the population with specific chronic diseases throughout the world. The SF-36 scales have scores between 0 and 100, with higher scores indicating a better quality of life in terms of health.[35]

Assessment and follow-up: During treatment, patients were followed for three consecutive weeks. During this period subjective parameters of offensive vaginal discharge, vulval itching and low back pain were assessed by using an arbitrary scale. Amsel's criteria; per speculum, homogenous vaginal discharge, vaginal pH, clue cells on wet mount, and whiff test were repeated after completion of the treatment. Additionally,

patients were asked if the medication had caused any side effects while it was being tested. Patients were instructed to follow up twice, with a 15-day interval between visits, once their treatment was finished to check for the return of their symptoms. For each adverse event, the features (onset, severity, and duration) and any potential cause-and-effect connections with medication delivery for the full trial period were noted.

Randomization and allocation: Using a straightforward randomization technique made possible by an online randomization generator (www.randomization.com), patients were randomly assigned in a 1:1 ratio to either the test group or the conventional control group. Patients were blinded.

Sample Size Estimation: From the previous literature and through expert survey, the proportion of subjects cured by test (*Hab Mufeed Sailan*) and control drug (metronidazole) was assumed 95% and 60% respectively with a clinically important difference of 35%. Based on these presumptions, a sample size of 36 participants, 18 in each group, was found to be enough to detect, with 80% power and a 5% level of significance, a clinically significant difference of 0.35 between the two groups in treating bacterial vaginosis. The necessary sample size, assuming a 10% dropout rate, was about 40 (20 in each group).

Statistical methods: While categorical measures are presented as numbers and percentages, results for continuous measurements are represented as mean standard deviation (minimum-maximum). At a 5% level, statistical significance was determined. Regarding the information, the following presumptions were made: 1. Samples should be taken at random from the population, 2. Dependent variables should have a normal distribution, and 3. Cases within the samples should be independent. For comparing two groups (intergroup analysis) based on metric parameters, a two-tailed, independent Student's t-test was used to determine the significance of research parameters on a continuous scale. Levene's test for homogeneity of variance was conducted to evaluate the equality of variances. For analyzing categorical data across two or more groups, the Chi-square test or Fisher's exact test was used, depending on the sample sizes and nature of the data. Fisher's exact test was used when the cell samples were very small, providing a non-parametric approach for qualitative data analysis.

Results and Discussion

Participant flow: Out of a total of 205 patients evaluated, 134 were found ineligible and eliminated from the study. The remaining 40 patients were randomized to their groups at random. (Figure 01.)

Baseline characteristics: Patients' baseline assessments included queries concerning their age, religion, education, socioeconomic status, occupation, diet, age of menarche, parity, and Mizāj Statistics revealed statistical similarities between the two groups (Table 1).

Primary Outcome: The test medication was discovered to be similarly successful at reducing vaginal discharge when compared with the standard drug as there was no significant changes were noted between the groups (Table 2). Improvement in vaginal discharge can be explained based on *daf'e jiryan wa sailan* and *qabiz* properties of *Acacia catechu* and *Quercus infectoria*.[36-39] Also, *Azadirachta indica* is found to be active against microorganisms in several in vivo and in vitro studies.[20-23] Besides it also showed anti-inflammatory activity in experimental studies.[24,25] A herbal formulation containing *Azadirachta indica* showed a significant reduction in the symptoms of *Trichomonal vaginitis*.[26] Similarly, *Acacia catechu*[27,28] and *Quercus infectoria*[29-31] were also found active against microorganisms as well as showed anti-inflammatory activity in animal studies.[32-34]

Both drugs were found equally effective in reducing vulval itching (Table 3). Kath has been advised by the Unani physicians to treat itching in the form of paste.[36]

Also, Ahmad et al., have reported a 100% reduction in pruritus vulvae with local application of *Phitkiree*, *Haldi* and *Barg Neem* and oral use of *Afsanteen*, *Kabab Chini*, *Bahroza* and *Mazu*.[26] Further, both groups showed equal improvement in low backache (Table 4). Table 5. Summarized the Amsel's criteria. The improvement in the pain can be explained as mentioned in Unani classical texts that the bark of *Azadirachta indica* possesses *Musakkin* (analgesic) property.[36,37] Further experimental studies have shown the analgesic properties.[25,40]

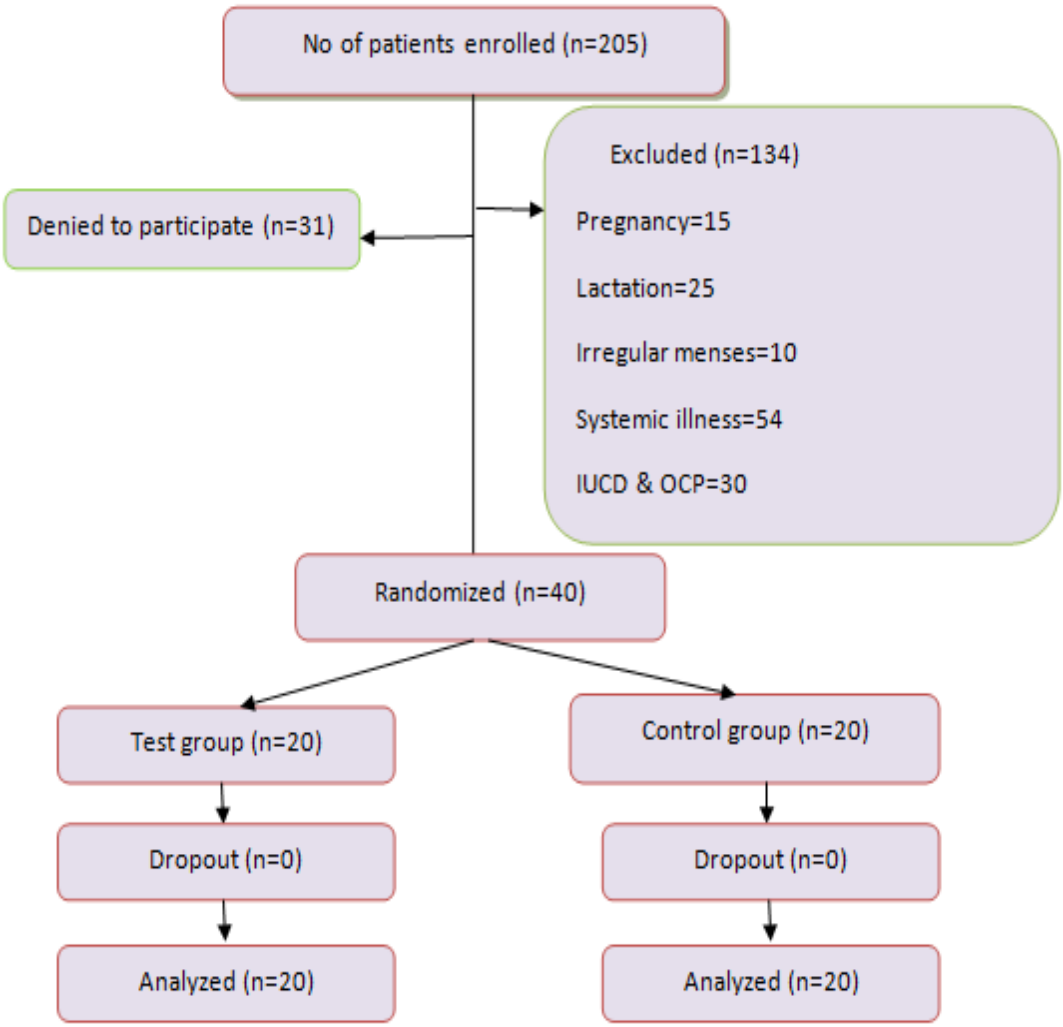

Figure 01. Flow chart of participants

Table 1. Baseline characteristics of the patients in test and control group

Basic variables	Test group	Control group	Total	P-value
Age in years				
<20	1(5%)	1(5%)	2(5%)	0.164
20-30	7(35%)	10(50%)	17(42.5%)	
31-40	11(55%)	9(45%)	20(50%)	
>40	1(5%)	0(0%)	1(2.5%)	
Total	20(100%)	20(100%)	40(100%)	
Mean ± SD	31.90±6.54	29.15±5.69	30.53±6.21	
Religion				0.342
Christian	1(5%)	0(0%)	1(2.5%)	
Hindu	3(15%)	1(5%)	4(10%)	
Muslim	16(80%)	19(95%)	35(87.5%)	
Occupation				1
House wife	18(90%)	19(95%)	37(92.5%)	
Professional	2(10%)	1(5%)	3(7.5%)	
Diet				1
Mixed	20(100%)	20(100%)	40(100%)	
Veg	0(0%)	0(0%)	0(0%)	
Habitat				1
Rural	1(5%)	0(0%)	1(2.5%)	
Urban	19(95%)	20(100%)	39(97.5%)	
Socioeconomic status				0.114
Upper Lower	9(45%)	3(15%)	12(30%)	
Lower middle	7(35%)	7(35%)	14(35%)	
Upper Middle	3(15%)	5(25%)	8(20%)	
Upper	1(5%)	5(25%)	6(15%)	
Education				
Illiterate	1(5%)	0(0%)	1(2.5%)	0.762
Primary	7(35%)	5(25%)	12(30%)	
Secondary	9(45%)	8(40%)	17(42.5%)	
High School	0(0%)	1(5%)	1(2.5%)	
Graduate	3(15%)	5(25%)	8(20%)	
Post Graduate	0(0%)	1(5%)	1(2.5%)	
Mizaj				
Balghami	5(25%)	7(35%)	12(30%)	0.063
Damvi	4(20%)	9(45%)	13(32.5%)	
Safravi	11(55%)	4(20%)	15(37.5%)	

Total	20(100%)	20(100%)	40(100%)	

Table 2. Comparison of vaginal discharge in two groups of the patients studied

Offensive vaginal discharge	**Before Treatment**	**After Treatment**	**% change**
Test Group (n=20)			
No discharge	0(0%)	12(60%)	60.0%
Scanty discharge	0(0%)	1(5%)	5.0%
Moderate discharge	18(90%)	7(35%)	-55.0%
Profuse discharge	2(10%)	0(0%)	-10.0%
Control Group (n=20)			
No discharge	0(0%)	16(80%)	80.0%
Scanty discharge	0(0%)	0(0%)	0.0%
Moderate discharge	18(90%)	4(20%)	-70.0%
Profuse discharge	2(10%)	0(0%)	-10.0%
P value	1.000	0.301	-

Table 3. Comparison of vulvovaginal pruritus distribution in two groups of patients studied

Vulvovaginal pruritus	**Before Treatment**	**After Treatment**	**% change**
Test Group (n=20)			
Not present (0)	0(0%)	11(55%)	55.0%
Mild (1)	2(10%)	4(20%)	10.0%
Moderate (2)	16(80%)	5(25%)	-55.0%
Severe (3)	2(10%)	0(0%)	-10.0%
Control Group (n=20)			
Not present (0)	0(0%)	16(80%)	80.0%
Mild (1)	8(40%)	0(0%)	-40.0%
Moderate (2)	12(60%)	4(20%)	-40.0%
Severe (3)	0(0%)	0(0%)	0.0%
P value	0.037	0.084	-

Table 4. Comparison of low back pain in two groups of patients studied

Low back pain	**Before Treatment**	**After Treatment**	**% change**

Test Group (n=20)			
No pain	1(5%)	6(30%)	25.0%
Mild pain	3(15%)	11(55%)	40.0%
Moderate pain	13(65%)	3(15%)	-50.0%
Severe pain	3(15%)	0(0%)	-15.0%
Control Group (n=20)			
No pain	9(45%)	14(70%)	25.0%
Mild pain	8(40%)	6(30%)	-10.0%
Moderate pain	3(15%)	0(0%)	-15.0%
Severe pain	0(0%)	0(0%)	0.0%
P value	<0.001**	0.018*	-

* Moderately significant (P value:0.01<P 0.05) ** Strongly significant (P value<0.01)

Table 5. Comparison of Amsel's criteria between the groups after treatment.

Amsel's criteria	**Test Group**	**Control Group**	***P* Value**
Positive	7(35%)	5(25%)	0.490
Negative	13(65%)	15(75%)	
Total	20(100%)	20(100%)	

Secondary Outcome Parameters: The quality of life was evaluated using the SF-36 questionnaire. All subdomains of quality of life were found to be affected in this study, with the general health scale showing the highest impact (Table 6). Similar findings were reported by Valsangkar et al., who observed that all domains of quality of life were affected in their study on RTI and STI, with the social and sexual domains experiencing the greatest impact.[41] Numerous studies have replicated the impairment of quality of life in various types of infections, such as recurrent vulvovaginal candidiasis, with research suggesting that women with this condition often face significant negative effects on their work and social life.[42] However, Zhu et al., reported that in recurrent vulvovaginal candidiasis, the SF-36 domain scores were significantly lower than the norms of the general population, particularly in the mental health domains.[43]

Both before and after treatment, safety profile measurements were discovered to be within normal ranges. Safety data between the groups did not significantly differ before or after treatment. Acacia catechu demonstrated an extremely substantial protective effect against CCI4-induced hepatotoxicity.[44] The biochemical enzyme levels and histological alterations caused by paracetamol in the liver of Wistar albino rats were substantially decreased following pretreatment with an ethanolic extract of Acacia catechu.[45]

Table 6. Comparison of quality of life in two groups of patients studied

Quality of life SF-36	Test Group	Control Group	Total	P value
Physical functioning				
Before Treatment	35.75±6.54	43.50±8.44	39.63±8.43	0.002**
After Treatment	74.65±7.80	85.50±7.59	80.08±9.38	<0.001**
difference	-38.9	-42	-40.45	-
P value	<0.001**	<0.001**	<0.001**	-
Role limitations due to physical health				
Before Treatment	51.25±9.85	52.50±24.20	51.88±18.25	0.832
After Treatment	100.00±0.00	100.00±0.00	100.00±0.00	-
difference	-48.75	-47.5	-48.125	-
P value	<0.001**	<0.001**	<0.001**	-
Role limitations due to emotional problems				
Before Treatment	56.67±15.70	58.35±14.84	57.51±15.10	0.73
After Treatment	100.00±0.00	100.00±0.00	100.00±0.00	-
difference	-43.33	-41.65	-42.49	-
P value	<0.001**	<0.001**	<0.001**	-
Energy/Fatigue				
Before Treatment	69.00±8.97	54.75±20.61	61.88±17.27	0.007**
After Treatment	88.50±19.54	93.25±10.17	90.88±15.56	0.341
difference	-19.5	-38.5	-29	-
P value	<0.001**	<0.001**	<0.001**	-
Emotional wellbeing				
Before Treatment	65.48±9.93	65.80±17.19	65.64±13.86	0.942
After Treatment	92.50±12.81	93.78±8.58	93.14±10.78	0.714
difference	-27.025	-27.975	-27.5	-
P value	<0.001**	<0.001**	<0.001**	-
Social Functioning				
Before Treatment	70.25±10.16	67.88±13.29	69.06±11.74	0.529
After Treatment	74.75±17.01	82.50±10.26	78.63±14.41	0.089
difference	-4.5	-14.625	-9.563	-
P value	0.165	0.001**	<0.001**	-
PAIN				
Before Treatment	65.25±13.40	62.50±18.76	63.88±16.15	0.597

After Treatment	78.86±21.58	90.88±16.94	84.87±20.09	0.058
difference	-13.61	-28.375	-20.993	-
P value	0.016*	<0.001**	<0.001**	-
General Health				
Before Treatment	7.00±5.48	6.50±8.13	6.75±6.85	0.821
After Treatment	68.60±10.88	72.75±7.86	70.68±9.60	0.175
difference	-61.6	-66.25	-63.925	-
P value	<0.001**	<0.001**	<0.001**	-

* Moderately significant (P value <0.01); ** strongly significant (P value <0.001)

Conclusion

The experimental medication demonstrated comparable effectiveness in alleviating the symptoms associated with bacterial vaginosis. However, the study was limited by its small sample size and the absence of long-term follow-up to assess both efficacy and safety. Therefore, it is recommended to carry out a future study with a larger sample size and extended follow-up duration to obtain more comprehensive findings.

Conflict of interest: None declared.

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