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Comparative efficacy of oral and vaginal probiotics in reducing the recurrence of bacterial vaginosis: a double-blind clinical trial

Mahnaz Boroumand Rezazadeh[1], Minoo Zanganeh[1], Lida Jarahi[2] and Zahra Fatehi[1*]

Abstract

Objective The primary goal of this study is to discern the optimal adjuvant treatment for patients diagnosed with bacterial vaginosis, focusing on reducing recurrence rates.

Methods This study is a double-blind clinical trial with no previous similar trials conducted to date. The study population consisted of non-pregnant, married women visiting teaching hospitals' clinics in Mashhad, complaining of vaginal discharge. After informed consent and questionnaire completion, samples were obtained from vaginal discharge surrounding the cervix of clinically diagnosed bacterial vaginosis patients. Using Gram staining, a gold standard method for bacterial vaginosis diagnosis, samples were examined under a microscope according to the Nugent score. After initial treatment with metronidazole, patients were divided into two groups receiving either vaginal or oral probiotics.

Results Of the 55 participating women, 20 were in the vaginal probiotic group and 35 were in the oral probiotic group. No significant demographic or clinical differences existed between groups at baseline. The Nugent score decreased from 8.5 to 3 in the vaginal group and from 9 to 3 in the oral group, suggesting the effectiveness of both treatments. While the difference between groups was not statistically significant, each group showed significant improvements from their initial states (p-value < 0.001).

Conclusion No significant difference was observed in the effectiveness of oral versus vaginal probiotics in reducing the recurrence of bacterial vaginosis after routine treatment. Therefore, the type of probiotic to be used could be chosen based on patient preference.

Keywords Bacterial vaginosis, Probiotics, Recurrence, Adjuvant treatment

*Correspondence:
Zahra Fatehi
zahraafatehi@gmail.com
[1]Department of Obstetrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Community medicine department, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Introduction

Bacterial vaginosis (BV) is a multifaceted clinical condition, commonly observed yet intricate in nature, often precipitated by a disruption in the natural balance of vaginal microbiota. BV tends to be prevalent among women in their reproductive years and is typically characterized by symptoms like unpleasant-smelling vaginal discharge and discomfort [1].

This condition, BV, is recognized as a recurrent polymicrobial syndrome that transpires from an alteration in the microbiota, which under usual circumstances, is dominated by Lactobacillus species. Instead, it is overpowered by an array of bacterial species such as Gardnerella vaginalis, Atopobium vaginae, among others [2]. Despite established treatments like metronidazole, the recurrence of BV continues to pose a significant challenge, with relapse rates of up to 50% within the initial three months post-treatment [3].

In the past few years, probiotics, administered either orally or vaginally, have gained traction as a promising supplement to conventional antibiotics therapy due to their beneficial impact on the vaginal microbiota [4, 5]. They have demonstrated potential in curbing the recurrence of BV by restoring and maintaining the balance of the natural vaginal microbiota [6, 7]. Nonetheless, the best mode of probiotic administration for managing BV remains to be determined.

The goal of this study is to assess the impact of oral versus vaginal probiotic administration on the recurrence rates of BV in nonpregnant women of reproductive age presenting with vaginal discharge. By pinpointing a more effective route for administering probiotics, this research could lead to more precise therapeutic strategies and enhance patient outcomes in the management of BV.

Method and materials

Trial design

This study was a randomized, controlled, single-center trial conducted at specialist clinics within Mashhad's, Iran educational hospitals. The objective was to evaluate the difference in bacterial vaginosis (BV) recurrence rates between two intervention groups: one receiving oral probiotics and the other vaginal probiotics, following a routine metronidazole treatment regimen.

Participants

Participants were nonpregnant, married women aged 18 years and older up to 50 years who sought treatment at the specialist clinics of Mashhad educational hospitals due to symptomatic vaginal discharge indicative of bacterial vaginosis (BV), which was confirm diagnosis by Gram stain. The diagnosis of BV was based on the Nugent scoring system, following the CDC guidelines for the diagnosis and treatment of BV [8]. The inclusion criteria included clinical confirmation of BV, no antibiotic use within the previous two weeks, and consent to participate. Patients with a known hypersensitivity to oral tinidazole, chronic diseases, immune deficiencies, abnormal vaginal bleeding, specific drug or hormone therapy usage within the last three months, or other vaginal infections were excluded. Other criteria included regular menstruation, normal gynecological status, non-lactating status, appropriate personal hygiene, and the cognitive ability for collaboration.

Sampling method for BV

Vaginal swabs were collected from participants to diagnose BV. Swabs were taken from the vaginal walls during the clinical examination and then processed for Gram staining. Laboratory technicians applied the Nugent scoring system to assess the results.

Sample size determination, randomization and participant Flow

Based on a two-sample t-test for a quantitative trait in two independent populations, an initial estimate suggested 32 participants per group. To account for potential attrition, we aimed to recruit between 35 and 40 participants per group.

Therefore, 66 participants were randomized to two groups: 35 participants to the first intervention group (oral probiotics) and 31 to the second intervention group (vaginal probiotics). All of the participants in these groups received the allocated intervention with using www.sealedenvelope.com website with block size.

Interventions

All patients diagnosed with bacterial vaginosis (BV) were initially treated with standard oral metronidazole (500 mg, twice daily) for one week. Following laboratory confirmation of BV, patients were randomly assigned to one of two groups (A and B) using an alternate distribution method. Group A received Lactovage® vaginal capsules (Zist Takhmir Company), a synbiotic formula suitable for women that contains beneficial Lactobacillus strains along with maltodextrin as a prebiotic. They administered one capsule vaginally each night for two weeks after completing the metronidazole treatment. Group B received Lactofem® oral capsules (Zist Takhmir Company), an oral synbiotic formula suitable for girls and women that contains high amounts of beneficial bacterial strains along with fructooligosaccharide (FOS) as a prebiotic. They took two capsules orally per day for four weeks.

The dosages were adjusted in both probiotic treatments to ensure equivalent probiotic intake between the two groups. The probiotic regimen commenced immediately after the week-long metronidazole course. In the vaginal

probiotic group, the use of Lactovage® was postponed until after menstruation, if applicable. Sexual intercourse was not prohibited during the treatment period; however, condom use was mandatory. The recurrence of bacterial vaginosis was assessed one month after the completion of probiotic treatment by a laboratory technician and a microbiology specialist using the Nugent score.

Outcomes

The primary outcome was the recurrence of bacterial vaginosis, diagnosed according to the Nugent criteria, one month after completing the probiotic treatment.

The Nugent scoring system evaluates Gram-stained vaginal smears, assessing the presence of three types of bacterial morphotypes: large Gram-positive rods (Lactobacilli), small Gram-negative rods (Gardnerella and Bacteroides), and curved Gram-negative rods (Mobiluncus). Each morphotype is scored from 0 to 4, with a total score of 7 or higher indicative of bacterial vaginosis. Considering the Nugent scale's sensitivity of 65.6% and specificity of 97.3% in comparison to the Amsel criteria with a sensitivity of 100% and specificity of 46%, the Nugent scale was chosen for its higher specificity [9–11]. Recurrence was assessed through Nugent criteria a month post treatment.

Blinding, randomization and allocation

The study was conducted as a double-blind trial. Thus, both the investigators who assessed the outcomes and the statisticians who analyzed the data were unaware of the treatment assignments.

The random allocation sequence was generated using a computer-based random number generator. This ensured a completely random and unbiased allocation of participants to the study groups. The allocation ratio was 1:1, with equal numbers of participants in each group.

We employed simple randomization without any restrictions such as blocking or stratification. This approach was chosen to maintain the unpredictability of the allocation sequence and to minimize potential selection bias.

To implement the random allocation sequence, we used sequentially numbered, opaque, sealed envelopes (SNOSE). Each envelope contained the group assignment and was opened only after the enrolled participant's details were recorded. This method was employed to ensure that the sequence was concealed until interventions were assigned, thus preventing selection bias and maintaining allocation concealment.

The random allocation sequence was generated by an independent statistician who had no clinical involvement in the trial. The enrollment of participants was conducted by the clinical research team, who were responsible for assessing participant eligibility and obtaining informed consent. Following enrollment, the assignment of participants to interventions was carried out by a separate member of the research team, who was not involved in the initial enrollment process. This separation of duties was maintained to ensure the integrity of the allocation concealment and to prevent any potential bias in participant assignment.

Statistical methods

Data analysis was performed using SPSS software, version 21. Quantitative variables were described using mean and standard deviation, while qualitative variables were presented by frequency and percentage.

The comparison of quantitative variables between the two groups was conducted using the Student's t-test. When more than two groups were compared, one-way ANOVA was utilized. In cases where the data did not follow a normal distribution which were evaluated by Kolmogorov-Smirnov test, equivalent non-parametric tests were employed.

The relationship between qualitative variables was assessed using the Chi-square test, and the correlation between quantitative variables was evaluated with the correlation test. All tests were two-tailed, and the level of significance was set at $p<0.05$.

Results

Participant flow

The study design and participant flow were summarized as per the CONSORT guidelines [Fig. 1]. Initially, 198 participants were assessed for eligibility. However, 132 were excluded because they did not meet the inclusion criteria ($n=72$), declined to participate ($n=60$), or for other reasons.

During the follow-up, six participants from the vaginal probiotics group were lost to follow-up, and five of these discontinued the intervention for various reasons. No participants from the oral probiotics group were lost to follow-up or discontinued the intervention.

Thus, the final analysis included 35 participants from the oral probiotics group and 20 participants from the vaginal probiotics group. No participant was excluded from the analysis.

Demographic and clinical characteristics

A total of 55 women participated in this study and were divided into two groups: the vaginal probiotic group ($n=20$) and the oral probiotic group ($n=35$). The baseline characteristics of the two groups are compared in Table 1.

The average age of the women in the vaginal probiotic group was 35.20 ± 7.19 years and 38.11 ± 8.57 years in the oral probiotic group. The difference was not statistically significant ($P=0.211$). The mean body mass index

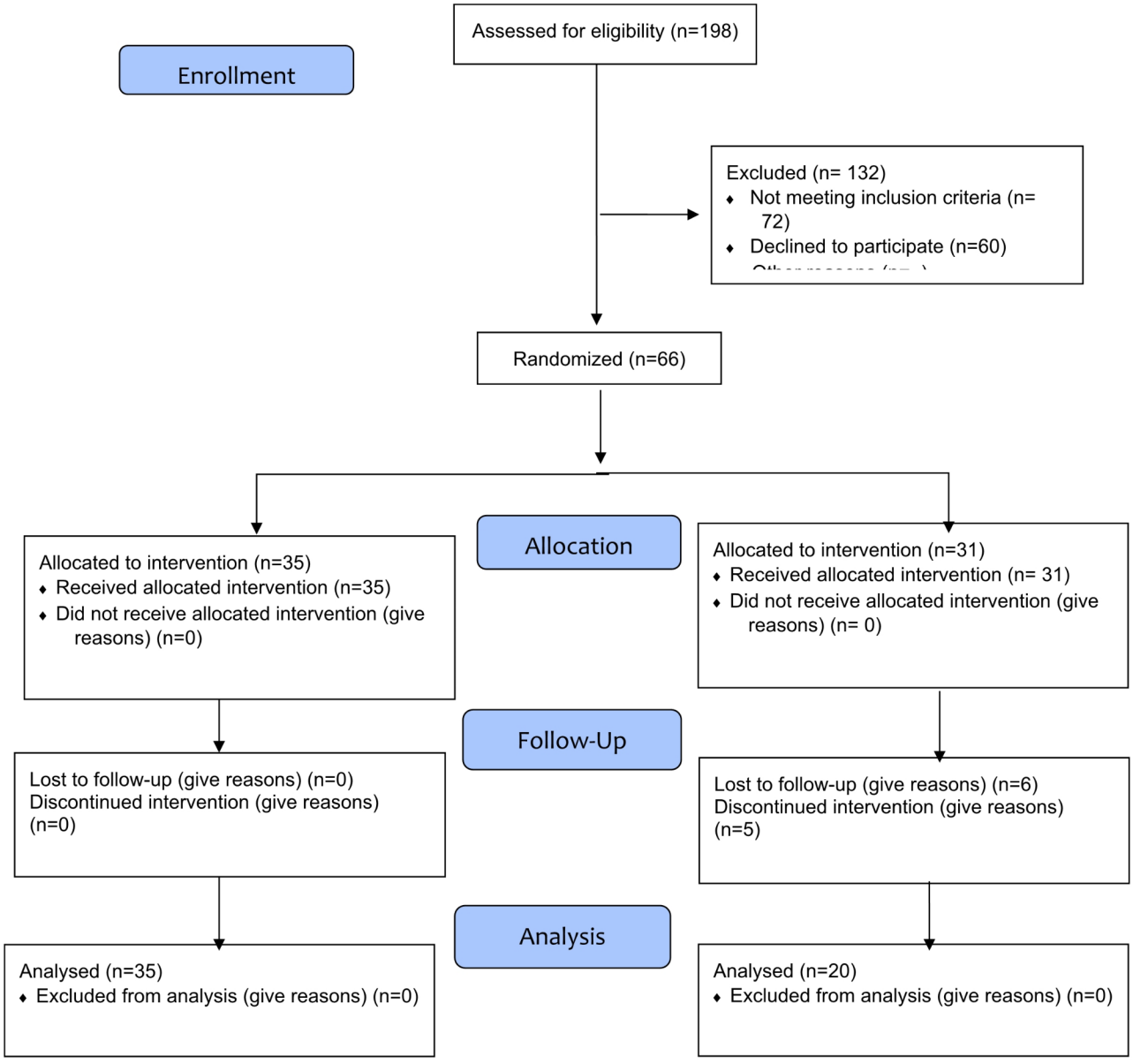

Fig. 1 The CONSORT Flowchart for the study

(BMI) of the participants in the vaginal probiotic group was 23.40±2.07, and in the oral probiotic group, it was 24.54±2.52, with no significant difference (P=0.850).

The duration of marriage varied among participants. The mean duration was 10.80±6.05 years in the vaginal probiotic group and 12.05±8.23 years in the oral probiotic group, with no significant difference (P=0.059).

Contraceptive methods varied among the participants. Natural methods were the most common in both groups, with 45% in the vaginal probiotic group and 42.9% in the oral probiotic group. The distribution of contraceptive methods did not differ significantly between the two groups (P=0.530).

Regarding the history of vaginal infection, 20% of women in the vaginal probiotic group and 17.1% in the oral probiotic group reported having had an infection in the past, with no significant difference between the groups (P=0.530). A history of infertility was reported by 15% of women in the vaginal probiotic group and 8.6% in the oral probiotic group, but the difference was not statistically significant (P=0.377).

Table 1 Comparison of demographic information of study participants

Characteristic	Vaginal Probiotic Group (*N* = 20)	Oral Probiotic Group (*N* = 35)	*P* Value
Age (years) Mean ± SD	35.20 ± 7.19	38.11 ± 8.57	0.211
Body Mass Index Mean ± SD	23.40 ± 2.07	24.54 ± 2.52	0.850
Duration of marriage (years) Mean ± SD	10.80 ± 6.05	12.05 ± 8.23	0.059
Contraceptive method			0.530
Natural	9 (45%)	15 (42.9%)	
Condom	5 (25%)	4 (11.4%)	
IUD	1 (5%)	4 (11.4%)	
Tubal ligation	1 (5%)	4 (11.4%)	
Pills	2 (10%)	5 (14.3%)	
Medroxyprogesterone Acetate Injection	1 (5%)	0	
No contraception	1 (5%)	3 (8.6%)	
History of vaginal infection			0.530
Yes	4 (20%)	6 (17.1%)	
No	16 (80%)	29 (82.9%)	
History of infertility			0.377
Yes	3 (15%)	3 (8.6%)	
No	17 (85%)	32 (91.4%)	
History of preterm birth			0.544
Yes	4 (20%)	8 (22.9%)	
No	16 (80%)	27 (77.1%)	
History of premature rupture of membranes in recent pregnancy			0.383
Yes	2 (10%)	6 (17.1%)	
No	18 (90%)	29 (82.9%)	

The independent t-test was used for comparing the two groups

Table 2 Nugent score at the beginning and end of the study

Group	Beginning of the Study Median (Q1-Q3)	End of the Study Median (Q1-Q3)	*P*-value (Within-group Comparison)
Oral Probiotic Group	8.5 (7–9)	3 (2–4)	< 0.001
Vaginal Probiotic Group	9.0 (8–9)	3 (2–4)	< 0.001
P-value (Between-group Comparison)	0.053	0.053	< 0.001

Q1 and Q3 represent the 25th and 75th percentiles, respectively. P-value (within-group comparison) refers to the comparison of Nugent scores at the beginning and end of the study within each group, while P-value (between-group comparison) refers to the comparison of Nugent scores between the two groups at each time point

In terms of obstetric history, 20% of the women in the vaginal probiotic group and 22.9% in the oral probiotic group had a history of preterm birth. This difference was not statistically significant ($P=0.544$). Similarly, there was no significant difference in the proportion of women who experienced premature rupture of membranes in recent pregnancy (10% in the vaginal probiotic group and 17.1% in the oral probiotic group, $P=0.383$).

Overall, the demographic and clinical characteristics of the participants did not differ significantly between the two groups at baseline, suggesting that the groups were comparable.

Outcome

At the end of the study, after the equalization of the two groups, the Nugent scoring form was completed for the members of each group. Due to the non-normal distribution of the data, the Mann-Whitney U test was utilized [Table 2].

In this test, the vaginal probiotic suppository group scored 7 at the 25th percentile (Q1) before starting the probiotic, which decreased to 2 after four weeks of probiotic use. The median score of this group was 8.5 at the start of the study, which decreased to 3 at the end. The score at the 75th percentile (Q3) for the vaginal probiotic suppository group also decreased from 9 at the beginning of treatment to 4 at the end.

In the oral probiotic group, at the start of treatment, the 25th percentile scored 8, which fell to 2 after the treatment. The median score for this group was 9 before the treatment and decreased to 3 after the treatment. The score at the 75th percentile decreased from 9 to 4.

The Wilcoxon signed-rank test was used to compare the score changes within each group. Although the changes between the two groups were not statistically significant, both groups showed significant changes compared to their initial state (p-value < 0.001).

Regarding side effects, no serious complication was reported in both groups.

Discussion

Bacterial vaginosis, characterized by the overgrowth of anaerobic bacteria and concurrent reduction of the normal vaginal flora, specifically lactobacilli, represents one of the most common gynecological complaints. Studies have estimated that bacterial vaginosis constitutes approximately 40–50% of all vaginal infections, underlining its clinical significance [12, 13]. Given its prevalence, the importance of prompt diagnosis and effective treatment cannot be overstated as untreated or improperly treated infections can trigger serious complications such as pelvic inflammatory diseases, infertility, chronic pelvic pain, preterm birth, and an elevated risk of HIV infection [14, 15].

Currently, metronidazole stands as the conventional treatment for bacterial vaginosis, but its application is associated with a number of side effects including gastrointestinal disturbances, alcohol intolerance, a metallic taste in the mouth, and occasionally, blood and nerve disorders. The existing challenges with current treatments revolve around unsuccessful pharmacological therapy,

rising resistance to treatment, and recurrent infection [16].

In the pathogenesis of bacterial vaginosis, a reduction in the number of lactobacilli constitutes the core mechanism. These bacteria play a vital role in maintaining vaginal health by converting glycogen present in vaginal mucosal cells into glucose and subsequently, lactic acid. This process acidifies the vaginal environment and thereby, restricts pathogenic growth. In addition, certain lactobacilli strains are capable of producing hydrogen peroxide, acting as an antimicrobial agent, thereby fortifying the vaginal defense mechanism [16, 17].

With this in mind, we embarked on this study to evaluate the effectiveness of both oral and vaginal probiotics as an alternative treatment option for bacterial vaginosis and to mitigate the issue of recurrence.

Our findings demonstrated significant improvement in bacterial vaginosis symptoms for patients treated with both oral and vaginal probiotics, as indicated by the reduced Nugent scores from baseline to the end of the study in both groups. Moreover, when comparing the effectiveness of the two treatment methods, there was no significant difference between the oral and vaginal probiotic groups ($p=0.053$). These results suggest that both administration methods were equally effective in reducing the symptoms of bacterial vaginosis and preventing recurrence, with neither method demonstrating superiority over the other.

This crucial finding adds to the growing body of evidence supporting the use of probiotics as an alternative or adjunct treatment option for bacterial vaginosis, offering a potential solution to the existing challenges associated with conventional antibiotic therapy such as treatment failure, antibiotic resistance, and recurrence.

The 2013 study by Heczko and colleagues [18] focused on oral probiotics in conjunction with metronidazole. They also found that probiotics enhanced the treatment process, similar to our findings. However, our study extended their research by comparing oral and vaginal administration methods, thereby adding more context to the use of probiotics in treating bacterial vaginosis.

The study conducted by Dobrohotova et al. (2021) [19] is intriguing in the sense that it adds another layer of complexity by examining patients with concurrent bacterial cystitis and bacterial vaginosis. They found significant improvements in the probiotics group, which strongly aligns with our findings. However, our research contributes to this field by directly comparing the two methods of probiotics administration, which was not the focus of their study.

Balaghi and colleagues (2020) [20] took a slightly different approach by examining the impact of probiotics on lactobacilli colonization and vaginal acidity. They didn't find any significant changes, contrasting with our study's findings where both oral and vaginal probiotics showed a beneficial effect. This discrepancy could be due to different strains of probiotics used or the patient selection criteria, emphasizing the need for further research to identify the most beneficial strains and populations.

The 2020 study by Wijgert et al. [21] and the 2021 study by Lin and colleagues [22] both examined the effectiveness of different strains of lactobacilli. While their focus was different from ours, they also reported a decrease in bacterial vaginosis, further strengthening the case for the use of probiotics. However, their studies' findings suggest that different strains might have different efficacies, indicating an avenue for future research. Our study adds to this body of work by comparing the administration methods, which could have implications on the effectiveness of different strains.

This study has several limitations that should be considered. Firstly, the sample size was relatively small, particularly in the vaginal probiotic group, which may have limited the statistical power to detect subtle differences between the treatment groups. Additionally, the follow-up period was relatively short (one month), which may not fully capture the long-term recurrence of bacterial vaginosis, as recurrence is commonly observed months after treatment.

Conclusions

In conclusion, this study aimed to compare the effectiveness of oral and vaginal administration of probiotics in treating bacterial vaginosis. The findings demonstrate that both methods significantly reduced bacterial vaginosis symptoms, with no significant difference in their effectiveness. This indicates that the choice between oral and vaginal probiotics can be based on patient preference and tolerance, potentially increasing adherence to treatment.

The results of this study contribute to the growing body of evidence on the efficacy of probiotics in treating bacterial vaginosis, expanding on previous research by directly comparing two administration methods. The study further demonstrates the key role of lactobacilli in maintaining vaginal health and combating bacterial vaginosis.

Author contributions

Mahnaz Boroumand Rezazadeh: Dr. Rezazadeh was pivotal in the study's conception, design, and manuscript drafting and revision. She approved the submitted and revised versions and is accountable for all aspects of her work in ensuring its integrity.Minoo Zanganeh: Dr. Zanganeh extensively contributed to data acquisition and analysis. She has approved the manuscript and commits to maintaining the integrity of her contributions and addressing accuracy and integrity issues in the study.Lida Jarahi: Dr. Jarahi was instrumental in developing new software for data analysis and contributed to data interpretation. She has approved the final manuscript and is responsible for ensuring the accuracy and integrity of her contributions.Zahra Fatehi: Dr. Fatehi played a key role in critically revising the manuscript, ensuring its scientific rigor. She has approved the final version and is dedicated to upholding the overall integrity of the work and resolving any related concerns.

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Data availability
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
The study procedures were carried out following the ethical standards of the institutional research committee and the Helsinki Declaration. Ethical approval for the study was granted by the Ethics Committee of Mashhad University of Medical Sciences, with the ethical code IR.MUMS.MEDICAL.REC.1398.736. The trial was also registered at the Iranian Registry of Clinical Trials with registration number IRCT20190202042596N1 which was registered on 2020-02-03.
Consent.
All patients participating in the study gave their informed consent after understanding the nature of the procedures involved. All patient data were anonymized and coded to maintain confidentiality.

Conflict of interest
The authors declare that there are no conflicts of interest in relation to the work presented in this study.

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