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Comparing Corifollitropin Alfa to Recombinant Follicle-STIMULATING Hormone in Poor Responder Patients Undergoing Intracytoplasmic Injection: A Randomized Clinical Trial

Nasrin Saharkhiz[1], Saghar Salehpour[1], Sedigheh Hosseini[1], Nazanin Hajizadeh[2*]

Abstract

Objectives: The high prevalence of poor ovarian response in women undergoing ovarian stimulation is a main therapeutic challenge that affects pregnancy outcomes in such patients. The current clinical trial aimed to compare the pregnancy outcome of corifollitropin alfa (CFA) versus recombinant follicle-stimulating hormone (rFSH) used in the gonadotropin-realizing hormone (GnRH) antagonist protocol in poor ovarian response patients.

Materials and Methods: We performed an open-label balanced block randomized clinical trial on 117 Iranian women with poor ovarian responses who were seeking treatment for infertility. Reporting followed the CONSORT 2010 guidelines for parallel group randomized trials. Patients were randomly assigned to the CFA group (a single injection of 150 µg CFA) or the rFSH group (300 IU rFSH on a daily basis). To avoid premature luteinizing hormone (LH) surges, treatment continued with a daily subcutaneous injection of 0.25 ganirelix, starting from day 6 of stimulation up to the hCG administration day. The primary investigated outcomes were the number of obtained oocytes and the number of metaphase II oocytes. Implantation rate, chemical pregnancy, and clinical pregnancy were the secondary outcomes examined, and study participants were followed up to ascertain the interested outcome.

Results: The average number of mature follicles in CFA was 5.0±2.1, which was significantly higher than the rFSH group (4.2±1.7) ($P=0.021$). The average number of puncture follicles and the number of embryos were significantly higher in the CFA group than in the rFSH group ($P<0.05$). Chemical pregnancy was observed in 32.2% and 30.5% of patients in the CFA and recombinant-FSH groups, respectively, and the observed difference was not statistically significant ($P=0.748$). We observed no statistically significant difference despite a relatively higher clinical pregnancy in the CFA group ($P=0.398$).

Conclusions: A single injection of CFA and a daily injection of rFSH could improve pregnancy outcomes in women with poor ovarian responses who underwent IVF. These two alternative treatments could be used interchangeably, and we highlighted no superiority between CFA and rFSH.

Trial Registration: Identifier: IRCT20221016056198N1; Iranian Registry of Clinical Trials (https://irct.behdasht.gov.ir/).

Keywords: Corifollitropin alfa, Recombinant FSH, GnRH antagonist, Assisted reproductive technology

Introduction

The high prevalence of poor ovarian responses in women undergoing ovarian stimulation is a main therapeutic challenge that affects pregnancy outcomes in such patients (1,2). Different treatment regimens have already been introduced to manage these patients; however, the previous studies are inconclusive regarding the most effective therapeutic approach (3,4). Recombinant follicle-stimulating hormone (rFSH) is the standard protocol that is used in the gonadotropin-realizing hormone (GnRH) antagonist protocol that provides beneficial pregnancy outcomes in poor respondent women (5-7). Corifollitropin alfa (CFA) is an alternative novel gonadotropin analogue with a promising pregnancy outcome in such patients (8). CFA is a recombinant dimeric glycoprotein that consists of recombinant FSH fused with the carboxyterminal peptide of the beta subunit of hCG (9). It has a prolonged half-life compared with FSH, and it provides sustainable follicle growth until seven days after the first rejection (10). Moreover, CFA provides a higher level of FSH, and it is faster in threshold achievement compared with rFSH (11).

Some previous studies compared CFA versus rFSH and showed similar pregnancy outcomes for these therapeutic approaches. In the ENGAGE trial, it has been shown that either a single injection of 150 µg CFA or 200 IU daily rFSH in the GnRH antagonist protocol could increase the ongoing pregnancy rate by over 35%, and there was no significant difference between these two alternatives (11). They also showed CFA as a tolerable and safe intervention in women younger than 36 years (11). Similar findings were also reported by Drakopoulos et

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[1]Department of Obstetrics and Gynecology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[2]Preventative Gynecology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
*Corresponding Author: Nazanin Hajizadeh, Tel: +989127298023, Email: hajizadeh.nazanin94@yahoo.com

al in the COMPORT trial, and they found no superiority for CFA over rFSH. However, the effect size of CFA and rFSH was considerably lower, and the pregnancy rate in both groups was less than 20% (12). Patients' baseline characteristics are the main reason for such heterogeneity, which highlights the importance of more investigation regarding the effect of CFA on pregnancy outcomes in poor respondent women. However, there are limited studies in this regard. Therefore, we aimed to compare the pregnancy outcome of CFA versus rFSH in a sample of Iranian women with poor ovarian responses who were seeking infertility treatment.

Material and Methods

Study Design

We employed a balanced block randomization method to allocate study participants into four distinct groups. Initially, we generated six blocks labeled A and B (e.g., AABB), numbered from 1 to 6. Subsequently, a dice was used to determine the intervention status for each participant. With each dice throw, we allocated intervention statuses to four participants based on the associated AB block and the dice number. This randomization process was repeated thirty times for all participants.

Group A represented the CFA intervention, while group B indicated the recombinant-FSH intervention, with the type of intervention written on each letter. Each case was assigned a number from 1 to 120 and subsequently received an 8-digit code comprising both numbers and letters. We meticulously documented these interventions on paper and placed them inside sealed envelopes, all of which were provided to the research group.

Following the enrollment of each participant, we announced the specific envelope code to be opened, consistently repeating this process until all participants were enrolled. Throughout the entire case enrollment period, we rigorously implemented routine quality control measures to ensure the integrity of the randomization process and prevent any deviations from the established randomization protocol. As the study was open-label, patients and physicians were aware of the type of intervention.

The current study was an open-label, phase III, randomized clinical trial that was conducted in Iran. This study was compatible with the Declaration of Helsinki (13), and its reporting is consistent with the CONSORT statement (14).

Study Participants

The study was performed on 130 women younger than 40 who were referred to the Taleghani Infertility Clinic in Tehran, Iran, 2022-2023. They had at least two of the following criteria: AFCL<5, AMH<1.2 ng/dL, at least three oocytes in the previous cycle, and fulfilled Bologna criteria for poor ovarian response (15,16). The exclusion criteria included uterine anomalies, a history of untreated endocrine problems, cardiovascular diseases, any disorder related to the lung and liver, severe and uncontrolled underlying diseases, unilateral or bilateral hydrosalpinx, and a prohibition of gonadotropin use. We also excluded patients who were egg donors, had severe male infertility (azoospermia, oligoasthenoteratospermia), stage 4 endometriosis, and patients with extremely low or high body mass index (BMI) <18 or >30. Out of the ten cases that were not included, five did not match the inclusion criteria, three did not consent to participate, and two had other reasons.

Intervention

We randomly assigned 117 eligible patients into the CFA group (group A = 59) and the recombinant-FSH stimulation hormone group (group B = 58) in a GnRH antagonist protocol.

Group A

Patients in group A received a single subcutaneous injection of 150 μg of CFA. To avoid premature luteinizing hormone (LH) surges, treatment continued with a daily subcutaneous injection of 0.25 ganirelix, starting from day 6 of stimulation up to the hCG administration day. The study participants in group A also received hp-HMG (300 IU/day) from day 8 of stimulation up to the hCG stimulation day (Figure 1).

Group B

The treatment protocol for group 2 was a daily injection of subcutaneous rFSH (300 IU/day) initiated on the second day of the menstrual cycle, followed by the hCG administration day. They also received a daily subcutaneous dose of 0.25 ganirelix started from Day 6 of stimulation up to hCG administration day to prevent premature LH surges. The intervention protocol for group B was also a subcutaneous 300 IU dose of hp-HMG on a daily basis, starting from day 8 of stimulation up to the day of hCG administration.

Both Groups

If no follicle measuring at least 11 mm was detected on ultrasound between stimulation days 8 and 10, the cycle would be canceled. When two follicle sizes reached ≥18 mm on ultrasound to induce final maturation of the oocyte, the administration of hCG at 10 000 IU was initiated on the same day or the day after. After 34-36 hours, patients underwent oocyte pick-up and intracytoplasmic sperm injection (ICSI). Progesterone started on the day of oocyte pick-up (Actogest® 200 mg, daily, suppository, intravaginally; and Progesterone, Amp, 50 mg/mL, IM, daily). Embryo transfer was performed on day six after oocyte pick-up, and for each patient, two oocytes were transferred at maximum. The quality

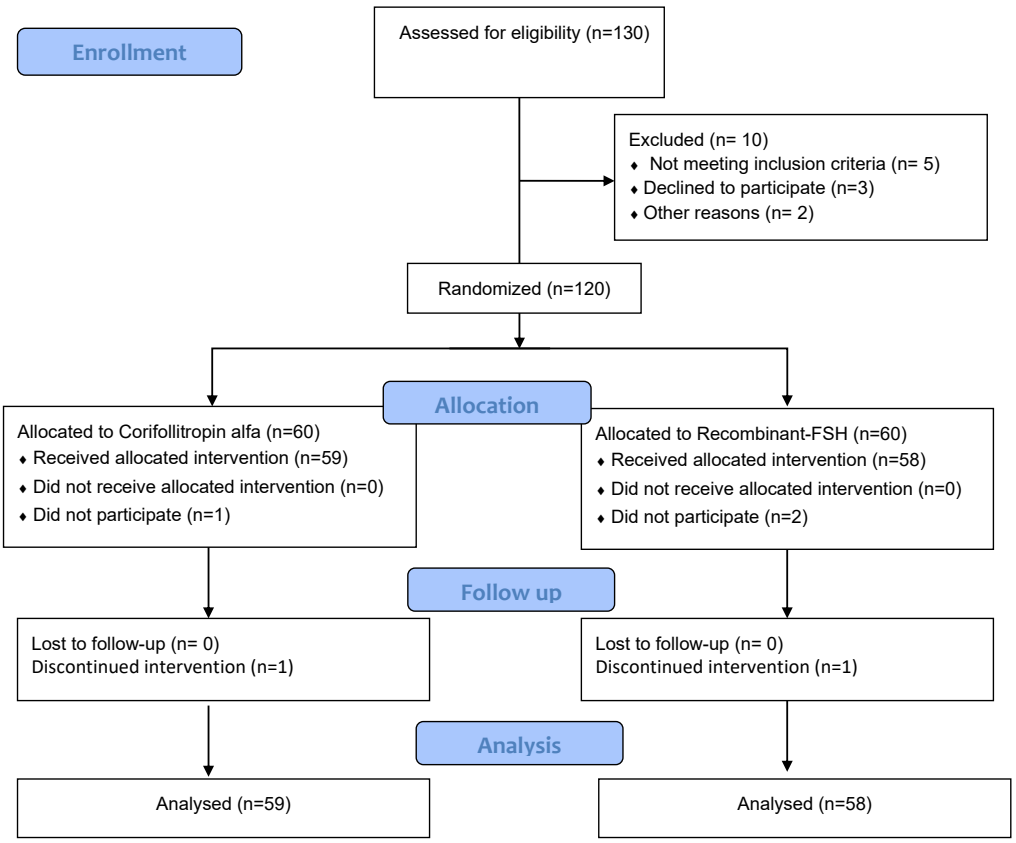

Figure 1. Consort Fellow Diagram of the Study.

of transferred embryos was assessed using the Istanbul consensus workshop, as previously described by Balaban et al (17) (Figure 1). Progesterone support continued until menses or a negative pregnancy test occurred.

Outcome Evaluation

The number of obtained oocytes and metaphase II oocytes were the primary outcomes of the current study. Chemical pregnancy, clinical pregnancy, and implantation rate were the secondary outcomes that we investigated. Chemical pregnancy was defined as a positive pregnancy test 2 weeks after embryo transfer, and the presence of an intrauterine gestational sac at seven weeks of gestation was referred to as clinical pregnancy. We also defined implantation rate as the number of gestational sacs/number of transferred embryos. We initially picked it because it is usually a big deal in these kinds of studies. However, as we went along, we learned some new things and had some unexpected issues with collecting data. So, we had to rethink what we were measuring to understand how well our treatment worked. We ended up focusing on something else that seemed to show better how effective the treatment was, based on what we found out during the study. Basically, while the ongoing pregnancy rate was a big part of our plan at the start, things changed as we learned more and ran into some unexpected challenges. We switched our main focus to get the most accurate picture of how well our treatment was actually working.

Sample Size Calculation

To calculate the sample size, we used data from previous studies. According to previous studies, ongoing pregnancy in the treatment group was 28%, while it was 8.5% in the standard treatment. With a significance level (α) of 0.5, a power of 80%, and an equal proportion of sample size in the compared group, the minimum sample size was calculated to be 120 and 60 in each group (12,18).

Out of the ten cases that were not included, five did not match the inclusion criteria, three did not consent to participate, and two had other reasons. Finally, we randomly assigned 117 eligible patients into the CFA group (group A=59) and the recombinant-FSH stimulation hormone group (group B=58) in a GnRH antagonist protocol.

Statistical Analysis

The statistical analysis was performed in an intention-to-treat fashion. We described continuous variables using mean and standard deviation (SD) and also provided median and interquartile range (IQR) when the distribution was skewed. Dichotomous variables were described as number, frequency, and proportion. We

used an independent t-test to compare the means of the continuous variables between Group A and Group B. The sample size estimation was conducted using the formula below.

$$N = 2 \times \left(\frac{Z_{1-\alpha} + Z_{1-\beta}}{\delta_0}\right)^2 \times S^2$$

To analyze non-parametric data, we used the Mann-Whitney test. Moreover, primary outcomes were compared using the chi-square test between the compared study arms. All statistical analyses were performed with a level of significance of 0.05 using Stata software (version 17.0, StataCorp, College Station, Texas, USA).

Results

Baseline Characteristics

The study included 117 women who were ovarian-poor responders. We compared the baseline characteristics of study participants in the CFA and recombinant-FSH groups. We observed no statistically significant difference in age, anti-Müllerian hormone level, antral follicle count, or duration of antagonist treatment. However, the number of stimulation days in the CFA (9.7) group was significantly lower than the r-FSH group (10.2) ($P=0.023$). The duration of hMG stimulation was significantly higher in rFSH (4.9 ± 0.9) than CFA (3.6 ± 0.9), as well ($P<0.001$) (Table 1). We also compared the quality of the transferred embryo and observed no statistically significant difference between the compared groups ($P=0.261$) (Figure 2).

Outcome Evaluation

The average number of mature follicles in CFA was 5.0±2.1, which was significantly higher than the rFSH group (4.2±1.7) ($P=0.021$). According to Table 2, the average number of puncture follicles and the number of embryos were significantly higher in the CFA group than in the rFSH group ($P<0.05$). Chemical pregnancy was observed in 32.2% and 30.5% of patients in the CFA and recombinant-FSH groups, respectively, and the observed difference was not statistically significant ($P=0.843$). The cumulative incidence of clinical pregnancy in the CFA group was 28.8%, and it was 22.0% in the recombinant-FSH group. We observed no statistically significant difference despite a relatively higher clinical pregnancy in the CFA group ($P=0.398$).

Discussion

The present clinical trial investigated the superiority of CFA versus rFSH in women with poor ovarian responses. Our data showed that both CFA and rFSH provided similar results in terms of chemical and clinical pregnancy, and CFA had no superiority over rFSH. The proportion of clinical pregnancy in the CFA and FSH groups was 28.8% and 22.0%, respectively. The results of previous studies indicated that either r-FSH or CFA could lead to promising outcomes in poor respondent women. The proportion of clinical pregnancy outcomes in the current study was comparable with the results of a pilot study conducted by Polyzos et al. They showed that either FSH or CFA could increase clinical pregnancy by over 28% (18). However, in the COMPORT trial, the proportion of clinical pregnancy in both groups was less than 20%, which was considerably lower than the value reported in the current study (18). Drakopoulos et al provided the following main reasons to justify the observed difference between the COMPORT trial and their initial findings: differences in case definition, the inadequacy of Bologna criteria, different mechanisms of ovarian aging, diversity in baseline characteristics of study participants in other studies, such as age and quality of oocytes, and potential biases and confounders (12). These reasons could also be related to a discrepancy between our findings and the COMPORT trial (12). Some other studies reported higher clinical pregnancy rates than our findings. In the study conducted by Devroey et al (11), the proportion of clinical pregnancy in both FSH and CFA groups was over 30%. Their study was conducted on younger women, and the number of retrieved oocytes in their trial was significantly higher. There is a strong direct association between age and the clinical prognosis of women with poor ovarian responses. The quality and quantity of the recruited oocytes are the other factors that affect the pregnancy outcome of such patients.

We also compared FSH and CFA regarding the clinical pregnancy outcome in women with poor ovarian responses. We observed no statistically significant difference between the compared groups, indicating that both CFA and FSH

Table 1. Study Participant's Line Characteristics in Two Different Treatment Groups

Characteristics	Group A: CFA	Group B: rFSH	*P* Value
Age, Mean (SD)	34.7 (4.6)	34.3 (4.5)	0.689
Anti-Mullerian hormone (ng/mL), Mean (SD)	0.7 (0.2)	0.7 (0.2)	0.685
Antral follicle count, Mean (SD)	2.8 (0.9)	2.7 (0.8)	0.502
N of stimulation days, Mean (SD)	9.7 (1.2)	10.2 (1.1)	0.023
Duration of antagonist treatment, Mean (SD)	4.3 (0.9)	4.5 (0.9)	0.099
Duration of hMG stimulation, Mean (SD)	3.6 (0.9)	4.9 (0.9)	<0.001

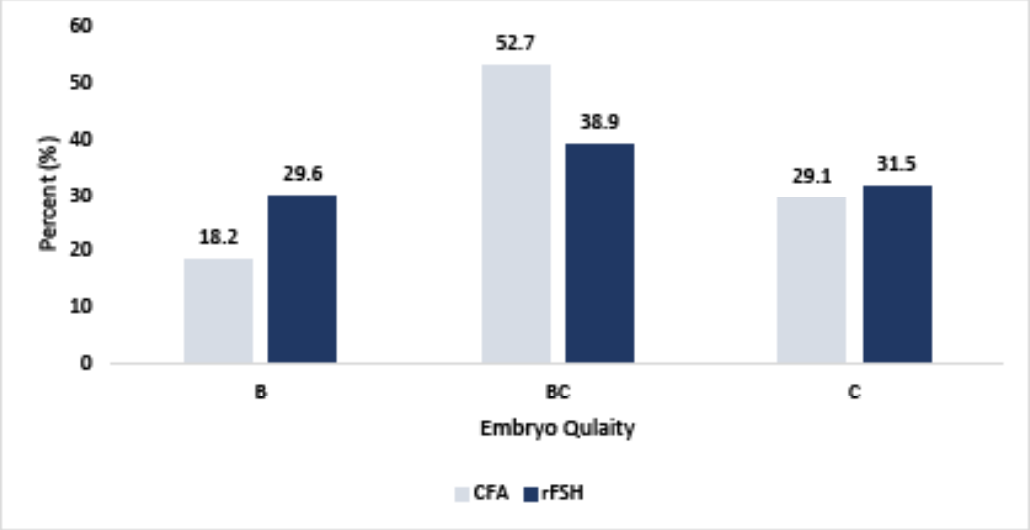

Figure 2. Quality of the Transferred Embryo in CFA and rFSH Groups.

treatments could be used as a co-treatment in the GnRH antagonist protocol to improve the outcome of pregnancy in poor ovarian respondent women. Regarding the equal number and quality of transferred embryos, it seems a single dose of CFA could increase pregnancy outcomes as much as rFSH. Drakopoulos et al reported similar findings, showing no significant difference in the effect of CFA compared to rFSH in poor respondent women (12). The results of Boostanfar et al supported our findings that CFA could provide similar pregnancy outcomes compared with daily r-FSH (10). Devroey et al have also shown a non-significant difference between CFA and rFSH in the ongoing pregnancy rate (11).

CFA consists of a C-terminal peptide fused with a beta-subunit of hCG, and it is considered a type of FSH (9,12). However, the absorption time is slower, and it has a longer half-life than r-FSH (10). A peak level of FSH activity after CFA injection occurs within two days, while it takes four to five days for daily FSH to reach the same level (19,20). It is argued that this pharmacokinetic feature could ease ovarian further stimulation and, therefore, lead to a relatively higher ovarian response during the first days of stimulation (8,11). A higher number of mature follicles in patients treated with CFA is attributed to this pharmacokinetic property that has already been reported in the ENGAGE trial and was similar to our findings (11). Other studies also showed that increasing doses of rFSH in the starting days could increase the number of recruited follicles (21,22). The COMPORT trial also showed increased supernumerary embryos in poor respondent women who received CFA, leading to an increased cumulative live birth rate despite no difference in pregnancy outcome (18).

Live birth was not our primary focus in this study, and our follow-up concluded upon achieving clinical pregnancy due to logistical challenges and budget constraints. Up until that point, there were no instances of lost follow-up in our study.

We recognize the significance of live birth rates and regret not extending our follow-up to encompass this outcome. However, due to resource limitations, our study design centered on clinical pregnancy as the primary endpoint. This decision was driven by constraints in resources and feasibility.

The current extensive clinical trial compared the effect of CFA to rFSH as the standard treatment in the GnRH antagonist protocol in women with poor ovarian responses. A robust study design, a valid case definition based on Bologna criteria, and a large sample size were the main strengths of the current study (23). However, our findings must be interpreted in light of our limitations. The main interesting outcome in the current study was clinical pregnancy, and we did not collect data on ongoing pregnancy or live births. The miscarriage rate was another outcome this study could examine. However, we could not collect data on these outcomes, mainly due to follow-up difficulties and a lack of resources.

Limitations

The main limitations of this study include the small sample size between comparators and the fact that only women younger than 40 were evaluated.

Conclusions

In conclusion, both a single injection of CFA and a daily injection of rFSH could increase follicle development and improve pregnancy outcomes in women with poor ovarian responses who underwent IVF. These two alternative treatments could be used interchangeably, leading to more oncocytes and an improved pregnancy rate. We emphasized that CFA is not superior to rFSH. In summary, our study revealed that both CFA and rFSH

improved follicle development and showed promise in enhancing pregnancy outcomes for women with poor ovarian responses in IVF. Although we didn't directly compare them to our standard treatment, both alternatives notably improved pregnancy rates. While we could not determine a clear superiority between CFA and rFSH in our study, their effectiveness in surpassing our standard protocol suggests they could be beneficial options for improving pregnancy rates in this group. Future research should directly compare these options to our standard treatment, which would provide a more comprehensive understanding.

Authors' Contribution

Conceptualization: Nazanin Hajizadeh, Nasrin Saharkhiz.
Data curation: Nazanin Hajizadeh, Nasrin Saharkhiz.
Formal analysis: Nazanin Hajizadeh, Nasrin Saharkhiz, Saghar Salehpour, and Sedigheh Hosseini.
Funding acquisition: Nazanin Hajizadeh, Nasrin Saharkhiz, Saghar Salehpour, and Sedigheh Hosseini.
Investigation: Nazanin Hajizadeh, Nasrin Saharkhiz.
Methodology: Nazanin Hajizadeh, Nasrin Saharkhiz, Saghar Salehpour.
Project administration: Nazanin Hajizadeh, Nasrin Saharkhiz.
Resources: Nazanin Hajizadeh, Nasrin Saharkhiz, Saghar Salehpour, and Sedigheh Hosseini.
Software: Nazanin Hajizadeh, Sedigheh Hosseini.
Supervision: Nasrin Saharkhiz, Saghar Salehpour.
Validation: Nasrin Saharkhiz, Saghar Salehpour.
Visualization: Nasrin Saharkhiz, Saghar Salehpour.
Writing–original draft: Nazanin Hajizadeh, Nasrin Saharkhiz.
Writing–review & editing: Nazanin Hajizadeh, Nasrin Saharkhiz, Saghar Salehpour, and Sedigheh Hosseini.

Conflict of Interests

The authors declare that they have no competing interests.

Data Availability Statement

All supporting data are available through the corresponding author.

Ethical Issues

All the women were informed about the quality of the project's implementation, the confidentiality of the information, and the project's purpose. They were not enrolled in the study unless they would like. According to the guidelines of the Iranian ethics committee, the participants were considered emancipated minors. Thus, written informed consent was received from the participants and/or their LAR. The study protocol was reviewed and approved by the Shahid Beheshti University of Medical Sciences ethics committee and review board (Ethics Code: IR.Sbmu.msp.RETECH.1401.520, 13/11/2022) and was conducted in accordance with the principles of the Declaration of Helsinki. It was also registered in the Iranian Registry of Clinical Trials (identifier: IRCT20221016056198N1, 22/11/2022). Written informed consent was obtained from each participant, and patients were liable to leave the study at any stage.

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