Efficacy of Prophylactic Intravenous Fibrinogen in Reducing Bleeding in Cesarean Section: A Randomized Controlled Trial

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Article Info

ABSTRACT

Background & Objective: Postpartum hemorrhage is the most common cause of maternal morbidity and mortality, which can occur unexpectedly without warning, and without any underlying causes. We hypothesized that administering fibrinogen concentrate to cesarean section patients before surgery would reduce perioperative blood loss.

Materials & Methods: In this double-blind randomized controlled parallel group study, a single dosage of fibrinogen concentrate or a placebo was given to 260 cesarean section patients at random (by G*Power software, Heinrich-Heine-Universität Düsseldorf, Germany) in a university-affiliated general hospital between November 11, 2022, to January 8, 2023. Individuals in the fibrinogen group received a dose of one gram of fibrinogen concentrate and those in the placebo group received normal saline solution with the same volume in the placebo group. Total blood loss was the primary outcome of this study.

Results: A total of 280 cases were screened and 260 were randomized. With a P-value of 0.001, the median (IQR) volume of bleeding in the fibrinogen group was 660 (341.25) mL, as opposed to 790 (475.00) mL in the placebo group. Comparatively, only 10 (7.7%) of the fibrinogen group and 26 (20%) of the placebo group required blood transfusions (P=0.006). No adverse event related to fibrinogen was reported.

Conclusion: Empiric treatment with fibrinogen concentrate results in reduced blood loss.

Keywords: Blood coagulation, Cesarean Section, Erythrocyte transfusion, Fibrinogen, Postpartum hemorrhage

Introduction

One of the most frequent and potentially fatal consequences of delivery that often happens unexpectedly is postpartum hemorrhage (PPH) (1, 2). PPH is mostly caused by uterine atony, retained placenta, and genital tract trauma. Even though they are less frequent, severe bleeding and coagulopathy are frequently caused by uterine rupture, placental abruption, and abnormal placentation. PPH accounted for about 25% of all maternal deaths worldwide in 2015, with more than 80,000 fatalities (3, 4). PPH has surged in most industrialized nations and has been associated with multiple births, obesity, aging mothers giving birth, and more obstetric procedures such as the use of oxytocin (5, 6).

The primary plasma protein involved in maintaining homeostasis, fibrinogen is the first coagulation factor to become critically elevated with significant surgical bleeding. Laboratory testing for fibrinogen takes around 60 minutes to complete, which is generally too long to guide therapeutic intervention. Advanced thromboelastometry results are available within 10–15
minutes following venesection and can be used to make therapeutic intervention decisions, but they are not widely available. Levels of 100–150 mg/dL are insufficient for effective hemostasis during continuous PPH (7-9) yet there is no established fibrinogen therapy trigger or target level. The majority of the existing guidelines are derived from studies of trauma victims. It is not apparent if it is better to adjust the fibrinogen levels to standard at the time of birth or to standard in the population that is not pregnant. The fact that fibrinogen drops earlier than other coagulation factors during PPH may explain why fibrinogen levels are low despite normal PT/aPTT (7-9).

Interest is shown in medications (like tranexamic acid) that lessen bleeding during all types of surgery (10, 11). Due to the significance of postpartum bleeding, fibrinogen concentrate is utilized in cases of severe postpartum hemorrhage. Fibrinogen concentrate promptly restores severe hypofibrinogenemia during PPH (12). A 200 mg/dL fibrinogen level or more should be kept throughout ongoing PPH, according to the practical view, even if PT and aPTT are normal. Some groups advise an empirical infusion of two cryoprecipitate pools (13). To increase by 100 mg/dL, approximately 3–4 g of fibrinogen concentrate (14, 15), 200 mL of cryoprecipitate (16), or 1500 mL of fresh frozen plasma (FFP) (15) are required. Additionally, there’s also a higher link between the dose of fibrinogen and the rise in fibrinogen level than there was with the dose of cryoprecipitate (17). Fibrinogen treatment was found to effectively minimize the bleeding and utilization of RBC and fresh frozen plasma (FFP) (12), but increasing the levels above 4 g/L has no benefit (18). There is a tendency for fibrinogen concentrate to be employed in preventing or treating PPH, even though some researchers disagreed with its use in postpartum hemorrhage (12, 19-21).

The therapeutic options for PPH control are currently mostly standardized; medical therapy is also required. Thus, fibrinogen replacement therapy for major bleeding is becoming more common. The purpose of this research is to look at the usage of fibrinogen concentrates in PPH.

**Methods**

Following permission from the … and Iranian Registry of Clinical Trials … and after participants gave written informed consent, this double-blind, placebo-controlled, randomized clinical study was performed for all pregnant women who underwent cesarean section in a university-affiliated general hospital between November 11, 2022, to January 8, 2023. Cases with a history of coagulopathy or who take anticoagulant drugs were excluded from the study. Cases that received coagulation-affecting drugs, such as tranexamic acid or colloid plasma expanders, were also excluded from the study. In addition, precipitants were withdrawn if placenta accreta was diagnosed antenatally or diagnosed with secondary postpartum hemorrhage (defined as abnormal bleeding 24 hours after the end of the surgery).

The sample size and the allocation sequence were generated by computer software (PASS 2021 Power Analysis and Sample Size Software, NCSS, LLC, Kaysville, UT, USA) with 1:1 parallel groups and blocks-of-four randomization with a set block size. By using sealed, numbered envelopes that were specifically made for this experiment, we were able to mask the patient trial ID and achieve the desired level of allocation concealment. Caretakers such as midwives, obstetricians, anesthesiologists, and nurse anesthetists were all blinded, as were participants, outcome assessors, study investigators, and statisticians. Participants were randomized and trial drugs were administered by an anesthetic professional who was not involved in patient care. Two 50 mL opaque blue syringes were brought to the operation room without revealing the allocation.

Participants were randomly assigned to either a placebo or P group (isotonic saline) and fibrinogen or F group which used one gram of fibrinogen concentrate (Haemocomplettan® P, CSL Behring GmbH, Marburg, Germany). Both of them were prepared in 50 mL volume and were administered over 10 minutes using an infusion pump 30 minutes before surgery. We employed a preset low dosage for all patients in the intervention group without prior clinical testing of fibrinogen levels to examine how this low dose impacts bleeding because low-dose fibrinogen concentrate administration has been proven to effectively increase fibrinogen levels (22). The primary focus was to reduce total blood loss, with a secondary goal of reducing the number of transfusions.

Blood samples were taken before surgery, in the recovery room, and 24 hours afterward. At all-time points, we employed routine assays such as hemoglobin, international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimer, platelet count, and plasma fibrinogen level. The Clauss method, which estimates fibrinogen plasma concentration using a calibration curve and evaluates the time to change in turbidity caused by fibrin formation, is used to measure fibrinogen levels. The fibrinogen concentrations estimated by Clauss’ approach and more contemporary methods like the FihTEM test show a great correlation, therefore it’s not a big concern (23).

The data were analyzed using chi-square, Kruskal-Wallis, and Spearman’s rho correlation coefficient. The relationship between bleeding quantities and baseline characteristics was examined using logistic regression. The results are displayed as a percentage, mean, median, and P. A P of 0.05 was defined as statistically significant for all analyses, which were carried out using SPSS software, version 17.
Results

The current study involved 280 pregnant women who were scheduled for elective cesarean surgery. Three cases were withdrawn from the study due to dissatisfaction with participation; five due to receiving tranexamic acid treatment, two due to receiving colloid volume expanders, and 10 more due to insufficient information, leaving 260 individuals to be divided into two groups at random: fibrinogen or placebo (Figure 1). The average age of the participants was about 30 years old, and their average BMI was 29 kg/m². There was no significant difference between the two groups in terms of age, education, job status, or nationality (P>0.05). Thirty-three patients (12.7%) required blood transfusions, four (1.5%) patients (two in the F group and two in the P group) experienced rebleeding, and ten (3.8%) patients were admitted to the critical care unit. There were no deaths among our patients. The baseline characteristics of the research participants are shown in Table 1.

Figure 1. Study flowchart

Table 1. Baseline characteristics of the population and Primary plus secondary outcomes

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fibrinogen</th>
<th>Placebo</th>
<th>Overall</th>
<th>P (Kruskal Wallis Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), year</td>
<td>31 (10)</td>
<td>31 (8)</td>
<td>31 (9)</td>
<td>0.624</td>
</tr>
<tr>
<td>BMI, median (IQR), kg/m²</td>
<td>29.38 (3.97)</td>
<td>28.70 (3.96)</td>
<td>29.07 (4.16)</td>
<td>0.190</td>
</tr>
<tr>
<td>History of abortion, median (IQR)</td>
<td>0 (1)</td>
<td>0 (1)</td>
<td>0 (1)</td>
<td>0.470</td>
</tr>
<tr>
<td>Number of deliveries, median (IQR)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0.811</td>
</tr>
<tr>
<td>Newborn weight, median (IQR), g</td>
<td>3135 (513)</td>
<td>3100 (513)</td>
<td>3110 (500)</td>
<td>0.768</td>
</tr>
<tr>
<td>Spinal anesthesia, n (%)</td>
<td>112 (86.2%)</td>
<td>109 (83.8%)</td>
<td>221 (85.0%)</td>
<td>0.729</td>
</tr>
<tr>
<td>Surgery duration, median (IQR), min</td>
<td>65.00 (15)</td>
<td>70.00 (20)</td>
<td>70 (20)</td>
<td>0.225</td>
</tr>
<tr>
<td>Total Bleeding, median (IQR), mL</td>
<td>660 (341.25)</td>
<td>790 (475.00)</td>
<td>750 (395.00)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total Bleeding, n (%)</td>
<td>115 (88.5%)</td>
<td>94 (72.3%)</td>
<td>209 (80.4%)</td>
<td>0.003</td>
</tr>
<tr>
<td>&lt;1000 mL</td>
<td>14 (10.8%)</td>
<td>30 (23.1%)</td>
<td>44 (16.9%)</td>
<td></td>
</tr>
<tr>
<td>1000-2000 mL</td>
<td>1 (0.8%)</td>
<td>6 (4.6%)</td>
<td>7 (2.7%)</td>
<td></td>
</tr>
<tr>
<td>&gt;2000 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb baseline, median (IQR), g/dL</td>
<td>11.60 (2.4)</td>
<td>11.60 (2.3)</td>
<td>11.60 (2.3)</td>
<td>0.593</td>
</tr>
<tr>
<td>Hb recovery, median (IQR), g/dL</td>
<td>10.50 (2.1)</td>
<td>10.00 (1.9)</td>
<td>10.20 (2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb 24 hours, median (IQR), g/dL</td>
<td>10.50 (1.4)</td>
<td>10.50 (1.4)</td>
<td>10.50 (1.4)</td>
<td>0.958</td>
</tr>
<tr>
<td>PLT baseline, median (IQR), /microliter</td>
<td>201.00 (68)</td>
<td>200.00 (72)</td>
<td>200.50 (70)</td>
<td>0.755</td>
</tr>
<tr>
<td>PT baseline, median (IQR), s</td>
<td>12.00 (1.7)</td>
<td>12.00 (1.5)</td>
<td>12.00 (1.7)</td>
<td>0.674</td>
</tr>
<tr>
<td>PTT baseline, median (IQR), s</td>
<td>31.05 (10.2)</td>
<td>29.00 (9.3)</td>
<td>30.50 (9.6)</td>
<td>0.948</td>
</tr>
<tr>
<td>INR baseline, median (IQR)</td>
<td>1.00 (0.1)</td>
<td>1.00 (0.1)</td>
<td>1.00 (0.1)</td>
<td>0.629</td>
</tr>
</tbody>
</table>
Effect of Fibrinogen on Cesarian Section bleeding

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fibrinogen (IQR)</th>
<th>Placebo (IQR)</th>
<th>Overall (IQR)</th>
<th>P (Kruskal Wallis Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen baseline, mg/dL</td>
<td>222.00 (76)</td>
<td>237.00 (92)</td>
<td>233.00 (92)</td>
<td>0.209</td>
</tr>
<tr>
<td>Fibrinogen recovery, mg/dL</td>
<td>238.00 (81)</td>
<td>220.98 (83.23)</td>
<td>231.00 (85)</td>
<td>0.002</td>
</tr>
<tr>
<td>Fibrinogen 24 hours, mg/dL</td>
<td>237.60 (68)</td>
<td>244.20 (67)</td>
<td>239.80 (65)</td>
<td>0.463</td>
</tr>
<tr>
<td>D-dimer baseline, ng/dL</td>
<td>744.50 (912)</td>
<td>790.00 (861)</td>
<td>779.00 (861)</td>
<td>0.819</td>
</tr>
</tbody>
</table>

IQR: interquartile range; BMI: body mass index; HB: hemoglobin, PLT: platelet count; PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalized ratio

According to Table 2 and Figure 2, the median blood loss was 750 (IQR=395.00) mL. The bleeding rate was considerably smaller in the F group (median=660, IQR=475.00, P=0.001) than in the P group (median=790, IQR=475.00, P=0.001). PPH and sPPH were detected in 44 (16.9%) and 7 (2.7%) of the individuals, respectively. PPH was found in 14 (10.8%) of the F cases and 30 (23.1%) of the P cases. In the F group, there was one (0.8%) case of sPPH and six (4.6%) cases in the P group. These variables have statistically significant differences (P=0.002). The Spearman's rho correlation coefficient was performed to examine the association between the quantity of bleeding and fibrinogen administration and found a significant correlation, although this correlation was weak (rs=.21, 95%BCa CI [.09,.32], p=.001, N=260). Table 2 summarized the primary and secondary outcomes.

### Table 2. Variable effects on PPH and sPPH

<table>
<thead>
<tr>
<th>Variables</th>
<th>PPH, median (IQR)</th>
<th>PPH, P (logistic regression)</th>
<th>sPPH, median (IQR)</th>
<th>sPPH, P (logistic regression test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>29.00 (6)</td>
<td>0.003</td>
<td>38.00 (6)</td>
<td>0.081</td>
</tr>
<tr>
<td>BMI, median, kg/m2</td>
<td>30.66 (40)</td>
<td>0.007</td>
<td>30.40 (45)</td>
<td>0.157</td>
</tr>
<tr>
<td>Newborn weight, g</td>
<td>3100.00 (625)</td>
<td>0.297</td>
<td>3400 (460)</td>
<td>0.042</td>
</tr>
<tr>
<td>Surgery duration, min</td>
<td>80.00 (20)</td>
<td>&lt;0.001</td>
<td>100.00 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PT baseline, s</td>
<td>12.00 (1.5)</td>
<td>0.352</td>
<td>11.90 (0.8)</td>
<td>0.796</td>
</tr>
<tr>
<td>PTT baseline, s</td>
<td>31.05 (10.1)</td>
<td>0.915</td>
<td>27.60 (3.4)</td>
<td>0.119</td>
</tr>
<tr>
<td>INR baseline</td>
<td>1.00 (0.1)</td>
<td>0.730</td>
<td>1.00 (0.0)</td>
<td>0.101</td>
</tr>
<tr>
<td>PLT baseline, /microliter</td>
<td>188.00 (56)</td>
<td>0.429</td>
<td>218.00 (44)</td>
<td>0.809</td>
</tr>
<tr>
<td>Fibrinogen baseline, mg/dL</td>
<td>198.00 (47)</td>
<td>0.001</td>
<td>147.00 (40)</td>
<td>0.002</td>
</tr>
<tr>
<td>D-dimer baseline, ng/dL</td>
<td>779.00 (861)</td>
<td>0.943</td>
<td>683.00 (913)</td>
<td>0.172</td>
</tr>
<tr>
<td>Hb baseline, g/dL</td>
<td>10.00 (2.3)</td>
<td>&lt;0.001</td>
<td>9.00 (1.4)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

PPH: postpartum hemorrhage; IQR: interquartile range; sPPH: severe postpartum hemorrhage; BMI: body mass index; PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalized ratio; PLT: platelet count; Hb: hemoglobin

Figure 2. The number of normal bleeding, PPH, and sPPH individuals
Logistic regression revealed a relationship between age, BMI, operating time, fibrinogen levels, preoperative anemia, and the incidence of PPH. Also, there was a relationship between operating time, fibrinogen levels, newborn weight, and anemia in the case of sPPH (Table 2).

The mean preoperative fibrinogen concentration was 244.68 mg/dL (SD=79.82). Of the individuals, 73 (28.1%) had fibrinogen levels under 200 mg/dL. A single 1 g fibrinogen concentrate dosage significantly boosted plasma fibrinogen concentration in the F group in the recovery room (Table 2), while fibrinogen concentration dropped in the P group (Figure 3). After 24 hours of surgery, the mean blood fibrinogen level in the F group was lower than in the recovery room but greater than the baseline level. At this time, the fibrinogen level in the P group was higher than in the recovery room, while being near the baseline value, with final values similar in both groups (Figure 3). Platelet count was lower in both groups postoperatively than before surgery, but there were no significant intergroup differences. Table 1 demonstrates that Hb levels in the recovery room were lower than in the baseline, with a significant difference between the F and P groups. There were no clinically detectable side effects of fibrinogen infusion.

![Figure 3. Median fibrinogen concentrations in F and P groups (mg/dL)](image)

As mentioned above, thirty-three (12.7%) cases received blood transfusions. Ten (7.7%) of group F participants and 26 (20%) of group P participants received blood transfusions. This difference was significant ($P=0.006$). Transfusion was required in 27 (61.4%) cases of PPH and all 7 cases of sPPH. For PPH and sPPH hemorrhage, the median number consumed of RBC units was 1 (IQR=1) and 4 (IQR=1), respectively. Additionally, there were substantial differences in the overall volume of blood transfused across groups ($P=0.021$). The F group used 10 units of blood, whereas the P group used 26. Furthermore, more patients in the P group require more than three units. The Spearman's rho correlation coefficient was also used to investigate the relationship between transfusing RBC and fibrinogen administration, and a modest but significant correlation was revealed ($r_s=-0.209$, 95% BCa CI [-0.32, -0.09], $p=0.001$, $N=260$).

Misoprostol was required by 20 (15.4%) of the subjects in group F and 30 (23.1%) of the subjects in group P. Despite group F having fewer receivers, there was no statistically significant difference between the two groups. ($P=0.156$).

**Discussion**

Postpartum hemorrhage greatly increases maternal morbidity and mortality. Plasma fibrinogen levels appear to be a useful biomarker for predicting PPH and the need for blood transfusion (7, 24); however, it is uncertain if restoring fibrinogen to peripartum levels may reduce bleeding and the need for transfusion during a persistent PPH. Despite a higher therapeutic acquisition cost, it was shown that the use of fibrinogen concentrates is a cost-saving treatment option due to savings in other hospital-based costs (25, 26). Furthermore, fibrinogen concentrate had a positive safety profile (17, 27, 28). The main objective of this study was to determine whether empiric low-dose fibrinogen may help patients undergoing cesarean sections avoid excessive bleeding and the need for blood transfusions. We do not have access to advanced thromboelastometry devices.

A total of 260 individuals of elective cesarean section were studied in this double-blind randomized controlled study. The main finding was that preoperative fibrinogen concentrate supplementation, regardless of preoperative fibrinogen level, decreased hemorrhage in cesarean section subjects. This was also linked to a considerable decrease in RBC transfusion needs. No clinical adverse events were shown to be causally associated with fibrinogen treatment. Because the numbers in this trial were small, the chances of thromboembolic events being recorded were likewise limited.

Several randomized studies have examined the hypothesis of fibrinogen supplementation to reduce bleeding intensity. Wikkelso and colleagues found that one gram infusion of this concentrate did not affect women with 500-1000 mL hemorrhages in the first randomized clinical study looking at the use of fibrinogen concentrate in acutely bleeding patients in an obstetric context (18). In another study, Wikkelso and colleagues found that giving two grams of fibrinogen in the early stages of postpartum hemorrhage did not affect bleeding or transfusion rate (21). In the study by Ducloy-Bouthors and colleagues, this outcome was reproduced with three grams of fibrinogen (29). However, the mean fibrinogen levels at the time of randomization were more than 400 g/dL in all of these investigations, which could account for the lack of effectiveness. In other studies, it has been demonstrated that administering fibrinogen can treat coagulation problems caused by postpartum hemorrhage (15, 17, 30-32). Fibrinogen has been proven to reduce postoperative hemorrhage in a variety of procedures (33-38). In our trial, administering fibrinogen significantly reduced the amount of
bleeding. Although the usual value for fibrinogen in the third trimester is 373-619 mg/dL (39), other studies observed levels ranging from 114 to 914 mg/dL (40-42). In our study, the average fibrinogen concentration was close to 245 mg/dL, which was comparatively low. Even though levels of fibrinogen lower than 200 mg/dL are not prevalent during PPH (19), approximately 28% of our individuals had levels that were. Ethnic differences may be responsible for this variation, but no studies that evaluated fibrinogen levels in pregnant women have been conducted in Iran.

The use of fibrinogen concentrates was linked to a reduction in the requirement for transfusions after various operations (34-36, 38, 43, 44) and postpartum hemorrhage (12, 15, 30), suggesting that using fibrinogen concentrate as the first-line treatment might be an acceptable strategy (35). Additionally, it is advised to consider preoperative fibrinogen level as a blood transfusion predictor (45). According to a Cochrane review, the administration of fibrinogen concentrates to bleeding patients was associated with a 53 percent decrease in the need for RBC transfusions (46). By the aforementioned studies, in contrast to Wikkelso and colleagues (21), Collins and colleagues (19), and Ducloy-Bouthors and colleagues (29), both the number of patients who received RBC transfusions and the number of blood units in the placebo group were significantly higher and more than two times as high as those in fibrinogen group.

Although early systematic fibrinogen replacement is not advantageous throughout the course of managing severe PPH, according to three significant randomized and controlled trials, FIB-PPH, OBS2, and FIDEL (19, 21, 29), some authors continue to support the efficacy of fibrinogen supplementation (31, 32, 47, 48). Since plasma fibrinogen concentrations were substantially lower than those seen in the studies mentioned above, this is not unexpected. This disparity might be attributed to the different research populations and their specific clinical conditions during fibrinogen infusion, such as the degree of hemodilution.

One of our study's limitations is that the accuracy of reported blood loss may have been influenced by significant interobserver variability. Additionally, it is not optimal to use blood loss as the main endpoint since other, clinically important endpoints including the need for transfusions, morbidity, and mortality would necessitate much larger research populations.

Conclusion

According to the evidence presented, fibrinogen concentrate may be useful in lowering postoperative bleeding and the need for RBC transfusions in cases of cesarean section. By eliminating the requirement for cross-matching, thawing, or both, fibrinogen concentrate has the potential to save time when compared to allogeneic blood products. Due to its safety, simplicity of use, and economic justification due to the decrease in complications related to bleeding and blood transfusion in cesarean sections, the use of low-dose empirical fibrinogen concentrate is strongly advised, particularly in areas with a high prevalence of low plasma fibrinogen levels and limited access to sophisticated thermometric devices.

Declarations:

We declare by signing the following letter:

1. The manuscript is the original work of the authors. All data, tables, figures, etc. used in the manuscript are prepared originally by the authors.

2. The manuscript has not been and will not be published elsewhere or submitted elsewhere for publication.

3. Authors mention that there is no conflict of interest in this study.

4. The final version of the paper I enclose is not substantially the same as any that I/we have already published elsewhere.

5. No more changes in the authors or main results are accepted from my side after submitting them to the journal.

Ethics approval and consent to participate:

This research received an ethical code (IR.SBMU.MSP.REC.1401.378) from the Ethics Committee of Shahid Beheshti University of Medical Sciences https://ethics.research.ac.ir/EthicsProposalView.php?&code=IR.SBMU.MSP.REC.1401.378

and RCT code (IRCT20120910010800N8) from the Iranian Registry of Clinical Trials (https://en.irect.ir/user/trial/11210/view).

Consent for publication

Not applicable.

Availability of data and materials

All data, tables, figures, etc. used in the manuscript are prepared originally by the authors and are available (by the corresponding author) if needed.

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**Authors' contributions**

Dariush Abtahi (guarantor) has conducted the design, execution, and management of the project, including writing and final approval of the manuscript; Shideh Ariana contributed translation to English and analyzed and interpreted the data; Arefzou Ashari, Maral Hosseinzadeh, Tannaz Yeganegi, and Ebtehaj Heshmatkhah cooperated in writing the manuscript; Shahram Sayadi and Shideh Ariana cooperated on design and writing the manuscript.

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**Conflict of Interest**

The authors state that they have no known financial or interpersonal conflicts that might have influenced the research presented in this paper.

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