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The effect of iron supplementation on menstrual bleeding volume and hemoglobin level during menstrual bleeding: A randomized clinical trial

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Abstract:

BACKGROUND: Many women around the world avoid taking iron supplements during their menstrual bleeding, thinking that menstrual bleeding will increase after taking these supplements. Due to the lack of relevant scientific evidence in this regard, this study was performed to determine the effect of iron supplementation on menstrual blood volume and hemoglobin level during menstrual bleeding.

MATERIALS AND METHODS: In this three-blind randomized clinical trial, 160 non-anemic female students of Rafsanjan University of Medical Sciences were selected through a public call and then they were randomly assigned to two intervention and control groups. The intervention group was given a ferrous sulfate tablet containsing 50 mg of elemental iron daily in the first four days of bleeding for three consecutive menstrual cycles, and the control group received a placebo simultaneously. Before and after the intervention, the level of hemoglobin was measured and the Higham chart was completed in each menstrual cycle by the participants of the two groups. The obtained data were analyzed using the SPSS software version 21 and Chi-square, independent *t*-test, paired *t*-test, analysis of variance with repeated measures, and nonparametric tests.

RESULTS: Before performing the intervention, the mean Higham score and hemoglobin level of the two groups were not statistically significant ($P = 0.307$, $P = 0.670$). The mean Higham score after each intervention was not statistically significant between the two groups over time or when considering the interaction of the time group ($P = 0.77$, $P = 0.916$). The hemoglobin level of these two groups did not change significantly after the intervention compared with that before the intervention ($P = 0.444$).

CONCLUSION: Compared with a placebo, taking iron supplements containing 50 mg of elemental iron during the first four days of menstrual bleeding in non-anemic women did not change the volume of menstrual bleeding and hemoglobin level.

Keywords:

Hemoglobin, iron, menstruation, students

Introduction

Iron deficiency anemia is a global health problem and the most common type of anemia.[1,2] More than 1.2 billion people worldwide suffer from iron deficiency anemia. Moreover, it is one of the top five causes of disability, which ranks first among women.[3] The World Health Organization (WHO) estimated that 43% of nonpregnant women in developing countries and 12% of them in developed countries have iron deficiency anemia.[4] One of the goals set by the WHO by 2025 is to reduce the frequency of anemia by 50%.[5] Iron deficiency anemia reduces mental concentration, learning ability, memory, resistance to diseases caused by weakened

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immune system, job performance, and quality of life and increases the rates of mortality among pregnant mothers, low birth weight, and premature children.[6] The causes of iron deficiency anemia are insufficient intake, insufficient absorption, and transport of iron and bleeding.[7] Dietary iron deficiency is very common, and 50% of women aged between 15 and 45 years suffer from it.[8,9] The values and preferences of the family or society are other causes of iron deficiency anemia that lead to low quality of diet.[10] Women of childbearing age lose about 1 mg of iron per day, and on average, at the age of childbearing, they may lose 1 mg more iron due to menstruation.[11] The average iron losses in patients with menorrhagia are, on average, five to six times higher than normal.[12] The WHO has recommended four basic strategies for the prevention and control of anemia, including iron supplementation, proper nutrition education, nutrient enrichment, and the control of infectious and parasitic diseases with iron compounds.[10] Iron supplementation is the most cost-effective and common strategy used by developed countries to control iron deficiency.[13] According to the WHO guidelines for the prevention of iron deficiency, nonpregnant women of childbearing age are recommended to take 30–60 mg of mental iron daily for three consecutive months in a year in locations where anemia is common.[14] In addition to regular iron supplementation, other factors are also effective in increasing the effectiveness of iron supplementation.[15] Blood loss during menses would also result in more iron loss, which would lead to lower hepcidin concentrations, so the release of stored iron in the body and the absorption of iron in the diet increase.[16] Cultural beliefs, defined as "a set of behavioral patterns related to thoughts, manners, and actions, which members of society have shared and passed on to succeeding generations," may also influence the decision-making of patients to take medication.[17] There is a significant positive or negative association between personal and cultural beliefs and medication adherence. Illness perceptions and other beliefs may influence the actions of the individual and negatively or positively affect his or her health and taking medication. Healthcare providers need to understand the impact of cultural and other beliefs on patients' adherence levels so that they can implement appropriate strategies to enhance adherence.[18,19]

Many women avoid iron supplementation during menstruation and believe that iron supplementation during this period increases the amount of bleeding. We did not find any scientific evidence to confirm this belief in the review of scientific documents. Therefore, this study was conducted with the aim of investigating the effect of iron supplementation on menstrual blood volume and hemoglobin level during menstrual bleeding in order to correct this common belief according to the results of the study. Since no study with a similar design was found in our search, this study is unique in its kind.

Material and Methods

Study design and setting

This study utilized a three-blind randomized clinical trial design to investigate the effect of iron supplementation during menstrual bleeding on menstrual bleeding and hemoglobin level of female students of Rafsanjan University of Medical Sciences. The participant recruitment was conducted from December 2020 to January 2021. We followed the CONSORT guidelines.

Study participants and sampling

Samples according to the study by Bani *et al*.,[20] 95% confidence level, and 80% statistical power as well as the relevant statistical formula samples were estimated to be 73 individuals in each group. By considering the probability of attrition, this number was finally estimated at 80 individuals for each group. The eligibility criteria of this study were as follows: not taking vitamin and iron supplements during the past 3 months; not taking oral or intravenous steroid hormonal drugs; not having liver, infectious, and parasitic diseases; not having blood diseases such as thalassemia and hemophilia; not having medical prohibition for taking iron; not being pregnant or lactating; not being smoker; BMI between 18.5 and 25 kg/m^2; hemoglobin greater than 12 grams per deciliter; normal menstrual cycle; no history of major surgery and blood transfusion; not using tampons or menstrual cups; and not having systemic diseases such as diabetes, thyroid problems, and overactive adrenal glands according to the individual herself. In case of any allergic reaction to iron tablets, forgetting to take more than one iron tablet per cycle, taking emergency contraceptive (EC) pills, being infected with coronavirus,[21] and injecting coronavirus vaccine,[22,23] they would be excluded from the study.

Data collection tool and technique

Female students of Rafsanjan University of Medical Sciences were invited to participate in this study through a public call. By taking 2.5 cc of blood from the volunteers before performing the intervention, the hemoglobin level was determined in a single laboratory. If the hemoglobin level was more than 12 mg/dl, they could enter the study. The participants were divided into two groups of intervention and control by picking up sheets with codes A and B, which were prepared according to the number of study samples and then placed inside the opaque box. For blinding of the study, iron tablets and placebo were made exactly the same by Amin Pharmaceutical Company and were given to the researchers anonymously with A and B codes. After analyzing the data of the study, it was determined that code A is related to placebo and

code B is related to iron tablets. Before conducting the intervention, the participants completed a demographic and menstrual profile questionnaire and the intervention group received 12 ferrous sulfate iron tablets, each one containing 50 mg[14] iron ions, and the control group received the same number of placebo for consumption during three menstrual cycles. The duration of the study was four menstrual cycles in total. In the first cycle, the individuals only recorded the amount of menstrual bleeding on the Higham chart[24] and confirmed its similarity to the pattern of the previous two cycles. Thereafter, they started taking iron and placebo pills from the next cycle. Notably, the Higham chart is used to assess the amount of bleeding.[25] A score of 100 or more is equivalent to bleeding greater than 80 ml, and a score of less than 100 indicates less bleeding amount.[26] The Higham score is valid and has more than 80 sensitivities and characteristics in adult women whose scores are more than 100.[27,28] Moukhah *et al*.[29] have confirmed the validity and reliability of the Higham chart. In this study, the researcher explained how to complete the Higham chart to the participants. To prevent forgetfulness of consumption and better digestive tolerance, it was recommended to take iron tablets at a specific time before going to bed. Daily consumption was also reminded to them with a reminder message. The intervention group took iron tablets once a day for the first 4 days of menstrual bleeding, and the control group took a placebo in the same way and in each cycle, and all of them recorded the amount of bleeding on the Higham chart. By passing one week of taking the last iron pill or placebo, the hemoglobin level was measured once again.[20]

Ethical consideration

This three-blind randomized clinical trial was approved by the Ethics Committee of the Rafsanjan University of Medical Sciences with the approval code IR.RUMS.REC.1399.077 and was registered at the Iranian Registry of Clinical Trials with the registration code IRCT20160308026971N11. We followed all the ethical principles of the World Medical Association Declaration of Helsinki for medical research involving human subjects. We obtained written informed consent from all study participants before their recruitment, which included the following information: the purpose of the research, the procedures to be followed during data collection, description of discomforts (if any) and benefits, confidentiality of the records, anonymity of the respondents, and the right of participation or withdrawal.

Statistical analysis

The data were analyzed using the SPSS version 16 software. The Chi-square test, independent *t*-test, paired *t*-test, Fisher's exact test, and repeated-measures analysis were used to compare the results at a statistically significant level of $P < 0.05$.

Results

In this study, 380 individuals were investigated to enter the research. Finally, 80 individuals were randomly assigned to each of the intervention and control groups. In addition, 18 individuals from the control group and seven individuals from the intervention group were excluded from the study, and finally, the analysis was performed with 73 people in the intervention group and 62 people in the control group [Figure 1].

There was no significant difference in demographic characteristics and menstrual history between the two study groups. There was no significant difference in hemoglobin levels between the two groups before the intervention ($P > 0.05$) [Table 1].

After performing the intervention, there was no significant difference in hemoglobin levels between the two groups based on the result of the independent *t*-test ($P = 0.681$). In addition, there was no statistically significant difference when comparing hemoglobin levels between the groups after the end of the intervention based on the paired *t*-test [Table 2].

There was no significant difference between the two study groups when considering the amount of menstrual bleeding by the Higham score before the intervention ($P = 0.307$). According to the results, there was no significant difference between these two groups after conducting each intervention. In the intragroup

Table 1: Demographic characteristics of subjects divided into intervention and control groups

Characteristic	Control (*n*=62)	Intervention (*n*=73)	Results
Weight	Mean (SD)	Mean (SD)	*P*=*0.875
	61.59±11.15	61.90±11.32	
Height	162.74±6.07	161.94±5.46	*P*=*0.424
Grade			
Bachelor's degree	38 (% 61.3)	36 (% 49.3)	*P*=**0.296
Master's degree	8 (% 12.9)	17 (% 23.3)	
Medicine and dentistry	16 (% 25.8)	20 (% 27.4)	
Place of residence			
Dormitory	15 (%24.2)	22 (%30.1)	*P*=**0.440
House	47 (%75.8)	51 (%69.9)	
Marital status			
Unmarried	33 (%53.2)	35 (%47.9)	*P*=**0.541
Married	29 (%46.8)	38 (%52.1)	
Body mass index**** (kg/m^2)	23.24±3.96	23.64±4.34	*P*=**0.424
Menarche age	13.66±1.36	12.75±1.25	*P*=*0.811
Duration of menstrual bleeding	6.64±1.50	6.61±1.19	*P*=**0.902
Hemoglobin level before intervention	13.05±0.89	13.67±0.94	*P*=*0.670

Independent *t*-tests*, Chi-square test**, Fisher's exact test***, ****Body mass index (BMI) obtained by dividing weight in kilograms by square of height in meters

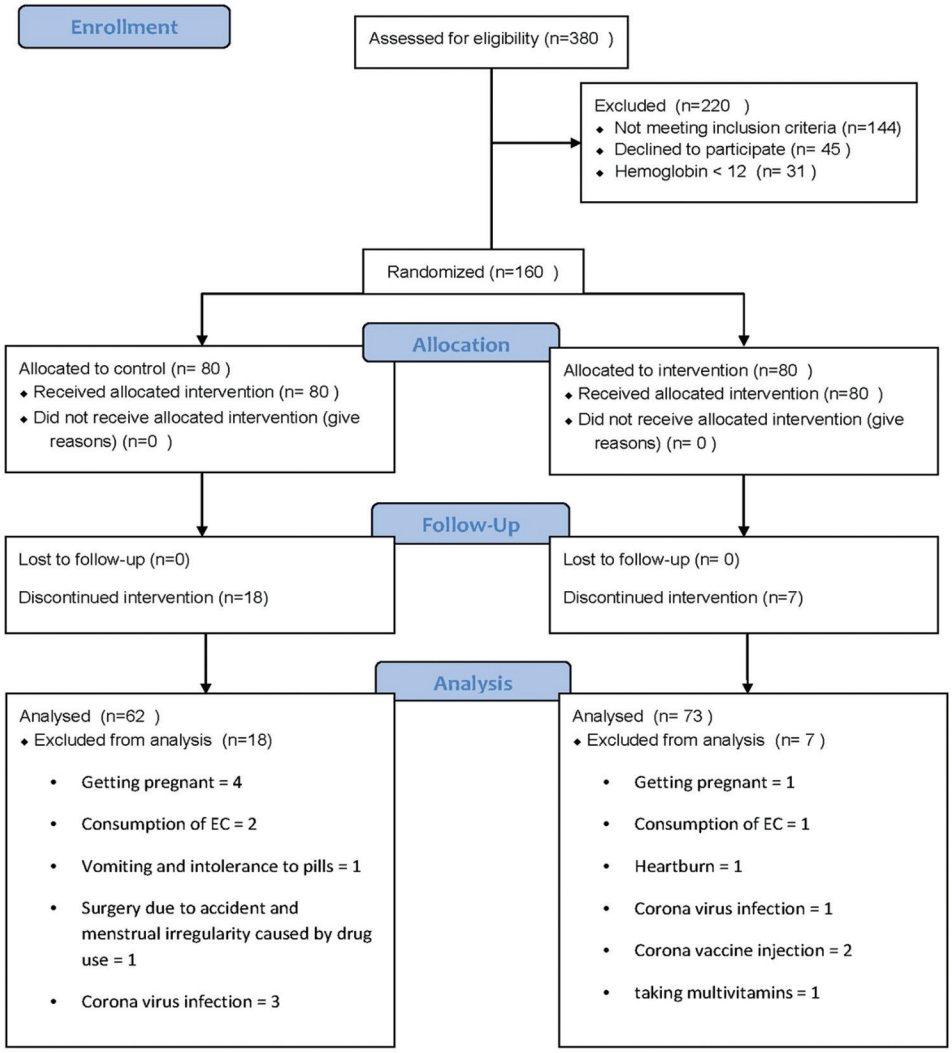

Figure 1: Flowchart of the participants' information in the study

Table 2: Comparison of hemoglobin levels before and after the intervention of the studied female students in the two intervention and control groups

Hemoglobin	Control Mean (SD)	Intervention Mean (SD)	*P*
Hemoglobin before the intervention	13.05±0.89	13.67±0.94	*0.670
Hemoglobin after the intervention	13.26±0.93	13.72±1.53	*0.681
P	**0.565	**0.444	Comparison of hemoglobin levels between the groups after completing the intervention

Independent *t*-tests*, paired *t*-test **

comparison, the amount of menstrual bleeding in the intervention group during four menstrual cycles showed no significant difference (P = 0.574). Additionally, in the control group, the amount of menstrual bleeding during four menstrual cycles had no significant difference (P = 0.382) [Table 3].

Based on the repeated-measures analysis test and considering the effect of measurement time, there was no significant difference among the average amounts of menstrual bleeding in the first menstrual cycle (before the intervention), the second menstrual cycle (intervention), the third menstrual cycle (intervention), and the fourth menstrual cycle (intervention) (P = 0.77). By comparing the two groups, no statistically significant difference was found between the average amounts of menstrual bleeding before and after the intervention based on the repeated-measures analysis test (P = 0.352). Also, by considering the interaction effect of time group, there was no significant difference between the average amounts of menstrual bleeding before and after performing the intervention (P = 0.916) [Table 4].

During four cycles in both the intervention and control groups, almost the same trend of Higham score was found [Chart 1].

Table 3: Intragroup and intergroup comparisons of menstrual bleeding in the two intervention and control groups before and after each intervention

Group Higham score	Control Mean (SD)	Intervention Mean (SD)	Comparison of the amounts of menstrual bleeding after each intervention *P*
The first cycle (before intervention)	69.72±44.84	78.30±51.18	*0.307
The second cycle (after intervention)	71.00±53.43	76.97±52.69	*0.515
The third cycle (after intervention)	69.69±49.35	79.27±57.33	*0.305
The fourth cycle (after intervention)	64.25±50.81	69.90±52.08	*0.527
Intragroup comparison	**0.382	**0.574	←*P*

Independent *t*-tests*, repeated measurement test**

Table 4: Intergroup comparison of changes in average bleeding amounts in the two groups during four menstrual cycles

	F	Average of squares	Df	Sum of squares	Repeated measurement *P*
Effect of measurement time	2.303	1687.58	3	5062.76	0.77
Interaction effect of time group	0.171	125.63	3	376.91	0.916
Comparison between two groups	0.874	7430. 42	1	7430.42	0. 352
Error	-----	732.93	399	292440.14	-----

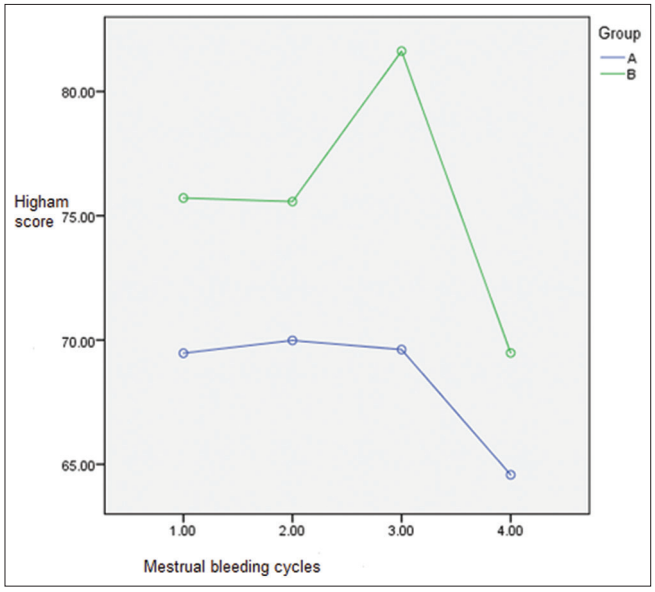

Chart 1: Higham score trends in the study groups at different measurement times based on the repeated measurement test

Discussion

This study was the first randomized clinical trial on the effect of iron supplementation on menstrual blood volume and hemoglobin level during menstrual bleeding. The results showed that taking iron tablets during menstrual bleeding did not lead to increased menstrual bleeding. In the study by Bani *et al*.,[20] there was no difference in the amount of hemoglobin level and menstrual bleeding between two consecutive and intermittent iron administration methods. In the study by Bani *et al*.,[20] the aim was to compare the two methods of iron supplementation (including iron and folic acid) among anemic individuals. In this regard, the intervention group was given iron supplements at the time of menstrual bleeding. Moreover, the control group received that on a specific day of the week, and there was a possibility that this day could coincide with the days of menstrual bleeding. However, in this study, the aim was to investigate the effect of iron supplementation (including only iron) on the amount of bleeding and hemoglobin level during menstrual bleeding in non-anemic people. In addition, to increase the accuracy of the study, the control group used a placebo on the same days of bleeding and at the same time as the consumption of iron pills in the intervention group. The design of our study was one of the strong points of the study because the consumed iron supplement did not include other vitamins and mineral salts, and the control group consumed an iron placebo at the same time of menstrual bleeding. In a study by Rahimi *et al*. (2010)[30] with the aim of investigating the effect of vitamin E on menorrhagia, the intervention group received vitamin E and iron and the control group received placebo and iron during their menstrual days. As a result, menstrual bleeding significantly reduced in both groups, but there was no significant difference between the two groups in terms of the amount of menstrual bleeding. Since the group of control received the vitamin E placebo, a decrease in the volume of menstrual bleeding was observed, which could be attributed to the use of iron tablets. Therefore, from the results of this study it can be concluded that the consumption of iron at the time of menstrual bleeding does not increase bleeding, which is in agreement with the result of our study, and even a decrease in bleeding was seen in the two groups. Another important factor that contributes to a negative iron balance in women at fertile age is menstruation. The normal monthly menstrual bleeding of women causes the loss of 10 to 40 mg of iron, stimulates the iron

regulatory system, and then leads to iron fluctuations during the menstrual cycle.[31] In the study by Chandra *et al*. (2017),[32] a significant difference was found in the iron status indicators including Hb, serum iron, TIBC, and MCV on different phases of the menstrual cycle with the highest values during the luteal phase and the lowest one during the menstrual phase. In the study by Frass (2015),[33] a significant association was found between the decreased hemoglobin level and postpartum hemorrhage. The increase in bleeding was expressed due to the role of heme in the structure of hemoglobin as well as the failure of oxygen transportation by hemoglobin to the uterus and cell function and tissue enzyme dysfunction, and as a result, a blood vessel constriction disorder was expressed.[33,34] The results of the study by Angeli *et al*. (2016)[16] also showed that blood loss during menses would result in more iron loss, which would consequently lead to lower hepcidin concentrations, so the release of stored iron in the body and the absorption of iron from the diet would increase. The results of the abovementioned studies can prove the appropriateness of taking iron pills during menstrual bleeding, and based on the results of this study, the public's concern about increased menstrual bleeding due to taking iron pills at this time is a false belief. There was no significant difference between the hemoglobin levels of the two intervention and control groups before and after the treatment, which could be due to the short period and low dose of iron consumed. Moreover, in the study by Bani *et al*.[20] and Rahimi *et al*.,[30] the hemoglobin levels of the two groups were not significantly different. Due to the limited number of available studies on the use of iron supplements during menstruation, we will discuss the results of some studies on the effect of other supplements, minerals, and vitamins on menstrual bleeding. In the study by Cueto *et al*. (2015),[35] there was no clear association among the consumption of folic acid supplements or multivitamins containing folic acid and iron, cycle regularity, and duration and intensity of menstrual bleeding compared with the control group. Since there was iron in multivitamins containing folic acid and its consumption did not increase menstrual bleeding, the result of this study is in agreement with the result of our study. The results of studies showed that some food sources rich in iron were effective in reducing menstrual bleeding according to the PBAC scores.[36,37] Therefore, from the results of these studies it can be concluded that the consumption of food sources rich in iron at the time of menstrual bleeding does not increase bleeding, which is in agreement with the result of our study, and even a decrease in bleeding was observed. However, because iron tablets were used in the present study and food sources rich in iron were used in these studies, the results of these studies may not be generalizable to the results of the present study. The results of the study by Gagnon *et al*. (2017)[38] showed that negative beliefs about medicines are as prevalent in the community as external barriers to accessing medicines, but negative beliefs were more significantly associated with adherence than external barriers. Physicians should identify and address patients' negative beliefs about medicines to improve adherence rates. Since negative beliefs about medicines can influence adherence rates, the result of this study shows the importance of conducting this study and correcting the beliefs of society about compliance and consumption of iron supplement. According to the results of the study by d'Arcangues *et al*.,[39] vitamin E and low-dose aspirin, alone or in combination, have no effect on the treatment of Norplant-induced prolonged bleeding or the vaginal bleeding patterns of these women. Łagowska (2018)[40] has shown that women with low vitamin D levels were almost five times more likely to have menstrual cycle disorders. Bahman *et al*.'s[41] study showed that vitamin D and calcium supplementations in women with PCOS can lead to better results in all PCOS symptoms, including regular menstruation and ovulation. It seems that the use of supplements during menstrual bleeding does not affect the amount of bleeding, but the lack of some of them, such as vitamin D and iron, can cause menstrual cycle disorders, including increased menstrual bleeding amount.

Limitations and recommendation

Due to the coronavirus pandemic, the closure of universities in Iran, and the unavailability of a large number of students, sampling was prolonged.

Conclusion

According to the results of this study, taking iron tablets containing 50 mg of iron ions in the first four days of menstrual bleeding in non-anemic women had no effect on menstrual bleeding and hemoglobin level compared with a placebo. Therefore, because iron absorption increases during menstrual bleeding[16] and the prevention of iron deficiency anemia is important, it is necessary to consider these points and correct their beliefs, if necessary, at the time of prescribing iron supplements to women. These findings emphasize the need to conduct more studies in this field.

Abbreviations

BMI: body mass index; EC: emergency contraception.

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Ethics approval and consent to participate

The Ethics Committee of the Rafsanjan University of Medical Sciences approved our study protocol with the ethics code IR.RUMS.REC.1399.077. We followed all the ethical principles of the World Medical Association Declaration of Helsinki for medical research involving human subjects. We obtained written informed consent from all study participants before their recruitment.

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Conflicts of interest

There are no conflicts of interest.

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