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Original Research

The Effect of Maternal Vitamin D Intake on the Incidence of Nonspecific Respiratory Distress in Infants: A Randomized Clinical Trial

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Abstract

Background: Vitamin D deficiency is associated with respiratory problems in neonates. The late preterm or near-term neonates who have been admitted for tachypnea and fully recovered before 12 h are called non-specific respiratory distress syndrome (NRDS) cases. The present study aimed to evaluate the effect of 25-hydroxy vitamin D administration in pregnant women at risk of preterm delivery on the incidence of NRDS in their newborns. **Methods**: This single-blind clinical trial was performed on mothers and neonates with a gestational age of 32–37 weeks who were referred with labor pains from February 20, 2021 to June 29, 2021 to the Obstetrics and Gynecology Department and intensive care unit of Ghaem Hospital, affiliated to Mashhad University of Medical Sciences, Iran. Within 72 h before premature delivery, a dose of 50,000 units of 25 hydroxyvitamin D was injected intramuscularly to pregnant women in the intervention group. A sample containing 1.5 mL of whole blood was collected from the umbilical cord of the infant and mother to assess the level of 25-hydroxy vitamin D. **Results**: In the present study, there was a significant difference between the two groups of control and intervention in terms of infant's weight (p = 001), 1-minute (p = 0.027) and 5-minute Apgar scores (p = 0.001), the incidence of NRDS (p = 0.001), and the maternal age (p = 0.004). However, the results showed no statistically significant difference between the two groups in terms of gender (p = 0.673), type of delivery (p = 0.299), level of 25-hydroxy(OH) vitamin D of the mother (p = 0.053), and infant (p = 0.805). **Conclusions**: A single injection of vitamin D into the mother prone to preterm birth over 31 weeks of gestation reduces transient respiratory problems in their newborns. **Clinical Trial Registration**: The study was also registered in the Iranian Clinical Trial Registration Center (IRCT20110807007244N7).

Keywords: non-specific respiratory distress syndrome (NRDS); vitamin D; infant; vitamin D deficiency

1. Introduction

In our several years of neonatal practice, we have seen many cases of late preterm or near-term neonates admitted for tachypnea who were fully recovered in a few hours. The initial tests, blood gas, radiography, and blood culture of these infants were all normal. Despite the good prognosis, separation of the mother and neonate in the first few hours imposes significant stress on the mother and deprives them of the benefits of indispensable mother-infant contact [1]. It would also be a nonessential burden on the medical and nursing staff. This condition is common in elective cesarean cases and in non-academic centers. We have used the term non-specific respiratory distress syndrome (NRDS) to describe this condition. Undoubtedly, the major cause of this problem is a disorder in the respiratory system in the transition from intrauterine to extrauterine life. The most important likely predisposing factors for NRDS are elective cesarean delivery and premature births.

During pregnancy, the fetal lung secretes fluid into the alveolar space through the chloride transport-driven liquid secretion mechanism. Na-K-2Cl channel inhibitors block this secretion. This fluid plays an important role in developing the lungs, providing a framework for preventing airway collapse and promoting them growth [2].

The fetus faces a challenge at birth because the fluid is emptied out of the airways quickly (secreted throughout the pregnancy) with an initial warning (labor) or even without any warning (elective cesarean delivery). A significant component of this process is the lung epithelium, which switches placental to pulmonary gas exchange. Effective gas exchange requires clearing the airways of fluid and increases pulmonary blood circulation to match ventilation and perfusion [3]. Any disturbance in the above process can lead to respiratory problems in the infant. If this respiratory problem lasts for more than 12 h but improves within 24 h to 48 h, transient tachypnea of the newborn (TTN) is suggested [4]. However, this condition often improves

within 12 h, which we called non-specific respiratory distress syndrome (NRDS). One way to mitigate this condition is to allow normal labor. Nevertheless, despite the countless benefits of normal labor, elective cesarean delivery is still very frequent. Therefore, before birth, the fetal lung must be well prepared for extrauterine life. Some studies have suggested the role of vitamin D in type-II pneumocyte cell maturation, fibroblast proliferation, surfactant synthesis, and alveolarization; therefore, vitamin D deficiency may be a risk factor for respiratory problems [5,6]. Premature birth increases the risk of vitamin D deficiency in the infant due to insufficient opportunity for vitamin D to pass from mother to fetus. In this respect, the prevalence of vitamin D deficiency in premature infants has varied in different parts of the world. For instance, vitamin D deficiency has been reported in 64%, 83%, and 82% of preterm infants in the United States, India, and Iran, respectively [7]. Numerous studies have been done on the relationship between vitamin D deficiency and respiratory diseases such as bronchopulmonary dysplasia (BPD), TTN, and respiratory distress syndrome (RDS), and vitamin D deficiency has been considered among the influential factors in the occurrence of these diseases in infants [6,8–11]. We hypothesize that vitamin D deficiency may also play a role in NRDS. Therefore, the present research aimed to assess the relationship between non-specific respiratory distress at birth and maternal intramuscular 25-hydroxy vitamin D intake.

2. Method

2.1 Study Design

This single-blind clinical trial was conducted from 20 February to 29 June 2021 on mothers (and their neonates) with a gestational Dage of 32–37 weeks who were admitted with labor pain to the Obstetrics and Gynecology Department and the intensive care unit of Ghaem Hospital, affiliated to Mashhad University of Medical Sciences (MUMS), Iran. The study was approved by the Ethics Committee of MUMS with the tags IR.MUMS.MEDICAL.REC.1399.613 and 990699. Informed consent was obtained from the participants. The study was also registered in the Iranian Clinical Trial Registration Center (IRCT20110807007244N7).

2.2 Inclusion and Exclusion Criteria

The inclusion criteria included pregnant women with a gestational age of 32 to 37 weeks and signs of premature labor, who had a normal fetal prenatal ultrasound, and no significant medical and obstetric problems (such as cardiovascular disorders, diabetes mellitus, epilepsy, and asthma).

The exclusion criteria included meconium aspiration syndrome, congenital anomaly, congenital infection, RDS, TTN, intubation in the delivery room, death in the delivery room, severe asphyxia, addicted mothers, pneumonia, and persistent respiratory distress in the newborn beyond the first 12 h after birth (Fig. 1).

2.3 Randomization

In this study, blocking randomization was used as a reliable method to reach a balanced allocation of individuals in treatment groups at the end of each block. For this purpose, a web-based online software(Sealed Envelope Ltd. 2022. Create a blocked randomisation list. [Online] Available from: https://www.sealedenvelope.com/simple-randomiser/v1/lists [Accessed 1 Jan 2023]) was used to determine the volume and number of random blocks. This online software can create random blocks with desired variable sizes. Twenty blocks with variable sizes of 6, 8, and 10 were introduced for a total of 160 samples. The blocks were marked with numbers 1 to 20. Each block included an equal number of intervention and control cases according to the size of that block. After selecting the first mother, one of the blocks was randomly selected. Then, it was assigned according to the order of the contents of the block to one of the groups. By referring to the next mother, the next item of the same block was selected. The remaining blocks were processed, and these steps were repeated until sampling was completed. This process continued until the completion of the first block. The next block was then selected randomly from the remaining blocks, and the above process was repeated until sampling was completed.

The neonates were followed up by a principal researcher, who did not know the relevant control or intervention groups, regarding the occurrence or non-occurrence of respiratory distress and the time of recovery and diagnosis of the respiratory distress. Data were classified as A and B in the SPSS software (version 23 SPSS Inc., Chicago, Illinois, USA), and the statistical analyst interpreted the analysis results without knowing the type of groups, to avoid any bias.

2.4 Intervention

Within 72 h before the preterm delivery, a single dose of 50,000 units of intramuscular 25-hydroxy vitamin D was injected into the pregnant mother in the intervention group who had not taken 25-hydroxy vitamin D in the last three months.

2.5 Laboratory Evaluation

A sample containing 1.5 mL of whole blood was collected from the umbilical cord of the infant and mother to assess the level of vitamin D. The prepared samples were centrifuged, the serum was kept at –20 °C, and they were sent to the central laboratory of Ghaem Hospital for evaluation. Serum 25-hydroxy vitamin D (25OHD) levels were measured using a competitive electroluminescence protein binding assay (Roche Diagnostics vitamin D total assay kit; Roche Diagnostics, Mannheim, Germany) on a Cobas e411 analyzer. The 25-hydroxy vitamin D below 30 ng/mL was considered 25-hydroxy vitamin D deficiency.

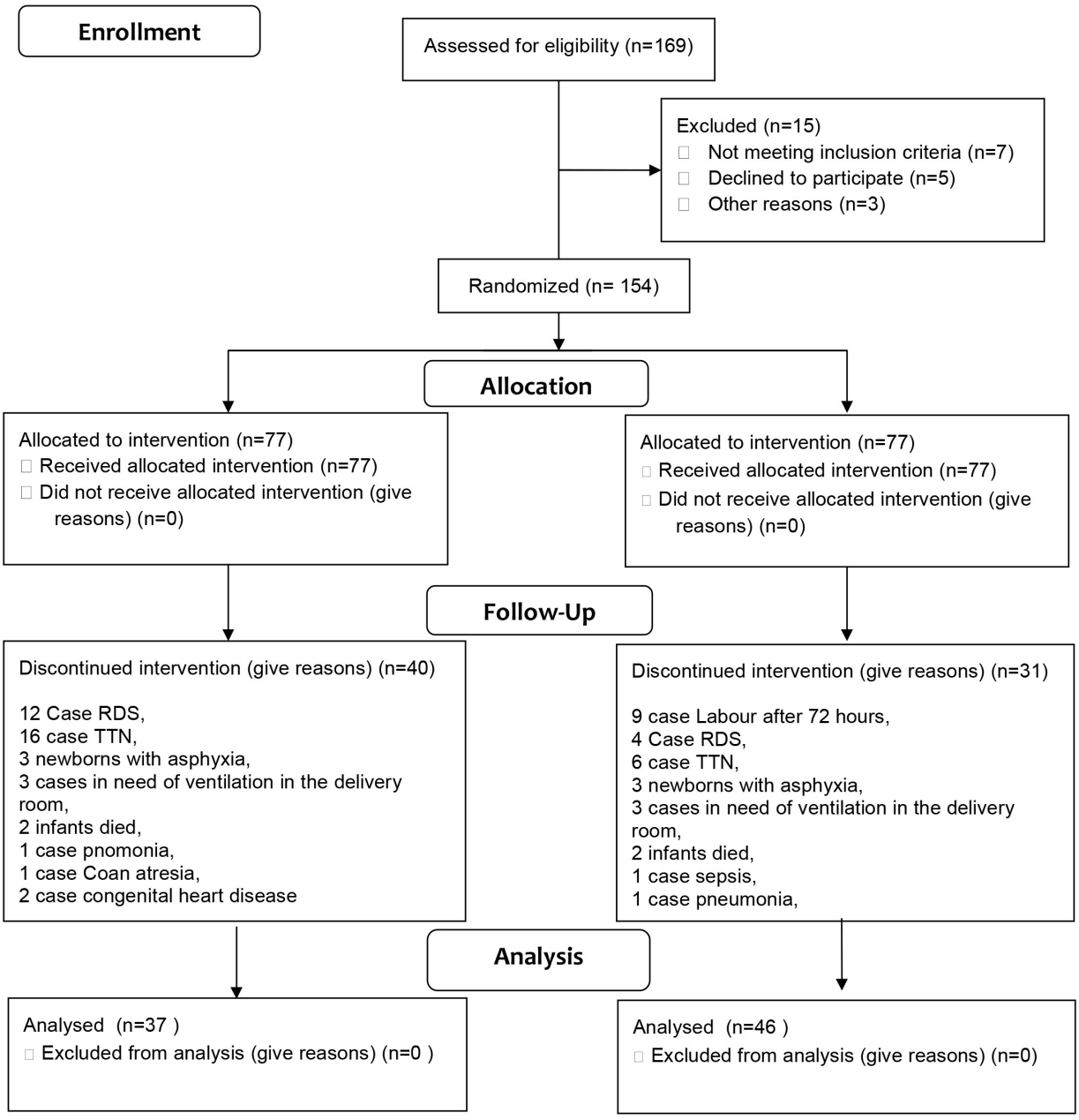

Fig. 1. CONSORT Flow Diagram.

2.6 Radiological Evaluation

Infants who had more than 2 h of respiratory distress and had been admitted to the neonatal ward underwent a chest radiographic examination. The cause of the neonatal respiratory distress was then determined based on imaging findings and the clinical course.

2.7 Outcomes

The primary outcome of the neonates in the study group was the incidence of non-specific respiratory distress. The diagnosis criteria included respiratory distress (tachypnea, intercostal muscle retraction, granting, and nasal flaring) lasting more than 2 h and less than 12 h, normal chest radiograph, and negative blood culture.

2.8 Data Collection

Complete characteristics of infants (birth weight, age, sex, gestational age, Apgar score, and clinical signs), maternal history (age, previous pregnancy, delivery problems, and delivery method), and laboratory results were collected and recorded in a questionnaire. The need for resuscitation, duration of respiratory distress, duration of oxygen therapy, duration of hospitalization in the Neonatal intensive care unit(NICU), and mortality were also recorded. The levels of vitamin D of the mother and newborn were also collected.

2.9 Patients and Methods

In this clinical trial, 169 infants were enrolled. Neonates with more than 2 h and less than 12 h respiratory distress, normal chest radiograph, and negative blood culture met the criteria for the study. The newborns were placed under oxyhood with continuous close monitoring for worsening respiratory symptoms. Pulse oximetry was performed by a probe at the right upper extremity, and respiratory symptoms were examined repeatedly. Blood gas analysis and oxygen saturation were the gold standards to detect infants at risk of respiratory failure.

2.10 Data Analysis

Statistical analysis was performed by the SPSS software (IBM SPSS Statistics, Version 23.0, IBM Corp., Armonk, NY, USA). The mean of quantitative variables between the two groups was compared using an independent *t*-test or Mann-Whitney U test, depending on the assumption about data distribution. Chi-square test and Fisher's exact test were used to compare qualitative variables between the studied groups. Quantitative data are expressed as mean $\pm$ standard deviation (SD). A *p*-value below 0.05 was considered statistically significant (at 95%).

3. Results

In this study, 14 of 169 mothers were excluded from the study, and the remaining 154 mothers were randomly equally divided into the intervention and control groups. Of 77 newborns in each group, 40 infants in the control group and 31 infants in the intervention group were eventually excluded from the study for different reasons as mentioned in Fig. 1. Finally, 37 infants in the control group and 46 infants in the intervention group were included in the study.

In the control group, 51.4% were boys and 48.6% girls, and in the intervention group, 53.3% were boys and 46.7% were girls. The results showed no statistically significant difference between the two groups in terms of gender ($p = 0.673$) and type of delivery (cesarean section and normal vaginal delivery) ($p = 0.299$). However, in both groups, the rate of cesarean delivery was higher. The mean duration between vitamin D injection and delivery was overall 23.68 $\pm$ 9.78 h in intervention group.

The mean weight of neonates in the control and intervention groups was 2017.64 $\pm$ 651.11 g and 2624.56 $\pm$ 639.70 g, respectively, and the difference between the two groups was significant. The mean gestational age was 34.81 $\pm$ 1.88 weeks in the control and 35.60 $\pm$ 1.87 weeks in the intervention group, with no significant difference.

The mean level of 25-hydroxy vitamin D of mothers in the control and intervention groups was both less than 30 ng/mL, and there was no significant difference between the two groups. However, there was a significant difference between the two groups in terms of infant's weight, 1-minute and 5-minute Apgar score, and maternal age. The details are provided in Table 1. Comparing two groups of neonates without respiratory distress and neonates with non-specific respiratory distress in terms of gestational age, weight, parity, maternal age, and serum levels of vitamin D in neonates and mothers showed no significant difference between the two groups.

On the mothers' side, a significant difference was observed between the two groups of mothers who received 25-hydroxy vitamin D and the control group, in terms of non-specific respiratory distress incidence in infants and improvement within less than 12 h. The results also indicated that maternal intake of 25-hydroxy vitamin D significantly reduced the incidence of non-specific respiratory distress in the infants (Table 2).

4. Discussion

Our results showed that injecting 50,000 units of 25-hydroxy vitamin D to a mother at risk of preterm delivery can reduce the transient respiratory problems of the infant. This result indicates the significance of vitamin D in accelerating the maturation of the lungs of newborns. Moreover, we may conclude that vitamin D enhances the development of the cardiorespiratory system and the successful transition from fetal to neonatal life during the delivery process. In the present study, for the first time, we investigated the effect of vitamin D on non-specific neonatal respiratory problems. We hope this study is a prelude to new efforts on reducing the respiratory problems of preterm infants. To the best of our knowledge, there is no similar study in the literature.

However, several articles on animals have suggested the role of vitamin D in fetal lung maturity [3,9]. A systematic review conducted in 2015 concluded that vitamin D stimulates fetal lung maturation in animals. These data support the hypothesis that vitamin D deficiency is a risk factor, as well as modifiable RDS and BPD [5]. Our results are consistent with those of this article in terms of improved lung function and faster adaptation to the extrauterine environment owing to vitamin D. This vitamin may also help to transform fetal lungs into neonates' by protecting the integrity of the pulmonary epithelial barrier in the premature or near-term infants. Lack of vitamin D receptors in the pulmonary epithelial barrier leads to acute lung injury caused by lipopolysaccharides. Vitamin D treatment reduces lipopolysaccharide-induced lung damage and

Table 1. Comparison of neonatal and maternal characteristics between the control and interventional group.

Variable	Control (Mean ± SD)	Intervention (Mean ± SD)	p value^{+}
Gestational age (weeks)	34.81 ± 1.88	35.60 ± 1.87	0.058
Weight (gr)	2017.64 ± 651.11	2624.56 ± 639.70	<0.001*
Maternal age (weeks)	29.56 ± 4.55	33.02 ± 6.19	0.004*
Parity	1.81 ± 0.93	2.24 ± 1.33	0.089
Apgar 1-minute	7.48 ± 1.87	8.32 ± 1.63	0.027*
Apgar 5-minute	8.98 ± 0.92	9.64 ± 0.81	0.001*
maternal 25(OH) vitamin D (ng/mL)	18.81 ± 11.40	23.68 ± 9.78	0.053
Neonatal 25(OH) vitamin D (ng/mL)	20.10 ± 13.58	20.95 ± 14.24	0.805

$^{+}$ Using an independent t-test. * $p < 0.05$ was considered statistically significant.

Table 2. Comparison of neonates in terms of non-specific respiratory distress between the control and intervention groups.

25(OH) vitamin D administration (mother)	No respiratory distress	Non-specific respiratory distress	p value^{+}
Control	21 (56.8%)	16 (43.2%)	0.001*
Intervention	41 (89.1%)	5 (10.9%)	

$^{+}$ Using chi-square test. * $p < 0.05$ was considered statistically significant.

maintains the alveolar barrier function. Thus, vitamin D treatment has been suggested as a potential treatment strategy in acute lung injury and RDS [12].

Hansdottir *et al.* [13] reported that the effects of vitamin D are very broad, including increased secretion of cathelicidin antimicrobial peptide, decreased chemokine production, inhibition of dendritic cell activation, and altered T-cell activation. All these cases effectively reduce inflammation and lung damage and are more important in preterm and near-term infants who are more prone to inflammatory conditions and lung damage. Numerous studies have indicated vitamin D deficiency as a risk factor for respiratory problems, such as RDS and TTN, in preterm infants [2,6].

A successful transition from fetal to neonatal life at delivery requires a series of extensive physiological changes in the cardiorespiratory system, leading to an adjustment in the gas exchange pathway from the placenta to the lungs. Replacement of intra-alveolar fluid with air, initiation of regular respiration, and increased pulmonary blood circulation are the most critical respiratory changes at birth. In this regard, normal and term labor are two fundamental factors that facilitate this important process. Numerous mechanisms are involved in alveolar fluid clearance, including the delivery process, initial respiration, and thoracic pressure. Secretion of chloride during pregnancy is vital in lung growth and development. In late pregnancy, the lung epithelium changes from the active secretion of chloride and fluid into the airways to the active absorption of sodium and fluid in response to the increased concentrations of catecholamines and other hormones. Increased oxygen pressure at birth increases sodium transfer and expression of the epithelial sodium channel gene and causes a high absorption of alveolar fluid [3,14].

Early effective breaths cause high transpulmonary pressures. The mean esophageal pressure is estimated to be –52 cm H_2O during inhalation and 71 cm H_2O during exhalation in the term infants. Increased pulmonary blood circulation occurs due to increased systemic vascular resistance and decreased pulmonary vascular resistance [14]. In a study, 49%, 78%, and 100% of infants over 35 weeks had complete airway clearance at 2, 4, and 24 h postpartum, respectively [15]. Prematurity and vitamin D deficiency may be two predisposing factors that delay this process, leading to respiratory distress in the early hours of life in preterm and near-term infants, although it lasts less than 12 h and all laboratory and radiological evaluations are normal. This phenomenon, which occurs probably due to the prolongation of the transition phase from the fetal stage to the neonatal, was called “non-specific respiratory distress”. Expression of vitamin D receptors in the lungs in late pregnancy in animals highlights the role of vitamin D in alveolar maturation [5]. Further, vitamin D may be involved in postpartum lung growth and alveolarization, but the evidence is limited in this regard. Premature infants have lower levels of 25-hydroxy vitamin D at birth and are at greater risk than term infants for postpartum vitamin-D deficiency. This problem, which is due to intestinal failure and comorbidities, theoretically puts them at risk for acute and chronic lung diseases [16].

According to our results, 25-hydroxy vitamin D injection into the mother improved the 1-minute and 5-minute Apgar scores in infants. Vitamin D affects the airways through several mechanisms, including increased resistance and airway smooth muscle mass, pulmonary parenchyma density, and alveolar septa [17]. Its effects on surfactant production have also been supported in human studies [18]. All of these can be considered effective factors in improv-

ing the neonatal Apgar score. A significant correlation was observed in another study between vitamin D levels and the 1-minute and 5-minute Apgar scores [6]. In a study, maternal vitamin D intake improved the 1-minute and 5-minute Apgar scores in the neonates [19]. However, Amegah *et al*. [20] reported that the relationship between vitamin D and Apgar score is contradictory.

Nevertheless, strongly attributing the incidence of these disorders in infants to vitamin D deficiency needs more research on the role of vitamin D in neonatal respiratory diseases. More research should also be done on the pathophysiology and cause of NRDS to prevent the occurrence.

The most significant limitation of the present study was the lack of measurement of vitamin D level before the administration. The second main limitation was that we did not control the injection time interval until delivery, which can explain the lack of difference in the serum vitamin D levels in infants of the two groups.

5. Conclusions

The results of the present study showed that a single injection of 25 hydroxyvitamin D to mothers with labor symptoms after the 31st week of pregnancy reduces transient respiratory problems in their infants. Therefore, proper vitamin D supplementation during pregnancy may reduce the respiratory problems of the neonates, although more studies are still required.

Statement

All methods were performed in accordance with the relevant guidelines and regulations.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

HB and NP participated in the design of the study. Statistical analyses were conducted by AD and MRS. All authors contributed to the interpretation of the results. NP and MHAN contributed to the drafting of the manuscript. All authors also contributed to the critical revision of the manuscript for important intellectual content, approved the final version, and are accountable for the integrity of its content.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Mashhad University of Medical Science (Ethics code: IR.MUMS.MEDICAL.REC.1399.613). The researchers obtained informed consent from the participating patients. The study was registered in the Iranian Clinical Trial Registration Center (IRCT20110807007244N7).

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Conflict of Interest

The authors declare no conflict of interest.

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