Short-term Outcomes of Launching Mother’s Milk Bank in Neonatal Intensive Care Unit: A Retrospective Study

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Abstract

**Background:** The WHO and UNICEF have suggested pasteurized donor milk (PDM) as the best alternative for infants who do not receive enough milk from their mothers.

**Objective:** This study aimed to assess the short-term outcomes of launching the first mother’s milk bank in North-West of Iran.

**Methods:** The present retrospective study included 366 premature infants (181 pre-launch and 185 post-launch) who were hospitalized in Al-Zahra Hospital of Tabriz, Iran. The study included infants with birth weight <2000 g and/or gestation age <32 weeks who were born before and after the launch of mother’s milk bank. Frequency of necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), late onset sepsis (LOS) and mortality rate were compared. Data were analyzed using SPSS 23 with the chi-square test, Fisher exact test, independent t test, and logistic regression test.

**Results:** In total, NEC grade ≥ 2 was reported in 9 cases; 8 cases (4.41%) in pre-launch and one case (0.54%) in post-launch (adjusted OR = 0.091; 95% CI = 0.010 to 0.849, P = 0.035). ROP was reported in 21 cases in two groups. Nineteen cases (10.5%) belonged to the pre-launch group and 2 cases (3.7%) to the post-launch group (adjusted OR = 0.105; 95% CI = 0.022 to 0.488, P = 0.004). LOS was also found in 17 cases (9.39%) in the pre-launch group and 4 cases (2.16%) in the post-launch period, suggesting a significant difference between the two groups (adjusted OR = 0.297; 95% CI = 0.089 to 0.995, P = 0.049). There was no significant difference in mortality of infants during hospitalization between the two groups (P = 0.789); however, it was decreased from 15 to 8.

**Conclusion:** Launching the human milk bank significantly improved the outcomes of premature infants.

**Keywords:** Milk bank, NICU, Premature infants, Short-term outcomes

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Introduction

Nutrition by human milk is fundamental for the growth and development of premature infants.1-6 The best food for each infant is his or her mother's own milk as suggested by World Health Organization (WHO) guideline on optimal feeding of low birth-weight infants.7 Feeding with human milk has protective effects against inflammations and infections.8 On the other hand, feeding with formula is a great danger for the death and morbidity of infants, especially premature ones.9 The risk of necrotizing enterocolitis (NEC) in high-risk infants, particularly in very low birth weight preterm newborns, increases with the use of artificial formula when compared to feeding with mother’s milk.10,11 Investigations have shown that donor milk in premature infants also protects them from NEC and infections.12 Other studies have suggested the benefits of using donor milk on long-term outcomes such as improvement in the cognitive function, neurological development, and lowering the risk of cardiovascular diseases.13-16 Another study in the United Sates has also indicated that those premature infants who are fed only by human milk without formula had a significantly lower rate of mortality.9 The American Academy of Pediatrics and the WHO recommend that every preterm infants should take human milk and that pasteurized donor milk (PDM) should be used if mother’s milk is nonexistent or its use is contraindicated.7,17 Despite limitations in assessing the effectiveness of utilizing donor milk, there is an increasing trend to use human milk in hospitals because the benefits of human milk are obvious.18 However, despite several investigations on the short- and long-term outcomes of donor milk (DM), few surveys have been conducted to analyze other potential advantages of access to DM in
neonatal units. In Iran, the first human milk bank was launched in Al-Zahra teaching hospital of Tabriz in July 2016.

The aim of this study was to assess the effect of establishing a mother’s milk bank on short-term outcome of premature infants. We hypothesized that feeding preterm infants with DM decreases the risk of short-term outcomes including NEC as the primary outcome as well as retinopathy of prematurity (ROP), late onset sepsis (LOS), and mortality rate as secondary outcomes.

**Materials and Methods**

**Design**

In this retrospective study, all premature infants admitted in the neonatal intensive care unit (NICU) of Al-Zahra teaching hospital of Tabriz who met the inclusion criteria were recruited from six months before launching the human milk bank (January 2016–June 2016) to six months after the launch (July 2016–December 2016). The inclusion criteria were birth weight < 2000 g and/or gestation age <32 weeks at birth, and being hospitalized in the NICU. Cases with any major congenital anomalies such as gastrointestinal anomalies, congenital heart diseases (CHDs), chromosomopathies, genetic disorders, and hypoxic ischemic encephalopathy were excluded from the study.

Based on a study by Vazquez-Roman et al., the sample size was calculated using the formula to estimate the difference between two proportions \[ \alpha = 0.05, \beta = 0.15, p_1 = 8.3\% \] (proportion of NEC before operation of the human milk bank), \[ p_2 = 2\% \] (proportion of NEC after operation of the human milk bank). It was calculated equal to 176 individuals; by estimating a drop-out rate of 3%, the final size was calculated at 181 infants for each group.

**Setting**

We performed a retrospective study to evaluate the short-term outcome of launching a human milk bank in the NICU on hospitalized premature infants. Availability of PDM following establishment of a human milk bank in the neonatal unit was the intervention that could meet the full needs of the population under survey. The primary outcome was the frequency of NEC and the secondary outcomes consisted of mortality rate during hospitalization, ROP, and LOS defined as: “positive result for blood or other sterile fluid of body cultures after 72 h from birth with clinical findings”, which were compared between the two groups.

**Samples**

During the pre-launch period, the enteral feeding of the infants consisted of their mother’s own milk (MM), infant formula and unpasteurized donor milk (UPDM) (prepared by the freeze thawing method: freezing at -20 degrees Celsius for 72 hours and then thawing in refrigerator for around 8 hours), separately or combined. After launching the donor milk bank, in addition to the mother’s own milk, PDM was used if needed at least during the first four weeks of life and use of UPDM and formula was stopped. All infants received total parenteral nutrition until enteral feeding provided at least half of the daily caloric needs of the infants. The criterion for discharge from the unit was the same during study period.

**Measurement**

Hospital information system and questionnaires were used to collect data. Maternal data included age, type of delivery, and place of residence (urban or rural) and their risk factors such as consanguineous marriage, hypertension, preeclampsia, maternal diabetes, thyroid disorders, history of intra-uterine fetal death, history of infertility, in-vitro fertilization, premature rupture of membrane, using prenatal steroids, and addiction were recorded. Infants’ characteristics such as gestational age, gender, first and fifth minutes APGAR score and resuscitation needs were also recorded.

Data about the type of milk used for feeding of infants included MM, artificial formula (F), PDM, UPDM. The data were recorded by the nursing staff in NICU charts and extracted by a research nurse at the end of each day.

**Data Analysis**

To evaluate normal distribution of data, we used the Kolmogorov-Smirnov test, normal probability plot, and measures of dispersion (standard deviation, skewness, kurtosis). Descriptive statistics including frequency and mean (SD) were utilized for data description. To compare maternal- neonatal features, the chi-square and Fisher’s exact tests were used for qualitative and the Independent \( t \) test was used for quantitative variables. To compare neonatal outcomes such as NEC, ROP, LOS, and mortality in premature infants in both groups, inferential data including bivariate, chi-square, and multivariable logistic regression with enter strategy were used. All confounders (all maternal and neonatal factors could influence both the exposure and the outcomes according to subject-matter knowledge) were entered into the model. The Hosmer–Lemeshow test was used to test the fit of the model. \( P < 0.05 \) was considered as statistically significant.

**Results**

In the current investigation, we recruited 198 preterm infants during the 6 months before launching the human milk bank, and 201 infants during the 6 months afterwards. During the period of the study, out of 198 infants, 8 were excluded due to major congenital anomalies and CHD who were transferred to a pediatric hospital, and 9 others died within 72 hours after birth. In the post-launch phase, 6 infants died within 72 hours after birth and 10 were excluded due to major congenital anomalies and CHDs, or being transferred to a pediatric hospital for surgical problems. Finally, 366 infants (181 and 185 infants, respectively for the pre- and post-launch
phases) were included (Figure 1). Due to twin or triplet childbirths, 166 mothers in the pre-launch phase and 159 in the post-launch phase were recruited. The average age of the mothers was 30.1 ± 6.2 years in the pre-launch group, and 29.9 ± 6.9 years in the post-launch group (P = 0.841). Both groups were homogenous (P > 0.05) in terms of demographics and maternal features, except for consanguineous marriage (P = 0.005) (Table 1).

Gestational age (weeks) did not have a significant difference between the two groups (P = 0.74). Infants were similar in the study groups in terms of gender (P = 0.599) and weight (P = 0.155). The mean ± SD of the first-minute APGAR score was 4.4 ± 2.2 in the pre-launch group, and 6.8 ± 2.1 in the post-launch group, which showed no statistical significance (P = 0.075).

In the pre-launch group, 33 (18.2%) infants were fed only their MM, 98 (54.1%) both artificial formula and MM, 23 (12.7%) MM and UPDM, 19 (10.5%) UPDM and artificial formula and MM, and 8 others only UPDM. In the post-launch group, 168 (90.8%) were fed both MM and PDM, 14 (7.6%) MM, and the other 3 only PDM (Table 2). Neonatal feeding with PDM and MM was continued for at least the first 28 days of life and if possible, until discharge. It was the parents’ preference to ask for PDM instead of formula if the mother did not have enough milk.

Stage 3 or higher ROP was reported in 21 cases across both groups, including 19 (10.5%) in the pre-launch group and 2 (3.7%) in the post-launch group; the difference was significant after adjustment of confounding variables (adjusted OR = 0.105; 95% CI = 0.022 to 0.488, P = 0.004). We found that the odds for ROP decreased 89.5% after launching the human milk bank.

The frequency of grade 2 or higher NEC was significantly different between the groups after adjustment of confounding variables. In the pre-launch group, eight premature infants (4.4%) and in the post-launch group, one infant (0.5%) had significant NEC (adjusted OR = 0.091; 95% CI = 0.010 to 0.849, P = 0.035). The rate of NEC decreased by 91% in the post-launch group compared to the pre-launch group. We also found that in the pre-launch group, 17 infants (9.4%) and in the post-launch group, 4 infants (2.2%) had LOS which was significant after the adjustment of confounding variables (adjusted OR = 0.297: 95% CI = 0.089 to 0.995, P = 0.049). In the current study, LOS was defined as symptoms compatible with sepsis with a positive culture of blood or other sterile body fluids after 72 h from birth time.20 In this study we, excluded the cases of early onset sepsis (EOS) which means a positive culture of blood or other sterile body fluid during the first 72 hours. Here, the presence of mothers’ milk bank was associated with a 70.3% decrease in the risk of LOS among premature infants.

The mortality of infants 72 hours after birth was not significantly different between the two groups (P = 0.789); however, the number of deaths in the pre-launch group decreased from 15 to 8 in the post launch group (Table 3).

Discussion
Establishment of the mother’s milk depository in the NICU facilitates early initiation of enteral feeding in preterm infants without the need to wait for MM to become available. This is the most important benefit

Table 1. Maternal Characteristics in Two Groups of Preterm Infants before and after Launching the Breast Milk Bank

| Characteristics                        | Before Milk Bank (n = 166) | After Milk Bank (n = 159) | P Value |
|----------------------------------------|----------------------------|---------------------------|---------|
| Maternal age (y), mean (SD)            | 30.1 (6.2)                 | 29.9 (6.9)                | 0.841*  |
| Residence                              |                            |                           |         |
| Urban                                  | 137 (82.5%)                | 138 (86.7%)               | 0.246*  |
| Rural                                  | 29 (17.4%)                 | 21 (13.2%)                |         |
| Mode of delivery                       |                            |                           |         |
| Vaginal                                | 41 (24.6%)                 | 26 (16.3%)                | 0.052*  |
| Cesarean section                       | 125 (75.3%)                | 133 (83.6%)               |         |
| Drug abuse                             | 0 (0%)                     | 1 (1.5%)                  | 1.000*  |
| Consanguineous marriage                | 18 (10.8%)                 | 5 (3.1%)                  | 0.005*  |
| Hypertension                           | 32 (19.2%)                 | 39 (7.8%)                 | 0.430*  |
| Preeclampsia                           | 53 (31.9%)                 | 60 (37.7%)                | 0.572*  |
| Thyroid disorders                      | 7 (4.2%)                   | 16 (10.06%)               | 0.83*   |
| Mother diabetes                        |                            |                           |         |
| Diabetes mellitus                      | 2 (1.2%)                   | 4 (2.5%)                  | 0.507*  |
| Gestational diabetes mellitus          | 7 (4.21%)                  | 11 (6.9%)                 | 0.456*  |
| Other diseases                         | 0 (0%)                     | 7 (4.4%)                  | 0.015*  |
| Assisted reproductive techniques       | 3 (1.8%)                   | 7 (4.4%)                  | 0.337*  |
| Infertility                            | 13 (7.8%)                  | 8 (5.0%)                  | 0.268*  |
| Intra-uterine fetal death              | 4 (2.4%)                   | 0 (0%)                    | 0.06*   |

*Independent t test; *Fisher’s exact.
Table 2. Neonatal Characteristics and Perinatal Interventions in Two Groups of Preterm Infants before and after Launching the Breast Milk Bank

| Characteristics                      | Before Milk Bank (n = 181) No. (%) | After Milk Bank (n = 185) No. (%) | P Value |
|--------------------------------------|-----------------------------------|----------------------------------|---------|
| Gender                               |                                   |                                  | 0.599<sup>a</sup> |
| Male                                 | 98 (54.1)                         | 106 (57.3)                       |         |
| Female                               | 83 (45.9)                         | 79 (42.7)                        |         |
| Gestational age (wk)                 |                                   |                                  | 0.240<sup>c</sup> |
| 20–24                                | 1 (0.6)                           | 1 (0.5)                          |         |
| 24–28                                | 39 (21.5)                         | 24 (13.0)                        |         |
| 28–32                                | 141 (77.9)                        | 160 (86.5)                       |         |
| Weight at birth (g)                  |                                   |                                  | 0.155<sup>c</sup> |
| Under 1000                           | 34 (18.7)                         | 27 (14.5)                        |         |
| 1000–1500                            | 72 (39.7)                         | 63 (34.05)                       |         |
| 1500–2000                            | 75 (41.4)                         | 95 (51.3)                        |         |
| Apgar 1/ mean (SD)                   | 4.4 (2.2)                         | 6.8 (2.1)                        | 0.075<sup>a</sup> |
| Apgar 5/ mean (SD)                   | 8.1 (1.7)                         | 8.5 (1.5)                        | 0.008<sup>b</sup> |
| PPROM                                |                                   |                                  | <0.001<sup>c</sup> |
| No                                   | 117 (64.6)                        | 171 (92.4)                       |         |
| >18 h                                | 42 (23.2)                         | 5 (2.7)                          |         |
| <18 h                                | 22 (12.2)                         | 9 (4.9)                          |         |
| Use of steroids during pregnancy     |                                   |                                  | < 0.001<sup>c</sup> |
| No use                               | 11 (6.1)                          | 1 (0.5)                          |         |
| Complete use                         | 96 (53.0)                         | 103 (55.6)                       |         |
| Incomplete use                       | 74 (40.8)                         | 81 (43.7)                        |         |
| Meconium staining                    | 3 (1.7)                           | 1 (0.5)                          | 0.368<sup>b</sup> |
| Neonatal feeding at least during the first 28 days of life | | | < 0.001<sup>c</sup> |
| 1. MM                                | 33 (18.2)                         | 14 (7.6)                         |         |
| 2. MM+F                              | 98 (54.1)                         | 0 (0)                            |         |
| 3. PDM                               | 0 (0)                             | 3 (1.6)                          |         |
| 4. MM + PDM                          | 0 (0)                             | 168 (90.8)                       |         |
| 5. MM + UPDM                         | 23 (12.7)                         | 0 (0)                            |         |
| 6. UPDM+MM+F                         | 19 (10.5)                         | 0 (0)                            |         |
| 7. UPDM                              | 8 (4.4)                           | 0 (0)                            |         |
| CPR                                  |                                   |                                  |         |
| Routine care                         | 45 (24.9)                         | 82 (44.3)                        | < 0.001<sup>b</sup> |
| The first steps of the resuscitation | 59 (32.6)                         | 55 (29.7)                        | 0.574<sup>b</sup> |
| CPAP                                 | 70 (38.7)                         | 105 (56.8)                       | 0.001<sup>b</sup> |
| PPV with bag and mask                | 28 (15.5)                         | 14 (7.6)                         | 0.021<sup>b</sup> |
| PPV through tracheal tube            | 53 (29.3)                         | 24 (13.1)                        | < 0.001<sup>b</sup> |
| Intubation and suction               | 5 (2.8)                           | 0 (0)                            | 0.029<sup>b</sup> |
| Comparison of chest                  | 2 (1.1)                           | 0 (0)                            | 0.244<sup>b</sup> |
| Drug epinephrine                     | 2 (1.1)                           | 0 (0)                            | 0.244<sup>b</sup> |

MM, Mother’s own milk; F, Formula; PDM, Pasteurized donor milk; UPDM, Unpasteurized donor milk; CPAP, continuous positive airway pressure; PPV, Positive pressure ventilation.

<sup>a</sup>Independent t-test; <sup>b</sup>Fisher’s exact; <sup>c</sup>Chi-square test.

of having human milk accessible from birth. Feeding endurance increases with use of mother’s milk (MM or PDM) compared to the formula. There is also evidence that feeding of preterm infants with formula enhances the risk of NEC, and several investigations have shown a relationship with other risks in the short- and long-term. In our study, most of the preterm infants in the pre-launch period were fed both artificial formula and MM (54.14%), but after launching the mother’s milk bank, the majority of infants received both MM and PDM (90.81%). It means that use of artificial formula was eliminated totally from the unit. This finding is consistent with the
Table 3. Comparison of Neonatal Outcomes before and after Launching the Milk Bank

| Outcome                                      | Before (n=181) No. (%) | After (n=185) No. (%) | Adjusted Odd Ratio* (95% CI) | P Value* | P-Value** |
|----------------------------------------------|------------------------|-----------------------|-----------------------------|----------|-----------|
| Retinopathy of prematurity stage 3 or higher | 19 (10.5)              | 2 (3.7)               | 0.105 (0.022 to 0.488)      | 0.004    | <0.001    |
| Necrotizing Enterocolitis grade ≥ 2          | 8 (4.4)                | 1 (0.5)               | 0.091 (0.010 to 0.849)      | 0.035    | 0.019     |
| Late onset sepsis                           | 17 (9.4)               | 4 (2.2)               | 0.297 (0.089 to 0.995)      | 0.049    | 0.003     |
| Death                                        | 15 (8.3)               | 8 (4.3)               | 0.860 (0.286 to 2.586)      | 0.789    | 0.135     |

*Logistic regression adjusted for Apgar, PPROM, Delivery mode, Use of steroid, CPR, Neonatal feeding, history of intra-uterine fetal death, weight at birth, and gestational age.

*Adjusted P value; ** Non-adjusted P value

Hosmer and Lemeshow Test: Chi-square = 10.788; df = 8; P = 0.215

findings of Vazquez-Roman and colleagues who reported the clinical effect of inauguration of a human milk bank in a NICU in 2014.19 They presented a before and after survey of the inauguration of a human milk bank, and two groups of preterm infants ≤ 32 weeks of gestational age were studied. They reported that after launching the mother’s milk bank, none of the preterm infants initiated feeding with preterm formula.

In the study by Vazquez-Roman et al, disposal to formula in the prime of 15 days of life was diminished from 50% to 16.6%, and its use during the first 28 days of life was significantly decreased after launching the mother’s milk bank.19 After launching the human milk bank, we did not use formula totally until discharge from hospital because of the availability of donor milk and family preference. We did not record the starting time of feeding with mother’s milk in the unit; however, after launching the human milk bank in the study by Vazquez-Roman et al, enteral nutrition was started 31 hours earlier (P<0.001), enteral feeding of 100 mL/kg/d was achieved 59.5 hours sooner (P<0.001) and volume of 150 mL/kg/d 52 hours earlier (P=0.002).

There is some concern that establishing mother’s milk banks in NICUs may lead to a drop in the rate of breastfeeding by mothers’ own milk or the mother’s desire for expressing mother’s milk for their infants. In our study, in the pre-launch group, 33 infants (18.23%) were fed only their MM which decreased to 14 (7.56%) in the post-launch period. In the study by Vazquez-Roman et al, MM intake was greater after initiating the bank in the primary days of life, but there was no significant difference during the hospitalization. So, it is a warning for the units with mother’s milk banks to try harder to promulgate breastfeeding in the units. Training the
nursing staff, facilitating skin to skin contact, supporting and encouraging mothers to feed their infants in the first days of life, and facilitating the expression of human milk by pumps can help mothers to prepare MM for their infants, regardless of the accessibility of DM.18,21 On the other hand, the 7.56% use of MM combined with the 90.81% use of mixed breastfeeding during hospital stay can be considered a success in our study. Arslanoglu et al evaluated a total number of 4277 very low birth weight infants in 83 Italian NICUs and found monopolized breastfeeding rate at discharge was significantly greater in NICUs with a human milk bank (HMB) than in NICUs without it (29.6% vs. 16.0 %, respectively).22

The rate of NEC was significantly different between the study groups and showed a significant decrease in the post-launch group (P=0.035). A study by Quitadamo et al also confirmed the protective impact of nutrition with mother’s or DM against NEC in low-birth weight infants.13 In a systematic review and meta-analysis, Miller and colleagues reviewed the literature after the year 1990 and evaluated the impact of human milk on morbidities, chiefly NEC, LOS, ROP, bronchopulmonary dysplasia, and neurodevelopment in infants born ≤28 weeks of gestation and/or average birth weight of ≤1500 g. Human milk demonstrated a clear protective impact on NEC, with an approximately 4% decline in occurrence. Human milk also caused a possible decline in LOS, severe ROP and severe NEC. Especially for NEC, any quantity of human milk is better than preterm formula, and greater volume will be more protective.23 A recent Cochrane Systematic Review showed that nutrition with formula in preterm infants (instead of donor mother’s milk when mother’s own breast milk does not exist) is related to rapid rates of growth, but with a near-doubling of the risk of progression of NEC.24 According to a research by Larena et al, after launching the mother’s milk bank, premature infants’ length and head circumference were significantly greater in comparison to premature infants in the pre-launch group. The occurrence of NEC was lower after the implementation of the milk bank.25 Fortunately in our unit, after training the nursing staff and families about the significance of the mother’s milk and its effect on short- and long-term outcome of the infants, they preferred to use human milk (MM, PDM, or mixed).

In the current study, the rate of ROP was significantly decreased in the post-launch group compared to the pre-launch period (P=0.004). In a study by Kreissl et al in Australia, ROP decreased from 13% to 4%, using DM in premature infants (P<0.01).26 This finding is in line with the findings of present study. A systematic review and meta-analysis by Miller et al found that totally, there is inconclusive evidence for the impact of any human milk vs. preterm infant formula on either ROP or severe ROP.22

The rate of LOS also had a significant decrease after launching the milk bank in this study (P=0.049). Our results appear consistent with many other studies. In Korea, Kim et al showed that in the donor milk group, the rate of LOS was significantly decreased.12 Other systematic reviews and meta-analyses have also found that feeding with mother’s milk significantly decreased LOS.24,27-29 A study by Cortez et al in the United States indicated that a smaller number of infants who were fed mother’s milk suffered from LOS compared to the group fed formula (9 vs. 19, P<0.05).30 Compared to formula, the mother’s or donor milk prevented LOS in premature infants.12,30 There was a relation between infection and nutrition in LBW and premature infants.31 Different studies have suggested a relation between infection and nutrition among premature and low-weight infants.32 The American Academy of Pediatrics suggested that in case of inaccessibility of mother’s milk in low-weight infants, it is advised to use donor milk because using donor milk significantly decreases infections and bronchopulmonary dysplasia compared to formula.15

The present study indicated that the rate of mortality among premature infants decreased from 15 in the pre-launch group to 8 cases after launching the milk bank, but this reduction was not statistically significant.

**Limitations**

The present study did not investigate bronchopulmonary disease or long-term outcomes such as neurodevelopment of premature infants using donor milk. This study was a retrospective case-control study; therefore, the relationship between study variables does not necessarily indicate a cause-effect relationship. Moreover, there is the possibility of sparse-data bias as an important limitation of the study due to very small counts as well as unrealistic very small OR estimates. So, readers should be attentive to this important and common problem in interpreting results in clinical research.33

In conclusion, launching a mother’s milk bank in the NICU significantly decreased the frequency of NEC grade ≥2, ROP, and LOS in premature infants with less than 32 weeks of gestation or 2000 g of weight. We suggest the implementation of human milk banks in other NICUs in Iranian hospitals.

**Authors’ Contribution**

Study concept and design: MBH, AZ, AFKh, NF; Acquisition, analysis and interpretation of data: AZ, NF, NH, ShT; Drafting of the manuscript: AZ, NF, NH, ShT; Critical revision of the manuscript for important intellectual content: MBH, AFKh; Statistical analysis: AFKh, AZ. All authors have read and approved the manuscript.

**Conflict of Interest Disclosures**

The authors of this research state no conflict of interest.

**Ethical Statement**

The research was confirmed by the committee of ethics of Tabriz University of Medical Sciences (TUOMS) (IR.TBZMED.REC.1397.876).

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