Packed Cell Transfusion and Feeding Tolerance in Well Preterm Infants: A Randomized Clinical Trial

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Abstract

Background: The correlation between necrotizing enterocolitis (NEC) and packed cell transfusion (PCT) has recently been identified. Based on some research, 25–35% of NEC has been linked to transfusion, we planned this study to determine, the association between PCT and feeding tolerance in well preterm newborns.

Method: Our study was a clinical trial study in preterm infants admitted to NICU of Mofid Children's Hospital from April 2017 to May 2018. Seventy well premature babies with a birth weight of <1500 grams and gestational age <32 weeks with enteral feeding, who need PCT were enrolled. The eligible patients divided by simple randomization to two groups, in the intervention group (35 patients) the baby's breastfeeding withholding just during the time of PCT and continue as usual after that, but in control groups (35 patients) feeding of neonates is given as usual regardless of PCT. The feeding tolerance during the first 72 hours after transfusion was compared between the two groups. Sick neonates exclude from the study. Data analysis was performed in SPSS version 20.

Results: The mean gestational age, birth weights, and postnatal age in the intervention group were 30.13 weeks, 1245.71 grams, and 17 days respectively and in the control group were 29.97 weeks, 1169.43 grams and 15.46 days respectively without any statistically significant difference between them. Except for hemoglobin and hematocrit pre-transfusion, other characteristics of patients were similar. In the evaluation of feeding tolerance after transfusion during 24, 48 and 72 hours, 32(91.2%), 33(94.73%), 34(97.1%) of both groups, had feeding tolerance with no significant difference. There were no statistically significant differences between neonates with and without the feeding tolerance in the patients of each group.

Conclusion: Our research showed that in well preterm neonates with a good general condition, during PCT, withholding of feeding, isn't necessary and continued breastfeeding seems to be safe.

Trial registration: All ethical considerations of the study were approved by the institutional review board and the research ethics committee at Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR. SBMU.RETECH.1395.1010) and granted ethical approval and the Iranian Registry of Clinical Trial code are IRCT20200419047136N1.

Approved by Iranian Registry of Clinical Trials

Trial Id: 47347

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Approved by Research Ethics Committee: IR. SBMU.RETECH.1395.1010
Background

One of the most important aspects of the care in premature infants is nutrition(1). Inability to oral feeding on the breast of the mothers with preterm delivery causes nutritional constraints in these high-risk babies(2). However by the gavage method, enteral feeding eliminates the nutritional needs of them, but the immaturity of the gastrointestinal tract(GI tract)can make the baby susceptible to some disorders such as necrotizing enterocolitis (NEC), dysmotility syndrome and feeding intolerance concurrent with sepsis, hypoxic-ischemic encephalopathy (HIE) or other common neonatal problems(3). NEC is a devastating complication of prematurity with a high rate of mortality and morbidities such as short bowel syndrome, failure to thrive, cholestasis, neurodevelopmental delay(4, 5).

So far, many risk factors have been identified for this disorder. Along with prematurity as the main risk factor, infection, inflammation, ischemia, feeding material, hyperviscosity is the other involved factors(6). In recent years, packed cell transfusion (PCT) in anemic preterm patients, is known as another risk factor of NEC during 48-72 hours after transfusion(5). Association between NEC and PCT as named TANEC (transfusion-associated NEC), was first defined from 1987 by McGrady et al, and following an outbreak of NEC in 33 preterm neonates was admitted to their neonatal intensive care unit. After that in 1998, Bednarek et al evaluated the transfusion practices in preterm neonates in six NICUs and they noted that lower incidence of NEC was observed at centers with fewer transfusions in comparison with the NICUS with a higher rate of transfusion(7). Since then, many researchers have been published their studies about this issue, such as a recent meta-analysis in 7 non-randomized clinical trials (RCT), that showed withholding the nutrition in peri-transfusion periods reduces the rate of NEC. Regard to the moderate quality of this research, they suggest adequately powered RCT for better results(8).

There is some hypothetical mechanism for the pathogenesis of TANEC such as immune mechanisms as responsible for the acute mucosal injury of the intestine by passive transfusion of biological response mediators from donor or activation of T-cell antigens of red blood cells(9). The other effective factors consist of the age of the blood products, the severity of anemia in the neonate, and the low levels of nitric oxides in stored red blood cells resulted in the vasoconstriction of the lower mesenteric vessels and decreased blood flow and resulted in mucosal injury(7). The changing of oxygenation in the vascular bed of the mesenteric system during the transfusion causes the disease(5). There are many studies with confounding and different results that evaluate the effect of holding of enteral feeding before during, and after the time of transfusion(10).

Unfortunately, until now, there is no specific protocol for the feeding of preterm neonates during the transfusion of the packed cell. Regard to the high probability of need to the PCT during the hospital course of these patients, the establishment of a precise and standard guideline, can help to provide the perfect care for improving the outcome of these babies. In spite of the majority of studies about the correlation between PCT and NEC, little research has been done about feeding intolerance (as a preliminary marker of NEC) and PCT especially in the well prematurely neonates. We planned this study...
for the assessment of the association between PCT and feeding tolerance in well preterm newborns admitted to the neonatal intensive care unit (NICU) of our hospital.

We hypothesize that feeding tolerance-related packed cell transfusion. Therefore, our study aimed to determine the correlation between packed cell transfusion and feeding tolerance in well preterm infants.

**Methods**

**Design**

This Quasi-experimental study was a randomized interventional clinical trial conducted in preterm infants admitted to the NICU of Mofid children's hospital from April 2017 to May 2018. Following the study by Qi Lu et al(5) with a confidence level of 95% and test power of 90% and according to the incidence of NEC in our study, 70 individuals were selected for this research, and they were divided into 35 participants for each group.

**Participants**

**Inclusion criteria:**

The inclusion criteria were all well premature babies with no abdominal distension and signs and symptoms of NEC, sepsis and birth weight of <1500 grams and gestational age <32 weeks with enteral feeding (per-oral or gavage) who needed PCT due to anemia. The postnatal age of neonates was not a limitation of enrollment in the study if enteral feeding was started in the patients.

**Exclusion criteria:**

Because of the multifactorial basis of feeding intolerance and NEC in preterm infants, for elimination, the effect of the other factors causing feeding problems rather than PCT, all sick patients, neonates with sepsis, history of previous feeding intolerance and NEC and neonates without enteral feeding exclude from the study and just well preterm infants which stay in the hospital for growing that needed to transfusion for severe anemia enrolled in the research.

**Randomization and Allocation:**

The randomization was performed using block randomization with the same block sizes by the central randomization unit at the Neonatal Health Research Center. All infants with inclusion criteria were allocated a number. Then the randomization numbers were given to the speech therapy student. He allocated eligible participants to intervention (A group) and control groups (A group) randomly. Every infant with code A withhold feeding during PCT and infants with code B had liberal feeding during the transfusion of the packed cell (Figure 1).

**Blinding:**
This study was a randomized, double-blind, controlled trial where neither the staff participants, care providers, those assessing outcomes (except for one researcher that run intervention) nor the researchers knew the randomization status of the participants during the study.

**Interventions**

Transfusion of the packed cell for the treatment of the anemic patients was ordered based on the restricted protocol of transfusion according to the general condition and cardiorespiratory status of the patients. Regarding that we select just well preterm neonates with no need for oxygen supplement or mechanical ventilation, based on the restricted protocols, hemoglobin lower than 7 g/dl and hematocrit lower than 21% was indicated for packed cell transfusion.

During the first 72 hours after transfusion, the feeding tolerance was evaluated by the report of special nurses of the patients and physical exams of them by attending neonatologist or responsible neonatal-perinatal fellowship of the NICU. The results of these measures were compared between two groups and any significant feeding intolerance means gastric residual more than 30-50% of feeding volumes, bilious vomiting, gastrointestinal bleeding, abnormal abdominal distension (detected by abdominal circumference measurement), necrotizing enterocolitis (NEC) were compared and analyzed between them. Despite the recommendations on the use of cytomegalovirus (CMV) negative and irradiated packed cells in very low birth weight infants, unfortunately, due to unavailability to these products we transfused our patients regardless of CMV status and unirradiated packed cell. The prescribed volume of the packed cell for transfusion was 10-15 cc/kg from a cross-matched product with the patients and preferentially not older than one week's age.

The material of feeding for the patients in our ward is the breast milk of own mother preferably. Given that we don't access to the milk bank, in the participants without access to breast milk inevitably preterm formula was used for the feeding of patients. When the volume of feeding was over 50 cc/kg-day, for the fortification of the milk, the human milk fortifier adds to breast milk.

**Outcomes**

The number of transfusions was not a limitation for enrollment in the analysis. In the patients with a history of the multiple packed cell transfusions at different times with an interval of more than one week, the analysis was done as the new participant. Feeding intolerance defined as gastric residual more than 30-50% of feeding volumes, bilious vomiting, gastrointestinal bleeding, abnormal abdominal distension (detected by abdominal circumference measurement) more than the normal examination of the neonate.

Variables such as birth weight, gestational age, postnatal age, sex, the level of hemoglobin and hematocrit before and after transfusion, blood group and Rh of the neonates, in two groups of intervention and control were assessed and the correlation between feeding tolerance and these variables with PCT were analyzed and compared.

**Data Analysis**
Data analysis was performed in SPSS version 20 (SPSS Inc., Chicago, IL) and the quantitative variables were expressed in mean and standard deviation (SD). In addition, repeated measures of ANOVA were used to evaluate the differences between the variables. P-value of less than 0.05 was considered statistically significant.

**Ethics Approval and Consent to Participate**

The present study was extracted from a thesis in pediatritionist at Shahid Beheshti University of Medical Sciences. All ethical considerations of the study were approved by the institutional review board and the research ethics committee at Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.RETECH.1395.1010) and granted ethical approval and the Iranian Registry of Clinical Trial code is IRCT20200419047136N1. All participants in the study were informed of the study objectives and signed a written informed consent form and were assured of the confidentiality of their personal information and the voluntary nature of participation.

**Results**

A total of 70 preterm infants were included in our research. The thirty-five (50%) neonates were in the intervention group and 35(50%) patients were in the control group. The comparison of demographic data between the intervention and control group were shown in Table 1. The mean gestational age, birth weights and postnatal age in the intervention group were 30.13 weeks (SD: 2.1), 1245.71 grams (SD: 256.736) and 17 days (SD: 23.42) respectively and in the control group were 29.97 weeks (SD: 2.32), 1169.43 grams (SD: 201.508) and 15.46 days (SD: 15.84) respectively without any statistically significant difference between two groups.

The mode of delivery in 91.4%(n=32) and 82.9%(n=29) patients in intervention and control group was caesarian section respectively with no significant difference (P=.239).

The mean level of hemoglobin and hematocrit before transfusion in the intervention and control was 8.25 mg/dl, 24.4 mg/dl, and 7.5 mg/dl, 22.6 mg/dl respectively with a statistically significant difference. (P=0.021 and 0.035 respectively), in the control group, there was a lower level of hemoglobin and hematocrit. The mean level of hemoglobin and hematocrit post-transfusion was 11.5 mg/dl and 33.8 mg/dl in intervention groups and 10.78 mg/dl and 31.95 mg/dl in the control group with no significant difference between two groups. (P=0.05 and 0.1 respectively).

As the table 1 showed there weren’t any significant statistically differences in sex (P=.595), gestational age(P=.784), birth weight(P=0.171), postnatal age at the time of transfusion(P=.739), the previous history of transfusion (P=.270) and mechanical ventilation(P=.401), blood group, and Rh of neonates (P=.368) and the feeding material (breast milk alone, formula, breast milk, and fortifier) (P=0.197) between two groups.
Interestingly, the most common blood group and Rh in neonates of both groups was B+ in 51.4% and 37.1% in the intervention and control group respectively.

Unfortunately, 60% and 57.2% of our preterm neonates in the intervention and control group respectively, were fed by the formula. This unacceptable percentage of neonates that are deprived of their mother's breast milk is an alarming sign for our healthcare providers for increasing their effort for enhancing the rate of breastfeeding.

In the evaluation of feeding tolerance after transfusion during 24 -72 hours, we monitor the feeding tolerance of the patients. In table- 2 we showed the comparison of the feeding tolerance during 1-3 days after transfusion, in the intervention and control groups.

The number of patients with feeding intolerance was very few and in 32(91.2%), 33(94.73%), 34(97.1%) of both of intervention and control groups, had no feeding intolerance and there was no statistically significant difference between two groups in feeding tolerance during 1,2 and 3 days after transfusion (P= 0.663, P= 0.693, P= 0.754). In spite of the higher number of exclusive formula-fed patients in the control group in relation to intervention groups (48.6% vs. 28.6%, P= 0.037), feeding intolerance was the same.

In another analysis of our data, we compare the feeding tolerance of patients in each group between the days one to three research periods. There was no correlation between the variables of postnatal age, the levels of hemoglobin and hematocrit pre and post-transfusion in feeding tolerance each day after transfusion of patients that participated in the research. (P> 0.05).

**Discussion**

Decreased the iron storage of preterm neonates at the time of birth, inability to enteral feeding with breast milk at the first days or weeks of life, frequent blood sampling and decreased the level of erythropoietin leading to anemia and packed cell transfusion frequently during the admission time of premature infants(11). Although packed cell transfusion is a lifesaving treatment modality, unfortunately can be lead to some complications. A recently known probable complication is NEC and feeding problems which for decreasing this complication, withholding enteral nutrition during the time of transfusion of preterm babies is suggested(8). In this clinical trial study, we aimed to evaluate the correlation between packed cell transfusions and feeding tolerance in well preterm infants. Our results showed that discontinuing feeding had no effect on the feeding tolerance of patients and it seems that the liberal protocol of feeding regardless of the time of transfusion in well premature babies is safe.

To remove, the effect of the other risk factors of feeding intolerance such as sepsis, NEC, HIE, we include just well premature infants without any history of mentioned problems. In some recent studies, 25–35% of NEC has been related to PCT(12). There is a lot of research on this issue but the results of them were inconclusive so far there isn't standard protocol for the feeding of preterm infants during transfusion(13).
Similar to our research, in the study by VT Le in case-crossover research for assessment of the NEC and the fortification and volume increase of milk, in 63 preterm infants<32 weeks of gestation, they did not detect any effect of the fortification and volume of the milk and GI problems(14), inversely some other studies such as Alfaleh showed that PCT was associated with the lower rate of NEC in preterm infants(15).

The mean age of the newborns in both of the intervention and control groups of our research was 17 and 15 days respectively, notably, the inclusion criteria of our research was well preterm infants, considering that, the first days of life in premature patients are concurrent with more systemic problems such as respiratory distress syndrome(RDS), need to mechanical ventilation and surfactant therapy or sepsis, which can cause feeding intolerance and confound the results of our research, most of our patients were older than 2 weeks which had a better general condition for including our research.

Many reports are indicating the impact of the delivery mode on the neonatal outcome of preterm babies. Intraventricular hemorrhage, hypoxic-ischemic encephalopathy (HIE), RDS are the neonatal problems affected by mode of delivery. Our research did not show any significant difference in the rate of NEC or feeding intolerance after transfusion in preterm babies delivered by C/S or NVD (P=.239) resembles the study by Monika Bajaj (P=0.37)(16).

Despite the emphasis on the feeding in preterm infants by expressed breast milk of own mothers Unfortunately, the overall rate of breastfeeding in the population of our research was 42%. Our hospital is a referral center without nursery and most of the patients referred from the distance areas, so we don’t access to breast milk all the times and due to the lack of milk bank in our hospital, the use of formula as an alternative substance is logical. In spite of the more using of formula in the control group of our patients, the rate of feeding intolerance was similar between the two groups.

There are inconclusive recommendations about the duration of withholding the nutrition and packed cell transfusion. Some research has recommended discontinuing enteral feeding in patients 1-4 hours before the time of transfusion, some the others studies don’t give milk to the baby during or after transfusion even to 24 hours later(7). We withheld feeding of neonates in intervention groups just during the transfusion and observed all patients in intervention and control groups 24-72 hours after transfusion, due to the definition of TANEC that is the appearance of the NEC during 48-72 hr after transfusion. As we mentioned we did not find any difference in feeding intolerance between two groups.

Anemia as an underlying risk factor for TANEC, cause the subclinical intestinal mucosal injury precedes the overt clinical signs and symptoms of enterocolitis. Probable mechanisms include immaturity of re-oxygenation injury in the anemic gut, the splanchnic vascular bed, and immune mechanisms similar to those seen in transfusion-related lung injury (TRALI)(17). Then transfusion of the packed cell may not be a primary cause of the intestinal injury rather, be an additive risk factor to underlying mucosal injury by severe anemia. By this hypothesis, the level of hemoglobin and severity of anemia can be effect the incidence of feeding intolerance.
Then, some research analyzed the effect of the level of hemoglobin on the occurrence of TANEC and resulted in a significant effect on the incidence and severity of the NEC. These studies concluded that lower levels of hemoglobin have been associated with an increased risk of NEC(18). In our research, the level of hemoglobin in the control group was significantly lower than the intervention group (7.56 mg/dl vs. 8.27 mg/dl, P=0.021), but there wasn’t any statistically significant difference in feeding intolerance between two groups. This result may be due to the low level of difference between the values of hemoglobin in two groups.

The study was done by Cris Derienzo in a retrospective cohort research in 148 very low birth weight infants; they compare transfusion-associated NEC (TANEC) with this problem without correlation with transfusion. They found that TANEC was observed in smaller premature patients and lower levels of hematocrit before transfusion, in other words, more severe anemia in premature infants was associated with a higher incidence of TANEC. The authors of this article recommended that in infants at higher risk of NEC, maintenance of the higher level of hemoglobin and hematocrit is a protective factor(19).

Also in research by Ravi M. Patel and colleagues in very low birth weight infants with the age of 0-5 days, they found that severe anemia (not packed cell transfusion) was associated with NEC(20). But in our study compared to this research, the mean age of neonates was higher than the age of our patients and the severity of anemia didn’t have any significant effect in the feeding intolerance.

The prolonged hospitalization time of preterm infants is concurrent with the repeated need for PCT. In our research 5(14.3%) of patients in intervention groups and 8(22.9%) of the control group had the previous history of transfusion without any significant effect on the rate of feeding intolerance. It is unclear whether repeated transfusion has an additive effect on feeding intolerance or NEC. However, the time interval between repeated transfusions is important for this effect. In research was done by Yu-Cheng Wang the number of RBC transfusions was higher in participants with NEC(21).

The limitation of our study was the low sample size of the patients, although, in spite of this limitation, the methodology of our research was suitable for judgment in this issue.

Conclusion

However, there is concern about the association between severe anemia and packed cell transfusion with NEC in preterm infants admitted in NICUs, but the precise timing of discontinuation of nutrition in neonates needed to packed cell transfusion, not yet been determined. While almost all research in this issue was done in sick preterm infants and evaluated the impact of PCT on NEC, there are little studies in well premature neonates with a stable condition for assessment of the feeding intolerance (not NEC) followed by PCT. Our randomized clinical trial study showed that in well preterm neonates with a good general condition, continuing the nutrition during the time of packed cell transfusion did not cause feeding intolerance and withholding of feeding, isn’t necessary then continued breastfeeding seems to be safe. However, in a sick preterm infant with other underlying risk factors for NEC, sepsis or GI problems, this result cannot be generalized.
Abbreviations

NEC: Necrotizing enterocolitis

PCT: Packed cell transfusion

NICU: Neonatal Intensive Care Unit

HIE: Hypoxic-ischemic encephalopathy

CMV: Cytomegalovirus

Declarations

Ethical approval and consent to participants:

The present study was extracted from a thesis in pediatritionist at Shahid Beheshti University of Medical Sciences. All ethical considerations of the study were approved by the institutional review board and the research ethics committee at Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR. SBMU.RETECH.1395.1010) and granted ethical approval and the Iranian Registry of Clinical Trial code are IRCT20200419047136N1. All participants in the study were informed of the study objectives and signed a written informed consent form and were assured of the confidentiality of their personal information and the voluntary nature of participation.

The trial Id was 47347 and Registration date was 2020-05-04, 1399/02/15IRCT Id. (The link directly for trial registration: [https://en.irct.ir/trial/47347](https://en.irct.ir/trial/47347))

Consent for publication: The written consent was obtained from the parents

Availability of data and materials:

The data of research are available.

Competing Interest: The authors have no conflicts of interest

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Authors contribution: Design study: MF, MK, Practical Performance: SHK, Data Dnalysis: ST, Manuscript Preparation: MF and ST, Critical Review Manuscript: NTT and MK

All authors have read and approved the manuscript.

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Tables

Table 1: Comparison of the demographic characteristic of the patients between intervention and control groups
| Variables                        | Intervention Group (NPO N=35) | Control Group (PO N=35) | P-Value |
|----------------------------------|------------------------------|------------------------|---------|
|                                 | Mean(SD)                     | Mean(SD)               |         |
| Gestational age(week)            | 30.11(2.083)                 | 29.97(2.256)           | 0.784   |
| Post-natal age(days)             | 17.06(23.422)                | 15.46(15.844)          | 0.739   |
| Birth weight(gram)               | 1245.71(256.736)             | 1169.43(201.508)       | 0.171   |
| Hemoglobin (pre-transfusion)     | 8.274(1.302)                 | 7.569(1.1829)          | 0.021   |
| Hematocrit (pre-transfusion)     | 24.494(3.6221)               | 22.620(3.6767)         | 0.035   |
| Hemoglobin (post-transfusion)    | 11.569(1.8293)               | 10.783(1.4480)         | 0.051   |
| Hematocrit (post-transfusion)    | 33.811(5.1211)               | 31.954(4.1299)         | 0.100   |
| Sex                              | Male 20(57.1%)               | Female 20(57.1%)       | 0.595   |
|                                 | Female 15(42.9%)             | 15(42.9%)              |         |
| Delivery mode                    | C/S 32(91.4%)                | NVD 6(17.1%)           | 0.239   |
| Blood Group/Rh                   | A 8(22.9%)                   | B 18(51.4%)            | 0.368   |
|                                 | AB 5(14.3%)                  | O 4(11.4%)             |         |
|                                 | A 8(22.9%)                   | B 13(37.1%)            |         |
|                                 | AB 10(28.6%)                 | O 6(17.1%)             |         |
| previous history of transfusion  | Yes 5(14.3%)                 | No 30(85.7%)           | 0.270   |
|                                 | No 30(85.7%)                 | 27(77.1%)              |         |
| Feeding material                 | Breast milk 11(31.4%)        | Breast milk 8(22.9%)   | 0.037   |
|                                 | Breast milk fortifier 3(8.6%) |Breast milk+ Formula 11(31.4%) |         |
|                                 | Formula 10(28.6%)            | 17(48.6%)              |         |
| Volume of feeding                | Full feed 6 (17.1%)          | No full feed 10(28.6%) | 0.197   |
|                                 | 29(82.9%)                    | 25(71.4%)              |         |
| History of mechanical ventilation| Yes 13. (37.1%)             | No 11(31.4%)           | .401    |
|                                 | No 22(62.9%)                 | 24(68.6%)              |         |

NPO: Nil per os, PO: Per oral

Table 2: Comparison of the feeding tolerance during 1-3 days after transfusion, in the intervention and control groups

| Feeding tolerance | Intervention group(n=35) | Control group(n=35) | P-value |
|-------------------|--------------------------|---------------------|---------|
| First 24 hour     |                          |                     |         |
| Yes               | 32(91.4%)                | 32(91.4%)           | 0.663   |
| No                | 3(8.6%)                  | 3(8.6%)             |         |
| 24-48 hour        |                          |                     |         |
| Yes               | 33(94.3%)                | 33(94.3%)           | 0.693   |
| No                | 2(5.7%)                  | 2(5.7%)             |         |
| 48-72 hour        |                          |                     |         |
| Yes               | 34(97.1%)                | 34(97.1%)           | 0.754   |
| No                | 1(2.9%)                  | 1(2.9%)             |         |
Figures

Figure 1
Follow-up Diagram of Patients (According to Consort Statement).

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist.doc