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Commentary: Is It Safe to Limit Allogeneic Red Blood Cell Transfusions to Neonates?

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Abstract

Two randomized clinical trials, conducted independently, have reported results of neonates transfused with red blood cells (RBCs) given per either liberal (relatively high pretransfusion blood hematocrit levels) or restrictive (relatively low pretransfusion blood hematocrit levels) transfusion programs. Both found fewer RBC transfusions given per restrictive programs and comparable outcomes for several clinical endpoints. However, the Iowa trial found significantly more problems with apnea, intraparenchymal brain hemorrhage and periventricular leukomalacia in infants transfused per the restrictive program – findings not found by the Canadian trial. A critical analysis of both trials and possible reasons for the discrepant findings are discussed. Until definitive data are reported by additional studies, it seems prudent not to severely restrict/limit allogeneic RBC transfusions to neonates – except in approved investigational settings.

Keywords

Neonatal RBC transfusions; RBC transfusion indications/guidelines; RBC transfusion triggers; Risks of undertransfusion, restrictive vs. liberal transfusion practices

Background

Most neonates with birth weight <1.0 kg need life-saving red blood cell (RBC) transfusions – especially if they have cardiorespiratory problems. Although many risks of allogeneic RBC transfusions have been strikingly decreased – by donor questioning and infectious disease testing, by prestorage leukocyte reduction, by γ -radiation and by dedicating a single unit of RBCs to each neonate (to limit donor exposure) – complete safety can never be guaranteed. Hence, a number of reports have been published touting the merits of decreased numbers/amounts of RBCs transfused when transfusions are prescribed using restrictive/conservative practice guidelines [1,2].

The basic concept assessed by clinical trials comparing liberal/standard RBC transfusion programs with restrictive/conservative programs is that the higher pretransfusion hematocrit (HCT) trigger of the liberal programs leads to more transfusions, with potentially greater risks of ‘overtransfusion’ – transfusions given for benefits that are not always clearly established – whereas the lower pretransfusion HCT trigger of the restrictive programs leads to fewer transfusions and provides benefits without risks of ‘undertransfusion’. The stated hypotheses tested by these trials, usually, are either that RBC transfusions can be decreased by restrictive transfusion programs/guidelines or that significant problems due to undertransfusion will not occur with restricted RBC transfusions. In addition to the primary endpoint, for which each

trial is statistically powered, several secondary endpoints are assessed for which, unfortunately, acceptable statistical power often is absent.

Two such trials have been conducted, independently, in preterm neonates given small-volume RBC transfusions per liberal versus restrictive transfusion programs [3,4]. Both trials successfully achieved their primary endpoints, and several findings are in agreement. However, they disagree in one alarming way – specifically whether restrictive RBC transfusion practice leads to brain injury due, in some undefined way, to undertransfusion – thus presenting a dilemma for physicians prescribing RBC transfusions for preterm neonates.

Iowa Trial [3]

To determine if restrictive RBC transfusion guidelines could reduce the number of RBC transfusions given (primary endpoint) without causing adverse consequences, 100 preterm neonates (0.5–1.3 kg birth weight) were randomly assigned to receive either liberal RBC transfusions (n = 51) or restrictive RBC transfusions (n = 49). For randomization, neonates were stratified by birth weight among three groups (0.5–0.75, 0.751–1.0, and 1.001–1.3 kg) to ensure even distribution of all weights of neonates between the two RBC transfusion programs. Neonates with conditions that might lead to unusual RBC transfusion needs or imminent death were excluded. With the exception of a slight increase in boys assigned to the restrictive transfusion program, there were no significant demographic differences between groups at the beginning of the study. With the exception of RBC transfusions, all other aspects of care were identical, and no neonates received recombinant erythropoietin.

Differences in RBC transfusion triggers between the liberal and restrictive programs were based on pretransfusion blood HCT and the extent of respiratory support needed by the neonate at the time of the RBC transfusion (table 1). Note that the pretransfusion HCT differences between the two transfusion programs were fairly large – 12 HCT percentage points during assisted ventilation, 10 HCT percentage points during continuous positive airway pressure (CPAP) or nasal supplemental oxygen, and 8 HCT percentage points when no oxygen or respiratory support were required. When the blood HCT fell below the transfusion trigger value, RBC transfusions were given consistently as 15 ml/kg (current weight) of RBCs packed by centrifugation – a method well studied at Iowa and known to increase the neonate's HCT value by an average of 12 HCT percentage points [5]. Although immediate posttransfusion HCT values were not reported, they can be estimated – based on the pretransfusion of HCT plus the expected posttransfusion increment – for neonates in the liberal transfusion group to be 58% for ventilated infants, 50% for those given CPAP and/or supplemental oxygen, and 42% for those receiving no oxygen or other respiratory support. Estimated values for neonates in the restrictive group are, respectively, 46, 40 and 34%. Thus, average differences between liberal and restrictive groups were 12 HCT percentage points for ventilated infants, 10 HCT percentage points for infants given CPAP and/or supplemental oxygen, and 8 HCT percentage points for those receiving no oxygen or respiratory support. At 6 weeks of age, mean blood hemoglobin levels still were significantly higher in neonates transfused per liberal guidelines (11.0 g/dl = 33% HCT) versus those in the restrictive group (8.3 g/dl = 25% HCT).

The primary endpoint of the trial was achieved with neonates in the liberal transfusion group receiving 5.2 ± 4.5 RBC transfusions vs. 3.3 ± 2.9 ($p = 0.025$) for neonates in the restrictive group. The number of neonates completely avoiding RBC transfusions was not different (12 and 10% in the liberal and restrictive transfusion groups, respectively). Of 161 RBC transfusions given to neonates in the restrictive group, 17 (11%) did not meet predetermined study criteria. The reasons for these 'out-of-study' transfusions were not reported, but likely they were given because physicians felt the neonate's clinical status required a higher HCT. There were no statistically significant differences between liberal and restrictive transfusion

groups in many secondary clinical endpoints including survival, length of hospitalization, time on ventilator and need for supplemental oxygen, rates of patent ductus arteriosus, retinopathy of prematurity and bronchopulmonary dysplasia, and the overall rate of intraventricular hemorrhage.

However, grade 4 intraventricular hemorrhage (i.e., parenchymal brain hemorrhage) was seen only in neonates given restrictive RBC transfusions (4 neonates vs. none in the liberal group). Periventricular leukomalacia, also, was seen only in the restrictive group of neonates (4 vs. 0). When viewed as a composite endpoint, 6 neonates given RBC transfusions per restrictive guidelines had parenchymal brain hemorrhage, periventricular leukomalacia, or both versus none of the neonates transfused per liberal guidelines ($p = 0.012$). These ultrasound findings were associated with significantly more apnea in the restrictive transfusion group of infants ($p = 0.004$). At the end of the study, 16% of neonates transfused per restrictive guidelines had either died or survived with brain injury versus 2% in the liberal transfusion group ($p \leq 0.05$) [6].

The authors concluded that fewer RBC transfusions were given to preterm neonates when restrictive guidelines were used versus more liberal guidelines. However, the finding of more frequent neurologic events suggested that giving RBC transfusions per restrictive guidelines may be harmful – presumably due to diminished oxygen delivery to the brain and possible compensatory responses (e.g., increased cerebral blood flow).

Canadian Trial [4]

To determine if restrictive RBC transfusion guidelines had an effect on the composite primary endpoint (death before discharge or survival with any of severe retinopathy, bronchopulmonary dysplasia, or brain injury on ultrasound), 451 preterm neonates (birth weight <1.0 kg) were randomly assigned to receive either liberal RBC transfusions ($n = 228$) or restrictive RBC transfusions ($n = 223$). For randomization, neonates were stratified by birth weight (≤ 0.75 or $0.751\text{--}0.999$ kg) and by center, as this was a multicenter trial. Neonates with conditions that might lead to unusual RBC transfusion needs or to imminent death were excluded. Demographic data from both groups were stated to be similar at the beginning of the study (p values not reported), and it is important to note that the Canadian neonates had a lower birth weight and gestational age than those from Iowa (respective means were 0.770 vs. 0.956 kg and 26.1 vs. 27.7 weeks). No neonates received recombinant erythropoietin.

Differences in RBC transfusion triggers between the liberal ('high threshold' as stated in the paper) and restrictive ('low threshold') programs were based on pretransfusion blood hemoglobin concentration (to facilitate comparisons with the Iowa trial, I multiplied hemoglobin values $\times 3$ to convert to HCT), extent of respirator support needed, and the age in days of the neonate (table 2). Note two things in comparison to the Iowa trial: (1) the pretransfusion HCT differences between the Canadian liberal and restrictive guidelines are fairly small – 6 HCT percentage points during respiratory support and only 3–6 HCT percentage points during periods of no respiratory support, and (2) the pretransfusion HCT triggering RBC transfusions to neonates in the Canadian liberal group was considerably lower than in the Iowa trial. RBC transfusions were given as 15 ml/kg of washed, packed RBCs, but details of the quantity of RBCs actually transfused after washing at each center are not reported. This may be important because up to 20% of RBCs can be lost by washing and, unless adjustments are made, the quantity/dose of RBCs transfused from transfusion to transfusion may vary considerably. Although immediate posttransfusion HCT increments were not reported, weekly mean HCT values ranged from high of 45% (week 1) to low of 34% (week 4) for neonates in the liberal transfusion group vs. a high of 43% (week 1) to a low of 30% (week 4) for those in the restrictive group – differences between infants in the two RBC

transfusion groups of only 2 HCT percentage points at week 1, and 4 HCT percentage points at week 4.

More neonates ($p = 0.037$) completely avoided RBC transfusions when transfused per restrictive guidelines (11%) vs. liberal guidelines (5%). However, the number of transfusions given per neonate were not significantly different between the liberal transfusion group (5.7 ± 5.0) and the restrictive group (4.9 ± 4.2). This was due, in part, to the fact that 16% (173/918) of transfusions given to neonates in the restrictive group were given for clinical reasons, rather than per predetermined study guidelines (i.e., physicians felt that the neonate's clinical status required a higher HCT).

There was no statistically significant difference ($p = 0.25$) in the composite endpoint of death or survival with any of severe retinopathy, bronchopulmonary dysplasia or brain injury by ultrasound – nor were there any differences with the individual components of the composite endpoint when they were compared. The percentage of neonates suffering the composite primary endpoint was quite high whether RBC transfusions were given per liberal (70%) or restrictive (74%) guidelines – likely reflecting the extreme prematurity of the infants studied. There were no significant differences in several secondary outcomes including growth, duration of ventilation, duration of supplemental oxygen, length of hospitalization, apnea, necrotizing enterocolitis or culture-proven sepsis.

The authors concluded that, for extremely low birth weight neonates, maintaining high hemoglobin levels results in more RBC transfusions with little evidence of benefit, and that RBC transfusion thresholds/triggers for preterm neonates can be lowered by at least 1.0 g/dl hemoglobin without incurring a clinically important increased risk of death or major morbidity.

Critical Analysis and Recommendations

In many respects, the Iowa and Canadian neonatal RBC transfusion trials reported similar findings. Restrictive RBC guidelines did, indeed, decrease RBC transfusions given in both trials – although in different ways. In the Iowa trial, the percentage of neonates avoiding all RBC transfusions did not differ between the two study arms, but among transfused neonates, those in the restrictive group received significantly fewer RBC transfusions per infant than did neonates transfused per liberal guidelines. In the Canadian trial, a significantly higher percentage of neonates transfused per restrictive guidelines avoided all RBC transfusions compared to those transfused per liberal guidelines. However, among infants transfused according to either transfusion program, there was no difference in the number of RBC transfusions given per infant. This last finding in the Canadian trial was almost certainly due to two factors: (1) the small difference in the pretransfusion blood hemoglobin/HCT threshold (trigger) between liberal and restrictive transfusion guidelines, and (2) the fact that 16% of RBC transfusions given to neonates in the restrictive group were prescribed for clinical reasons – rather than per predetermined hemoglobin/HCT guidelines. Such 'out-of-study' transfusions are permitted in many clinical trials assessing transfusion practices because extra/urgent transfusions are believed by prescribing physicians to be necessary to ensure patient safety. Nonetheless, these 'extra' transfusions often confound results.

All of these factors led to the critical finding, in the Canadian trial, that differences in infant blood hemoglobin/HCT values were very small between neonates transfused per liberal versus restrictive guidelines. The difference in mean values reported at weekly intervals usually was only 1.0 g/dl hemoglobin (or slightly higher) which corresponds to 3–4 HCT percentage points. Although these small differences in hemoglobin/HCT values between the two groups of neonates were statistically significant, the clinical significance/importance of such a slightly higher value in the liberal transfusion group can be questioned.

In contrast, the HCT differences between Iowa neonates transfused per either liberal versus restrictive guidelines were much greater. Although the HCT differences between the two groups of infants were not reported on a weekly basis during the study period, they can be estimated (as described earlier) to range from 8 to 12 HCT percentage points higher in the liberal transfusion infants versus those in the restrictive group. Even at 6 weeks of age, when the effects of the RBC transfusions given earlier in life per different transfusion guidelines tended to dissipate, the reported difference was still 6 HCT percentage points. Thus, one can conclude that the Iowa neonates truly were clinically/hematologically distinct, in terms of blood HCT values, whereas the Canadian infants were fairly similar clinically/hematologically – perhaps too similar to detect possible differences in outcomes dependent on blood hemoglobin/HCT values.

Most clinical endpoints in both trials were, in fact, similar in neonates whether transfused per liberal or restrictive RBC transfusion guidelines – with the very important exception of severe brain injury. Significantly more infants in Iowa, transfused per restrictive RBC guidelines, suffered grade 4 (not overall grades) intraventricular hemorrhage and/or periventricular leukomalacia – ultrasound findings associated clinically with more severe apnea. The Canadian study did not find such differences, but most of the Canadian neonates studied, whether transfused per liberal or restrictive RBC guidelines, either died or suffered severe complications of prematurity – making it difficult to detect any possible differences. The high percentage of Canadian neonates with severe outcomes likely was due to their extreme prematurity – although the mechanisms responsible were not reported and might include multiple factors in their care, including RBC transfusion practices. Clearly, Canadian neonates were undertransfused when compared to the Iowa neonates (or the Iowa neonates were overtransfused, depending on one's point of view). Iowa neonates transfused per liberal RBC transfusion guidelines had high HCT values throughout the study period, and from about 2 weeks of age and thereafter, estimated and reported posttransfusion blood HCT levels were higher in Iowa neonates, transfused per *restrictive guidelines*, than were HCT values in *either group* of Canadian neonates (i.e., either liberal or restrictive)!

When considering how the results of these trials should influence RBC transfusion practices for preterm neonates, several factors should be considered. First, the difference in ultrasound severe brain injury in the Iowa trial was a secondary composite endpoint. The trial was not designed or powered to definitively assess this endpoint. To do so would require more extensive/systematic ultrasound and, perhaps, other imaging studies designed as a primary endpoint. Second, the Canadian neonates, although transfused per two different RBC transfusion programs, differed only slightly in respect to their blood hemoglobin/HCT values, raising the question as to whether they differed sufficiently to permit meaningful comparisons – particularly with a composite primary endpoint that was met by a very high percentage of infants in both groups (i.e., whether transfused per liberal or restrictive guidelines). Finally, insufficient oxygen delivery to the brain, quite possibly, is a mechanism involved in hemorrhage and leukomalacia.

Two studies will be discussed briefly to illustrate this last factor. Kissack et al. [7] reported an association between high cerebral fractional oxygen extraction and intraventricular hemorrhage and/or hemorrhagic parenchymal infarction in a comparative study of 25 preterm infants – who were overall similar, except 13 had brain injury and 12 did not. They concluded that high cerebral oxygen extraction reflected low cerebral oxygen delivery that was evidence of brain hemorrhage. Since one of the factors involved in oxygen delivery to tissues is the blood hemoglobin/HCT content, the findings support the possibility that hemorrhagic brain injury in preterm infants might be influenced by RBC transfusions. Following a similar rationale, Mercer et al. [8] reported that delayed umbilical cord clamping (30–45 s) in preterm infants decreased rates of intraventricular hemorrhage (14% in the delayed vs. 36% in the immediate clamping

groups, with 36 infants studied in each group). They concluded that the transfusion of autologous placental blood, consequent to the delayed cord clamping, protected the neonatal brain from hemorrhage – although the possible mechanisms were not defined.

Because of the discrepant/contrary findings of the Iowa and Canadian RBC transfusion trials, the questions/criticisms that can be raised about both trials, and the need for more definitive information, physicians prescribing RBC transfusions for preterm neonates are in a quandary at this time. In my view, the possible risks of undertransfusion, when prescribing RBC transfusions per very restrictive guidelines, exceed the risks of more frequent RBC transfusions – particularly when given per ‘single-donor’ transfusion programs [5]. Thus, in the day-to-day (routine) management of preterm neonates, RBC transfusions should be given per conventional guidelines, which are fairly liberal. However, in efforts to improve the safety of transfusion practices, it is reasonable to investigate restrictive RBC transfusion guidelines, but only by well-designed studies that are approved and monitored by human-investigation committees, and when parental informed consent has been given.

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Table 1

Liberal vs. restrictive RBC transfusion programs used in Iowa trial (RBC transfusions as 15 ml/kg packed RBC concentrate)

Clinical condition	Liberal ^I	Restrictive ^I
Mechanical ventilation	46%	34%
CPAP or nasal oxygen	38%	28%
No respiratory support	30%	22%

CPAP = Continuous positive airway pressure.

^I HCT threshold (trigger) prompting RBC transfusion.

Table 2

Liberal vs. restrictive RBC transfusion programs used in the Canadian trial (RBC transfusions as 15 ml/kg washed, packed RBCs)

Clinical condition			Age	Liberal ^I	Restrictive ^I
Yes	Respirator support	≤7 days		41%	35%
Yes	Respirator support	8–14 days		36%	30%
Yes	Respirator support	≥15 days		30%	26%
No	Respirator support	≤7 days		36%	30%
No	Respirator support	8–14 days		30%	26%
No	Respirator support	≥15 days		26%	23%

^I HCT threshold (trigger) prompting RBC transfusion per capillary blood sample.