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RBC storage and avoiding hyperkalemia from transfusions to neonates & infants

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A “benchmark” is a standard or measure by which others can be assessed and/or compared. Benchmarking is the process of gathering information (ie, data and/or expert opinions) to set the benchmark. The greater the care, precision and validation taken during the benchmarking process, the more accurately the benchmark will reflect the optimal practices/issues in question and, in turn, allow the best point of reference for comparing/judging/instructing/advising others.

In this issue of *Transfusion*, Fung et al report results of a benchmarking survey performed by the University HealthSystem Consortium (UHC) to assess the acceptability of various RBC anticoagulant/storage solutions and to determine the existence, or lack thereof, of policies to avoid possible hyperkalemia during RBC transfusions given to infants at member institutions.(1) The authors state in the title that this is a “benchmarking study” — which by convention implies that the results will serve as a standard by which others may be measured and/or as a point of reference from which other measurements can be made.

Although the need to establish benchmarks for the issues raised (ie, RBC anticoagulant/storage solutions for infant transfusions and policies to avoid potential problems with transfusion-induced hyperkalemia) are well stated in the introduction by Fung et al,(1) the limitations/shortcomings of the benchmarking survey are multiple (as pointed-out by the authors in the discussion section). Thus, the extent to which the findings, conclusions and recommendations of Fung et al should be directly applied to neonatal/infant transfusion practices can be questioned.

The basis for my opinion pertaining to limitations/shortcomings, is summarized by the following critical points — many of which were mentioned by the authors themselves,(1) but warrant emphasis here. First, response to the survey by institutions surveyed was only modest (47 of 107 UHC members = 44% for the RBC anticoagulant/preservative section and 45 of 107 = 42% for the hyperkalemia section), with no explanation offered as to why nonresponders failed to reply — other than mentioning that only 77 UHC members are “benchmarking program members” and noting that “no attempt was made at increasing response rate” beyond a few modest efforts.(1) Because UHC members are academic medical centers, one might assume that their practices would be as “evidence-based” as possible. Accordingly, to avoid possible misinformation due to reporting bias, more efforts should have been made to increase response rates to get a complete and accurate picture of member practices — to establish benchmarks that most likely reflect best/optimal practices.

Second, one should question whether the most knowledgeable people completed the survey. The respondents were not neonatologists/pediatricians and only 21% were transfusion/pathology physicians. The remaining 79% of respondents were supervisors/managers/administrators.(1) Although these non-physician respondents can review blood bank/laboratory policies/procedures to answer survey questions, it is likely that they will not have in depth knowledge of transfusion practice guidelines/policies of the Departments of Pediatrics and Neonatology Divisions or of the Departments of Nursing. Moreover, they likely will not be familiar with the preferences/practices of physicians prescribing RBC transfusions for infants — particularly pertaining to potassium concerns.

Third, to extend the second point, collecting data for which RBC anticoagulant/preservative solutions are “acceptable” provides only limited benchmarking data. For purposes of planning educational programs and recommending evidence-based guidelines/practices, it would be much more informative to know which anticoagulant/preservative solutions are “preferred” and, in the many institutions accepting multiple solutions, what percentage of RBC transfusions are actually given with the “accepted” anticoagulant/preservative solutions. In 19 of 47 responding institutions, four or five different anticoagulant/preservative solutions were “acceptable” with no indication as to which one(s) the prescribing physicians preferred and/or to what extent RBCs stored in different solutions were transfused. Simply acknowledging a solution is “acceptable” does not mean it is preferred or even actually used at an institution.

Fourth, no mention is made as to how, or even whether, the survey answers were validated for completeness or accuracy. The authors stated that although no formal validation was performed, all participating UHC members were given opportunities to review and make corrections after close of the survey.(1) It would have increased credibility to report the number/percentage of UHC members who actually did review the completed survey and made corrections — and, in particular, to document whether answers to the survey were ever reviewed by physicians and nurses actually involved in RBC transfusions given to infants.

Regarding the acceptability of anticoagulant/preservative solutions, the authors state that the decision to transfuse RBCs stored in additive solutions (AS-1, AS-3, AS-5) should be made by the medical director of the transfusion service, in consultation with institutional neonatologists — a point with which all would agree. The authors then make a rather feeble case for recommending RBCs stored in additive solutions as the best practice for low volume (<20 mL/kg) transfusions given to infants and, then, mention the “boilerplate” comment that because there is not universal acceptance for this practice, there may be need for more education or more substantive evidence-based safety data. Were my mentor of years ago, at the Children’s Hospital Research Foundation in Cincinnati, to hear this last oft-used phrase about need for more education and data, he would exclaim “BALDERDASH!! Data are available, so educate!!” — a comment with which I fully agree.

As previously reviewed(2–6), a great deal of data exist in peer-reviewed journals to establish both the efficacy and safety of transfusing RBCs stored in additive solutions for low/small volume transfusions (generally 10–15 mL/kg) to neonates/infants. Moreover, there are no definitive data to establish superior efficacy and/or safety of RBCs stored in CPD or CPDA (citrate-phosphate-dextrose-adenine) solutions — the ones often demanded by neonatologists — over RBCs in additive solutions for low/small volume transfusions. Accordingly, there is no scientific/medical justification for physicians to insist on RBCs stored in CPD or CPDA for low/small volume transfusions given to neonates/infants, and it is an unwarranted use of institutional resources for blood banks to maintain separate RBC inventories for infants needing such transfusions.

RBC STORAGE AND POTASSIUM – TRANSFUSION ISSUES FOR NEONATE/INFANTS

Legitimate concerns have been raised about transfusing RBCs in additive solutions — particularly, if stored longer than 7 to 14 days — for large volume transfusions (generally >25 mL/kg) given to critically-ill infants, especially if rapid infusion is a possibility. Accordingly, I would have preferred Fung et al(1) to firmly recommend — based on strong evidence that RBCs stored in additive solutions are efficacious, safe and diminish allogeneic donor exposures PLUS their own benchmarking data documenting that the majority of UHC institutions accept RBCs in these solutions — that low/small volume RBC transfusions to neonates/infants should consist of RBCs stored in additive solutions. This recommendation would then be followed by the caveat that exceptions should be made for larger volume transfusions, for which physicians could select either RBCs stored in anticoagulant/preservative solutions believed to be safer by local blood bank and neonatology physicians — although, there are only anecdotal data to establish the safety of RBCs stored in CPD or CPDA solutions for such transfusions — or RBCs stored in additive solutions from which the anticoagulant/preservative solution is largely removed from the RBCs before transfusion either by washing or by centrifugation, followed by resuspension of the RBCs in saline, albumin solution or fresh plasma.

Regarding the possible risks of hyperkalemia in infants given low/small volume transfusions of RBCs stored for prolonged periods of time and/or irradiated, there is little, if any risk, of clinically significant hyperkalemia when RBCs are infused slowly over the customary 2 to 4 hours; this is true even for RBCs irradiated and then stored as long as the permitted 28 days post-irradiation.(7) Accordingly, I cannot agree with Fung et al(1) that institutions should develop policies dealing with transfusion-induced hyperkalemia in regards to low/small volume RBC transfusions infused slowly. Clearly, physicians and nurses involved in transfusing neonates/infants should be educated about the possible risks of hyperkalemia, particularly, in infants who already have elevated plasma potassium levels and/or impaired renal function. In contrast, I strongly agree that policies should be developed/implemented for large volume RBC transfusions (≥ 25 mL/kg), particularly, if rapid infusion is possible (eg, surgery). The rationale(1–7) for such a policy is described in the following paragraphs. I suggest that some of these points/calculations be included in institutional policies/guidelines for RBC transfusions given to neonates/infants.

First, for the following calculations, assume that the hematocrit of a unit of RBCs stored in additive solution is 57%; that a 10 mL transfusion from such a RBC unit consists of 5.7 mL RBCs + 4.3 mL extracellular fluid; that the expected potassium concentration in the extracellular fluid of a unit of RBCs stored in additive solution for the maximum 42 days is 50 mEq/L and, if irradiated and stored for ≥ 2 days, is 72 mEq/L; that when considering potassium concentrations, milliequivalents per liter (mEq/L) and millimoles per liter (mmol/L) are the same; and that numbers in calculations will be “rounded-off” at the third decimal place.

Second, the daily potassium requirement for normal infants is 2 to 3 mEq/kg/24 hrs. Thus, the infusion rate for intravenous maintenance potassium is $3 \text{ mEq/kg} \div 1440 \text{ min} = 0.002 \text{ mEq/kg/min}$. For hypokalemic infants, the therapeutic infusion rate will be higher, but generally not above 0.004 mEq/kg/min. These infusion rates are safe for the vast majority of neonates/infants, even those who are critically ill.

Third, when a one kg infant receives a low/small volume transfusion of 10 mL/kg RBCs stored in additive solution for 42 days, the potassium dose (assuming a 3 hour infusion) is

0.001 mEq/kg/min, and a 20 mL/kg RBC transfusion potassium dose is 0.002 mEq/kg/min. Calculations are:

- 10 mL transfusion consists of 5.7 mL RBCs + 4.3 mL extracellular fluid containing potassium at 0.05 mEq/mL. Thus, the potassium “dose” is $4.3 \times 0.05 = 0.215$ mEq/kg.
- 3 hour infusion = 180 minutes.
- $0.215 \text{ mEq/kg potassium} \div 180 \text{ min} = 0.001 \text{ mEq/kg/min}$ for a 10 mL/kg RBC transfusion infused over 3 hours.
- A similar RBC transfusion given as 20 mL/kg will deliver twice the potassium dose (ie, 0.002 mEq/kg/min).
- Either potassium dose does not exceed the normal maintenance infusion rate.

Fourth, when a one kg infant receives a low/small volume transfusion of 10 mL/kg RBCs stored in additive solution with the unit irradiated ≥ 2 days before transfusion (assuming a 3 hour infusion), the potassium dose is 0.002 mEq/kg/min, and a 20 mL/kg RBC transfusion dose is 0.003 mEq/kg/min. Calculations are:

- 10 mL/kg transfusion consists of 5.7 mL RBCs + 4.3 mL extracellular fluid containing potassium at 0.072 mEq/mL. Thus, the potassium “dose” is $4.3 \times 0.072 = 0.310$ mEq/kg.
- $0.310 \text{ mEq/kg potassium} \div 180 \text{ min} = 0.002 \text{ mEq/kg/min}$ for 10 mL/kg RBC transfusion infused over 3 hours.
- The potassium “dose” for a similar RBC transfusion given as 20 mL/kg is $0.620 \text{ mEq/kg potassium} \div 180 \text{ min} = 0.003 \text{ mEq/kg/min}$.
- Either potassium dose does not exceed safe infusion rates.

Fifth, for large volume RBC transfusions (>25 mg/Kg), particularly if infused rapidly, potassium that increases in the extracellular fluid during RBC storage poses a significant danger. Transfusions of this type are similar to the situation for many drugs in which intravenous infusion rates must not exceed limiting rates to ensure safety. Whenever possible, fresh RBC units (stored no more than 7 days since collection) should be issued for large volume RBC transfusions. Alternatively, older RBC units can be washed before transfusion. However, washed RBCs suspended in isotonic saline do not store well and, although storage is permitted for 24 hours at refrigerator temperature, potassium readily leaks into the extracellular fluid. Therefore, if RBC units are washed to remove extracellular potassium, they should be transfused shortly after washing — in my opinion, always within 12 hours to minimize potassium reaccumulation.

If neither fresh (ie, < 7 days storage) nor washed RBC units are available — as may occur during surgery or when other critically ill infants experience unexpected massive bleeding — physicians must transfuse whatever RBC units are available, regardless of storage age. For RBC units issued routinely (ie, without advance consideration to be stored < 7 days), I suggest an infusion rate of 0.5 mL/Kg/min (eg, a 10 Kg infant would receive additive RBCs stored longer than 7 days at an infusion rate of 5 mL/min). This recommendation is not based on results of clinical trials investigating rapid infusion RBC emergency transfusions, because they do not exist, but per the following calculations:

- During storage, potassium in the extracellular fluid of RBC units stored in additive solutions increases linearly over time to a maximum concentration of approximately 50 mEq/L (0.05 mEq/mL) after the complete 42 days of storage. Because of blood bank/center inventory management policies and the extent to

which available RBC units are used (ie, rapidity of RBC inventory turnover), the age of RBC units issued for transfusion often is 20 to 22 days since collection. The extracellular fluid potassium concentration of 20 day units is approximately 30 mEq/L (0.03 mEq/mL). Because the HCT of AS-1, AS-3 and AS-5 units is $\cong 57\%$, each milliliter issued for transfusion consists of 0.57 mL RBCs + 0.43 mL extracellular fluid — with the extracellular fluid containing about 0.013 mEq of potassium. Thus, when the “usual” AS-1, AS-3 or AS-5 RBC unit is issued after 20 to 22 days storage and is transfused at a rate of 0.5 mL/Kg/min, the potassium in the extracellular fluid is being infused, on average, at 0.007 mEq/Kg/min.

- A 10 kg infant experiencing life-threatening bleeding would, then, be transfused with the usual RBC units available at a rate *not to exceed* 5 mL/min; a 20 kg infant would be transfused at a rate *not to exceed* 10 mL of RBCs/min. Obviously, additional crystalloid and/or colloid fluids can be infused separately, as needed to restore/maintain blood pressure (ie, RBCs transfusions alone are not the optimal management of hemorrhagic shock).
- Although there are no data from clinical trials to document the safety of transfusing stored AS-1, AS-3 or AS-5 RBCs at a rate of 0.5 mL/Kg/min to treat massive bleeding in infants, in my opinion, it is a reasonable practice for two reasons: (1) the clinical situation is grave, with a life-saving need for RBCs for which taking a possible risk is justified; and (2) the potassium infusion rate of 0.007 mEq/Kg/min is not greatly different than the accepted potassium maintenance rate of 0.002 mEq/Kg/min or the replacement rate for hypokalemia of 0.004 mEq/Kg/min (ie, only 3 to 5 thousandths of one mEq/Kg/min!!). Thus, in grave bleeding situations, the potential risk of infusing potassium at a rate slightly higher than rates accepted to be safe seems reasonable. Perhaps infusion rates faster than 0.5 mL/kg/min might be tolerated by some infants, but in my opinion, this infusion rate should be used only with “fresh” RBC units stored < 7 days. The practice of limiting RBC infusion rates is analogous to limitations followed to avoid toxicity of drugs and other substances infused intravenously. In-line filters have been shown to remove extracellular potassium during rapid infusion, but their efficacy and possible toxicity in neonatal/infant RBC transfusions requires more extensive study.(8)

Benchmarks provided by the results of Fung et al.(1) when considered within the context of additional published literature, permit conclusions/guidelines helpful for neonatal/infant RBC transfusion practices.

Acknowledgments

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