Transfusion-Associated Hyperkalemia

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The supernatant potassium concentration [K +] of red blood cell (RBC) units is frequently much higher than normal human plasma potassium levels, especially in units nearing the end of their storage life. Clinical hyperkalemia resulting from RBC transfusions has been recognized as a transfusion complication for decades, and there have been reported cardiac arrests attributed to transfusion-associated hyperkalemia. This review summarizes the evidence surrounding RBC [K +] levels, effects of irradiation and washing on [K +], the evidence for clinical hyperkalemia and cardiac arrests resulting from transfusion, predictors of post-transfusion hyperkalemia, and their preventative strategies. Key points include: (*a*) the [K +] (in mmol/L) increases linearly and is approximately equal to the number of days of RBC unit storage; (*b*) irradiation causes a rapid increase in [K +]; (*c*) there is potentially sufficient potassium in the supernatant of current RBC preparations to lead to hyperkalemia with large transfusion volumes; (*d*) any rise in patient potassium after transfusion is usually transient due to the redistribution of the potassium load; (*e*) transfusion-associated hyperkalemic cardiac arrests probably do occur, although it is difficult to prove this fact conclusively; and (*f*) promising strategies to combat transfusion-associated hyperkalemia include RBC washing, the use of in-line potassium filters, and the use of traditional treatments for hyperkalemia such as the use of insulin.

INCREASING ATTENTION HAS recently been given to the noninfectious complications of transfusion.[1-3] Transfusion of red blood cells (RBCs) is associated with a wide range of unintended consequences, including but not limited to circulatory overload, bradykinin-mediated hypotension, allergic reactions,[1] altered coagulation,[2] acute lung injury, infections, and death.[3] At transfusion, the composition of the red cell unit is very different from the composition of the blood initially taken from the donor. Over time, stored RBCs undergo numerous biochemical and membrane changes that result in a dramatic increase in the number of irreversibly deformed RBCs.[4] Recent research has focused on this "storage lesion," and there has been growing concern that the age of an RBC unit (even within the currently accepted shelf life of 42 days) may affect its safety profile. A large multicenter clinical trial is underway to determine the effects of standard storage-age RBCs as compared to fresh blood (<8 days old) (Age of Blood Evaluation [ABLE] trial, ISRCTN44878718). Another trial aims to evaluate the effect of RBC age on outcomes after cardiac surgery (Red Cell Storage Duration Study [RECESS] Trial, NCT00991341).

One of the consistent changes during RBC storage is increasing potassium concentration [K+] of the RBC supernatant. Although the volume of the supernatant in current RBC preparations is small (less than 40% of the total volume), the [K+] can be substantially higher than that of normal human plasma [K+].

Hyperkalemia can result in multiple negative effects in humans. These include muscle weakness, including respiratory muscle weakness if severe. However, the most feared consequences of hyperkalemia are its potentially fatal cardiac effects. Low-grade elevations in [K+] may result in electrocardiographic changes such as peaked T waves, loss of P-wave amplitude, and prolonged PR interval and QRS duration. With more severe hyperkalemia, a sine-wave electrocardiographic pattern and ventricular fibrillation or asystole may ensue, leading to mechanical arrest of the heart and death.[5]

The purpose of this review is to examine the published evidence relating to transfusion-associated hyperkalemia in an attempt to answer several questions. What is the K+ content of RBC units? How is the supernatant [K+] affected by processing methods such as irradiation or washing? Could this potassium load be significant relative to human blood volume? Does increased [K+] in transfused blood actually translate into increased serum [K+]? What is the evidence for hyperkalemia causing cardiac arrests? How might transfusion-associated hyperkalemia be prevented? Key points presented in this article are summarized in Table 1.

Table 1. Key Messages

- The supernatant potassium concentration of CPD-SAGM RBCs increases linearly from approximately 2 to 45 mEq/L over 42 days of storage.
- Stored RBC units may contain a sufficient amount of supernatant potassium to result in hyperkalemia if large volumes are transfused.
- The rise in a patient's serum potassium level is usually transient due to the redistribution of the potassium load.
- While it is difficult to prove conclusively that RBC transfusions lead to cardiac arrest, available evidence suggests that transfusion-associated hyperkalemic cardiac arrest is a real phenomenon.
- Several investigators have reported on interesting strategies to prevent post-transfusion hyperkalemia, including the use of fresh blood, insulin, in-line potassium filters, and washing RBCs with cell salvage devices prior to transfusion.
- There is a distinct lack of high-quality data on the incidence of hyperkalemia following transfusion and this area warrants further study.

There are many case reports of transfusion-associated hyperkalemia and transfusion-associated hyperkalemic cardiac arrests, most frequently in the anesthesia literature, usually in the setting of a large-volume transfusion. A smaller number of papers explore these issues more systematically. We present here what is known to date on transfusion-associated hyperkalemia.

WHAT IS THE POTASSIUM CONTENT OF RBC PREPARATIONS IN CURRENT USE?

In the United States, blood donation and collection is performed by different agencies and hospitals which often use different anticoagulants and pre-servatives. The American Red Cross lists several different examples in its practice guidelines, including AS-1, AS-3, AS-5, citrate-phosphate-dextrose-adenine (CPDA-1), citrate-phosphate-dextrose (CPD), and CP2D.[6] Current British and Canadian nation-wide practices are to use CPDA or CPD anticoagulants with sodium-adenine-glucose-manni-tol (SAGM) added to the RBCs.[7,8] The [K+] of the supernatant bathing the RBCs increases with storage time. RBCs rely on membrane sodium-potassium pumps to maintain intracellular electrolyte concentrations. These pumps are energy-dependent, using adenosine triphosphate, and highly temperature-sensitive. With refrigeration, there is a gradual leak of sodium into, and potassium out of, the RBCs.[9]

The change in [K+] with time has been described for CPDA-1 and SAGM preparations. From the first day until the 35th day of RBC storage, the [K+]

of CPDA-1 whole blood increases from 5.1 to 78.5 mmol/L.[10] Citrate-phosphate-dextrose SAGM RBCs have also been studied during storage from 0 to 42 days.[11] The [K+] initially is 2.1 mEq/L and increases to 45.3 ± 3.7 mEq/L on the 42nd day of storage. The increase in [K+] appears to be roughly linear with time, suggesting that the [K+] of CPD-SAGM RBCs might be estimated as approximately equaling the number of days of storage.

A study of RBCs stored in RAS-2 (citrate-adenine-mannitol-adenine-glucose) storage medium with CPD anticoagulant showed a change in [K+] from 3.8 ± 0.5 to 66.5 ± 5.3 mmol/L between days 1 and 49.[12]

Work done in the 1970s involved whole blood or anticoagulant acid-citrate-dextrose packed RBCs over 21 days of storage.[13] The plasma [K+] of both types of blood was approximately 4 mmol/L initially. [K+] rose to about 46 mmol/L by day 21 for packed RBCs and to about 20 mmol/L for whole blood. The whole blood units studied were of a 500-mL volume, and the packed RBC units consisted of approximately 300 mL. The total plasma load of potassium was therefore slightly higher for the whole blood despite the lower concentration because of the larger volume of supernatant.

In the same set of investigations, intracellular [K+] was calculated across the first 21 days from the potassium measured in the supernatant versus that in the total unit. The calculated intracellular value for whole blood on day 0 was 89.1 ± 6.8 mEq/L and on day 21 was 65.1 ± 4.0 mEq/L. For the packed RBCs, it was 90.5 ± 3.8 mEq/L on day 0 and 73.6 ± 3.5 mEq/L on day 21. Values at days 1, 3, 7, and 14 were also provided in this report. The results suggested a gradual release of the intracellular potassium in the stored blood to the surrounding supernatant, by leak and/or by RBC lysis.

The supernatant potassium content of blood may not be the only factor responsible for a post-transfusion potassium load. A portion of transfused RBCs lyse, mostly within the first 2 hours after transfusion, and the portion of RBCs that lyse in the recipient increases with storage time of the blood. Intracellular potassium from these RBCs may contribute to the post-transfusion rise in the patient's [K+].[14]

Summary

Supernatant [K+] in RBC units increases sub-stantially with time because of the potassium leak

from the RBCs and RBC lysis. For SAGM RBCs, the [K+] in mmol/L is roughly approximated by the number of days of storage. In Canada, the average age of RBCs transfused is 18.2 days.[15] After transfusion, an additional potassium load may be delivered to the patient's circulation due to post-transfusion RBC lysis, particularly relevant with older units of blood.

HOW IS THE [K+] AFFECTED BY PRODUCT MANIPULATION, PARTICULARLY IRRADIATION OR WASHING?

Weiskopf et al[16] studied the effects of irradiation (25 Gy) and washing on [K+] of 26 recently outdated CPDA-1 and AS-1 (additive solution–1) RBC preparations at 0, 6, 12, and 24 hours. They found that after washing and after γ-irradiation, [K+] increased with each time interval. The [K+] of irradiated units increased more rapidly than that of nonirradiated units. The [K+] of RBC units washed after irradiation increased more slowly than that of RBC units washed before irradiation.

Nonirradiated, washed RBC units had [K+] at 24 hours of 5.9 ± 1.4 mmol/L. The [K+] of RBC units irradiated then washed was 1.6 ± 0.3 mmol/L at 0 hours, 5.3 ± 0.5 mmol/L at 6 hours, 8.6 ± 1.0 mmol/L at 12 hours, and 14.3 ± 1.3 mmol/L at 24 hours. Post-wash hematocrit of the RBC units was $75.5\% \pm 4.1\%$. (Total extracellular potassium was 0.11 ± 0.03 mmol immediately after washing, and 0.35 ± 0.09 mmol at 6 hours.) The initial K+ concentration of nonoutdated RBC units of various storage ages was also tested after irradiation and washing. The age of the RBCs did not significantly affect its post-treatment [K+], suggesting that these experimental results may be applicable to in-date RBCs.

Davey et al[17] stored AS-1 RBCs for 42 days after 30 Gy irradiation on day 0. At 42 days, the [K+] of the irradiated RBCs was 78 ± 4 mmol/L. The [K+] of nonirradiated RBCs was significantly lower at 43 ± 9 mmol/L at 42 days ($P < .01$). The current Canadian standard[18] for expiry of irradiated RBCs is 28 days after irradiation or the original expiry date, whichever is shorter.

Summary

Irradiation substantially increases RBC supernatant [K+] versus that of nonirradiated RBCs, both in the first 24 hours, and over 42 days of storage. Washing the RBCs reduces supernatant potassium

concentration. If irradiated RBCs are washed after irradiation, the K+ concentration remains low for the first 6 hours.

COULD THIS POTASSIUM LOAD BE SIGNIFICANT RELATIVE TO HUMAN BLOOD VOLUME?

The blood volume of human adults and children can be estimated from the subject's body weight. Term neonates have approximately 80 to 90 mL/kg of blood. Premature neonates have a blood volume of as much as 100 mL/kg. Older children have an estimated blood volume of 70 mL/kg,[19] similar to that of lean adults.[20] At 70 mL/kg, a typical 70-kg adult has a blood volume of 4900 mL, or approximately 5 L. A 500-g preterm newborn has an estimated blood volume of approximately 50 mL (100 mL/kg).

Red blood cell transfusions given to adults are typically administered by the unit. One unit of SAGM RBCs prepared by Canadian Blood Services contains 289 ± 56 mL, with a hematocrit of 0.50 to 0.70.[8] The volume of the supernatant SAGM suspending the RBCs is thus approximately 110 mL. The transfusion of 1 U of RBCs should raise the hemoglobin concentration by about 10 g/L.[21] For infants and children, RBCs are usually transfused as milliliters per kilogram: 10-15 mL/kg of RBCs should increase the hemoglobin concentration by approximately 20 to 30 g/L.

The following calculations demonstrate estimates of plasma potassium changes with RBC transfusions for either an adult or a premature infant. The calculations assume high values for the potassium content in the transfused RBCs, such as seen at 42 days of storage and a supernatant volume of 110 mL. The model is based on complete mixing of the patient's entire plasma volume with the entire RBC supernatant volume, with no K+ shifts occurring intracellularly.

If a euvolemic adult (see Fig 1) is given one 300-mL unit of RBCs, his blood volume will increase from 4900 mL to 5200 mL. His initial plasma volume is about 30 to 35 mL/kg.[22] Using 33 mL/kg, this gives his total plasma volume as 2310 mL (2.31 l). If his baseline [K+] is 4.0 mmol/L, he has a total of 9.24 mmol of potassium in his plasma, pre-transfusion.

With the transfusion of a single RBC unit containing 110 mL of supernatant (0.11 L), at a concentration of 45 mmol/L of potassium, he will receive 4.95 mmol of additional plasma potassium.
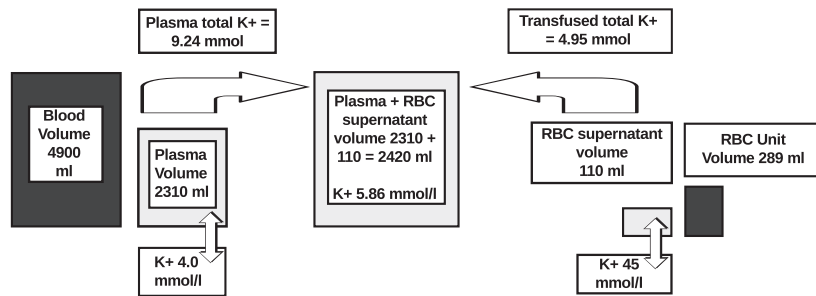
Fig 1. Adult weighing 70 kg (plasma [K+] baseline 4.0 mmol/L) transfused with 1 U of RBCs (supernatant [K+] of 45 mmol/L), model of instantaneous mixing. Resulting [K+] of mixture = 5.86 mmol/L.

The resulting total potassium in his plasma will be 4.95 + 9.24 = 14.19 mmol. His resulting plasma volume will be 110 + 2310 = 2420 mL. The resulting [K+] concentration in his plasma will be 14.19 mmol/2.42 l, which gives a [K+] of 5.86 mmol/L. The single-unit transfusion will thus increase his plasma potassium concentration by about 1.9 mmol/L over baseline. Using this model, additional units of the same supernatant volume and [K+] would increase the concentration similarly. It is apparent from this "worst case" calculation that multiple units of RBCs could potentially lead to a dangerous post-transfusion [K+] elevation. It is perhaps surprising that serious hyperkalemia does not result more frequently.

The situation for a 500-g premature infant with a baseline [K+] of 5.0 mmol/L is different (see Fig 2). (Recall, the normal laboratory range for serum potassium is generally higher in preterm neonates: approximately 4.5-6.5 mmol/L). The estimated blood volume is thus 50 mL. The normal hematocrit range for neonates is 0.46 to 0.70 L/L, so the plasma fraction of the blood volume is 0.30 to 0.54 L/L. If a mid-range fraction of 0.42 is assumed, the plasma volume of the infant will be 21 mL. A transfusion of 15 mL/kg to this infant would be 7.5 mL (about 1/40 of the volume given to the adult patient). The transfusion would contain 1/40 of the unit's 110-mL supernatant volume, or 2.8 mL. If the same RBC unit as above ([K+] = 45 mmol/L) were used, it would mean 45 mmol/L × 0.00275L = 0.124 mmol potassium will be delivered with the infant's RBC transfusion. The infant's total plasma volume post-transfusion is 21 + 2.8 = 23.8 mL. The infant's total plasma potassium content will be 0.105 + 0.124 = 0.229 mmol. The new plasma [K+] post-transfusion will be 0.229 mmol/0.0238 L = 9.6 mmol/L. The infant's plasma potassium concentration will thus be almost doubled with a single transfusion. Hence, transfusion-associated hyperkalemia would occur much more readily in this patient population with typical RBC transfusion volumes.

Summary

In summary, a basic plasma/supernatant mixing model for RBC transfusion shows that it is plausible (especially in infants and small children) that clinically significant hyperkalemia could result after the infusion of a number of RBC units.
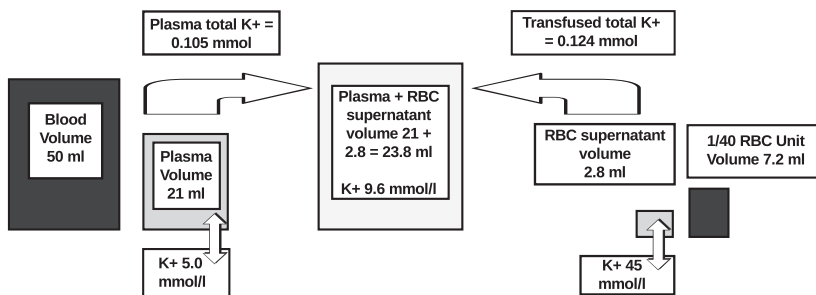

Fig 2. Premature infant weighing 500 g (plasma [K+] baseline 5.0 mmol/L) transfused with 15 mL/kg RBCs (supernatant [K+] of 45 mmol/L), model of instantaneous mixing. Resulting [K+] of mixture = 9.6 mmol/L.

However, so many other factors may influence a recipient's actual post-transfusion [K+] that prediction is not possible without knowledge of other relevant clinical and physiologic information.

DOES K+ IN BLOOD TRANSLATE INTO INCREASED SERUM [K+] WHEN TRANSFUSED?

The preceding calculations assume instantaneous mixing of the transfused RBCs with the blood volume of the recipient and that no other forces act to increase or decrease the concentration of potassium once transfused. In reality, the situation is not so straightforward. RBC transfusion often occurs via a catheter. If this is a central venous catheter, it is conceivable that the composition of blood "seen" by the heart (especially during a rapid transfusion) is more like that of the stored blood than a mixture.

In 1962, Schweizer and Howland[23] concluded from a study of massive blood replacement that tissue trauma and acidemia may be major determinants of hyperkalemia in these circumstances. Another study found that pH did not explain the increase in patients' [K+] after massive transfusion.[24] This same retrospective study found that, in 9 children who became hyperkalemic in the setting of intraoperative massive transfusion, a simple mixing model did not predict accurately the actual [K+] at 1 to 2 hours. At one extreme, a child had 82.5% less [K+] increase than expected, and at the other extreme, one child had 18.2% more increase in [K+] than could be explained by the potassium administered in the transfused blood.[24]

Forces other than simple mixing may thus be in play. Only about 1.4% of total body potassium is contained within the blood. Shifts into or out of tissue cells may be important within the time scale of the RBC transfusion. Even warming RBCs for transfusion may alter the [K+]. Cold temperatures can cause potassium to exit the RBCs, and warming may cause it to reenter the RBCs.[23] However, full recovery of potassium in transfused RBCs takes several days, and only minimal recovery occurs by 8 hours.[24] Remarkably, there are reports of several cases where patients became hypokalemic after transfusion.[25,26] The definitive cause of the hypokalemia seen in such cases is not known, but several possible mechanisms have been proposed: a rise in plasma catecholamines, hypothermia, alkalemia, shock-related inhibition of body cell membrane sodium-potassium pumps, and (to a small extent in the short term) return into the transfused RBCs.

The theory that RBC transfusions increase serum [K+] makes mathematical sense. However, in vivo data are important in confirming or refuting the ability of K+ in RBC transfusions to alter a patient's actual resulting serum potassium level. Some studies did not find the occurrence of hyperkalemia in transfused subjects, even with massive transfusions,[23,27] whereas other studies reported hyperkalemia.

Experiments in dogs have demonstrated that hyperkalemia can result from RBC transfusions. LeVeen et al[28] followed 3 groups of adult dogs, 5 dogs per group, given blood transfusions. All dogs underwent 10 cycles of bloodletting and transfusion: 100 mL of blood was phlebotomized from an animal, and 100 mL of banked blood was then retransfused. The composition of the banked blood was not described, but it is listed as containing 25 mmol/L of potassium. The control group underwent 10 cycles of bloodletting as described, whereas 2 experimental groups had additional amounts phlebotomized prior to the cycles of bloodletting. This additional amount left dogs in these groups mildly and moderately hypovolemic, respectively, throughout the rest of the experiment. It should be noted that the hypovolemia in both experiment groups was considered "compensated," (ie, the dogs' vital signs normalized before the transfusion cycles). Although vital signs were monitored, no specific markers of tissue hypoperfusion were reported.

In the control group, the dogs' serum potassium levels were unchanged (average 4.2 mEq/L baseline, 4.4 mmol/L after 10 transfusion cycles.) However, hyperkalemia was noted in the other 2 groups of dogs. The post-transfusion potassium levels in the compensated mildly and moderately hypovolemic dogs were elevated: 7.4 and 9.8 mmol/L, respectively. These experiments suggest that hyperkalemia may result from blood transfusions but that normovolemia may be protective against transfusion-associated hyperkalemia. No equivalent study has been performed in humans, but the process involved in exchange transfusions bears some similarity to what was done in the work of Leveen et al.[28] Two common indications for treatment with exchange transfusion are hyperbilirubinemia in infants and sickle cell disease in older children and adults. In these procedures, small

volumes of blood are repeatedly removed from a patient and replaced with banked RBCs. Often a total of 1 to 2 blood volumes are replaced over approximately 2 hours.[29,30] Those who have reviewed these procedures have not identified hyperkalemia among the observed complications.[29-32] There is one published case report of a fatal hyperkalemic arrhythmia with exchange transfusion in a 1.1-kg premature infant, who received 160 mL of blood for the treatment of disseminated intravascular coagulation.[33]

Several published articles address the outcome of hyperkalemia after transfusion in humans in both pediatric and adult populations. A chart review involving extremely low-birth-weight infants in their first week of life demonstrated a linear correlation between K+ administration via transfusion and post-transfusion plasma [K+]. The larger the volume per weight of RBCs transfused, the higher was the resulting [K+] level ($r = 0.442$, $P = .008$).[34] This was true even with the study's design whereby the patient potassium level was not measured until 1 hour after transfusion, suggesting that more severe hyperkalemia may have been detected if [K+] had been measured immediately post-transfusion. Of the 61 patients studied, 3 developed hyperkalemia. All were treated successfully without symptoms.

A pediatric intensive care unit study examined the effects of blood transfusion on serum potassium levels in critically ill babies and children.[35] These investigators followed up 28 children receiving 54 RBC transfusions. No change in post-transfusion serum [K+] was observed, nor were any adverse clinical events seen. However, the RBC transfusions were administered over an average of more than 2 hours, and the post-transfusion potassium values were measured more than an hour after the transfusions were completed. Transfusion volumes were also modest (11.8 ± 2.8 mL/kg of packed RBCs). It is possible that the potassium loads were too small to see increments in the serum values, or that re-equilibration of the potassium in the patients caused observers to "miss" changes when measured later.

One report compared potassium levels in children who underwent surgery, 10 not requiring RBC transfusions and 11 who were massively transfused (>1 blood volume) during major craniofacial surgery.[24] The mean intraoperative plasma [K+] values were not significantly differ-ent between the 2 groups. The RBC-transfused group had a mean baseline [K+] of 3.9 ± 0.4 mmol/L and final [K+] of 4.2 ± 0.8 mmol/L. These values were not significantly different. However, the reviewers identified that 10 of the 11 massively transfused patients had intraoperative spikes in [K+] (range 4.4-6.7 mmol/L), and 9 of the 10 were temporally related to RBC transfusion. This observation may support the idea of a temporary hyperkalemia coinciding with RBC administration, resolving rapidly with redistribution of the potassium load. Finally, analysis of frequent intraoperative blood samples did find a relationship between plasma potassium levels and hematocrit. The authors propose that the observed increases in potassium may therefore be attributable to the RBC transfusions.

In a study of pediatric cardiac bypass primes, there is evidence for transfusion causing hyperkalemia.[36] Two groups of 11 patients had bypass primes made from either unwashed irradiated RBCs (within 14 days of irradiation) or cell-saver-washed irradiated RBCs. The washed RBC prime had a significantly lower [K+]: 2.6 ± 0.1 mmol/L vs 8.1 ± 0.4 mmol/L. Peak patient [K+] early after initiating bypass was also significantly different: washed 3.1 ± 0.1 mmol/L vs unwashed 4.9 ± 0.3 mmol/L ($P < .001$). This laboratory's upper limit of normal serum [K+] was 4.6 mmol/L. Four of the patients in the unwashed RBC group had peak potassium levels higher than 6 mmol/L, and 2 of these patients had ventricular fibrillation during the hyperkalemia period that responded to electrical defibrillation in both cases. Results from this small study suggest that a potassium load can translate into a transient but significant hyperkalemia. The fact that two patients developed dangerous arrhythmias is worth noting.

A third study of pediatric extracorporeal life support circuits with infants below 10 kg demonstrated no relationship between the [K+] level of the primed circuit and the patient serum potassium after initiation.[37] However, initial [K+] were not measured until 30 minutes after cannulation for extracorporeal life support. It is conceivable based on information from other studies suggesting rapid re-equilibration of potassium loads that an initial potassium spike might have been missed with the 30-minute measurement.

Perhaps the strongest evidence for the ability of transfused RBCs to increase plasma [K+] comes

from a military trauma study in adults.[38] The report involved 131 trauma victims studied in an American combat hospital in Iraq for the development of transfusion-associated hyperkalemia. Patients with crush injury, an insult known to cause hyperkalemia, were excluded from this report; 38.5% of transfused patients developed hyperkalemia. Two important conclusions can be drawn from the data presented. First, the investigators examined several factors for possible association with the development of hyperkalemia, including baseline base deficit; baseline plasma bicarbonate level, total transfused blood products, total transfused RBCs, platelet transfusions, cryoprecipitate transfusions, and fresh whole blood transfusions. Of these, the only independent predictor of hyperkalemia was the number of RBC units transfused. Transfusion of other types of blood products did not impact on the incidence of hyperkalemia.[38]

The other key finding was that the number of RBC units needed to cause hyperkalemia (defined as >5.5 mmol/L in this study) was 7, suggesting that hyperkalemia may be a concern in adults but only with large to massive RBC transfusions in the setting of hypovolemic shock. Of note, the study did not look at clinical outcomes from transfusion-associated hyperkalemia.[38]

Tempering the results of the military report are those of a more recent civilian retrospective cohort study.[39] Massively transfused (>10 U RBC) patients at an American trauma center were compared with nontransfused patients. Again, noncrush trauma patients were studied. The maximum [K+] values recorded in the preoperative, immediate postoperative, and 12-hour time frames were compared. Hyperkalemia was significantly more common in the massively-transfused patients in the immediate post-operative period (4.6% vs 1.8%, P = .036), although not at 12 hours. A multivariate analysis was performed to control for several variables: age, sex, injury severity score, preoperative [K+], renal function, acid base, and glycemic statuses. Controlling for these factors, they no longer found an association between massive transfusion and hyperkalemia. Only preoperative [K+] and postoperative pH were associated with postoperative hyperkalemia in their multivariate analysis.

Differences existed between the civilian and military reports. First, the median age of blood in the civilian study was 20 days versus a mean of 30 to 34 days in the military study. Younger blood may have reduced the likelihood of hyperkalemia. Second, intraoperative [K+] was not examined in the civilian report. If a K+ redistribution phenomenon exists, postoperative and 12-hour measurements may fail to capture hyperkalemia that occurs during peaks of transfusion. Finally, the retrospective nature of the civilian study makes it possible that the hyperkalemia was recognized and treated without knowledge of those performing the chart review.

Summary

The question of whether RBC supernatant [K+] affects recipient post-transfusion potassium level has been examined in dogs, children, and adults. Results are mixed. Some studies do not show a relationship. However, several studies do indicate that potassium in transfused RBCs can elevate serum potassium, potentially to dangerous levels. Factors that may predispose to hyperkalemia include high potassium load (either due to high volume, or high [K+] of transfused blood), and hypovolemia.

WHAT IS THE EVIDENCE FOR HYPERKALEMIA CAUSING CARDIAC ARRESTS OR CLINICAL DANGER?

Although it may be plausible that hyperkalemia could result from RBC transfusions, it is important to examine whether clinically important morbidity or mortality has been observed. Reports of transfusion-associated hyperkalemia have been made to hemovigilance organizations. The Public Health Agency of Canada has two reports on record—one of a life-threatening nature in 2002 and a less serious one in 2004 (personal communication, Ms Jenni Vik). The United Kingdom's SHOT (Serious Hazards of Transfusion) reports from 1996 to 2009 include no mention of hyperkalemia as a complication of transfusion. The Australian Hemovigilance Reports (2008 and 2010) similarly describe no hyperkalemic complications.

Studies in dogs of potassium infusions have demonstrated levels at which cardiac arrest occurs. Work done in 1965 by Smith et al[40] involved infusions designed to deliver potassium loads approximating those of potassium given with rapid transfusions. These investigators studied normal dogs and a group treated with reserpine to deplete cardiac catecholamines before potassium

administration. Potassium infusions were continued and increased until the dogs died. Normal dogs died at a mean serum potassium level of 9.79 ± 0.78 mmol/L. Dogs in the reserpine group died at a serum potassium level of 15.00 ± 2.25 mmol/L, although indices of cardiovascular function (cardiac output, total peripheral resistance, mean transit time) worsened earlier in this group. These findings suggest interactions between a patient's catecholamine state and their potassium level, indicating that both protective and harmful interactions may exist. It is interesting to note that normal dogs died of ventricular fibrillation, the commonly described mechanism of hyperkalemic cardiac arrest. However, reserpine-treated dogs died of asystole, suggesting there may be more than one possible sequence of electrocardiographic changes with different biochemical states. Potassium values in both groups were higher than those reported during clinical RBC transfusions. However, LeVeen et al[41] did experiments showing that less than half the infused potassium is required to cause cardiac arrest if dogs are even mildly hypovolemic, instead of normovolemic.

One pediatric study looked at the relationship between blood transfusion, hyperkalemia, and cardiac arrest. Brown et al[42] performed a retrospective review of cardiac arrests over four years at a children's hospital. Two groups were identified: children who were receiving RBC transfusions at the time of the cardiac arrest and those who were not. To be included, cases had to have had a plasma [K+] on record before and during arrest. The mean prearrest [K+] were similar between the transfused (4.59 mmol/L) and nontransfused (4.58 mmol/L) groups. However, the [K+] during the arrest were significantly different: 8.23 mmol/L transfused vs 5.63 mmol/L nontransfused ($P < .05$). (The 5.63 mmol/L arrest value for the nontransfused group was not statistically different from the group's baseline value. This fact suggests that cardiac arrest in itself does not cause hyperkalemia.) These findings do not definitively lead to the conclusion that potassium from RBCs caused the cardiac arrests. In all 7 transfused-arrest cases, the arrest was in the setting of intraoperative hemorrhage being treated with RBC transfusions. Only 3 of these patients had an arrhythmia (2 had ventricular fibrillation, one asystole). Presumably, the other 4 cardiac arrests were due to pulseless electrical activity.[42] It is conceivable that these 4 cardiac arrests might have resulted from hypovolemia rather than hyperkalemia. Hypovolemia is a classic cause of pulseless electrical activity arrest, and also, basic science research done in chickens suggests that hemorrhage itself may lead to a degree of hyperkalemia.[41] The report by Brown et al does seem to indicate that all 7 transfused children were resuscitated. However, profound hyperkalemia may be a barrier to resuscitation in a cardiac arrest situation. Even if the [K+] in the RBC supernatant is not the direct cause of the cardiac arrests, it is likely to aggravate an already dangerous situation.

Interestingly, none of the transfused cardiac arrest patients received specific treatment for hyperkalemia, but all had plasma potassium levels under 5.5 mmol/L within 30 minutes of the arrest.[42] This suggests that the potassium associated with the RBC transfusions may be redistributed within minutes. Another interesting finding in this analysis was the pH during the cardiac arrest. Acidosis is traditionally taught as causing an extracellular shift of potassium. The postcardiac arrest pH of the transfused group was 7.34 ± 0.27, and that of the nontransfused group was 7.27 ± 0.25. Although these pH values were not compared statistically, their similarity implies that the hyperkalemia in the transfused group is likely not secondary to a greater degree of acidemia.

Retrospective reviews looking for transfusion-associated hyperkalemic arrests (TAHA) have also been done at other hospitals.[43] A review of one institution's perioperative (operating room and postanesthetic unit) computerized database of critical incidents was conducted examining an 18-year period from 1988 to 2006. Investigators excluded cases with cardiopulmonary bypass, extracorporeal membrane oxygenation, or liver transplantation. They identified arrests in patients undergoing rapid or massive RBC transfusions by finding either laboratory [K+] of 5.5 mmol/L or greater, or an anesthesiologist's note (eg, describing electrocardiographic evidence of hyperkalemia) that the arrest was due to hyperkalemia. A total of 16 patients were identified. The total number of patients in the database was not given. Most of the patients were adults. The types of operative cases were varied: trauma, vascular, neurosurgical, urologic, hepatobiliary, and others. Mean serum [K+] for the patients was 5.1 ± 1.0 mmol/L before their arrests. All patients received

multiple units of RBCs (or multiple weight-based RBC doses in the case of children). During or immediately after the cardiac arrests, mean serum [K+] was 7.2 ± 1.4 mmol/L.

While the design of this single institutional review does not help us grasp the incidence of TAHA, or specific factors that predispose to it, it does provide evidence that such an entity might exist. However, because the exact details of the cardiac arrests are not conveyed in the article, one might still remain skeptical: perhaps the RBC transfusions (and hence the hyperkalemia) were only associated to the ultimate cause of the cardiac arrests (eg, hypovolemia).

Another single institutional database review (which looks to be from the same database as just discussed) examined perioperative pediatric cardiac arrests.[44] Over a 7-year period there were 88, 639 pediatric non–cardiac surgeries at the institution. There were a total of 26 cardiac arrests amongst the non–cardiac surgery patients. The investigators attributed 8 of these arrests to "hypovolemia, including the consequences of massive blood transfusion, ie, hyperkalemia" and indicated that the latter was the most common cause of cardiac arrest. If all of these 8 cardiac arrests were due to hyperkalemia, it would give an incidence of about 9 per 100 000 hyperkalemic arrests in pediatric noncardiac surgical procedures. However, RBC transfusions are typically uncommon in pediatric noncardiac operations. If only operations where RBC transfusions actually occurred were included in the denominator, the incidence of cardiac arrests might be substantially higher.

Some institutions have already instituted blood bank policies and procedures that limit patient exposure to high-potassium-content RBCs. At Canada's largest children's hospital, supernatant depletion and selection of fresh or very fresh blood (<21 or <7 days from collection) are measures used to limit potassium loads to the smallest patients (personal communication, Dr. Wendy Lau). At Canada's largest trauma center, point-of-care blood-storage refrigerators (operating room, trauma room) are routinely stocked with younger red cell units, rather than oldest stock (personal communication, Dr. Jeannie Callum). Procedures such as these may be associated with reducing the apparent risk of hyperkalemia from RBC transfusions, but this association is still unclear at this time.

Summary

It appears that RBC transfusions can lead to hyperkalemia, and that hyperkalemia-associated cardiac arrests have been observed in the setting of rapid/massive transfusions. The definitive human experiment that would be needed to show causation of TAHA, in patients without confounding factors (otherwise healthy, hemodynamically stable), would of course be highly unethical. What we are able to glean from the available literature is that RBC transfusions probably can cause hyperkalemic cardiac arrests and that these arrests usually happen with large or rapidly transfused volumes, particularly in patients with an associated hypovolemia.

WHAT ARE SOME OF THE PREDICTORS OF TRANSFUSION-ASSOCIATED HYPERKALEMIA?

Patient factors, the storage age of RBC units, and other transfusion factors (ie, speed of infusion) may all have an impact. Some important patient and blood unit factors have already been discussed. Based on animal studies, patients with hypovolemia may be more prone to hyperkalemia that nonhypovolemic patients. Other possible patient factors such as acid-base status, pretransfusion [K+], and renal failure have not specifically been studied. RBC unit factors such as storage age, irradiation, and washing definitely affect supernatant [K+], which may in turn affect the degree of hyperkalemia occurring after transfusion.

The transfusion factor of total volume transfused has already been addressed, with larger volumes having the potential to cause a greater predisposition to hyperkalemia. The other most discussed transfusion factor is the rate of infusion of the RBC transfusion.

There has been interest in the rate of transfusion as it relates to the degree of resulting hyperkalemia. Finnish investigators followed 2 groups of patients undergoing major surgery.[45] The 2 groups compared were one with RBC transfusion rates over 0.3 mL/kg per minute vs patients receiving RBCs at slower infusion rates. There were 11 patients in the former group and 20 in the latter. Serum [K+] was measured before and during transfusion, as well as at the end of anesthesia and after 1 to 2 hours of postoperative recovery. Peak [K+] for both groups occurred during the RBC transfusions. There was a higher rate of hyperkalemia (serum [K+] over 5.5 mmol/L) in the rapidly transfused group. Two of

these patients developed peaked T waves. However, the rapid-infusion group received on average 5864 ± 1021 mL of blood, compared to 1275 ± 156 mL in the slow infusion group, creating a confounding factor. The correlation between rate and degree of potassium rise was poor, whereas the correlation between total potassium load and serum [K+] rise was statistically significant.

Other information from this study points indirectly to the role of infusion rate in developing clinically important hyperkalemia.[45] For both groups, [K+] measurements at the end of anesthesia and during recovery had returned to pre-transfusion levels. This latter finding suggests that there is a redistribution of the potassium load from RBC transfusions over a period less than a few hours. (Mean anesthesia duration was 6.1 ± 0.6 and 5.0 ± 0.3 hours for the more rapidly and less rapidly transfused groups, respectively.) It would therefore be logical to hypothesize that the rate of RBC transfusion is important inasmuch as transfusions may carry a greater risk of causing hyperkalemia if the rate of K+ administration via RBCs exceeds the rate of redistribution of the K+ in the body.

An earlier report from the same group looked back at 21 cases of intraoperative massive transfusion of at least 10 U of whole blood.[46] Eleven of the patients had developed hyperkalemia (defined as >6 mmol/L). Peak values for 5 of the patients were above 7 mmol/L. Three of the hyperkalemic patients experienced cardiac arrests (one ventricular fibrillation and 2 asystole), and 1 died. The cardiac arrests were reported to have occurred during peak transfusion rate and peak potassium measurements. There is mention of a significant correlation between transfusion rate and degree of hyperkalemia, although the rates of transfusion are not indicated. This report also found that post-transfusion [K+] returned to pre-transfusion levels, suggesting that the redistribution of potassium occurs quickly. Therefore, another important transfusion factor impacting on hyperkalemia may be time elapsed since the RBC transfusion.

Summary

Factors that may contribute to transfusion-related hyperkalemia include patient hypovolemia; RBC unit irradiation, increased storage age, and lack of washing; increased transfusion volume; and rate of RBC infusion. Many other factors could be important, including the acid-base status of the recipient, their renal function, and the mode of RBC transfusion (ie, central catheter versus peripheral intravenous), but these factors have not been studied particularly well.

HOW MIGHT TRANSFUSION-ASSOCIATED HYPERKALEMIA BE PREVENTED?

The clinical treatments of hyperkalemia might also be effective in preventing transfusion-associated hyperkalemia and its consequences. For example, agents to enhance potassium elimination or intracellular potassium shift (insulin, β-agonists, bicarbonate), and calcium administration might be helpful in this regard.

The use of fresh blood, which has lower supernatant [K+], might theoretically prevent symptomatic hyperkalemia. A study comparing patient potassium while receiving younger and older RBCs has not yet been reported.

Xia et al[47] studied insulin regimens for prevention of hyperkalemia after reperfusion in liver transplant patients. One of their regimens utilized insulin dosing based on the number of RBC units transfused: 1 to 2 U of insulin with each RBC unit. This regimen was compared retrospectively with large bolus insulin given at the discretion of the anesthesiologist. Although a lower total dose of insulin was used in the RBC-linked protocol, less reperfusion hyperkalemia occurred. Although there were some limitations in the design of the study (including the fact that the potassium load in liver transplant patients is not only from blood but also from the transplanted organ and from tissue metabolism during hypoperfusion), this study suggests that insulin may be an effective way to reduce the risk of transfusion-related hyperkalemia. It also suggests that frequent or possibly continuous administration of insulin may be preferable to bolus infusion.

A commercial bedside potassium adsorption filter has been developed and tested.[48] It has a similar appearance to a standard inravenous tubing and blood filter but uses a sodium polystyrene sulfonate resin to absorb potassium, releasing sodium in its place. When tested at a transfusion rate of 20 ± 9.9 mL/min, it removed about 95% of supernatant potassium from a RBC unit. Potassium removal is high for the first 2 units then drops to 64.4% for the third RBC unit.[49]

Another possible method of removing potassium from RBC units was described in a clinical case report.[50] A patient undergoing nephrectomy had an

initial serum potassium of 5.4 mmol/L, which increased to 6.7 mmol/L intraoperatively. The patient had received 2 U of RBCs after his hematocrit fell to 20%. Further transfusion was required intraoperatively, and there was concern that additional units of RBCs might further increase his serum [K+]. The operative team therefore made use of a continuous autotransfusion (cell saver) device to wash the banked blood prior to transfusion. They reported a 35 minute time to wash 4 U of RBCs, with a reduction in average RBC unit [K+] from 39.6 to 2.3 mmol/L. The patient's serum [K+] fell from 6.7 to 5.9 mmol/L after transfusion of the processed units.

Washing of RBCs before transfusion is commonly performed by blood banks for the purpose of removing various components of the supernatant plasma and additives. However, this process takes considerably longer than the RBC washing described using a cell saver device. When there is advance warning that RBC transfusions will be required, RBC washing is an option. However, the nature of large-volume rapid RBC transfusions is that they are frequently required with little advance notice. In addition, once an RBC unit is washed by the blood bank, it must typically be used within 24 hours (and some suggest 12 hours,[51] limiting the possibility of routine storage of large numbers of pre-washed RBC units.

Avoidance of hemolysis with rapid transfusion might also prevent an unnecessary potassium load. Miller and Schlueter[52] found that rapid administration via needles of 23, 24, and 25 gauge sizes resulted in hemolysis and higher [K+] in the blood passed through the needles versus 18 and 20 gauge needles. However, the change in [K+] was only significant in very fresh units of RBCs, and was not significantly different from baseline in RBC units stored for more than 2 weeks, limiting the clinical relevance of these findings.

Summary

Several methods are available to help clinicians avoid transfusion-associated hyperkalemia when facing high-risk situations. Red blood cell washing is an obvious way to remove supernatant potassium, but is usually impractical for massive RBC transfusions. Transfusing through large-bore needles, selecting fresh blood, using inline potassium adsorption filters, and using cell saver devices to wash RBCs all may reduce the potassium load. Traditional treatments for hyperkalemia may also be effective (eg, insulin).

FUTURE DIRECTIONS

A number of the important facts surrounding transfusion-associated hyperkalemia still need clarification. First, it would be helpful to establish whether RBC transfusions cause hyperkalemia, or whether only an association exists. Strong evidence for causation could come from a prospective trial where blood of different potassium levels (eg, regular stored RBC units versus washed RBCs) are evaluated in patients requiring massive transfusions.

Other relevant questions that should be addressed include the following:

1. Is there a rate of RBC administration above which hyperkalemia is more likely to complicate a transfusion or a rate below which hyperkalemia is very unlikely to occur?
2. Should there be a RBC transfusion trigger (eg, volume transfused per weight) above which antihyperkalemia measures might need to be instituted?
3. What are the safest, most effective, and least expensive ways to prevent hyperkalemic complications associated with RBC transfusions?

ACKNOWLEDGMENT

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