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TRANSFUSION COMPLICATIONS

TRANSFUSION

Transfusion-associated hyperkalemia in pediatric population: Prevalence, risk factors, survival, infusion rate, and RBC unit features

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Abstract

Background: Hyperkalemia is a rare life-threatening complication of red blood cell (RBC) transfusion. Stored RBCs leak intracellular potassium (K+) into the supernatant; irradiation potentiates the K+ leak. As the characteristics of patients and implicated RBCs have not been studied systematically, a multicenter study of transfusion-associated hyperkalemia (TAH) in the pediatric population was conducted through the AABB Pediatric Transfusion Medicine Subsection.

Study Design: The medical records of patients <18 years old were retrospectively queried for hyperkalemia occurrence during or ≤12 h after the completion of RBC transfusion in a 1-year period. Collected data included patient demographics, diagnosis, medical history, timing of hyperkalemia and transfusion, mortality, and RBC unit characteristics.

Results/Findings: A total of 3777 patients received 19,649 RBC units during the study period in four facilities. TAH was found in 35 patients (0.93%) in 37 occurrences. The patient median age and weight were 1.28 years and 9.80 kg, respectively. All patients had multiple serious comorbidities. There were 79 RBC units transfused in the TAH events; 62% were irradiated, and the median age of the units was 10 days. The median total RBC volume transfused ≤12 h before TAH was 24% of patient estimated total blood volume, and the median infusion rate (IR) was19.6 ml/kg/h. Mortality rate within 1 day after the TAH event was 20%.

Conclusions: The prevalence of TAH in children was low; however, the 1-day mortality rate was 20%. Patients with multiple comorbidities may be at higher risk for TAH. The IR was higher for patients who had TAH than the IR threshold for safe transfusion.

KEYWORDS

non infectious, RBC transfusion, transfusion complications, transfusion practices (neonatal, pediatrics)

1 | BACKGROUND

Transfusion-associated hyperkalemia (TAH) is a rare but potentially life-threatening complication of red blood cell (RBC) transfusion that may lead to cardiac arrest due to arrhythmia and depressed cardiac contraction.[1, 2] Stored RBCs leak intracellular potassium (K+) in the supernatant of the RBC units due to inhibition of the membrane Na-K-ATPase pump in cold temperature, and gamma irradiation to prevent graft-versus-host disease potentiates the K+ leak. Although the supernatant mean K+ level in the RBC unit can climb to as high as 78.5 mmol/L in CPDA-1 RBC units (storage day 35);[3] 50.0 and 46.0 mmol/L in AS-1 and AS-3 RBC units, respectively (storage day 42);[3] and 80.7 mmol/L in irradiated AS-1 RBC units (storage day 28 with irradiation day 26),[4] Strauss[5] states that 15 ml/kg RBC transfusion over 5 h would not cause hyperkalemia in neonates. Neonatal K+ levels were also not significantly affected by the low volume of RBC transfusion at normal infusion rates (IRs)[6–8] because the total transfused K+ dose is small and does not exceed the normal physiologic amount of K+ intake required by the neonate. To prevent TAH, most transfusion services that care for neonatal and pediatric patients have established practices to select RBC units for large-volume transfusion that have shorter storage age and that are irradiated close to the time of issue, and RBC units are sometimes washed with normal saline to remove the supernatant. Those practices are based on the fact that older RBC units have higher K+ concentrations and are decided by each transfusion service.

Serious repercussions of TAH with or without cardiac arrest have been reported,[9–18] raising concerns for the risks of TAH from large-volume transfusions with or without a rapid IR for pediatric patients, especially for infants.[19, 20] Patients who are undergoing procedures such as cardiac surgeries using cardiopulmonary bypass (CPB), extracorporeal membrane oxygenation (ECMO), RBC exchange, and liver transplantations may receive large-volume RBC transfusions rapidly and may be at increased risk for TAH. Because fresher units may not be available, and a waiting time of 30 min or more for supernatant removal may be too long in emergencies, the possibility of transient hyperkalemia may not be eliminated.

As the occurrence of TAH and characteristics of patients and implicated blood products in the pediatric population have not been studied systematically, a multicenter retrospective study for TAH was conducted through the AABB Pediatric Transfusion Medicine Subsection to determine the prevalence of this adverse event, as well as the patient and RBC unit characteristics associated with laboratory-confirmed TAH.

2 | STUDY DESIGN

2.1 | Data collection

The medical records of patients who received RBC transfusion and were younger than 18 years at the time of transfusion in a 1-year period (9/1/15 to 8/31/16) were retrospectively queried for hyperkalemia occurrence in four facilities (3 children's hospitals in large academic medical facilities and 1 large academic children's hospital, all in the United States) after local internal review board approvals were obtained. TAH was defined as K+ levels above the institutional reference range (upper limit of 4.9–5.5 mmol/L depending on the patient's age and facility) during or within 12 h after completions of RBC transfusion(s). Patients with minor K+ increase, defined as ≤0.2 mmol/L between the prior K+ level and K+ level at the time of hyperkalemia occurrence, were excluded as an acceptable variable even if K+ level increased to above the reference range. Patient demographics; diagnosis; medical history and comorbidities; and the date and time of K+ levels at the most recent K+ level before the transfusions, at the time hyperkalemia occurred, and follow

TABLE 1 Number of transfused red blood cell (RBC) units and patients by patient age in four facilities

Patient age (years old)	<1	1–5	6–10	11 - <18	Total
NO of RBC units transfused	7467	3620	3139	5423	19 649
NO of patients who received RBC	1523	892	553	809	3777
NO of patients who had hyperkalemia	15 (0.98%)	12 (1.35%)	1 (0.18%)	7 (0.87%)	35 (0.93%)
p	.876	.265	.079	1.00	
p for trend	.385				
Mortality within 1 day of hyperkalemia	3 (20.00%)	3 (25.00)	0 (0%)	1 (14.29%)	7 (20.00%)
p	1.00	.713	N/A	1.00	
p for trend	.846				

TABLE 2 Demographics, comorbidities, and features of transfusion in 35 patients who had hyperkalemia episode(s)

		N (%) or results
Gender	Female	20 (57.14)
	Male	15 (42.86)
Race	Caucasian	13 (37.14)
	African American	6 (17.14)
	Hispanic	1 (2.86)
	Asian	1(2.86)
	Other/non-Hispanic/unknown	14 (40.00)
Median	Age	1.28 years old
	Weight	9.80 kg
	Estimated total blood volume	637.00 mL
Comorbidities	Prematurity	**10 (28.57)**
	Cardiac dysfunction	**10 (28.57)**
	Congestive heart failure	4 (11.43)
	Cardiac arrhythmias	4 (11.43)
	Respiratory dysfunction	**10 (28.57)**
	Kidney dysfunction	**17 (48.57)**
	Liver dysfunction	**8 (22.86)**
	Intracranial disorders/surgery	4 (11.43)
	Orthopedic surgery	1 (2.86)
	Blood loss/iron deficiency anemia	**10 (28.57)**
	Sepsis	4 (11.43)
	Dialysis	3 (8.57)
Priming of life support when hyperkalemia occurred	ECMO	6 (17.14)
	CPB	2 (5.71)
Types of access	Central line	7 (20.00)
	Peripheral veins	8 (22.86)
	Unknown	20 (57.14)
Mortality after hyperkalemia occurrence	In 1 day	7 (20.00)
	In 2–7 days	4 (11.43)
	Within 7 days	11 (31.43)

Abbreviations: CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation.

up when available were recorded. Data on the types of treatment for hyperkalemia, creatinine (Cr) level at the closest time of but before hyperkalemia occurrence, and mortality within 1 day and 7 days after the hyperkalemia occurrence were also collected.

Each RBC unit that was administered within 12 h prior to hyperkalemia occurrence was reviewed in each patient who had TAH. The storage age, volume of the unit, blood type and modification of the units (leukoreduced, irradiated, washed, supernatant reduced), total volume of RBCs transfused within 12 h, and date and approximate start and end times of transfusion of each unit were also recorded when available. Irradiation of RBC units was performed based on each facility's protocol; universal irradiation of RBC unis for pediatric patients by default in three facilities and on request in one facility in study period.

Estimated total blood volume (eTBV) in each patient was calculated based on patient age at the time of transfusion as follows: premature infant 100 ml/kg, <1 month old 85 ml/kg, <4 months old 75 ml/kg, and ≥4 months old male 70 ml/kg and female 65 ml/kg. The RBC IR was calculated from the volume of RBCs transfused and start/end time of transfusion.

2.2 | Statistical analysis

After completion of data collection from four facilities, analysis was performed in aggregate. Due to skewed distribution of the investigated patients' age (most patients were younger than 5 years old), results in median are mainly used for analysis. The patients were divided into four groups by age (Tables 1 and 4), into two groups with hyperkalemia occurrence during or after the transfusion (Table 5-A), and into two groups with or without 1-day mortality (Table 6). RBC units were also divided into two groups with hyperkalemia occurrence during or after the transfusion for analysis on irradiation effect (Table 5-B).

In addition to basic descriptive analysis, further statistical analyses were performed using R Software (R-Project, R Foundation for statistical computing, version 4.0.0; Vienna, Austria). Results were considered statistically significant when p value was <.05. Associations between categorical variables were assessed using Fisher's exact test and Chi-squared test for trend in proportions, as appropriate. The relationship between death within 1 day of hyperkalemia (dependent variable) and other variables (independent variables) collected during the study was assessed using univariate and multivariate binomial regression models. Univariate or multivariate regression analyses were also performed for predictability of death within 1 day of hyperkalemia occurrence.

3 | RESULTS

There were 3777 patients who received 19,649 units of RBC transfusions during the study period in four facilities (Table 1). Hyperkalemia during or within 12 h after RBC transfusion was found 37 times in 35 patients (0.93% of total number of patients who received RBC transfusions). Two patients had a second TAH event after K+ level on the first TAH was returned to normal. These were investigated and analyzed as two occurrences. Mortality within 1 day after TAH among the patients who developed TAH was 20% (7 patients) overall, with the highest occurrence in the 1–5 years age group (25.00%, 3 patients in 12 patients who had TAH). Notably, among three patients who died within 1 day in the <1 year age group (42.86% of seven mortalities), two patients were neonates, less than 28 days of age (28.57% of total seven mortalities). Between age groups, the number of the patients who had TAH and 1-day mortality after hyperkalemia were not statistically different. The trend of the result in each age group from the <1 year age group to 11 to < 18 years age group was also not statistically significant (p for trend: 0.385 and 0.846).

Patients who developed TAH had a median age and weight at the time of transfusion of 1.28 years (0-16.2 years) and 9.80 kg (0.70–45.8 kg), respectively (Table 2). All patients had multiple serious comorbidities; comorbidities that affected more than 20% of

TABLE 3 The features of hyperkalemia in 37 occurrences in 35 patients

		N (%)	p	p for trend
Timing of hyperkalemia (K+ > 1.4 mmol/L from previous normal)	During	18 (48.65)	**.029**	**<.001**
	≤30 min	6 (16.22)	.810	
	30 min to 1 h	3 (8.11)	.197	
	1 to 6 h	8 (21.62)	.821	
	6 to 12 h	2 (5.41)	.107	
	Total	37 (100)		
Any treatments performed for hyperkalemia	Yes	19 (51.35)	.87	
	No	18 (48.65)		

TABLE 4 Patients and red blood cell (RBC) units on transfusions

		Age groups of the patients					
		< 1 yo	1–5 yo	6–10 yo	11– < 18 yo	Total	p or p for trend (*)
Patients (N or median)	Patients (N)	15	12	1	7	35	
	Weight (kg)	3.03	11.70	28.00	48.46	9.80	
	Creatinine (mg/dL)	0.86	0.39	1.50	0.70	1.01	.149
	K+ increase (mmol/L)	0.70	1.65	2.00	1.40	1.40	.119
	Hyperkalemia occurrences (N)	17	12	1	7	37	**.001***
RBC units and Transfusion (N or median)	Units transfused (N)	25	29	1	24	79	.072*
	Units with transfusion time available (N)	21	22	1	19	63	
	Age of units (days)	5.00	11.00	6.00	14.00	10.00	**.021**
	tV-12 (ml)	51.00	263.00	280.00	750.00	250.00	**<.01**
	tV-12/eTBV	0.26	0.25	0.15	0.24	0.24	.710
	IR (ml/h)	40.00	1050.00	227.03	819.00	191.25	**<.001**
	IR/weight (ml/kg/h)	16.56	50.92	8.11	23.81	19.57	.414
	IR/eTBV (/h)	0.22	1.33	0.12	0.35	0.29	**.021**

Note: Creatinine, creatinine closest of but before hyperkalemia occurrence (mg/dL); eTBV, estimated total blood volume; IR, infusion rate; K+ increase, median increase of K level at the time of hyperkalemia from previous K+ level; tV-12, transfused RBC volume within 12 h before hyperkalemia occurrence; yo, years old.

patients were prematurity; anemia; and cardiac, respiratory, renal, and liver dysfunctions. All 35 patients had at least two comorbidities. A high volume of RBCs was used for priming extracorporeal circuits in eight patients; ECMO in six patients, and CPB in two patients.

TAH occurred during transfusion 48.65% of the time ($p = .029$, Table 3). Overall, 64.86% (24/37 occurrences) of TAH occurred during or within 30 min of transfusion. Hyperkalemia was treated in 51.35% of occurrences. Two occurrences were not treated because the patients died before the treatment could be initiated. The details of treatments are fluid bolus, furosemide, albuterol, insulin, calcium gluconate, sodium bicarbonate, stop potassium drip, hook up with continuous renal replacement therapy, and a combination of those.

The group of 6–10-year-olds includes only one patient; therefore, this group does not have a statistical power. Median pretransfusion Cr was within the normal limit (0.20–6.9 mmol/L) except in the 6–10 years of age group with one patient, and median K+ increase from pretransfusion K+ level was 1.40 mmol/L (0.4–4.3 mmol/L, Table 4). Median age of the RBC units was 10.0 days old (3–28 days). Times of transfusion start and end were available in 63 units of the total 79 transfused units. Age of the units, transfused RBC volume within 12 h before TAH occurrence (tV-12), IR, and IR adjusted by eTBV (IR/eTBV) were statistically different between age groups. Median tV-12 was 24% of eTBV, and IR/Kg was 19.57 ml/kg/h.

The transfused volume and IR in each patient and the age and irradiation status of RBC units, along with the timing of TAH occurrences, were analyzed in four groups: TAH during transfusion, TAH after transfusion, data from the specific unit when TAH occurred, and the total occurrences (Table 5). Table 5-A shows the timing of TAH occurrence with transfusion in cases where IR could be calculated (N = 33). The median tV-12/eTBV,

TABLE 5 Comparison of timing of TAH occurrence: during transfusion and after transfusion (data represents median)

A: IR and hyperkalemia occurrence in cases IR could be calculated

	Hyperkalemia occurrence during transfusion (N = 14)	Hyperkalemia occurrence after transfusion (N = 19)	*p*	On specific red blood cell unit when TAH occurred (N = 14)	Hyperkalemia occurrences with available infusion rate (N = 33)
tV-12 (ml)	255	176	.716		215
tV-12/eTBV	0.56	0.17	**.045**		0.24
IR (ml/h)	474.00	100.87	.176	96.69	127.27
IR/weight (ml/kg/h)	30.24	8.48	**.049**	26.18	22.11
IR/eTBV (/h)	0.39	0.11	**.019**	0.34	0.33

Note: eTBV, estimated total blood volume of the patient; IR, infusion rate; TAH, transfusion-associated hyperkalemia; tV-12, transfused RBC volume within 12 h of hyperkalemia occurrence.

B: Effects of irradiated units

	Units when hyperkalemia occurred during transfusion (N = 46)	Units when hyperkalemia occurred after transfusion (N = 33)	*p*	Specific unit at the time of hyperkalemia (n = 14)	Total number of units (N = 79)
Irradiated units (% in each group's total)	30 (65.22)	19 (57.58)	.620	11 (78.57)	49 (62.03)
Age of the units (day)	12.00	9.00	.253	7.00	10.00
Time from irradiation to transfusion (min)	87.00	147.00	.666	87.00	

TABLE 6 Comparison of individual data of patients with mortality within 1 day after hyperkalemia and others (for analyses, numbers represent median)

		Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pts with 1-day mortality (N = 7)	Pts without 1-day mortality (N = 28)	*p*	Total (N = 35)
Patient	Age (year old)	1 day	5 day	39 days	2.1	2.2	3.3	13.0	2.12	1.27	.808	1.28
	Weight (kg)	2.8	0.68	1.03	10.40	12.39	9.80	25.0	9.80	9.90	.257	9.80
	eTBV (ml)	280	68.0	103.0	676.0	805.6	637.00	1625.0	637.0	643.5	.375	637.0
	Creatinine (mmol/L)	1.4	0.93	1.6	0.9	0.2	0.63	0.2	0.9	0.7	.951	1.01
	K+ increase	0.4	0.9	0.6/1.1	2.6	1.8	1.9	4.3	1.45	1.40	.577	1.40
RBC units	Age of unit(s)	9.0	4.0	4.5	9	24.0	16	17.0	9.0	10.0	.622	10.0
	tV-12 (ml)	60.0	38.0	15.0/9.0	250.0	176.0	530.0	1566.0	118.0	276.0	.549	250.0
	tV-12/eTBV	0.21	0.56	0.15/0.09	0.37	0.22	0.83	0.96	0.29	0.24	.349	0.24
	IR (ml/h)	55.38	NA	3.81/2.77	2100.00	54.43	67.13	756.00	917.50	105.88	.343	191.25
	IR/weight (ml/kg/h)	19.78	NA	3.70/2.69	201.92	4.39	6.85	30.24	36.70	14.75	.360	19.57
	IR/eTBV (/h)	0.20	NA	0.04/0.03	3.11	0.07	0.11	0.47	0.56	0.21	.083	0.29
Timing of hyperkalemia recorded during or after the transfusion		120 min	During	10 min/ During	During	30 min	During	During	During 5 (71.43%)	During 12 (42.86%)	.352	
Treatment for hyperkalemia		1, 2	2, 3, 4	1, 2, 5/N	1, 2	6	N	1, 2, 3				
Main comorbidities		Prem. DIC Seizure	Prem. Sepsis C/P-d	Prem. K-d	ECMO Trisomy C/L-d	K-d CRRT	Sepsis K-d R-d	Encephalopathy R-d Ventilator				

Note: Treatment: 1. Sodium Bicarbonate, 2. Calcium, 3. Insulin, 4. Albuterol, 5. Fluid, 6. Continuous renal replacement therapy, N: none.

Comorbidities: Prem.: prematurity, DIC: disseminated intravenous coagulopathy, ECMO: extracorporeal membrane oxygenation.

Abbreviations: C, L, K, R-d, Cardiac-, Liver-, Kidney-, Respiratory dysfunction; Creatinine, creatinine before hyperkalemia occurrence (mg/dL); CRRT, continuous renal replacement therapy; eTBV (ml), estimated total blood volume; IR, Infusion rate; Pt, patient; tV-12 (ml), transfused red blood cell volume within 12 h before hyperkalemia occurrence.

IR/Kg, and IR/eTBV were higher in TAH occurrences during the transfusion than TAH occurrence after the transfusion (p .045, .049, and .019, respectively). Table 5-B shows the irradiation status and storage age of transfused RBC units in the same groups. The number of the irradiated units and median age of the units were slightly higher in the group with TAH occurrences during the transfusion, but the time from irradiation to transfusion was shorter in this group. None of those data were statistically significantly different ($p > .05$).

A total of 79 RBC units were transfused for 35 patients who experienced TAH. Thirty-four units (43.04%) were AS-1 RBC units, and 45 units (56.96%) were AS-3 units. Sixty-three units (79.75%) were blood type O (45 Rh + and 18 Rh-). Blood types of the units were all compatible with the patients; however, 36 type O units were transfused to 17 type non-O patients (48.57% of total 35 patients). All units were leukoreduced, and 49 units (62.03%) were irradiated (Table 5-B). None of the units were either washed or plasma reduced.

Mortality occurred in seven patients within 1 day of hyperkalemia occurrence with multiple comorbidities; three of them had prematurity, and three of them had kidney dysfunction. The details of those 7 patients (Pt 1-7) were compared with 28 other patients who survived at least 1 day after the TAH event and with the total of 35 patients who had TAH (Table 6). Pt 3 had two episodes of TAH; therefore, two data points were divided by a slash (/). Five patients (71.43%) died during the transfusion, and two patients died before the initiation of treatment. Comparing data between the groups of these 7 patients and the 28 other patients, the median IR, IR/Kg, IR/Kg/h, and the prevalence of TAH event during the transfusion were all higher in the 7-patient group; however, the differences were not statistically significant. Overall, none of the collected variables were predictive of 1-day mortality after hyperkalemia occurrence in univariate or multivariate analysis regression analysis (all $p > .05$).

4 | DISCUSSION

Although cases of TAH have been reported, and the occurrence of TAH has been recognized for quite some time, especially in pediatric anesthesiology,[21] the prevalence is low. Available literature is mainly case reports or case series from one facility. Our study is the first multicenter systematic review in a large cohort of pediatric population.

In previous reports of TAH, many patients were pediatric patients, especially neonates;[9–14] however, a significant amount of the literature reported adult patients who developed TAH.[14–18] Our study also shows that the age group of 1–5 years had the biggest prevalence of TAH, but seven patients were in the age group of 11 to <18 years, some of whom had an adult body size. Therefore, TAH may occur not only in the patients with a smaller body size, as we expected, but also in the patients with an adult body size. However, the median age of the patients with TAH was 1.28 years, and the median body weight was 9.80 kg; 27 of 35 patients (77.14%) who had TAH were ≤ 5 years old (0–5.6 years old), which may still suggest that the patients with a smaller body size rather than bigger size are at higher risk of TAH in the pediatric population. In addition, of the seven patients who died within 1 day after a TAH episode, six patients (85.71%) were ≤5 years old. Among them, two patients (28.6%) were neonates (≤28 days old), which is high and consistent with the majority of published cases reporting cardiac arrest due to TAH occurring in neonates.[9, 10, 12]

Our study found that all patients who had TAH had multiple comorbidities. Understandably, the comorbidity with the highest frequency was history of kidney dysfunction, although the laboratory data (Cr) do not suggest that most of these patients were in renal failure before the TAH episode. However, considering the lower reference range of Cr for patients ≤4 years old (0.2–0.6 mg/dL), five of seven patients with 1-day mortality had a slightly higher pretransfusion Cr level above this reference range, which suggests they might have a lower K+ excretion. Prematurity, blood loss/iron deficiency anemia, and cardiac/respiratory/liver dysfunctions were also commonly seen in patients with TAH.

We also investigated the role of RBC volume on the prevalence of TAH. A small volume of RBC transfusion in the normal IR (generally 10–15 ml/kg) is reported not to cause TAH, but massive transfusion is often linked to TAH occurrence.[10, 11, 22] Brown et al.[22] reported that 10 of 11 pediatric patients who underwent massive blood transfusion in craniofacial surgery had an increase in K concentration. Vohra et al.[23] reported that smaller patients (<5 kg) who underwent cardiac surgery with CPB experienced hyperkalemia, but larger patients did not. On the other hand, in adult patients, Carmichael et al.[24] reported that 47% of the adult patients had postoperative hypokalemia, not hyperkalemia, after transfusion of more than 10 RBC units. The reason for hypokalemia is thought to be an intake of K+ by K+ depleted RBCs with restored Na-K-ATPase pump, but hypokalemia is not reported in the pediatric population. Therefore, the risk of TAH from a high volume of transfusion may be specific for young patients with a smaller body size who have low total blood volume and immature kidneys, which may cause low K+ excretion. Our data showed that mean transfused RBC volume within 12 h before

hyperkalemia occurrence was only 24% of eTBV. However, we found that a high volume of RBC transfusion for priming of ECMO and CPB devices was associated with TAH. In addition, the patients on ECMO or CPB who had TAH during the transfusion were ≤ 5 years old (1 day to 5.6 years old) with median weight of 7.58 kg (2.57–21.7 kg). Our results may support previous accounts, and massive RBC transfusion may be a bigger risk factor of TAH in smaller patients. In addition, the patients who developed hyperkalemia during transfusion received larger amounts of transfusions adjusted by eTBV than patients who developed hyperkalemia after transfusion. These data may suggest that higher transfusion volume may also be contributing to TAH occurrence during the transfusion.

Rapid transfusion is also often linked to TAH occurrence.[2, 16, 17] In addition to the fact that hyperkalemia causes suppression of electrical activity, Brown et al.[2] reported that rapid RBC transfusion might depress cardiac output due to ineffective cardiac contraction, resulting in an acute increase in the K+ concentration in hypovolemic children (10–15 kg). They also reported that higher K+ levels were found in those children with rapid blood transfusion than children without rapid transfusion at the time of cardiac arrest. Our patients did not receive a high volume of RBCs but received transfusion in much higher IR than the safe transfusion threshold of 15 ml/kg/5 h (3 ml/kg/h) that Strauss[5] stated. Our study also demonstrates that the age group of 1–5 years had the highest prevalence among the four age groups and had the highest median IR and 1-day mortality rate after the TAH episode. Among the patients with 1-day mortality, IR greater than 3 ml/kg/h was found in six of eight TAH occurrences (75.0%), while one patient had routine IR at the time of death, and another had no data available. Moreover, our study shows significantly higher IR adjusted by patient weight and eTBV in the TAH occurrences during the transfusion than those after the transfusion. These results may suggest that IR might be an important factor to predict TAH occurrence.

Strikingly, most of the patients in this study with TAH received *fresher* RBC units (3–28 days), and the median age of the units transfused was only 10 days, which should not contain extremely high K+. Irradiation was performed in 62% of total transfused units in 35 patients; however, the number of irradiated units and time from irradiation to transfusion did not reveal statistically significant differences between units of TAH occurrence during the transfusion and after the transfusion. These results may imply that the features of the units might not be as influential as we originally expected.

There are several limitations in this study. First, the start and end times of each RBC transfusion may not be precise in some cases because those times were manually entered in most facilities, and in some cases, only time of issue from blood bank and general time of use during surgery/massive transfusion were captured. Therefore, the IR might not be perfectly accurate. Second, it was difficult to assess if the transfusion caused hyperkalemia and if TAH is the cause of mortality because all patients had multiple comorbidities. The need for the rapid and large volume of RBC transfusion suggests the patient had medical or surgical issues unrelated to transfusion that could have caused their demise. Third, the control group (patients who received RBC transfusion but did not develop hyperkalemia) necessary to analyze multivariate analysis for prediction of risk factors of TAH occurrence was not investigated at this time. Therefore, multivariate analysis for risk factors could not be performed. Four, as this is a retrospective study, the K+ concentration of each RBC units was not available. Therefore, the direct correlation between K+ level of the RBC unit and posttransfusion serum K+ level or TAH occurrence could not be analyzed.

5 | CONCLUSIONS

The overall prevalence of TAH in the pediatric population is 0.93%, which means 1 in 108 patients may experience TAH with RBC transfusions. The 1-day mortality after TAH is high (20%) in such patients. Causes of TAH are multifactorial, and all affected patients in our study had multiple comorbidities that could potentiate TAH and its associated complications. Our data show that TAH can occur with an RBC transfusion of only 24% of patient eTBV within 12 h, but median IR/weight was 19.57 ml/kg/h. The highest prevalence of TAH occurrence and 1-day mortality was also found in the 1–5 years age group, with the highest median IR in four age groups. High transfusion volume may not necessarily cause TAH; however, it may be a greater risk factor of TAH in small patients. Higher IR may be an important factor to predict TAH occurrence, especially during the transfusion. Importantly, the irradiation status and storage age of RBC units may not be as influential as expected. The study demonstrates the scope and importance of TAH in the pediatric population. Knowledge and mitigation of the identified risk factors for TAH are critical to prevent adverse consequences.

CONFLICT OF INTEREST

I should like to mention here that I and all of my coauthors have read the AABB's policy on Conflict of Interest

and none of us have any conflicts of interest or financial interests related to this manuscript.

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