Predictors of transfusion outcomes in pediatric complex cranial vault reconstruction: a multicentre observational study from the Pediatric Craniofacial Collaborative Group

Les prédicteurs des besoins transfusionnels lors d'une reconstruction de la voûte crânienne complexe chez l'enfant : une étude observationnelle multicentrique du *Groupe collaboratif craniofacial pédiatrique*

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Abstract

Purpose Pediatric patients undergoing complex cranial vault reconstruction (CCVR) are at risk of significant perioperative blood loss requiring blood product transfusion. Minimizing allogeneic blood product

transfusion is an important goal because of the associated risks and cost. The impact of patient and surgical variables on transfusion is unknown in this population. Our primary aim was to examine relationships between demographic and perioperative variables and blood product transfusion outcomes in CCVR.

Methods The multicentre Pediatric Surgery Perioperative Registry was checked for children undergoing CCVR between June 2012 and September 2016. Univariable and multivariable analyses were performed examining patient,

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procedure, and blood conservation variables and their relationship to three outcomes: intraoperative red blood cell-containing product (RBC-CP) transfusion, total perioperative blood donor exposures, and transfusion-free hospitalization.

Results The registry search returned data from 1,814 cases. Age and surgical duration were the only variables significantly associated with all three outcomes studied. Predictors of reduced RBC-CP transfusion included lower American Society of Anesthesiologists (ASA) physical status and antifibrinolytic administration. Total cranial vault reconstruction, intraoperative vasoactive infusion, and presence of a tracheostomy predicted increased donor exposures. Increased body weight, higher preoperative hematocrit, and utilization of intraoperative cell saver and transfusion protocols were associated with transfusion-free hospitalization.

Conclusion Clinical factors associated with increased allogeneic blood product transfusion in pediatric CCVR include: age ≤ 24 months, ASA status $\geq III$, preoperative anemia, prolonged surgical duration, lack of intraoperative antifibrinolytic use, lack of intraoperative cell saver use, and the lack of transfusion protocols.

Résumé

Objectif Les patients pédiatriques subissant une reconstruction complexe de la voûte crânienne courent un risque de pertes sanguines périopératoires importantes nécessitant la transfusion de produits sanguins. La minimisation de la transfusion de produits sanguins allogènes constitue un objectif majeur étant donné les risques et les coûts associés. L'impact des variables liées au patient et à la chirurgie sur la transfusion est inconnu dans cette population. Notre objectif principal était d'examiner les liens entre les variables démographiques et périopératoires, et les résultats des transfusions sanguines suite à une reconstruction complexe de la voûte crânienne.

Méthode Le Registre périopératoire multicentrique de chirurgie pédiatrique (Pediatric Surgery Perioperative Registry) a été consulté afin d'en extraire les dossiers de tous les enfants ayant subi une reconstruction complexe de la voûte crânienne entre juin 2012 et septembre 2016. Des analyses univariées et multivariées ont été réalisées et ont examiné les variables concernant les patients, l'intervention et la conservation du sang ainsi que les relations entre ces données et trois critères : la transfusion peropératoire de produits contenant des érythrocytes, l'exposition durant toute la période périopératoire aux dons de sang, et l'hospitalisation sans transfusion.

Résultats L'examen du Registre a permis d'extraire les données de 1814 cas. L'âge et la durée de la chirurgie étaient les deux seules variables à afficher une association

significative aux trois critères à l'étude. Les prédicteurs d'une transfusion réduite d'érythrocytes étaient un statut physique ASA (American Society of Anesthesiologists) plus bas et l'administration d'agents antifibrinolytiques. La reconstruction totale de la voûte crânienne, la perfusion peropératoire d'agents vasoactifs et la présence d'une trachéostomie constituaient des prédicteurs d'exposition plus importante aux dons de sang. Un poids corporel accru, un hémocrite préopératoire plus élevé et l'utilisation de systèmes d'autotransfusion peropératoire et de protocoles de transfusion étaient associés à une hospitalisation sans transfusion.

Conclusion Les facteurs cliniques associés à une augmentation des transfusions de produits sanguins allogènes dans les cas de reconstruction complexe de la voûte crânienne chez l'enfant sont : un âge ≤ 24 mois, un statut ASA $\geq III$, une anémie préopératoire, la durée prolongée de la chirurgie, l'absence d'utilisation peropératoire d'antifibrinolytiques, l'absence d'utilisation de systèmes d'autotransfusion peropératoire, et l'absence de protocoles de transfusion.

Pediatric patients undergoing complex cranial vault reconstruction (CCVR) are at risk of significant blood loss and perioperative transfusion. Minimizing blood loss and blood product transfusion is an important goal given the risks and costs of allogeneic blood transfusion.¹⁻⁶ Numerous blood management strategies have been employed in craniostomy surgery, including antifibrinolytics, cell saver, preoperative erythropoietin, acute preoperative normovolemic hemodilution, and the use of restrictive transfusion protocols. The strength of evidence supporting the efficacy and safety of these techniques varies, while knowledge of the impact of other patient and surgical factors on perioperative transfusion, such as patient age, American Society of Anesthesiologists (ASA) physical status, surgical duration, or intraoperative complications, is generally lacking.⁷

In 2011, a consortium of international collaborators from the United States and Canada formed the Pediatric Craniofacial Collaborative Group under the auspices of the Society for Pediatric Anesthesia. This group then established the Pediatric Craniofacial Surgery Perioperative Registry (PCSPR), which has become the largest pediatric craniofacial surgery registry worldwide. It was designed to collect data pertaining to the perioperative course, management, and outcomes in this patient population. A further goal was to foster multicentre research and quality improvement of pediatric anesthesia for reconstructive craniofacial surgery.

We conducted this study to evaluate the relationships between demographic and perioperative variables and transfusion outcomes of CCVR in the multicentre PCSPR; we have not previously examined variables associated with transfusion outcomes using this database. Three outcomes were evaluated: intraoperative red blood cell-containing product (RBC-CP) transfusion, total perioperative blood donor exposures, and the occurrence of an allogeneic transfusion-free hospitalization course. We hypothesized that patient-related variables (e.g., age, weight, ASA physical status), procedure-related variables (procedure type, surgical duration, redo operation) and specific blood management techniques (use of antifibrinolytics, cell saver, and transfusion protocols) would be independently associated with these transfusion outcomes. The primary aim of this study was to report independent predictors of the transfusion outcomes mentioned.

Methods

We searched the PCSPR for subjects undergoing CCVR. Complex cranial vault reconstruction was defined as fronto-orbital advancement/anterior cranial vault reconstruction, middle/posterior cranial vault reconstruction, or total cranial vault reconstruction. All procedures involved a craniotomy. Neuro-endoscopic procedures, spring-mediated cranioplasties, and modified Pi procedures were excluded. Data extracted included demographic and surgical data, fluid and transfusion data, perioperative management data, and complications. The study analysis plan was submitted to the Pediatric Craniofacial Collaborative Group scientific review committee and approved prior to the conduct of the analysis. Appropriate institutional review board (IRB)/research ethics committee approval was obtained at each study site as well as written informed consent when required; at some study sites, the requirement for written informed consent was waived by the IRB. The study was conducted in accordance with STROBE guidelines.⁸

Pediatric craniofacial surgery perioperative registry

Participating institutions began entering data following local institutional ethical review board or equivalent approval. Study data were collected and managed using REDCap electronic data capture tools hosted at the Children's Hospital of Philadelphia.⁹ Data entry began on June 25, 2012. A de-identified dataset with data through to September 30, 2016 was analyzed. Individual institutions were represented using an institution code and were not identifiable.

Data collection, entry, and validation

Thirty-three institutions contributed data over the study time period. Sites were required to provide quarterly reports quantifying case capture rates to avoid reporting bias. The median (25th, 75th interquartile range) reported case capture rate across all participating institutions was 100% (98%, 100%). All participating institutions were required to report data collection and auditing processes to ensure accuracy.¹⁰ Perioperative blood management strategies captured by the registry included the preoperative use of erythropoietin, the intraoperative use of antifibrinolytics (tranexamic acid or aminocaproic acid), deliberate hypotension, cell saver utilization, and acute preoperative normovolemic hemodilution. Intraoperative and postoperative transfusion protocols were also used.

In addition to the above, the study's principal investigator at the Data Coordinating Center audited data prior to analysis. This included scrutinizing cases for omissions of critical data (e.g., age, weight) and identifying outlier data. Cross-validation of data within individual records was performed to optimize data accuracy. Queries based on omissions, outliers, and discrepancies identified through this process were aggregated and sent to site investigators for rectification.

Outcomes and statistical analysis

Demographic data and data describing perioperative management were analyzed using descriptive statistics. Our primary objective was to use univariable and multivariable analysis to identify independent factors associated with three transfusion outcomes: total perioperative blood donor exposures, total volume of intraoperative RBC-CPs, and the occurrence of a transfusion-free hospital course. Red blood cell-containing products included packed red blood cells (PRBCs), whole blood, and reconstituted blood composed of PRBCs and fresh frozen plasma (FFP).¹¹ Hemostatic blood products included non-reconstituted FFP, cryoprecipitate, and platelets.

Independent variables in the analyses included age, weight, sex, race, ethnicity, ASA physical status, preoperative tracheostomy presence, procedure category, cranial distractor placement, history of prior craniofacial surgery, preoperative evidence of elevated intracranial pressure, preoperative hematocrit, use of deliberate hypotension, use of intraoperative cell saver, antifibrinolytic administration (tranexamic acid or aminocaproic acid), use of a standardized protocol to guide either intraoperative or postoperative red cell transfusion, diagnosis of syndromic craniosynostosis or craniosynostosis with three or more sutures involved,

duration of surgery, intraoperative administration of a vasopressor infusion, occurrence of intraoperative hypothermia (nadir temperature of $< 35^{\circ}\text{C}$), hypothermia on arrival to the intensive care unit or recovery room ($< 35^{\circ}\text{C}$), and whether or not one or more major intraoperative cardiorespiratory complications occurred. Major intraoperative cardiorespiratory complications were specific itemized data elements on the registry case report form that were identified prior to analysis. These complications included administration of an intravenous epinephrine bolus, cardiac arrest (defined as any case in which chest compressions were initiated), suspected venous air embolism with cardiovascular collapse, dural venous sinus bleed, suspected transfusion reaction, pulmonary edema, and re-intubation in the operating room.

Data measured on a continuous scale were presented as mean (standard deviation [SD]) or median [interquartile range (IQR)]; categorical variables were presented as frequencies and percentages. Univariable and multivariable analyses were performed for variables potentially associated with the three outcomes described above. For univariable analyses of intraoperative RBC-CP volume and total perioperative blood donor exposure outcomes, the Wilcoxon-Mann-Whitney test was used for dichotomous independent variables and the Kruskal-Wallis test was used for multi-level independent variables. Independent variables with a univariable significance of $P < 0.1$ were included in the multivariable model. Because three outcomes were evaluated, a corrected P value of < 0.0167 ($0.05/3$) was considered statistically significant for the multivariable analysis. For the volume of intraoperative RBC-CP and total perioperative blood donor exposure outcomes, multivariable analysis was performed using a generalized linear mixed effect negative binomial model accounting for the effect of institution with a random effect. For the transfusion-free hospital course outcome, the Chi-square test or Fisher's exact test (when the expected counts were less than 5) was used in the univariable analysis. Logistic regression was used in the multivariable analysis for this binary outcome. For the multivariable analyses, case wise deletion was employed in cases of missing data (available as Electronic Supplementary Material; eTable). Statistical analysis was done with the statistical package SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Demographics

Search of the PCSPR yielded 1,814 subjects from 33 institutions; 75% (1,377) of these were under 24 months of

age (infant group). Detailed demographic data are presented in Table 1. Single-suture metopic and sagittal craniosynostosis were the most common diagnoses. Anterior cranial vault reconstruction/fronto-orbital advancements accounted for greater than 60% of cases. Craniofacial reoperation accounted for 20% of cases for all ages and 11% of cases in the infant group.

Intraoperative blood product transfusion

Intraoperative transfusion data for specific blood products are presented in Table 2. One thousand five hundred and ninety-two (88%) of CCVR patients were transfused a mean (SD) volume of 29.7 (25.9) $\text{mL}\cdot\text{kg}^{-1}$ of allogeneic RBC-CP intraoperatively. Fourteen percent of all patients received an autologous erythrocyte transfusion from intraoperative cell saver (similar in both age groups). With respect to hemostatic blood products, discrete FFP transfusion was the most common, being administered to 22% of all patients. Platelets and cryoprecipitate were transfused relatively infrequently (2% and 3% of cases, respectively).

Intraoperative RBC-containing product transfusion outcome

Univariable and multivariable analyses of selected independent variables and their relationship to intraoperative RBC-CP transfusion are presented in Table 3, with variables organized into three categories: patient variables, procedure variables, and blood conservation variables. Patient variables independently associated with increasing intraoperative RBC-CP transfusion included younger age, decreasing weight, and increasing ASA physical status. Procedure-related variables that were associated with increasing intraoperative RBC-CP transfusion in multivariable analysis included procedures not involving distractor placement, longer surgical duration, use of a vasoactive infusion intraoperatively, and the occurrence of a major intraoperative cardiorespiratory complication. Lack of antifibrinolytic administration was the only blood conservation variable independently associated with higher RBC-CP transfusion.

Blood product donor exposure outcome

Univariable and multivariable analyses for variables associated with total perioperative blood donor exposures are shown in Table 4. Younger patient age and the presence of a tracheostomy were the only patient variables that independently correlated with increased donor exposures. Procedural variables that were

Table 1 Patient demographic data

Variable ^a	All ages	≤ 24 months
Number of subjects	1,814	1,377
Number of institutions represented	33	33
# of cases by institution	41 [16–78]	36 [12–53]
Age (months)	23.7 (30.6)	10.6 (5.0)
Weight (kg)	12.0 (8.9)	9.0 (2.6)
Sex (Male/female)	1,104/710	837/540
Race:		
White/Caucasian	1,315 (73%)	1,040 (76%)
Black/African American	198 (11%)	115 (8.5%)
Asian	53 (3%)	38 (3%)
Other	228 (13%)	168 (12%)
Not recorded	20 (1%)	16 (1%)
Diagnosis:		
Sagittal	417 (23%)	317 (23%)
Metopic	384 (21%)	352 (26%)
Syndromic	275 (15%)	165 (12%)
Unicoronal	272 (15%)	241 (18%)
Multiple (≥ 3 sutures)	174 (10%)	93 (7%)
Bicoronal	94 (5%)	74 (5%)
Lambdoid	54 (3%)	50 (4%)
Sagittal and metopic	47 (3%)	34 (2%)
Sagittal and unicoronal	18 (1%)	8 (0.6%)
Sagittal and lambdoid	16 (0.9%)	10 (0.7%)
Metopic and unicoronal	11 (0.6%)	9 (0.7%)
Unicoronal and lambdoid	3 (0.2%)	2 (0.1%)
Other/not recorded	49 (3%)	22 (1.6%)
Procedure category:		
Anterior cranial vault/ fronto-orbital advancement	1,128 (62%)	888 (64%)
Mid/posterior cranial vault	489 (27%)	373 (27%)
Total cranial vault	197 (11%)	116 (8%)
Distractor placement	214 (12%)	137 (10%)
Prior craniofacial surgery	370 (20%)	147 (11%)
Craniosynostosis syndrome ^b	278 (15%)	167 (12%)
Tracheostomy present	55 (3%)	32 (2%)
Preoperative evidence of elevated intracranial pressure	252 (14%)	84 (6%)
Preoperative hematocrit (%)	35.7 (3.3)	35.3 (3.2)
ASA ^c physical status	II (II–III)	II (II–II)
Plastic surgeon operated	1,760 (97%)	1,327 (96%)
Neurosurgeon operated	1,805 (99%)	1,372 (99%)
Other discipline procedure performed	95 (6%)	61 (5%)

^a Data presented as median [interquartile range] for # of cases by institution, ASA physical status. Data presented as mean (standard deviation) for age, weight, and preoperative hematocrit. All other variables reported as *n* and *n* (%)

^b Craniosynostosis syndrome included Apert, Crouzon, Pfeiffer, Saethre-Chotzen, Muenke, Antley-Bixler, and Carpenter syndromes

^c ASA = American Society of Anesthesiologists = I (normal healthy patient), II (patient with mild systemic disease), III (patient with severe systemic disease), or IV (patient with severe systemic disease that is a constant threat to life)

associated with increasing blood donor exposures in multivariable analysis included procedures not involving distractor placement, longer duration of surgery, vasoactive infusion administration, and total cranial vault reconstruction (vs mid/posterior cranial vault reconstruction). None of the blood conservation variables examined were independently associated with this outcome.

Transfusion-free hospital course outcome

Univariable and multivariable analyses for the binary transfusion-free hospital course outcome are presented in Table 5. Patient-related variables independently associated with this outcome included age greater than 24 months (odds ratio [OR], 4.5; 95% confidence interval [CI], 2.2 to 9.14), weight greater than 11 kg (OR, 3.5; 95% CI, 1.6 to 7.9), ASA physical status III–IV (OR, 0.42; 95% CI, 0.25 to 0.72), and preoperative hematocrit greater than 36 (OR, 2.7; 95% CI, 1.7 to 4.2). Procedure variables that were significantly associated with the occurrence of a transfusion-free course in multivariable analysis included shorter duration of surgery, while total cranial vault reconstruction was associated with a decreased likelihood of this outcome (OR, 0.32; 95% CI, 0.14 to 0.75, vs mid/posterior cranial vault reconstruction). With respect to blood conservation variables, intraoperative red cell transfusion was associated with a lower likelihood of a transfusion-free course (OR, 0.10; 95% CI, 0.05 to 0.21), while intraoperative cell saver use (OR, 4.62; 95% CI, 2.8 to 7.7) and postoperative transfusion protocols (OR, 2.23; 95% CI, 1.3 to 3.8) were independently predictive of a transfusion-free hospital course.

Discussion

Significant variability exists in the amount of bleeding and transfusion in pediatric CCVR, ranging from massive intraoperative transfusion to a transfusion-free hospitalization.¹⁰ We evaluated patient, surgical, and blood conservation variables and three perioperative transfusion outcomes in a large multicentre pediatric CCVR dataset to identify independent predictors of transfusion outcomes. The vast majority (88%) of patients were transfused with a mean RBC-CPs transfusion volume of 30 mL·kg⁻¹. In multivariable analysis, patient age and surgical duration were the only independent variables associated with all three outcomes. Conversely, prior craniofacial surgery, elevated intracranial pressure, syndromic or multi-suture craniosynostosis, intraoperative hypothermia, sex, race, and ethnicity were not associated with these outcomes.

Table 2 Intraoperative transfusion data

	All ages (<i>n</i> = 1,814)		≤ 24 months (<i>n</i> = 1,377)	
	<i>n</i> (%) Receiving	Volume ^a (mL·kg ⁻¹)	<i>n</i> (%) Receiving	Volume ^a (mL·kg ⁻¹)
RBC-containing product	1,592 (88%)	29.7 (25.9)	1,245 (90%)	32.3 (26.7)
PRBCs ^b	1,335 (74%)	30.7 (20.7)	1,076 (78%)	31.9 (20.8)
Reconstituted blood ^b	79 (4%)	63.6 (35.8)	57 (4%)	72.8 (36.5)
Whole blood	178 (10%)	44.8 (27.5)	112 (8%)	53.1 (29.1)
FFP ^b	394 (22%)	26.8 (18.1)	319 (23%)	27.6 (17.7)
Platelets	56 (3%)	16.8 (10.9)	42 (3%)	18.4 (12)
Cryoprecipitate	37 (2%)	5.9 (7.4)	28 (2%)	7.4 (8)
Cell saver	246 (14%)	7.8 (12.5)	188 (13%)	8.7 (14)

^a Volume data presented as mean (standard deviation). Volume data are reported for those patients who received the blood product

^b Number of patients and volumes administered of PRBCs and FFP does not reflect PRBC or FFP component of reconstituted blood. Similarly, data reported for reconstituted blood includes PRBCs and FFP that are not included in the data for these individual components. FFP = fresh frozen plasma; PRBC = packed red blood cells; RBC = red blood cells

Intraoperative RBC-containing product transfusion

We found that younger age, decreasing weight, and higher ASA physical status were each independently associated with increased intraoperative RBC-CP transfusion. This inverse relationship between age and weight with transfusion is consistent with prior reports.¹²⁻¹⁵ The association between higher ASA physical status and increased transfusion has not been previously reported in CCVR. While age and weight are not directly modifiable, our data suggest the possibility that when appropriate, performing surgery in older children may be a strategy to reduce transfusion. Our findings suggest that increased transfusion requirements might be anticipated in younger, smaller, and more medically complex patients.

Surgical variables associated with increased intraoperative transfusion included longer operations, surgeries without distractor placement, and the occurrence of a major intraoperative cardiorespiratory event or intraoperative vasoactive infusion administration. The correlation of distractor placement with less transfusion is consistent with the less complex nature of these procedures. The association of longer operations with increased transfusion has been described.¹²⁻¹⁴ The underpinnings of this relationship are unclear; for example, it is unknown whether it relates to procedure complexity, or if the operations are longer because more time is required to achieve hemostasis.

Intraoperatively, both the occurrence of a major cardiorespiratory complication and administration of a vasoactive infusion were associated with increased transfusion. We suspect that this association was observed because patients with more hemorrhage (and therefore transfusion) were more likely to develop hypotension requiring a vasoactive infusion and/or suffer a related complication.

Antifibrinolytic administration was the only blood conservation variable associated with decreased intraoperative transfusion. Antifibrinolytic administration is the only readily modifiable variable we studied that was associated with transfusion requirements. In the context of the evidence supporting antifibrinolytic efficacy and safety in CCVR, our findings support more widespread use of antifibrinolytic agents in these children.¹⁶⁻²⁰

Perioperative blood donor exposures

Because CCVR may entail postoperative transfusion, we studied total blood donor exposures to capture the entire perioperative course. Additionally, this outcome captures hemostatic blood products not included in the intraoperative RBC-CP outcome. Demographic variables associated with increased blood donor exposures included age over 24 months and preoperative tracheostomy. It is likely that tracheostomy presence is indicative of increased patient complexity in this outcome; similar to increased ASA status. Indeed, greater ASA status was associated with increased blood donor exposure in univariable analysis but fell out following multivariable analysis. Lower weight did not predict blood donor exposures despite its association with higher intraoperative transfusion volumes. This makes sense given that a standard unit of PRBC (i.e., one blood donor exposure) represents a progressively increasing volume (in mL·kg⁻¹) as patient weight decreases.

Similar to the intraoperative RBC-CP transfusion outcome findings, longer operations and vasoactive infusion administration were associated with increased perioperative donor exposures. Total cranial vault reconstruction was associated with more donor exposures, an expected finding given the greater extent and

Table 3 Univariable and multivariable analysis for the outcome “intraoperative red blood cell-containing product transfusion (mL·kg⁻¹)” among all age patients

	Univariable				Multivariable			
	<i>n</i>	Mean	SD ^a	<i>P</i> value	Adjusted mean in (count) ^b	lower 95% CI ^c	upper 95% CI ^c	<i>P</i> value
Patient variable								
Age				< 0.001				
≤ 24 months	1,377	32.3	26.7		38.5	29.7	49.9	
> 24 months	437	21.7	21.5		26.6	20.3	35.2	< 0.001
Weight (kg) tertile				< 0.001				
1 (3.2–8.6)	605	34.8	27.9		39.3	30.0	51.4	
2 (8.57–10.9)	605	31.3	27.1		31.5	24.0	41.3	< 0.001
3 (11–129)	604	23.1	20.8		26.6	20.5	34.8	< 0.001
Sex				0.1				
Female	710	30.1	27.3					
Male	1,104	29.5	25.0					
Race				0.12				
Black/African American	198	29.9	23.9					
Other	301	33.5	30.0					
White	1,315	28.8	25.1					
Ethnicity				0.18				
Non-Hispanic	1,469	30.2	26.3					
Hispanic	321	28.4	24.9					
ASA physical status				< 0.001				
I–II	1,290	27.6	23.7		28.8	22.2	37.7	
3–4	509	35.1	30.4		35.5	27.4	46.1	0.002
Tracheostomy				<0.001				
No	1,759	29.3	25.6		28.2	22.2	35.9	
Yes	55	43.9	33.0		36.2	26.0	50.4	0.08
Preoperative elevated ICP				< 0.001				
No	1,562	30.6	25.9		31.8	24.3	41.3	
Yes	252	24.6	25.5		32.5	24.8	42.5	0.95
Preoperative hematocrit median split (%)				0.13				
Below median (22–35)	847	30.2	25.0					
Above median (36–52)	840	29.6	27.2					
Syndromic/multi-suture synostosis				0.72				
No	1,366	29.2	24.5					
Yes	448	31.5	29.7					
Intraoperative hypothermia (T < 35)				0.91				
No	1,323	29.7	26.2					
Yes	448	29.7	24.7					
Hypothermia on arrival to ICU/PACU (T < 35)				0.96				
No	1,537	29.7	26.4					
Yes	13	27.7	20.3					
Procedure variable								
Procedure category (anterior reference)				< 0.001				
Anterior/FOA	1,128	32.0	27.5		31.8	24.3	41.7	
Mid/posterior	489	24.8	21.9		29.7	22.9	38.9	0.21
Total	197	28.9	24.2		34.8	26.3	46.5	0.24
Procedure category (mid reference)				< 0.001				
Mid/posterior	489	24.8	21.9		29.7	22.9	38.9	

Table 3 continued

	Univariable				Multivariable			
	<i>n</i>	Mean	SD ^a	<i>P</i> value	Adjusted mean in (count) ^b	lower 95% CI ^c	upper 95% CI ^c	<i>P</i> value
Anterior/FOA	1,128	32.0	27.5		31.8	24.3	41.7	0.21
Total	197	28.9	24.2		34.8	26.3	46.5	0.07
Procedure category (total reference)				< 0.001				
Total	197	28.9	24.2		34.8	26.3	46.5	
Anterior/FOA	1,128	32.0	27.5		31.8	24.3	41.7	0.24
Mid/posterior	489	24.8	21.9		29.7	22.9	38.9	0.07
Distractor placement				< 0.001				
No	1,600	30.4	25.6		36.9	28.8	47.9	
Yes	214	25.0	27.9		27.7	20.9	36.6	< 0.001
Prior craniofacial surgery				0.87				
No	1,444	29.5	25.0					
Yes	370	30.7	29.4					
Duration of surgery median split (min)				< 0.001				
Below median (44–225)	883	24.7	22.0		25.8	19.7	33.4	
Above median (226–725)	887	35.2	28.5		40.0	30.9	51.9	< 0.001
Intraoperative vasoactive infusion				0.011				
No	1668	29.0	24.5		28.2	21.8	36.6	
Yes	146	38.6	37.3		36.2	27.4	48.4	0.006
Major intraoperative cardiorespiratory complication				< 0.001				
No	1,728	29.0	25.0		27.4	21.3	35.5	
Yes	86	43.6	37.5		37.3	27.7	50.4	< 0.001
Blood conservation variable								
Deliberate hypotension				0.35				
No	1,734	29.6	25.8					
Yes	80	32.6	28.6					
EPO use				0.31				
No	1,804	29.7	25.6					
Yes	10	38.8	65.7					
Cell saver				< 0.001				
No	1,535	31.7	25.8		31.8	24.5	41.3	
Yes	279	18.7	23.8		32.5	23.6	44.3	0.95
Antifibrinolytic				< 0.001				
No	564	26.9	26.2		34.8	26.6	46.1	
Yes	1,214	31.3	25.6		29.4	22.6	38.1	0.009
Intraoperative RBC protocol				< 0.001				
No	1,227	26.9	23.3		30.0	23.1	39.3	
Yes	587	35.7	29.9		34.1	25.8	45.6	0.17

^a SD = standard deviation, ^bPredicted intraoperative red blood cell (RBC)-containing product transfusion (mL·kg⁻¹) for each independent variable based on the multivariable model, ^cCI = confidence interval.; EPO = erythropoietin; FOA = fronto-orbital advancement; ICP = intracranial pressure; ICU = intensive care unit; PACU = postanesthesia care unit; T = temperature

complexity of these procedures. Interestingly, none of the blood conservation variables were associated with a greater number of blood donor exposures, suggesting that the effects of patient and procedural variables predominated.

Transfusion-free hospital course

Achieving a safe, transfusion-free hospital course is a laudable goal. We found that increasing age, increasing body weight, and higher preoperative hematocrit were each

Table 4 Univariable and multivariable analyses for the outcome “total perioperative blood donor exposures” among patients of all ages

	Univariable				Multivariable			
	<i>n</i>	Mean	SD ^a	<i>P</i> value	Adjusted mean in (count) ^b	lower 95% CI ^c	upper 95% CI ^c	<i>P</i> value
<i>Patient variable</i>								
Age				0.005				
≤ 24 months	1,377	1.8	1.7		3.0	2.4	3.7	
> 24 months	437	1.8	2.4		2.5	2.0	3.2	0.003
Weight (kg) tertile				0.22				
1 (3.2–8.56)	604	1.8	1.6					
2 (8.57–10.9)	605	1.8	1.7					
3 (11–129)	605	1.9	2.2					
Sex				0.41				
Female	710	1.8	2.1					
Male	1,104	1.8	1.7					
Race (black reference)				0.001				
Black/African American	198	2.0	1.8		2.7	2.1	3.5	
Other	301	2.0	2.0		2.6	2.1	3.2	0.30
White	1,315	1.7	1.8		2.9	2.3	3.7	0.47
Race (white reference)				0.001				
White	1,315	1.7	1.8		2.9	2.3	3.7	
Black/African American	198	2.0	1.8		2.7	2.1	3.5	0.7
Other	301	2.0	2.0		2.6	2.1	3.2	0.019
Race (other reference)				0.001				
Other	301	2.0	2.0		2.6	2.1	3.2	
Black/African American	198	2.0	1.8		2.7	2.1	3.5	0.30
White	1,315	1.7	1.8		2.9	2.3	3.7	0.02
Ethnicity				0.54				
Non-Hispanic	1,469	1.8	1.8					
Hispanic	321	1.8	2.1					
ASA physical status				< 0.001				
I-II	228	1.6	1.5		2.4	1.9	3.0	
III-IV	1,062	2.3	2.5		3.1	2.5	3.9	0.05
Tracheostomy				0.001				
No	1,759	1.8	1.8		2.2	1.8	2.8	
Yes	55	3.4	3.6		3.4	2.6	4.3	<0.001
Preoperative elevated ICP				0.33				
No	1,562	1.8	1.8					
Yes	252	1.9	2.3					
Preoperative hematocrit median split (%)				0.6				
Below median (22–35.7)	847	1.8	1.6					
Above median (35.8–52)	840	1.9	2.1					
Syndromic/multi-suture synostosis				0.004				
No	1,366	1.7	1.7		2.7	2.1	3.4	
Yes	448	2.1	2.3		2.8	2.2	3.5	0.40
Intraoperative hypothermia (T < 35)				0.61				
No	1,323	1.8	1.9					
Yes	448	1.8	1.8					
Hypothermia on arrival to ICU/PACU (T < 35)				0.78				
No	1,537	1.8	1.9					

Table 4 continued

	Univariable				Multivariable			
	<i>n</i>	Mean	SD ^a	<i>P</i> value	Adjusted mean in (count) ^b	lower 95% CI ^c	upper 95% CI ^c	<i>P</i> value
Yes	13	2.2	3.1					
<i>Procedure variable</i>								
Procedure category (anterior reference)				< 0.001				
Anterior/FOA	1,128	1.9	2.0		2.7	2.1	3.3	
Mid/posterior	489	1.5	1.4		2.5	2.0	3.2	0.31
Total	197	2.0	2.0		3.1	2.4	3.9	0.04
Procedure category (mid reference)				< 0.001				
Mid/posterior	489	1.5	1.4		2.5	2.0	3.2	
Anterior/FOA	1,128	1.9	2.0		2.7	2.1	3.3	0.31
Total	197	2.0	2.0		3.1	2.4	3.9	0.02
Procedure category (total reference)				< 0.001				
Total	197	2.0	2.0		3.1	2.4	3.9	
Anterior/FOA	1,128	1.9	2.0		2.7	2.1	3.3	0.04
Mid/posterior	489	1.5	1.4		2.5	2.0	3.2	0.02
Distractor placement				< 0.001				
No	1,600	1.9	1.9		3.1	2.5	3.8	
Yes	214	1.4	1.5		2.5	1.9	3.1	0.003
Prior craniofacial surgery				0.03				
No	1,444	1.7	1.7		2.6	2.1	3.3	
Yes	370	2.2	2.4		2.9	2.3	3.6	0.05
Duration of surgery median split (minutes)				< 0.001				
Below median (44–225)	883	1.3	1.0		2.2	1.8	2.8	
Above median (226–725)	887	2.3	2.3		3.4	2.7	4.2	< 0.001
Intraoperative vasoactive infusion				< 0.001				
No	1,668	1.7	1.7		2.2	1.8	2.8	
Yes	146	2.7	3.0		3.4	2.6	4.3	< 0.001
Major intraoperative cardiorespiratory complication				< 0.001				
No	1,728	1.8	1.8		2.5	2.0	3.1	
Yes	86	2.6	2.4		3.0	2.3	3.8	0.03
<i>Blood conservation variable</i>								
Deliberate hypotension				0.60				
No	1,734	1.8	1.8					
Yes	80	1.9	2.4					
EPO use				0.83				
No	1,804	1.8	1.8					
Yes	10	2.9	4.2					
Cell saver				< 0.001				
No	1,535	1.9	1.9		2.4	2.0	3.0	
Yes	279	1.2	1.7		3.1	2.3	4.1	0.05
Antifibrinolytic				0.005				
No	564	1.8	2.0		2.9	2.3	3.7	
Yes	1,214	1.9	1.8		2.6	2.1	3.2	0.03
Intraoperative RBC protocol				0.12				
No	1,227	1.9	2.1					
Yes	587	1.6	1.4					

Table 4 continued

	Univariable				Multivariable			
	<i>n</i>	Mean	SD ^a	<i>P</i> value	Adjusted mean in (count) ^b	lower 95% CI ^c	upper 95% CI ^c	<i>P</i> value
Postoperative transfusion protocol				0.003				
No	1,318	1.9	2.0		2.8	2.3	3.5	
Yes	496	1.5	1.3		2.7	2.1	3.5	0.53

^a SD = Standard deviation, ^b Predicted total perioperative blood donor exposures for each independent variable based on the multivariable model, ^c CI = confidence interval; EPO = erythropoietin; FOA = fronto-orbital advancement; ICP = intracranial pressure; ICU = intensive care unit; PACU = postanesthesia care unit; RBC = red blood cell; T = temperature

Table 5 Univariable and multivariable analyses for the binary outcome “transfusion-free hospital course (yes/no)” among patients of all ages

	Univariable			Multivariable			
	No <i>n</i> (%)	Yes <i>n</i> (%)	<i>P</i> Value	OR ^b	lower 95% CI ^c	upper 95% CI ^c	<i>P</i> value
Patient variable							
Age			< 0.001				
≤ 24 months	1,291 (93.8)	86 (6.3)		1 (reference)			
> 24 months	350 (80.1)	87 (19.9)		4.48	2.20	9.14	<.001
Weight (kg) rank			< 0.001				
1 (3.2–8.56)	574 (95.0)	30 (5.0)		1 (reference)			
2 (8.57–10.9)	561 (92.7)	44 (7.3)		2.16	1.13	4.15	0.02
3 (11–129)	506 (83.6)	99 (16.4)		3.53	1.57	7.96	0.002
Sex			0.11				
Female	652 (91.8)	58 (8.2)					
Male	989 (89.6)	115 (10.4)					
Race (black reference)			0.007				
Black/African American	189 (95.5)	9 (4.6)		1 (reference)			
Other	279 (92.7)	22 (7.3)		1.63	0.61	4.34	0.33
White	1,173 (89.2)	142 (10.8)		2.62	1.12	6.16	0.03
Race (white reference)			0.007				
White	1,173 (89.2)	142 (10.8)		1 (reference)			
Black/African American	189 (95.5)	9 (4.6)		0.38	0.16	0.90	0.03
Other	279 (92.7)	22 (7.3)		0.62	0.33	1.16	0.14
Race (other reference)			0.007				
Other	279 (92.7)	22 (7.3)		1 (reference)			
Black/African American	189 (95.5)	9 (4.6)		0.62	0.23	1.64	0.33
White	1,173 (89.2)	142 (10.8)		1.61	0.86	3.02	0.14
Ethnicity			0.44				
Non-Hispanic	1,325 (90.2)	144 (9.8)					
Hispanic	294 (91.6)	27 (8.4)					
ASA physical status			0.04				
I-II	1,155 (89.5)	135 (10.5)		1 (reference)			
III-IV	472 (92.7)	37 (7.3)		0.42	0.25	0.72	0.0015
Tracheostomy			0.48 ^a				
No	1,589 (90.3)	170 (9.7)					
Yes	52 (94.6)	3 (5.5)					

Table 5 continued

	Univariable			Multivariable			
	Non (%)	Yesn (%)	P Value	OR ^b	lower 95% CI ^c	upper 95% CI ^c	P value
Preoperative elevated ICP			< 0.001				
No	1,432 (91.7)	130 (8.3)		1 (reference)			
Yes	209 (82.9)	43 (17.1)		1.07	0.61	1.87	0.81
Preoperative hematocrit median split (%)			< 0.001				
Below median (22–35.7)	801 (94.6)	46 (5.4)		1 (reference)			
Above median (35.8–52)	741 (88.2)	99 (11.8)		2.66	1.68	4.23	< 0.001
Syndromic/multi-suture synostosis			0.54				
No	1,239 (90.7)	127 (9.3)					
Yes	402 (89.7)	46 (10.3)					
Intraoperative hypothermia (T < 35)			0.03				
No	1,190 (90.0)	133 (10.1)		1 (reference)			
Yes	418 (93.3)	30 (6.7)		0.80	0.46	1.37	0.41
Hypothermia on arrival to ICU/PACU (T < 35)			1 ^a				
No	1,389 (90.4)	148 (9.6)					
Yes	12 (92.3)	1 (7.7)					
Procedure variable							
Procedure category (anterior reference)			<0.001				
Anterior/FOA	1,038 (92.0)	90 (8.0)		1 (reference)			
Mid/posterior	420 (85.9)	69 (14.1)		1.44	0.89	2.32	0.14
Total	183 (92.9)	14 (7.1)		0.46	0.20	1.04	0.06
Procedure category (mid reference)			<0.001				
Mid/posterior	420 (85.9)	69 (14.1)		1 (reference)			
Anterior/FOA	1,038 (92.0)	90 (8.0)		0.70	0.43	1.12	0.14
Total	183 (92.9)	14 (7.1)		0.32	0.14	0.75	0.008
Procedure category (total reference)			<0.001				
Total	183 (92.9)	14 (7.1)		1 (reference)			
Anterior/FOA	1,038 (92.0)	90 (8.0)		2.17	0.96	4.91	0.06
Mid/posterior	420 (85.9)	69 (14.1)		3.13	1.34	7.31	0.008
Distractor placement			< 0.001				
No	1,467 (91.7)	133 (8.3)		1 (reference)			
Yes	174 (81.3)	40 (18.7)		1.59	0.87	2.89	0.13
Prior craniofacial surgery			< 0.001				
No	1,326 (91.8)	118 (8.2)		1 (reference)			
Yes	315 (85.1)	55 (14.9)		1.01	0.58	1.76	0.98
Duration of surgery median split (minutes)			< 0.001				
Below median (44–225)	758 (85.8)	125 (14.2)		1 (reference)			
Above median (226–725)	851 (95.9)	36 (4.1)		0.25	0.15	0.43	< 0.001
Intraoperative vasoactive infusion			0.39				
No	1,506 (90.3)	162 (9.7)					
Yes	135 (92.5)	11 (7.5)					
Major intraoperative cardiorespiratory complication			0.13 ^a				
No	1,559 (90.2)	169 (9.8)					
Yes	82 (95.4)	4 (4.7)					

Table 5 continued

	Univariable			Multivariable			
	Non (%)	Yesn (%)	P Value	OR ^b	lower 95% CI ^c	upper 95% CI ^c	P value
Blood conservation variable							
Deliberate hypotension			0.89				
No	1,569 (90.5)	165 (9.5)					
Yes	72 (90.0)	8 (10.0)					
Cell saver			< 0.001				
No	1,427 (93.0)	108 (7.0)		1 (reference)			
Yes	214 (76.7)	65 (23.3)		4.62	2.77	7.69	< 0.001
Antifibrinolytic			< 0.001				
No	491 (87.1)	73 (12.9)		1 (reference)			
Yes	1,128 (92.9)	86 (7.1)		1.39	0.86	2.25	0.18
Intraoperative RBC protocol			< 0.001				
No	1,075 (87.6)	152 (12.4)		1 (reference)			
Yes	566 (96.4)	21 (3.6)		0.10	0.05	0.21	< 0.001
Postoperative transfusion protocol			< 0.001				
No	1,211 (91.9)	107 (8.1)		1 (reference)			
Yes	430 (86.7)	66 (13.3)		2.23	1.31	3.81	0.003

^a Fisher exact test *P* value was used where expected counts were less than 5, ^bOR = odds ratio, ^cCI = confidence interval; EPO = erythropoietin; FOA = fronto-orbital advancement; ICP = intracranial pressure; ICU = intensive care unit; PACU = postanesthesia care unit; RBC = red blood cell; T = temperature

associated with an increased likelihood of a transfusion-free hospitalization. Children with a preoperative hematocrit above the median of 35% were nearly three times more likely to avoid transfusion. This highlights the potential value of optimizing preoperative hematocrit and treating anemia when present; a concept supported elsewhere in the adult and pediatric perioperative literature.²¹⁻²⁴

More medically complex patients (ASA physical status III or IV) were less likely to experience a transfusion-free hospital course, similar to data previously reported for pediatric surgical patients.²⁵ The only procedural variable associated with a transfusion-free hospitalization was shorter duration of surgery, consistent with our other findings.

Use of cell saver and transfusion protocols were predictive of a transfusion-free hospitalization. Interestingly, despite evidence of efficacy, transfusion protocols are underutilized.¹⁰ Counterintuitively, intraoperative transfusion protocols were associated with a reduced likelihood of a transfusion-free course. This may be because we did not account for the effect of institution in this outcome, as centres with greater transfusion may also have implemented intraoperative transfusion protocols.

Limitations

Limitations of this study include those inherent to clinical databases including inaccurate or missing data.²⁶ Associations and not cause and effect relationships can be established with observational data. Additionally, the registry may not capture all management strategies that have an impact on outcomes. While the effect of institution was accounted for in the RBC-CP transfusion and blood donor exposure analyses, it was not accounted for in the transfusion-free hospitalization outcome because it is a binary variable with a low frequency of occurrence. For this outcome, the effects of variables for which there was little within-institutional heterogeneity could not be separated from institution-specific outcomes. Finally, the number of patients who experienced a transfusion-free hospitalization was small and so conclusions should be drawn cautiously regarding this outcome.

Conclusion

In this large, multicentre dataset we identified significant predictors of relevant transfusion outcomes in CCVR. The significant demographic variables may help physicians preoperatively identify patients with greater transfusion requirements. Patient variables independently associated

with increasing blood transfusion included younger age, decreasing weight, and increasing ASA physical status. Procedure-related variables that were associated with increasing blood transfusion included the more complex total cranial vault remodeling procedures, longer surgical duration, use of a vasoactive infusion intraoperatively, and the occurrence of a major intraoperative cardiorespiratory complication. Lack of antifibrinolytic administration was the only blood conservation variable independently associated with higher blood transfusion. Our findings of increased blood donor exposures for longer procedures and total cranial vault reconstruction and reduced transfusion with procedures involving distractor application provide information to be considered in surgical planning. Some of the identified predictors are directly modifiable and can serve as substrates for future investigation of improvement efforts.

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