Predictors of Clinically Significant Postoperative Events after Open Craniosynostosis Surgery

Susan M. Goobie, M.D., F.R.C.P.C., David Zurakowski, Ph.D., Mark R. Proctor, M.D., John G. Meara, M.D., Petra M. Meier, M.D., Vanessa J. Young, R.N., B.N., Gary F. Rogers, M.D.

ABSTRACT

Background: Craniosynostosis surgery is associated with clinically significant postoperative events requiring intensive care unit (ICU) admission. The authors investigate specific variables, which might influence the risk for these events, and thereby make recommendations regarding the need for postoperative ICU admission.

Methods: A retrospective review of 225 children undergoing open craniosynostosis repair at a single center during a 10-yr period is reported. The primary outcome measure was the incidence of predefined clinically relevant postoperative cardiorespiratory and hematological events requiring ICU admission.

Results: The incidences of postoperative cardiorespiratory and hematological events requiring ICU care were 14.7% (95% CI, 10.5 to 20.1%) and 29.7% (95% CI, 24.0 to 36.3%), respectively. Independent predictors of cardiorespiratory events were body weight less than 10 kg, American Society of Anesthesiologists physical status 3 or 4, intraoperative transfusion of greater than 60 ml/kg packed erythrocytes, and the occurrence of an intraoperative complication. The independent predictors of hematological events were body weight less than 10 kg, American Society of Anesthesiologists physical status 3 or 4, intraoperative transfusion of greater than 60 ml/kg packed erythrocytes, transfusion of hemostatic products (fresh-frozen plasma, platelets, and/or cryoprecipitate), and tranexamic acid not administered.

Conclusions: Children undergoing craniosynostosis surgery are at increased risk for clinically significant postoperative events requiring ICU admission if they are less than 10 kg body weight, American Society of Anesthesiologists physical status 3 or 4, require intraoperative transfusion of greater than 60 ml/kg of packed erythrocytes, receive hemostatic blood products, or if they develop a significant intraoperative complication. Tranexamic acid administration was associated with fewer postoperative events. A predictive clinical algorithm for pediatric patients having major craniosynostosis surgery was developed and validated to risk stratify these patients. **(Anesthesiology 2015; 122:1021-32)**

PROCEDURES to correct craniosynostosis have become safer during the last 3 decades. The morbidity and mortality rates of these procedures, once reported to be as high as 16.5 and 1.6%, respectively, have declined to approximately 0.1% for each.[1–4] Improvements in operative techniques and training as well as advancements in anesthesia care and patient blood management strategies have driven this trend.

In a retrospective review of 8,101 children undergoing craniofacial surgery in two centers in the United States, Czerwinski *et al.*[1] reported a mortality of 0.1% with 50% of the deaths being directly attributed to blood loss. A 2013 study, using a national database of 3,426 patients from 131 American teaching hospitals, reported a 10% acute postoperative complication rate from craniosynostosis surgical repair, most commonly due to hematological events, hemorrhage or hematoma (4%), and airway/respiratory failure (3%).[2] Lee *et al.*[3] published in 2012 a 30-yr retrospective review of 796 children having primary cransynostosis surgery from Australia and concluded that there was a combined 14% intraoperative and postoperative complication rate, higher

What We Already Know about This Topic

- Craniosynostosis surgery is associated with clinically significant postoperative events requiring intensive care unit admission.
- This study determined specific postoperative cardiorespiratory and hematological events after craniosynostosis surgery, which would require intensive care unit admission.

What This Article Tells Us That Is New

- Children undergoing craniosynostosis surgery are at increased risk for clinically significant postoperative events requiring intensive care unit admission if they are less than 10 kg body weight, have American Society of Anesthesiologists physical status 3 or 4, require intraoperative transfusion of greater than 60 ml/kg of packed erythrocytes, receive hemostatic blood products, or develop a significant intraoperative complication. Tranexamic acid administration was associated with fewer postoperative events.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). Presented at the International Society of Craniofacial Surgery Annual Meeting, September 10-14, 2013, Jackson Hole, Wyoming, and the International Anesthesia Research Society Meeting, May 17-20, 2014, Montreal, Quebec, Canada.

Submitted for publication March 1, 2014. Accepted for publication December 15, 2014. From the Department of Anesthesiology, Perioperative, and Pain Medicine (S.M.G., D.Z., P.M.M., V.J.Y.), Department of Neurosurgery (M.R.P.), and Department of Plastic Surgery (J.G.M.), Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts; and Department of Plastic Surgery, Children's National Medical Center, Washington, D.C. (G.F.R.).

 Anesthesiology 2015; 122:1021-32

in the syndromic/complex multisuturial craniosynostosis, age older than 9 months, longer surgical operating times, and in patients requiring a greater volume of blood transfused. Seruya *et al.*[4] in a 2013 retrospective review of 117 infants from a single U.S. tertiary care institution reported that 4.7% of patients had major events or interventions requiring intensive care unit (ICU) care after fronto-orbital advancement surgery. Predictors included preexisting end-organ dysfunction and higher intraoperative blood loss.

Despite the decreased risk of perioperative complications, most craniofacial centers routinely admit patients to the ICU after major cranial vault procedures. ICU admission provides a measure of additional safety after these large operations, but this step may be unnecessary for many patients. Bypassing the ICU stay has the potential to decrease treatment costs, decompress ICU bed usage, and provide a more comfortable setting for the family.[5] These four recent surgical reports support the decreased morbidity and mortality associated with these procedures; however, further data pertaining to risk stratification is needed to safely optimize and guide clinical care.

We conducted a retrospective chart review to investigate specific patient characteristics that might alter the risk for clinically significant postoperative events, specifically cardiorespiratory and hematological events, which would require ICU admission.

Materials and Methods

With Boston Children's Hospital institutional review board (Boston, Massachusetts) approval, the records of consecutive patients treated surgically for craniosynostosis at our institution from 2002 to 2012 were retrospectively reviewed by two independent examiners. The billing database was cross-referenced to surgical and anesthesia database records to ensure all patients were recorded. Documents evaluated included clinic notes, anesthesia record, surgical report of operation, ICU and inpatient documentation, laboratory values, and discharge summary. Patients who had undergone endoscopic strip craniectomies or who had other concurrent procedures were excluded. The appendix defines the preoperative, intraoperative, and postoperative variables collected.

Two clinically significant postoperative event categories (*i.e.*, occurring within the first 24 h), which would necessitate ICU stay, were predefined as follows:

1. Cardiorespiratory events that require ICU admission were defined as major respiratory events including postoperative intubation, reintubation, respiratory distress or failure, significant apnea, or significant upper airway obstruction, and/or a major cardiac event, including significant hemodynamic instability.
2. Hematological events that require ICU admission[6] were defined as the requirement for postoperative packed erythrocyte transfusion due to hemodynamic instability and/or significant anemia (defined as hematocrit <24%), postoperative clinical coagulopathy requiring hemostatic blood product transfusion (platelets, fresh-frozen plasma, and/or cryoprecipitate) as defined and treated by standard guidelines,[7,8] and/or significant bleeding (defined as >30 ml/kg of blood in the surgical drain during the first 24 h postoperatively).

Minor events, which could be routinely managed on the floor, are listed and defined in the appendix. These minor events were not considered to require ICU admission and were not included in the analysis.

The primary outcome measure was the incidence of clinically significant postoperative cardiorespiratory and hematological events, which require ICU admission.

Statistical Analysis

Univariate analysis was performed using Fisher exact test to identify associations between demographic and anesthesia variables and the occurrence of postoperative cardiorespiratory and hematological events. Cutoff values for continuous variable were determined using the Youden J-index in receiver operating characteristic curve analysis.[9] To control for any possible confounding among variables, multivariate logistic regression using backward selection was applied to determine the independent predictors of each category of postoperative event (cardiorespiratory or hematological) using a univariate cutoff value of P less than 0.20 for inclusion and P less than 0.10 for removal. The likelihood ratio test was used to assess significance of each variable and the odds ratio (OR) and 95% CI calculated for multivariate predictors.[10] Based on the final fitted multivariate models, maximum likelihood estimation was used to derive predictive algorithms with 95% CIs for estimating the risk of postoperative events.[11] The *c*-index, ranging from 0.500 (no discrimination) to 1.000 (perfect discrimination), was used as the criterion to judge the quality of multivariate model with a *c*-index of 0.750 or greater considered as excellent predictive accuracy indicating a useful algorithm in a practical clinical sense.[12] Power analysis was conducted *a priori* and indicated that a total sample size of 200 or more patients would provide 80% power to detect a minimum 20% difference in the incidence of a cardiorespiratory or hematological events between subgroups for each of the clinically relevant covariates being tested including American Society of Anesthesiologists (ASA) physical status, body weight, intraoperative packed erythrocyte transfusion, hemostatic blood product transfusion, occurrence of an intraoperative complication, and the use of tranexamic acid (TXA) based on Fisher exact test for univariate analysis and based on multivariate logistic regression modeling to capture an effect size defined as an OR of 2.5 or greater (version 7.0, nQuery Advisor; Statistical Solutions, USA).

To assess the influence of the evolution of practice over time, the incidences of clinically significant postoperative events over the time intervals 2002–2005, 2006–2009, and 2010–2012 yr were analyzed.

To assess the likely performance of the models for predicting cardiorespiratory and hematological events, we used an internal validation strategy based on the validate.lrm function in the R Design package (version 2.4.1 of R statistical software; R Foundation for Statistical Computing, Austria). For each event prediction model, we instructed the function to compute bias-corrected measures for model assessment based on the bootstrapping technique with 500 bootstrap resamples.[13] Statistical analysis was performed using IBM SPSS Statistics (version 21.0; IBM, USA) with two-tailed values of *P* less than 0.05 considered statistically significant.

To determine the generalizability of our model in predicting the incidence of clinically significant major postoperative events that might necessitate a postoperative ICU stay, using the independent risk factors determined, the multivariate predictive algorithm was also validated on an independent external cohort of patients.

Results

The charts of 225 successive patients who underwent craniosynostosis surgery at Boston Children's Hospital during the years 2002 to 2012 were analyzed. The characteristics of the study cohort undergoing craniosynostosis surgery are detailed in table 1.

The median age at surgery was 13 months (interquartile range, 9 to 34). The median weight was 10 kg (interquartile range, 8.6 to 12.7). The number of patients with the diagnosis of a craniosynostosis syndrome was 39 of 225 (17%). The mean duration of surgery was 5.4 ± 1.4 h. Intraoperatively, 91% of patients received a blood transfusion. The average volume of packed erythrocytes transfused was 32.5 ± 22.8 ml/kg. TXA was given to 64% (143 of 225) of patients. The average perioperative calculated blood loss in 24 h was 69 ± 44 ml/kg (median = 62 ml/kg; interquartile range, 44 to 84). Intraoperative hemostatic blood products were given to 8.4% (19 of 225) of patients. Standard practice dictated that all patients were admitted to the ICU postoperatively. The median length of stay in ICU was 1 day (interquartile range, 1 to 2); full range was 0 to 14 days. Seventy percent of patients spent only 1 day in the ICU postoperatively.

The two major categories of postoperative events, cardiorespiratory and hematological, requiring ICU management had the following incidence:

Cardiorespiratory Events. Within the entire cohort, the incidence of clinically significant cardiorespiratory events requiring postoperative ICU admission was 14.7% (95% CI, 10.5 to 20.1%) with 13.4% being respiratory and 1.3% being cardiac.

Univariate analysis identified six variables (table 2) that were associated with these cardiorespiratory postoperative events: body weight less than 10 kg, ASA physical status 3 or 4, intraoperative transfusion packed erythrocytes greater than 60 ml/kg, hemostatic blood product transfusion, significant intraoperative complication (see the appendix

Table 1. Characteristics of Study Cohort Undergoing Craniosynostosis Surgery (N = 225)

Variable	Value or No. Patients	Percentage
Age at procedure, months, median (IQR)	13 (9–34)	
Weight, kg, median (IQR)	10 (8.6–12.7)	
<10 kg	112	50
Gender		
Male	119	53
Female	106	47
ASA		
1 or 2	173	77
3 or 4	52	23
Procedure		
FOA	158	70
TCR	67	30
Number of sutures		
1	170	76
2	37	16
3	16	7
4	2	2
Craniofacial syndrome*	39	17
Intraop. packed erythro., ml/kg, mean ± SD	32.5 ± 22.8	
Intraop. albumin, ml/kg, mean ± SD	23.2 ± 22.1	
Intraop. hemostatic products	19	8.4
Surgical duration (h) mean ± SD (range)	5.4 ± 1.4 (2.2–10.6)	
TXA given	143	64

* Craniofacial syndromes = Aperts, Crouzan, Pfeiffer, Saethre-Chotzen, and Trisomy 21.

ASA = American Society of Anesthesiologists physical status; erythro. = erythrocytes; FOA = fronto-orbital advancement; hemostatic products = fresh-frozen plasma, platelets, and/or cryoprecipitate; Intraop. = intraoperative; IQR = interquartile range; TCR = total calvarial remodeling; TXA = tranexamic acid.

Table 2. Univariate Analysis of Candidate Predictors Associated with Clinically Significant Postoperative Cardiorespiratory Event

Variable	Event (n = 33)	No Event (n = 192)	*P* Value
Weight <10 kg	25 (76%)	87 (45%)	<0.001*
ASA 3 or 4	15 (46%)	37 (19%)	0.003*
Intraop. packed erythrocytes >60 ml/kg	13 (39%)	16 (8%)	<0.001*
Intraop. hemostatic products	7 (21%)	12 (6%)	0.011*
Intraop. complication†	14 (42%)	44 (23%)	0.029*
TXA not given	16 (49%)	66 (34%)	0.17

* Statistically significant (Fisher exact test). † Intraoperative complication = refer to the appendix for detailed definitions.

ASA 3 or 4 = American Society of Anesthesiologists physical status 3 (a patient with severe systemic disease) or 4 (a patient with severe systemic disease that is a constant threat to life); hemostatic products = fresh-frozen plasma, platelets, and/or cryoprecipitate; Intraop. = intraoperative; TXA = tranexamic acid.

for definition), and the absence of TXA administration intraoperatively.

All six variables significant by univariate analysis were tested using multivariate logistic regression analysis to determine independent risk factors of these postoperative cardiorespiratory events. Four significant independent predictors of postoperative cardiorespiratory events which require ICU admission were identified: body weight less than 10 kg ($P < 0.001$), ASA physical status 3 or 4 ($P = 0.003$), intraoperative packed erythrocyte transfusion greater than 60 ml/kg ($P < 0.001$), and occurrence of an intraoperative complication ($P = 0.029$). The ORs are given in table 3.

Hematological Events. Within the entire cohort, the incidence of clinically significant hematological events requiring postoperative ICU admission was 29.8% (95% CI, 24.0 to 36.3%). Patients requiring packed erythrocyte transfusion due to hemodynamic instability or significant anemia represented 5.8% of the total, with 11% of children requiring postoperative hemostatic blood product transfusion to treat significant clinical coagulopathy as defined and treated by standard guidelines[7,8] and 12.9% having significant postoperative bleeding. (See the appendix for definitions.)

Univariate analysis identified four variables (table 4) that were associated with a significant hematological postoperative event, requiring ICU admission: weight less than 10 kg, intraoperative packed erythrocyte transfusion greater than 60 ml/kg, intraoperative hemostatic blood product transfusion, and TXA not given.

All four variables significant by univariate analysis were tested using multivariate logistic regression analysis to determine independent risk factors for a postoperative hematological event requiring ICU admission. All four were identified as significant independent predictors of postoperative hematological events: body weight less than 10 kg ($P < 0.001$), intraoperative packed erythrocyte transfusion greater than 60 ml/kg ($P < 0.001$), intraoperative transfusion of hemostatic blood products ($P < 0.001$), and TXA not given ($P < 0.001$). The ORs are given in table 5.

Furthermore, algorithms were developed based on multivariate regression as a practical clinical tool to predict the probability of clinically significant postoperative cardiorespiratory and hematological events requiring ICU admission (tables 6 and 7). This multivariate model indicates that a patient with body weight less than 10 kg, ASA 3 or 4, intraoperative packed erythrocyte transfusion greater than 60 ml/kg, and the occurrence of an intraoperative complication would have a 90% probability (95% CI, 70 to 97%) of incurring a clinically significant postoperative cardiorespiratory event requiring ICU admission compared with only a 3% probability (95% CI, 1 to 7%) for a patient weighing greater than 10 kg, ASA 1 or 2, receiving intraoperative packed erythrocyte transfusion 60 ml/kg or less, and with no intraoperative complication (table 6). Furthermore, this multivariate model predicts that a patient with a body weight less than 10 kg, intraoperative packed erythrocyte transfusion greater than 60 ml/kg, intraoperative hemostatic blood products given, and TXA not given has a 97% probability (95% CI, 85 to 99%) of incurring a clinically significant postoperative hematological event requiring ICU admission compared with only a 10% probability (95% CI, 6 to 18%) for a patient weighing 10 kg or more, receiving packed erythrocyte transfusion 60 ml/kg or

Table 3. Significant Independent Multivariate Predictors of Clinically Significant Postoperative Cardiorespiratory Event

Predictor	LRT	*P* Value	Odds Ratio (95% CI)
Weight <10 kg	4.24	0.039	2.7 (1.1–6.8)
ASA 3 or 4	12.52	<0.001	5.1 (2.1–12.8)
Intraop. packed erythrocytes >60 ml/kg	12.56	<0.001	6.2 (2.3–17.1)
Intraop. complication*	7.49	0.006	3.5 (1.5–8.7)

* Intraoperative complication = refer to the appendix for detailed definition.

ASA 3 or 4 = American Society of Anesthesiologists physical status 3 (a patient with severe systemic disease) or 4 (a patient with severe systemic disease that is a constant threat to life); Intraop. = intraoperative; LRT = likelihood ratio test from multivariate logistic regression analysis.

Table 4. Univariate Analysis of Candidate Predictors Associated with Clinically Significant Postoperative Hematological Event

Variable	Event (n = 67)	No Event (n = 158)	*P* Value
Weight <10 kg	47 (70%)	65 (41%)	<0.001*
ASA 3 or 4	14 (21%)	38 (24%)	0.73
Intraop. packed erythrocytes >60 ml/kg	25 (37%)	4 (3%)	<0.001*
Intraop. hemostatic products	15 (22%)	4 (3%)	<0.001*
Intraop. complication†	21 (31%)	37 (23%)	0.24
TXA not given	39 (58%)	43 (27%)	<0.001*

* Statistically significant (Fisher exact test). † Intraoperative complication = refer to the appendix for detailed definitions.

ASA 3 or 4 = American Society of Anesthesiologists physical status 3 (a patient with severe systemic disease) or 4 (a patient with severe systemic disease that is a constant threat to life); hemostatic products = platelets, fresh-frozen plasma, and/or cryoprecipitate; Intraop. = intraoperative; TXA = tranexamic acid.

Table 5. Significant Multivariate-independent Predictors of Clinically Significant Postoperative Hematological Event

Predictor	LRT	*P* Value	Odds Ratio (95% CI)
Weight <10 kg	4.57	0.033	2.2 (1.2–4.3)
Intraop. packed erythrocytes >60 ml/kg	16.08	<0.001	9.2 (2.8–30.6)
Intraop. hemostatic products	6.24	0.013	5.3 (1.4–20.1)
TXA not given	7.37	0.007	2.6 (1.4–5.2)

Hemostatic products = platelets, fresh-frozen plasma, and/or cryoprecipitate; Intraop. = intraoperative; LRT = likelihood ratio test from multivariate logistic regression analysis; TXA = tranexamic acid.

less, not requiring hemostatic blood products, and receiving TXA intraoperatively (table 7).

The predictive accuracy of the four variable multivariate algorithms for postoperative cardiorespiratory events (table 6) and hematological events (table 7) was judged to be excellent based on the *c*-index = 0.818 (95% CI, 0.737 to 0.900) and *c*-index = 0.821 (95% CI, 0.755 to 0.888), respectively.

A simplified algorithm for predicting a clinically significant postoperative event requiring ICU based on the number of significant multivariate risk factors identified is presented in table 8. Patients with six of six risk factors were predicted to have a 97% chance (95% CI, 91 to 99%) of having a clinically significant postoperative event, whereas those with only one risk factor were predicted to have a 22% chance (95% CI, 56 to 75%) and those with no risk factors were predicted to have a 10% chance (95% CI, 5 to 17%).

Figure 1 shows the ORs for multivariate predictors of any clinically significant postoperative event requiring ICU

Table 6. Probability Algorithm of Clinically Significant Postoperative Cardiorespiratory Event

Significant Multivariate Clinical Predictor					
Body Weight <10 kg	ASA Class 3 or 4	Intraop. Packed Erythrocytes >60 ml/kg	Intraoperative Complication*	Probability (%)	95% CI
Yes	Yes	Yes	Yes	90	70–97
Yes	Yes	Yes	No	68	46–85
Yes	No	Yes	Yes	60	35–80
Yes	Yes	No	Yes	55	31–77
Yes	No	Yes	No	30	16–50
Yes	Yes	No	No	25	14–43
Yes	No	No	Yes	20	10–35
Yes	No	No	No	7	3–12
No	Yes	Yes	Yes	75	45–91
No	Yes	Yes	No	45	20–72
No	No	Yes	Yes	36	15–67
No	Yes	No	Yes	31	15–54
No	No	Yes	No	14	5–35
No	Yes	No	No	12	5–25
No	No	No	Yes	8	3–20
No	No	No	No	3	1–7

Algorithm developed using multivariate logistic regression.

* Intraoperative complication = refer to the appendix.

ASA class 3 or 4 = American Society of Anesthesiologists physical status 3 (a patient with severe systemic disease) or 4 (a patient with severe systemic disease that is a constant threat to life); Intraop. = intraoperative.

Table 7. Probability Algorithm of Clinically Significant Postoperative Hematological Event

Significant Multivariate Clinical Predictor					
Body Weight <10 kg	Intraop. Packed Erythrocytes >60 ml/kg	Intraop. Hemostatic Products	TXA Used	Probability (%)	95% CI
Yes	Yes	Yes	No	97	85–99
Yes	Yes	Yes	Yes	93	68–98
Yes	Yes	No	No	86	66–95
Yes	No	Yes	No	78	45–93
Yes	Yes	No	Yes	70	42–88
Yes	No	Yes	Yes	58	26–84
Yes	No	No	No	40	25–56
Yes	No	No	Yes	20	13–31
No	Yes	Yes	No	94	68–99
No	Yes	Yes	Yes	85	45–98
No	Yes	No	No	74	42–92
No	No	Yes	No	62	26–88
No	Yes	No	Yes	53	21–82
No	No	Yes	Yes	39	13–73
No	No	No	No	24	12–37
No	No	No	Yes	10	6–18

Algorithm developed using multivariate logistic regression.

Hemostatic products = platelets, fresh-frozen plasma, and/or cryoprecipitate; Intraop. = intraoperative; TXA = tranexamic acid.

admission. Figure 2 shows the percentage of clinically significant postoperative events requiring ICU admission for the multivariate risk factors identified. Figure 3 shows the percentage of any clinically significant postoperative event requiring ICU admission for the multivariate risk factors identified. Figure 4 shows the probability of any clinically significant postoperative event requiring ICU admission given the number of significant multivariate risk factors present.

There was no significant difference between the incidences of those clinically significant postoperative events during the time intervals of the study. Specifically, the incidence for hematological events in the year intervals 2002–2005, 2006–2009, and 2010–2012 was 23, 33, and 34%, respectively (x =2.62, P = 0.269) and the incidence of cardiorespiratory events 10, 16, and 18%, respectively, for those time intervals (x = 1.95, P = 0.377).

Table 8. Simplified Algorithm for Predicting a Clinically Significant Postoperative Event* Requiring ICU Admission Based on the Number of Significant Multivariate Risk Factors†

Number of Risk Factors	Probability of a Postoperative Event, %	95% CI
All 6	97	91–99%
Any 5	93	84–97%
Any 4	84	72–91%
Any 3	67	56–75%
Any 2	43	36–50%
Any 1	22	16–30%
None	10	5–17%

* Postoperative event can be either hematological or cardiorespiratory or both. Area under the receiver operating curve based on the simplified algorithm shows very good predictive accuracy (c-index, 0.785; 95% CI, 0.715–0.855).

† The six multivariate risk factors include body weight <10 kg, American Society of Anesthesiologists class 3 or 4, packed erythrocyte transfusion >60 ml/kg, intraoperative complication, hemostatic blood products (platelets, fresh-frozen plasma, and/or cryoprecipitate), and not using tranexamic acid.

ICU = intensive care unit.

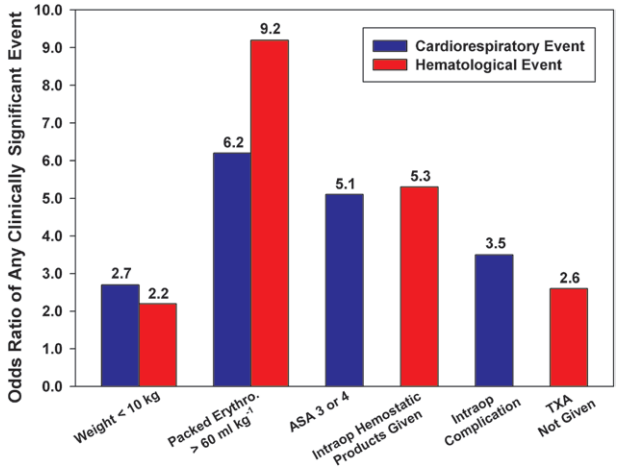

Fig. 1. Odds ratios for the six multivariate predictors of any clinically significant postoperative event requiring intensive care unit admission. The multivariate risk factors include body weight <10 kg, ASA class 3 or 4, packed erythrocyte transfusion >60 ml/kg, intraoperative complication, hemostatic blood product transfusion (platelets, fresh-frozen plasma, and/or cryoprecipitate), and tranexamic acid (TXA) not given. Any clinically significant postoperative event = cardiorespiratory and/or hematological; ASA 3 or 4 = American Society of Anesthesiologists physical status 3 (a patient with severe systemic disease) or 4 (a patient with severe systemic disease that is a constant threat to life); hemostatic products = platelets, fresh-frozen plasma, and/or cryoprecipitate; Intraop. = intraoperative; intraoperative complication = refer to the appendix for detailed definition; Packed Erythro = intraoperative packed erythrocyte transfusion.

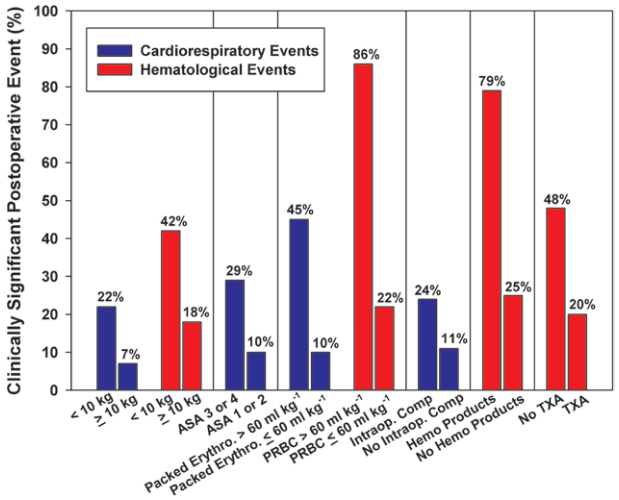

Fig. 2. Percentage of clinically significant postoperative events requiring intensive care unit admission for the multivariate risks factors identified. Clinically significant postoperative event = cardiorespiratory and/or hematological event. The multivariate risk factors include body weight <10 kg, ASA class 3 or 4, packed erythrocyte transfusion >60 ml/kg, intraoperative complication, hemostatic blood product transfusion (platelets, fresh-frozen plasma, and/or cryoprecipitate), and tranexamic acid (TXA) not given. ASA 3 or 4 = American Society of Anesthesiologists physical status 3 (a patient with severe systemic disease) or 4 (a patient with severe systemic disease that is a constant threat to life); Hemo. Products = platelets, fresh-frozen plasma, and/or cryoprecipitate; Intraop. = intraoperative; Intraop. Comp. = intraoperative complication (refer to the appendix for detailed definition); Packed Erythro (PRBC) = intraoperative packed erythrocyte transfusion.

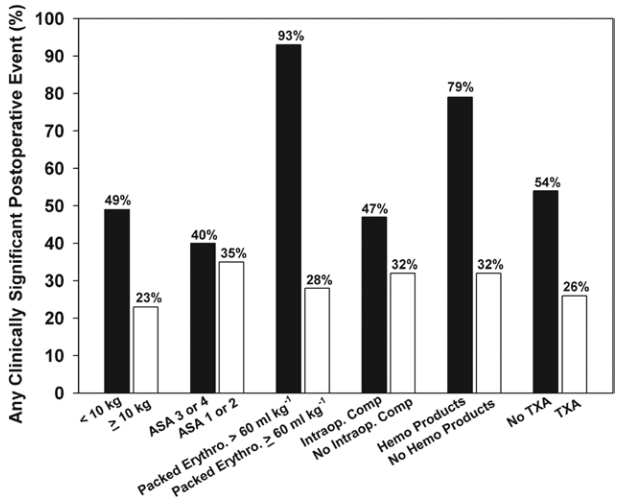

Fig. 3. Percentage of any clinically significant postoperative event requiring intensive care unit admission for the multivariate risk factors identified. Clinically significant postoperative event = cardiorespiratory and/or hematological event. The multivariate risk factors include body weight <10 kg, ASA class 3 or 4, packed erythrocyte transfusion >60 ml/kg, intraoperative complication, hemostatic blood product transfusion (platelets, fresh-frozen plasma, and/or cryoprecipitate), and tranexamic acid (TXA) not given. ASA 3 or 4 = American Society of Anesthesiologists physical status 3 (a patient with severe systemic disease) or 4 (a patient with severe systemic disease that is a constant threat to life); Hemo. Products = platelets, fresh-frozen plasma, and/or cryoprecipitate; Intraop. = intraoperative; Intraop. Comp. = intraoperative complication (refer to the appendix for detailed definition); Packed Erythro = intraoperative packed erythrocyte transfusion.

Individual patients having both cardiorespiratory and hematological clinically significant postoperative events accounted for 23% (19 of 81) of those who had such events. This high-risk group had a statistically significantly ($P < 0.05$) higher incidence of having one or more of the independent risk factors identified; 90% weighed less than 10 kg, 58% received greater than 60 ml/kg packed erythrocytes, 58% did not get TXA, 47% were ASA 3 or 4, 42% had an intraoperative complication, and 37% received intraoperative hemostatic blood products.

Internal Validation of Predictive Algorithms

Our validation results using the bootstrapping technique indicated for cardiorespiratory events, a bias-corrected Somers' D rank correlation measure of 0.543, corresponding to a c-statistic or area under the curve of 0.771. The Nagelkerke R^2 measure was 0.247. The intercept and slope of an overall logistic calibration equation were −0.099 and 0.913, respectively. The maximum absolute difference in predicted and calibrated probabilities, or E_{max}, was 0.038. The discrimination index D was 0.145, and the unreliability index U was 0.004, resulting in an overall quality index or logarithmic probability score Q = 0.142. The Brier quadratic probability score B was 0.102. For hematological events, the Somers' D was 0.553, equivalent to a c-statistic or area under the curve of 0.776. The R^2 measure was 0.325. The logistic calibration equation intercept and slope were −0.084 and 0.909, and E_{max} was 0.036. A discrimination index D value of 0.254 and an unreliability index U of 0.009, resulted in an overall quality index or logarithmic probability score Q = 0.244. The Brier quadratic probability score B was 0.154. Overall, the predictive accuracy was reasonable based on the validation results for the cardiorespiratory and the hematological algorithms, suggesting that our predictive models contain good internal validity, particularly judging from the c-index values, which are approaching 0.800. See Supplemental Digital Content 1, http://links.lww.com/ALN/B138, which represents the internal validation bootstrapping results using R software (R Foundation for Statistical Computing) for the original multivariate algorithms in predicting clinically significant postoperative cardiorespiratory complications and hematological complications.

External Validation of Multivariable Predictive Algorithm

The multivariate predictive algorithm was validated on an independent external sample of patients to determine the generalizability of our model in predicting the incidence of

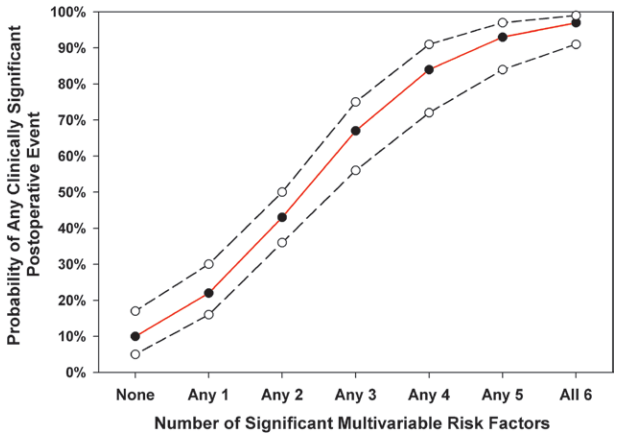

Fig. 4. Probability of any clinically significant postoperative event requiring intensive care unit admission for the number of multivariate risk factors identified. Clinically significant postoperative event = cardiorespiratory and/or hematological event. The six multivariate risk factors include body weight <10 kg, American Society of Anesthesiologists class 3 or 4, packed erythrocyte transfusion >60 ml/kg, intraoperative complication, hemostatic blood product transfusion (platelets, fresh-frozen plasma, and/or cryoprecipitate), and tranexamic acid not given. *Red line* indicates predicted probability with *dashed line* indicating 95% CI around the predicted probability.

clinically significant major postoperative events that might necessitate a postoperative ICU stay using the independent risk factors determined. The external validation cohort consisted of 40 consecutive patients from the years 2012 to 2014 who underwent craniosynostosis surgery at Boston Children's Hospital. There were a total of 12 unique patients with clinically significant postoperative events (8 hematological, 6 cardiorespiratory, and 2 patients had both kinds of events). The prognostic model was validated based on five of six of our predicted risk factors as all of the 40 patients in the new cohort received TXA. This is now the standard of care as supported by the fact that patients who did not receive TXA in our original cohort had an incidence of a major postoperative event that was double those receiving TXA: 44 of 82 patients not receiving TXA (54%) as compared with 37 of 143 patients receiving TXA (26%) and due to the recent literature on the efficacy of TXA in this population.[14] The event rate in the new validation cohort is similar to our original cohort of patients receiving TXA with respect to the percentage of patients who developed a postoperative hematological or cardiorespiratory event: new cohort 12 of 40 = 30%; original cohort 37 of 143 = 26%.

Table 9 shows the results of the external validation. The prognostic model accurately predicted the incidence of postoperative clinically significant events based on the five independent risk factors.

Table 10 shows the results for the external validation of the predictive algorithm based on the number of significant multivariate risk factors identified. Of the 40 new patients, 10 had three or more risk factors, and all of these 10 patients had a significant postoperative event. With a cutoff of three or more risk factors, sensitivity is 83%, specificity is 100%, and overall accuracy is 95%. Combining all five predictors together into multivariate logistic regression model and saving the predicted probabilities of having a postoperative event, the area under

Table 9. External Validation of Prognostic Algorithm to Predict Probability of a Clinically Significant Postoperative Event* Requiring ICU Admission Based on the Multivariate Risk Factors Identified† (n = 40)

Risk Factor	Any Clinically Significant Postoperative Event (n = 12)	No Major Postoperative Event (n = 28)	*P* Value
Weight			0.018‡
<10 kg	9 (75%)	9 (32%)	
≥10 kg	3 (25%)	19 (68%)	
ASA			0.041‡
1 or 2	2 (17%)	15 (54%)	
3 or 4	10 (83%)	13 (46%)	
Intraop. transfusion packed erythrocytes			<0.001‡
>60 ml/kg	5 (42%)	28 (100%)	
≥60 ml/kg	7 (58%)	0	
Intraop. transfusion hemostatic products			<0.001‡
Yes	5 (42%)	28 (100%)	
No	7 (58%)	0	
Intraop. complication§			0.006‡
No	7 (58%)	27 (96%)	
Yes	5 (42%)	1 (4%)	

* Postoperative event can be either hematological or cardiorespiratory or both. † The multivariate risk factors include body weight <10 kg, ASA class 3 or 4, packed erythrocyte transfusion >60 ml/kg, intraoperative complication, and hemostatic blood product transfusion (platelets, fresh-frozen plasma, and/or cryoprecipitate). All patients received tranexamic acid; therefore, this was not used as a variable in the validation. ‡ Statistically significant (Fisher exact test). § Intraoperative Complication = refer to the appendix for detailed definition.

ASA 3 or 4 = American Society of Anesthesiologists physical status 3 (a patient with severe systemic disease) or 4 (a patient with severe systemic disease that is a constant threat to life); hemostatic products = platelets, fresh-frozen plasma, and/or cryoprecipitate; ICU = intensive care unit; Intraop. = intraoperative.

Table 10. External Validation of Algorithm for Predicting a Clinically Significant Postoperative Event* Requiring ICU Admission Based on the Number of Significant Multivariate Risk Factors† (n = 40)

Number of Risk Factors	Postoperative Event*	
	Yes (n = 12)	No (n = 28)
All 5	2 (17%)	0
Any 4	2 (17%)	0
Any 3	6 (50%)	0
Any 2	1 (8%)	5 (18%)
Any 1	0	13 (40%)
None	1 (8%)	10 (36%)

* Postoperative event can be either hematological or cardiorespiratory or both. Area under the receiver operating curve based on the simplified algorithm shows very good predictive accuracy (area under the curve, 0.924; 95% CI, 0.793–1.000; $P < 0.001$). † The five multivariate risk factors include body weight <10 kg, American Society of Anesthesiologists class 3 or 4, packed erythrocyte transfusion >60 ml/kg, intraoperative complication, and hemostatic blood products (platelets, fresh-frozen plasma, and/or cryoprecipitate). All patients received tranexamic acid.

ICU = intensive care unit.

the receiver operating characteristic curve (*i.e.*, the *c*-index) indicates excellent predictive accuracy (area under the curve, 0.924; 95% CI, 0.793 to 1.000; $P < 0.001$).

Discussion

Our 10-yr retrospective review of 225 children undergoing open craniosynostosis surgery identified a 14.7% rate of postoperative cardiorespiratory events and a 29.7% rate of postoperative hematological events, which are clinically significant enough to require ICU monitoring postoperatively as opposed to routine monitoring on the surgical floor. These rates are in keeping with other reports[1–4]; the majority of problems arising from blood loss or airway/respiratory failure,[2] and the incidence of major postoperative complications being highest in medically complex and syndromic patients.[3] Within our cohort, 64% of patients did not have a clinically significant event requiring ICU care postoperatively and 70% spent only 1 day in the ICU. This low-risk group would be predicted to have an uneventful postoperative course, not requiring an ICU admission. Our goal was to identify those specific patients who are at higher risk for significant postoperative events and thereby, through risk stratification, make practical clinical recommendations for postoperative care to optimize ICU bed usage while maximizing patient safety.

Identified in this analysis are independent predictors of clinically significant postoperative events for children undergoing craniosynostosis surgery. We present a clinically relevant predictive algorithm based on the presence of six multivariate risk factors (body weight <10 kg, ASA physical status 3 or 4, intraoperative packed erythrocyte transfusion >60 ml/kg, intraoperative complication, intraoperative hemostatic blood product administration, and not administering TXA) which can be used to predict patients who are at an increased risk of a clinically relevant postoperative event requiring ICU admission.

Clinical Relevance

We developed useful predictive clinical algorithms (tables 6–8) for pediatric patients having craniosynostosis surgery to predict the risk for clinically significant postoperative events that might require an ICU stay. A simplified algorithm that predicts the probability of any significant postoperative event (table 8) highlights six important multivariate risk factors which can be used to risk stratify patients: body weight <10 kg, ASA physical status 3 or 4, packed erythrocyte transfusion greater than 60 ml/kg, a significant intraoperative complication, intraoperative transfusion of hemostatic blood products (fresh-frozen plasma, platelets, and cryoprecipitate; given to manage clinical coagulopathy as defined and treated by standard guidelines),[7,8] and not using TXA. These algorithms can be used by physicians to risk stratify these patients postoperatively and to more efficiently plan ICU bed usage. Patients having all six variables have a 97% (CI, 91 to 99%) probability for having a postoperative complication. Those in the lower risk category (body weight >10 kg, ASA physical status 1 or 2, receiving <60 ml/kg packed erythrocytes, no intraoperative complications, not receiving hemostatic blood products, and given TXA) have a 10% probability (CI, 5 to 17%) of having a clinically significant postoperative event and therefore may be considered good candidates to go to the floor instead. While beyond the scope of this study, the role of a step down unit or high dependency unit should also be considered as an alternative and reasonable option to ICU in some centers.[15]

Study Limitations

The limitations of this study are common for retrospective studies of this type: minor complications were not included, no set intraoperative/postoperative transfusion guidelines, no set anesthetic regime, potential change in practice over 10 yr as intraoperative and surgical care evolved over time, and underreporting or not identifying all complications, as is the nature of a retrospective review.

However, despite the potential evolution of therapeutic protocols and practice changes over time (including transfusion practices), there were no significant differences between the distributions of major postoperative events during the study time period.

To minimize any potential bias or confounding, a multivariate modeling analysis was performed to identify independently predictive risk factors of these events (*i.e.*, predictors that are unbiased and not confounded by other variables). Also, an internal validation was conducted to attest to the precision and calibration of our algorithm. Finally, an external validation with a cohort of all the patients from 2012 to 2014 who underwent craniosynostosis surgery at Boston

Children's Hospital was performed to confirm that the proposed multivariate predictive algorithms are robust and generalizable. These three methods provide more solid evidence that the conclusions are unbiased and internally consistent and that the algorithms are valid.

Our multivariate analysis did not identify any statistically significant correlation between increased postoperative adverse events and factors such as age, calculated blood loss, surgical duration, type of surgical procedure, number of sutures involved, intraoperative albumin administration, and/or the presence of a craniofacial syndrome as other investigators have found.[3,16,17] One explanation is that although these variables were significant in univariate analysis, through multivariate analysis they were eliminated as independent predictive factors.

Furthermore, although we have shown that the risk of clinically significant adverse postoperative event is low when the patient does not have one of the six major independent risk factors identified, there still remains some risk which may be difficult to predict or may be unexpected. This prognostic algorithm is a tool to help guide decision making. Clinical care should still be guided by expert clinical opinion.

Finally, although we have internally and externally validated these clinical algorithms within our institution, they have not been validated prospectively in other institutions, and their application to modern clinical practice and generalizability to different patient populations need to be tested. Going forward, the next steps are to establish external validity prospectively in another independent craniosynostosis cohort, focusing particularly on the evaluation of sensitivity and specificity (*i.e.*, capturing and correctly classifying clinically relevant events and nonevents), and then testing the performance and generalizability of these clinical algorithms for other craniofacial centers and patient populations.

Conclusion

Procedures for open craniosynostosis repair are safe, but certain patients are at increased risk for clinically significant events and will require or benefit from postoperative ICU monitoring. These risk factors include weight less than 10 kg at the time of surgery, ASA physical status 3 or 4, intraoperative transfusion of packed erythrocytes greater than 60 ml/kg, a significant intraoperative complication, or administration of intraoperative fresh-frozen plasma, platelets, or cryoprecipitate (given to manage clinical coagulopathy as defined and treated by standard guidelines). TXA administration is associated with less postoperative clinically significant events and may reduce the requirement for ICU admission. Patients who are less than 10 kg or ASA physical status 3 or 4 at the time of surgery should be scheduled for postoperative ICU admission to maximize safety. The clinically relevant predictive algorithms presented can be used as prognostic tools to risk stratify patients postoperatively and guide decision making regarding the need for postoperative ICU admission.

Acknowledgments

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Goobie: Department of Anesthesiology, Perioperative, and Pain Medicine, Boston Children's Hospital and Harvard Medical School, 300 Longwood Avenue, Boston, Massachusetts 02115. susan.goobie@childrens.harvard.edu.

Appendix. Types and Definitions of Preoperative, Intraoperative, and Postoperative Variables Collected

Types of Variables

Preoperative variables recorded included age at procedure, weight, height, body surface area, race, surgical diagnosis, types and numbers of cranial sutures involved, syndromic *versus* nonsyndromic craniosynostosis and specific type of syndrome, comorbid illnesses, American Society of Anesthesiologists (ASA) physical status, revision *versus* primary craniosynostosis repair, and preoperative clinical and laboratory test results.

Intraoperative variables collected included incidence of hypotension, hypertension, tachycardia, bradycardia, use of vasopressors (type: continuous and bolus), air embolus and classification, hypothermia, hyperthermia, difficult intubation, desaturation, respiratory distress, bronchospasm (and treatment), ventilation difficulties, unplanned extubation, length of surgery, crystalloids and colloids given (ml/kg), packed erythrocytes transfused (amount in ml/kg), type and amount of other blood products transfused (fresh-frozen plasma, platelets, and cryoprecipitate), amount of intraoperative blood loss (estimated and calculated[18] in ml/kg), urine output, antifibrinolytic given and dose, intraoperative complications, and if the patient was extubated *versus* remained intubated.

Postoperative intensive care unit (ICU) and neurosurgical floor data recorded included hypotension, hypertension, tachycardia, bradycardia, use of vasopressors (type: continuous and bolus, and reason), desaturation, airway obstruction and treatment, oxygen therapy (type, amount, and duration) respiratory distress or failure, if the patient remained intubated or reintubated, laboratory data, anemia (defined as hematocrit <24%), colloids administered, blood product transfusion (packed erythrocytes, fresh-frozen

plasma, platelets, and cryoprecipitate), postoperative bleeding (as recorded by amount of blood in surgical drain), hypothermia, fever, neurological events (such as seizures), reoperation (type and reason), pain, length of stay in ICU (hours and reason if >2 days), readmission to ICU and reason, length of hospital stay, and reason for prolonged stay (>2 days on floor).

Definitions of Variables

Hypotension: systolic blood pressure <20% baseline or mean arterial pressure <40 mmHg for two consecutive measurements over 5 min as measured continuously and derived from electronic medical records.

Hypertension: systolic blood pressure >20% baseline or mean arterial pressure >60 mmHg for two consecutive measurements over 5 min as measured continuously and derived from electronic medical records.

Tachycardia: heart rate >180 for three consecutive measurements or 20% baseline for three consecutive measurements over 5 min as measured continuously and derived from electronic medical records.

Bradycardia: <80 for three consecutive measurements or 20% baseline for three consecutive measurements over 5 min as measured continuously and derived from electronic medical records.

Air embolism: defined as type 1 (change in precordial Doppler), type 2 (change in precordial Doppler plus decrease in end-tidal carbon dioxide by ≥5 mmHg), or type 3 (change in precordial Doppler plus decrease in end-tidal carbon dioxide by ≥5 mmHg plus decrease in systolic blood pressure >20% baseline).

Desaturation: saturation of oxygen <90% for two consecutive intervals measured over 5 min as measured continuously and derived from electronic medical records.

Respiratory distress or failure with diagnosis including upper airway obstruction (stridor, croup, and apnea) and/or lower airway pathology (pneumonia, pulmonary edema, or reactive airway disease) and characterized as desaturations with saturation of oxygen <90% for two consecutive measurements over 5 min as measured continuously and derived from electronic medical records requiring oxygen treatment of >50% for over 12 h and/or necessitating airway support by nasal/oral airway, continuous positive airway pressure or biphasic positive airway pressure, or intubation.

Postoperative bleeding amount (in ml and ml/kg) in surgical drain routinely recorded by nursing staff per shift and documented in electronic medical record and totaled for the first 24 h postoperatively.

Significant bleeding defined as blood in surgical drain >30 ml/kg during the first 24 h postoperatively.

Significant apnea defined as apnea resulting in desaturations with saturation of oxygen <90% for two consecutive measurements over 5 min as measured continuously and derived from electronic medical records and necessitating airway support by nasal/oral airway, continuous positive airway pressure or biphasic positive airway pressure.

Significant upper airway obstruction defined as inspiratory stridor requiring at least one dose of racemic epinephrine or upper airway obstruction requiring continuous positive airway pressure or biphasic positive airway pressure.

Significant hemodynamic instability defined as sustained tachycardia (or other arrythmia) and hypotension >20% baseline over 5 min as measured continuously and derived from electronic medical records and not responding to the standard clinical practice of a crystalloid bolus of 10–20 ml/kg and requiring blood products and/or vasopressors (ephedrine, phenylephrine, or dopamine; intermittent or continuously administrated).

Significant anemia defined as hematocrit <24%.

Significant clinical coagulopathy defined as clinical bleeding (blood in surgical drain >30 ml/kg during the first 24 h postoperatively) with supporting abnormalities on standard clinical laboratory tests. Standard clinical care is as follows: Fresh-frozen plasma administered if prothrombin time/partial thromboplastin time >1.5 times normal, platelets given if count <50,000, and cryoprecipitate given if fibrinogen level <150 as recommended by published guidelines.[8]

Hypothermia defined as temperature <35°C for two consecutive measurements as measured continuously intraoperatviely and postoperatively in the ICU by nursing staff every hour and derived from electronic medical records.

Hyperthermia defined as temperature >38°C for two consecutive measurements as measured continuously intraoperatviely and postoperatively in the ICU by nursing staff every hour and derived from electronic medical records.

Neurological events (such as seizures), reoperation, type and reason, and swelling (cannot open eyes or nurses/medical doctor comment documented on facial swelling).

Pain: significant pain score >5 for three consecutive times as measured every hour in the ICU by nursing staff and record on electronic medical record.

Intraoperative complication defined as a clinically significant intraoperative complication such as air embolism (grade >2), intraoperative respiratory event (significant desaturation, significant bronchospasm requiring bronchodilators, unplanned extubation, and clinically significant ventilation difficulties) or intraoperative cardiac event (cardiac arrest, severe bradycardia requiring atropine, significant hypotension requiring vasopressors, significant hypertension, or hemodynamically significant arrhythmia).

Minor events, which could be routinely managed on the floor, were defined as fever, pain, mild anemia (hematocrit >24%), minor bleeding, hypothermia, mild upper airway obstruction, hypotension responding to fluid boluses (following the standard clinical practice of a crystalloid bolus of 10–20 ml/kg), transient apnea, or desaturation. These were

not considered to require ICU admission and therefore were not included in the analysis.

References

1. Czerwinski M, Hopper RA, Gruss J, Fearon JA: Major morbidity and mortality rates in craniofacial surgery: An analysis of 8101 major procedures. Plast Reconstr Surg 2010; 126:181–6
2. Nguyen C, Hernandez-Boussard T, Khosla RK, Curtin CM: A national study on craniosynostosis surgical repair. Cleft Palate Craniofac J 2013; 50:555–60
3. Lee HQ, Hutson JM, Wray AC, Lo PA, Chong DK, Holmes AD, Greensmith AL: Analysis of morbidity and mortality in surgical management of craniosynostosis. J Craniofac Surg 2012; 23:1256–61
4. Seruya M, Sauerhammer TM, Basci D, Rogers GF, Boyajian MJ, Myseros JS, Yaun AL, Keating RF, Oh AK: Analysis of routine intensive care unit admission following fronto-orbital advancement for craniosynostosis. Plast Reconstr Surg 2013; 131:582e–8e
5. Abbott MM, Rogers GF, Proctor MR, Busa K, Meara JG: Cost of treating sagittal synostosis in the first year of life. J Craniofac Surg 2012; 23:88–93
6. Drews RE: Critical issues in hematology: Anemia, thrombocytopenia, coagulopathy, and blood product transfusions in critically ill patients. Clin Chest Med 2003; 24:607–22
7. Practice guidelines for blood component therapy: A report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. Anesthesiology 1996; 84:732–47
8. Roback JD, Caldwell S, Carson J, Davenport R, Drew MJ, Eder A, Fung M, Hamilton M, Hess JR, Luban N, Perkins JG, Sachais BS, Shander A, Silverman T, Snyder E, Tormey C, Waters J, Djulbegovic B; American Association for the Study of Liver, American Academy of Pediatrics, United States Army, American Society of Anesthesiology, American Society of Hematology: Evidence-based practice guidelines for plasma transfusion. Transfusion 2010; 50:1227–39
9. Zhou XH, Obuchowski NA, McClish DK: Statistical Methods in Diagnostic Medicine, 2nd edition. New York, John Wiley & Sons, 2011, pp 24–63
10. Katz MH: Multivariable Analysis: A Practical Guide for Clinicians and Public Health Researchers, 3rd edition. New York, Cambridge University Press, 2011, pp 140–61
11. Harrell FE: Regression Modeling Strategies with Applications to Linear Models, Logistic Regression, and Survival Analysis. New York, Springer, 2001, pp 215–67
12. Hosmer DW, Lemeshow S: Assessing the Fit of the Model in Applied Logistic Regression, 2nd edition. New York, John Wiley & Sons, 2005, pp 143–202
13. Miller ME, Hui SL, Tierney WM: Validation techniques for logistic regression models. Stat Med 1991; 10:1213–26
14. Goobie SM, Meier PM, Pereira LM, McGowan FX, Prescilla RP, Scharp LA, Rogers GF, Proctor MR, Meara JG, Soriano SG, Zurakowski D, Sethna NF: Efficacy of tranexamic acid in pediatric craniosynostosis surgery: A double-blind, placebo-controlled trial. Anesthesiology 2011; 114:862–71
15. Jaimovich DG; American Academy of Pediatrics Committee on Hospital Care and Section on Critical Care: Admission and discharge guidelines for the pediatric patient requiring intermediate care. Pediatrics 2004; 113:1430–3
16. Stricker PA, Shaw TL, Desouza DG, Hernandez SV, Bartlett SP, Friedman DF, Sesok-Pizzini DA, Jobes DR: Blood loss, replacement, and associated morbidity in infants and children undergoing craniofacial surgery. Paediatr Anaesth 2010; 20:150–9
17. White N, Marcus R, Dover S, Solanki G, Nishikawa H, Millar C, Carver ED: Predictors of blood loss in fronto-orbital advancement and remodeling. J Craniofac Surg 2009; 20:378–81
18. Kearney RA, Rosales JK, Howes WJ: Craniosynostosis: An assessment of blood loss and transfusion practices. Can J Anaesth 1989; 36:473–7