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Early postoperative follow-up after craniosynostosis surgery

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Background/aim: Declined morbidity rates after craniosynostosis surgery indicate bypassing the pediatric intensive care unit (PICU) course to minimize treatment costs and bed usage. The aim of this study is to examine the incident rates of PICU admission and assess its necessity.

Materials and methods: A retrospective analysis of 41 patients (operated on by open surgical techniques) between July 2011 and December 2015 was carried out. Intraoperative/postoperative vital signs, hemodynamic and metabolic parameters, estimated blood loss (EBV_{loss}), blood transfusions, length of PICU, and hospitalizations were recorded.

Results: Major and minor events reached 51.2% and 82.9%, respectively. EBV_{loss} within 24 h was calculated as 39.58 ± 8.19 (median: 38.44, 25.68–66.34) with 75.6% blood transfusion rate. Hypotension and hypothermia were associated with prolonged surgery (P = 0.001 and P = 0.007, respectively), but were not related to age (P = 0.054, P = 0.162) or procedure types (P = 0.558, P = 0.663). Prolonged surgery and younger age had an impact on the complications. One patient died of persistent hemorrhage at 96 h.

Conclusion: Monitoring cardiovascular and metabolic dynamics at PICU during the first 24 h after surgery is crucial. Additional studies are needed to define the threshold values of several metabolic and hemodynamic markers in risk assessment after cranial vault surgery.

Key words: Craniosynostosis, complications, postoperative

1. Introduction

Craniosynostosis is the premature fusion of cranial sutures. It leads to restriction of calvarial growth and results in functional and cosmetic problems. It can be spontaneous, usually affecting one of the sutures, with an incidence of 1:2000 at live birth, or syndromic, resulting in failure of growth of the entire brain and multiple sutures (1). Surgery is the treatment of choice to enhance psychosocial development, especially in nonsyndromic craniosynostosis.

There are numerous articles on craniosynostosis, including operational techniques, intraoperative course, and complications. However, few address the pediatric intensive care unit (PICU) course (2–5). Based on the recommendations of the guidelines on patients with open craniosynostosis surgery, most craniofacial centers routinely admit patients to PICU (6); however, declining morbidity rates due to advances in procedures (endoscopic approaches) have given rise to the idea of bypassing the ICU stage to minimize bed usage or treatment costs and not all patients might need intensive care admission (2,7,8). Addressing the previous hypothesis, the aim of this retrospective study was to examine the rates of incidents and related complications not only for hematological events, but also for hemodynamic and metabolic problems, in order to elucidate whether all infants need intensive care admission or not.

2. Materials and methods

Following ethical approval by the local institutional board, the medical records of 48 patients, operated by open surgical procedures at Akdeniz University Hospital between July 2011 and December 2015, were obtained. To exclude surgical experience and technical variability of different surgeons, a total of 41 nonsyndromic infants, who were operated on by only one neurosurgeon specializing in pediatric neurosurgery, were included in the study. Patient demographics and intraoperative data included age, sex, medical history, preoperational coagulation abnormality, type of procedure, length of surgery (LOS), intraoperative complications, administration of intraoperative fresh frozen plasma (FFP), packed red

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blood cell (PRBC), and platelets. Postoperative variables covered the first 24 h of PICU and included hypotension (minor/severe), hypothermia, metabolic acidosis, base excess (BE), estimated blood volume loss (EBV_{loss} in mL/kg, derived from Vamcavas formulation) (9), necessity of blood product transfusions, cranial imaging by computed tomography (CT), seizures, hospital-acquired infections (data obtained from previously recorded infection-positive infants), and antibiotherapy. Rate of mortality, length of conventional mechanical ventilation (MV), and PICU stay were recorded. All methodological definitions are presented in the Appendix.

With respect to institutional policy for small infants undergoing major surgery, all patients were directly transferred to the PICU. Maintenance fluids and prophylactic antibiotherapy were administered. Once the hemodynamic and metabolic balance was achieved, we initiated weaning from artificial respiration. Complications were evaluated as clinically significant major complications and minor events. Major complications included significant anemia, significant bleeding from drains, severe hypotension, metabolic acidosis, MV requirement over 24 h, and mortality. We classified minor events as hypothermia, hyperglycemia, electrolyte imbalance, fever of unspecified origin, hospital-acquired infections, and seizures.

The statistics of this retrospective study were analyzed using SPSS 23. Descriptive analyses were expressed as frequency (n), percentage (%), mean, standard deviation, and median with minimum and maximum values. Categorical data were assessed using χ^2 and Fisher's exact test. The Shapiro–Wilks test was used for normality distribution. Continuous variables were analyzed with the Mann–Whitney U test or independent samples t test. One-way ANOVA and/or Kruskal–Wallis tests (if significant, post hoc Bonferroni test) were applied to compare mean values or center of location parameters in the three groups. Wilcoxon rank sum tests or paired samples t test were used for statistical comparisons. $P < 0.05$ indicated statistical significance.

3. Results

Forty-one nonsyndromic patients were eligible for the study. The study included 26 males (63.4%) and 15 females (36.6%) with a median age of 7 months (4.5–24 months). To elucidate the postoperative events, the subjects were divided into age groups as follows: 1–6 months (22%), 7–12 months (36.6%), and 13–24 months (41.5%). Weight ranged from 5.2 to 13.75 kg (mean 9.36 ± 2.92 kg). Five patients (12.2%) had a history of epilepsy and were receiving antiseizure drug therapy. None had preoperational coagulation anomaly. Descriptive categories on synostosis subtypes were trigonocephaly (53.7%), scaphocephaly (24.4%), anterior plagiocephaly (17.1%), and brachiocephaly (4.9%). The assessment of procedure types revealed 26.8% of frontoorbital advancement (FOA), 39% of calvarial reconstruction, and 34.1% of strip craniectomy. We observed a median procedure length of 170 min (90–320 min) and length of PICU stay as 2.63 ± 0.88 days. Only one patient (2.4%) died of uncontrolled hemorrhage and metabolic disturbance. Table 1 represents the demographics of the population.

3.1. Intraoperative course

Procedure types were related to LOS ($P < 0.001$): longest duration in FOAs and shortest in strip craniectomy. Age did not contribute to LOS ($P = 0.141$). All patients received PRBC transfusions to achieve a hemoglobin level of 10 g/dL with PRBC volume < 10 mL/kg, except for one

Table 1. Demographics of the study population.

Variables	n (%)	Variables	n (%)
Male sex	26/41 (69.4%)	Craniosynostosis type	
Age (median)	7 (4.5–24) months	Trigonocephaly	22/41 (53.7%)
Age groups		Scaphocephaly	10/41 (24.4%)
1–6 months	9/41 (22%)	Anterior plagiocephaly	7/41 (17.1%)
7–12 months	15/41 (36.6%)	Brachiocephaly	2/41 (4.9%)
13–24 months	17/41 (41.5%)	Operation type	
Weight (kg) (mean ± SD)	9.36 ± 2.92	Frontoorbital advancement	11/41 (26.8%)
Epilepsy history	5/41 (12.2%)	Calvarial reconstruction	16/41 (39%)
Intubation at admission	41/41 (100%)	Strip craniectomy	14/41 (34.1%)
Length of intubation (median)	6 (3–96) h	Duration of surgery*(median)*	170 (90–320) min
Length of PICU stay (mean)	2.63 ± 0.88 days	Mortality	1/41 (2.4%)

(transfused over 20 mL/kg due to severe hemorrhage). FFP was administered to 12 (29.2%) patients to maintain hemostasis. Table 2 represents the descriptives of the study group. Unfortunately, intraoperative EBV_{loss} could not be calculated due to missing data of the intraoperative hematocrit (Hct) values.

3.2. Postoperative course

3.2.1. Cardiovascular dynamics

Initial vital signs demonstrated that 82.9% of the study population was hypothermic. A total of 73.2% (30/41) manifested intravascular volume deficit and required 0.09% NaCl replacement to achieve normotension, whereas four infants (9.8%) necessitated inotropic support (severe hypotension). Table 3 represents the descriptives of the complications. Hypotension and hypothermia were significantly associated with prolonged surgery (P = 0.001 and P = 0.007, respectively), but were not related to age (P = 0.054, P = 0.162) or procedure types (P = 0.558, P = 0.663) (Table 4). Median urine output within 24 h was 2.1 mL/kg per hour (0.4–4 mL/kg per hour) overall. Only two severely hypotensive infants with metabolic acidosis were oliguric (urine < 1 mL/kg per hour). Twelve infants (29.3%) had elevated lactate (median: 3.75 mmol/L; 2.5–13 mmol/L). Prolonged surgery, metabolic acidosis, hypotension, low BE, and significant anemia were statistically related to elevated lactate in the following order: P < 0.001, P = 0.004, P = 0.003, P = 0.006, and P = 0.037. However, a similar relation was not observed with EBV_{loss} (P = 0.563). Although the distribution of lactate-elevated patients among procedure types was too small to perform statistical analysis, clinically 64% of the FOA group had elevated lactates (31.3% in calvarial reconstruction and none in strip craniectomy groups).

3.2.2. Ventilation

All patients were intubated and on conventional MV on arrival. The median length of MV was 6 (3–96) h. Thirty-eight infants had been intubated less than 24 h prior; intubations lasted more than 24 h only in three (7.3%) patients with hemodynamic imbalance and persisting metabolic acidosis. Among these patients, one died of persistent hypotensive shock resulting in renal failure, which later progressed to multiple organ dysfunctions at 96 h. No reintubation occurred.

3.2.3. Hematologic events

During the postoperative follow-up, 31 (75.6%) patients received PRBC and two (4.8%) had FFP transfusions to maintain hemostasis (Table 2). Blood loss over 30 mL/kg per 24 hours from surgical drainage occurred in 14.6% of the infants. None had hematoma (confirmed by CT scans) or spinal fluid leakage. Prolonged surgery and younger age were clearly associated with postoperative PRBC requirement (P = 0.003, P = 0.023); however, procedure

Table 2. Descriptives of the population.

Intraoperative course	
Hct_{preop} (median) (%)	32 (28–36)
PRBC transfusion (n)	41/41 (100%)
FFP transfusion (n)	12/41 (29.2%)
Postoperative Course	
$Hct_{initial}$ (mean ± SD) (%)	33.58 ± 2.83
Hct_{final} (mean ± SD) (%)	26.59 ± 4.33
EBL_{loss} (mean ± SD) (mL/kg)	39.50 ± 8.19
PRBC transfusion (n)	31/41 (75.6%)
FFP transfusion (n)	2/41 (4.8%)
Urine output (median) (mL/kg per hour)	2.1 (0.4–4)
BE value (mean ± SD)	−8.39 ± −2.89
Lactate overall (median)(mmol/L)	1.5 (0.5–13)
Elevated lactate (median) (mmol/L)	3.75 (2.5–13)

Table 3. Postoperative complications.

Variables	*n (%)*
Hemodynamic	
Minor hypotension	30/41 (73.2%)
Severe hypotension	4/41 (9.8%)
Urine output less than 1 cc/kg per h	2/41 (4.9%)
Elevated lactate	12/41 (29.3%)
Metabolic	
Metabolic acidosis	20/41 (48.8%)
Hypothermia	34/41 (82.9%)
Hyperglycemia	6/41 (14.6%)
Electrolyte imbalance	0
Hematological	
Blood loss from drains ≥ 30 mL/kg per day	6/41 (14.6%)
Significant anemia (Hct_{final})	9/41 (22%)
Ventilation	
Mechanical ventilation over 24 h	3/41 (7.3%)
Reintubation	0
Other	
Fever of unspecified origin	10/41 (24.4%)
Culture positive infection	4/41 (9.8%)
Surgical site infection	2/41 (4.9%)
Ventilator-associated pneumonia	2/41 (4.9%)
Antibiotherapy	
Monoantibiotherapy	9/21 (42.9%)
Combined antibiotherapy	1/20 (5%)
Seizures	5/41 (9.8%)

Table 4. Descriptives and morbidity of the subtype surgery groups.

Variables	FOA [a] (n = 11)	Calvarial reconstruction[b] (n = 16)	Strip craniectomy[c] (n = 14)	P
Age (months) (median)	7 (4.5–24)	9 (5–24)	14.5 (5–24)	0.209
Length of surgery (min) (mean ± SD)	227 ± 45.85	164 ± 27.50	124 ± 25.79	***< 0.001****
Length of intubation (hours) (median)	6 (5–96)	6 (4–30)	6 (3–9)	0.761
Length of PICU stay (days) (mean ± SD)	2.93 ± 1.18	2.5 ± 1.09	2.5 ± 0.52	0.085
Morbidities				
Hemodynamic				
Hypothermia (%)	10 (90.9%)	15 (93.8%)	9 (64.3%)	NA
Severe hypotension (%) Minor hypotension (%)	2 (18.1%) 8 (72.7%)	2 (12.5%) 12 (72.0%)	0 10 (71.4%)	NA NA
Metabolic acidosis (%)	9 (81.8%)	9 (56.3%)	2 (14.3%)	NA
Base excess (mean ± SD)	–10.06 ± –2.42	–9.03 ± –1.95	–6. 35 ± –3.09	***0.006*****
Lactate elevated patients (%)	6 (54.4%)	3 (18.8%)	**0**	NA
Hematological				
PRBC transfusion (%)	10 (90.9%)	14 (87.5%)	7 (50%)	NA
$Hct_{initial}$ (mean ± SD)	32.35 ± 2.37	33.68 ± 3.09	34.42 ± 2.68	NA
Hct_{final} (mean ± SD)	25.57 ± 4.58	25.70 ± 4.04	28.72 ± 3.31	0.190
EBV_{loss} (mean ± SD)	39.64 ± 11.63	*1.58* ± 8.18	37.40 ± 3.69	0.069
Blood loss from drains (%)	2 (14.3%)	4 (25%)	0	0.674
Other				
Fever of unspecified origin (%)	2 (18.2%)	5 (31.3%)	3 (21.4%)	NA
Seizure (%)	3 (27.3%)	1 (6.3%)	1 (7.1%)	NA
Hyperglycemia (%)	3 (27.3%)	2 (12.5%)	1 (7.1%)	NA

*Analysis of length of surgery within three groups: P < 0.001 for a–b; P < 0.010 for a–c; P = 0.005 for b–c.
**Analysis of base excess within three groups: P > 0.999 for a–b; P = 0.012 for a–c; P = 0.026 for b–c.

type did not impact the necessity of PRBC transfusion (P = 0.922) (Table 4). EBV_{loss} within 24 h was calculated as 39.58 ± 8.19 mL/kg (median: 38.44; 25.68–66.34) overall; procedure type, surgery length, age, or sex did not seem to affect $EBVl_{oss}$ (P = 0.674, P = 0.635, P = 0.793, and P = 0.060, respectively). By August 2015, the intraoperative coagulation policy included administration of tranexamic acid (TXA) in patients with 50 mg/kg loading dose, following 5 mg/kg per hour infusion rate during surgery. Six patients (14.6%) received TXA intraoperatively; none needed postoperative PRBC.

3.2.4. Metabolic imbalance

Clinically significant metabolic acidosis (pH < 7.30) was observed in 21/41 (51.2%) patients with a mean BE value of –8.39 ± –2.89 (Tables 2 and 3). We found that lower BE was related to prolonged surgery, hypotension, and younger age (P < 0.001, P < 0.001, and P = 0.009, respectively) (correlations for BE and length of operation, r = –0.629; for BE and age, r = 0.404). Electrolyte monitoring revealed no abnormalities for hyponatremia, hyperpotassemia, or hypocalcemia.

3.2.5. Infections

The initial prophylactic antibiotic spectrum consisted of single third-generation cephalosporin in 51.2% of patients. The rest received combination antibiotherapy as third-generation cephalosporin + vancomycin due to the possible risks of dural tears informed by the surgeon. Fever of unspecified origin occurred in ten patients (24.4%), whereas four infants (9.8%) developed culture-positive infections (*Pseudomonas aeruginosa* in tracheal aspirates; methicillin-sensitive *Staphylococcus aureus* in cultures of blood or surgical site fluids) (Table 3). Antibiotics were

escalated to carbapenem and/or vancomycin combinations. Prolonged PICU stay and MV were not related to fever (P = 0.819, P = 0.213). All four culture-positive infants belonged to the monoantibiotherapy group.

3.2.6. Rare complications

Five infants (9.8%) with previous epilepsy history developed febrile seizures, whereas hyperglycemia, which was another problem faced in the first hours of PICU admission, occurred in six infants (14.6%). Normoglycemia was achieved after a short period of insulin infusions.

4. Discussion

Despite the varying range of complications in the literature (2–5,10–13), the assessment of incidents in this cohort demonstrated clinically significant metabolic or hemodynamic events. This required close monitoring of such infants for at least the first 24 h after surgery. Major complications included 22% of significant anemia at 24 h during the PICU stage, 14.6% of significant bleeding from drains, 9.8% of severe hypotension, 51.2% of metabolic acidosis at arrival, 7.3% of MV support over 24 h, and 2.4% of mortality. Apart from metabolic acidosis, our rates for major complications resembled the previous reports by Goobie et al. with 14.7% for postoperative cardio-respiratory and 29.7% hematological events (2). Blood loss constitutes the major determinant in hematological events after open surgery procedures and extends to the postoperative period (14). In fact, postoperative blood loss can be approximately equal to the intraoperative period, which can be explained by the oozing of blood from exposed bone surfaces (15). Our intraoperative and postoperative transfusion rates of 100% and 75.6%, respectively, were concordant with the rates of 1.7%–100% reported in the literature (5,16). Type of procedure and LOS affect the necessity of blood transfusion (1,11,17–18). In the present study, the postoperative PRBC requirement was clearly related to younger age and LOS. There are conflicting results on the topic of age in the literature. Akingbola et al. reported higher consumption rates in older infants, whereas the results published by Eaton et al. were opposite (1,17). KIDS database in 2012 report EBV_{loss} can be as high as 60%–100% during the intra- and postoperative period (4). Our calculation of 38.44 mL/kg per day (25.68–66.3 mL/kg) for the median postoperative EBV_{loss} was almost half the EBV_{loss} (69 ± 44 mL/kg/day) reported by Goobie et al. (2). This difference can be explained by their calculations, which covered the perioperative 24 h, whereas we only focused on blood loss during the postoperative 24 h. As expected, different open surgical procedures influence the amount of blood loss: EBV_{loss} of 100% for total calvarial reconstructions and 25% for strip craniectomy (1,11,18), whereas our data for procedure type and surgery length did not have an impact on $EBV_{loss.}$

The monitoring of cardiovascular and metabolic dynamics carries another perspective of ICU course. In most patients, metabolic acidosis develops intraoperatively and extends to the postoperative period (14). BE reaches its lowest values at the end of surgery and normalizes between 9.5 and 12 h in the postoperative stage (19,20). Lower base deficits and higher lactate levels can be expected due to infants' relatively large head/body surface area, which contributes to additional fluid and blood loss and results in hypothermia, hypotension, and inadequate tissue perfusion (19). Prolonged surgery is another factor for hypotension and metabolic acidosis (11,21). BE values in the present study were –8.9 ± –2.0 mmol/L, similar to the BE values of 7.74 mmol/L reported by Ali et al. (19), and were directly related to hypotension and length of surgery, regardless of age or procedure type.

Lactate is a well-established indicator of tissue perfusion. The American Society of Anesthesiologists' guidelines report 'tolerated anemia' when Hct levels are between 18% and 25%. Hct less than 25% (15%–25%) is known to initiate lactate production in a normovolemic healthy individual (22). During the follow-up, nine patients developed lactate elevation with a median of 3.75 mmol/L (2.5–13 mmol/L). Elevated lactate was associated with LOS, significant anemia, hypotension, and metabolic acidosis.

Perceptions of the term 'minor event' should not underestimate outcomes in terms of hypothermia, infections, hyperglycemia, seizures, electrolyte imbalance, which we categorized as minor events. Rates of minor events were 82.9% for hypothermia, 24.4% for FUO, 9.8% for infections, 14.6% for hyperglycemia, and 9.8% for seizures. Maintaining normothermia and normoglycemia is equally important in metabolic monitoring (14,19). Hypothermia is a known factor of coagulopathy and metabolic acidosis due to blood loss at surgery, refrigerated blood transfusions, room temperature changes, inadequate end organ perfusion, or heat loss from infants' relatively large head/body surface area (11,14). Hypothermia observed in this cohort was far beyond the previously reported rates of 10%–19.4% (23,24), which was probably due to our definition for hypothermia as axillary temperature less than 36 °C for this study. The operating room's (OR) inconvenient conditions to achieve normothermia, a relative distant transfer from OR to PICU (OR and PICU are localized at different blocks of the facility) may be factors that contribute to hypothermia rates.

The impact of postoperative fever and infections is considerable. Both are associated with prolonged PICU and hospital stays (1,24–26). The rates of fever without an identifiable source or etiology range from 5% to 24% (1,24). Consuming intraoperative blood products, prolonged surgery for over 2 h, and stress stimuli driven

by surgery might have an impact on fever in small infants after craniofacial surgery (27). The results of this study demonstrated that 24.4% of postoperative fever and 9.8% of infection rates were in the form of ventilator-associated pneumonia and surgical site infections. Our infection rates remained slightly higher than those reported in the literature, ranging from 1.5% to 8% (11,26–29); however, they were not related to prolonged PICU stay or ventilator support, which was quite the opposite of Yeung's report on 2 more days of ICU stay (OR, 10.8; 95% CI, 2.2–53.3) and prolonged intubation (OR, 4.8; 95% CI, 1.2–18.6) (30). We think that this conflicting result occurred because of our approach towards infants requiring critical care. Once the hemodynamic and metabolic balance is achieved and the patient's neurological and respiratory condition is good enough to comprehend, we initiate the weaning process from artificial ventilation. Furthermore, fever alone is a not a parameter for elongating the ICU stay. Only if clinical suspicion of infection (not only fever, but the presence of purulent body fluid) occurs are routine laboratory tests investigated (procalsitonin, CRP, white blood cell counts, peripheral blood smears, and cultures of body fluids). Then, if necessary, we escalate the antibiotherapy regimen. We did not interpret the impact of infection on total hospitalization period, since this study focuses on the early postoperative intensive care period of craniosynostosis surgery.

The final minor event we addressed was electrolyte abnormality. Close monitoring of electrolytes (hyponatremia due to secretion of ADH hormone or inappropriate hypotonic fluid infusions; hypocalcemia and hyperpotassemia due to citrated or overexpired blood transfusions) is essential (14,31). Despite hyponatremia's highest incidence within electrolyte abnormalities, which contributes to the development of cerebral edema, seizures, and even death (31), we did not observe such sodium abnormality, probably due to the application of more hypertonic maintenance fluids (5% dextrose in 0.9% or 0.045% sodium chloride solutions).

Length of PICU stay was 2.63 ± 0.88 days (median: 2 days, 2–6 days) in the present study. Despite the high incidence of events (regardless of major or minor), the length of stay was concordant with other reports by Ali et al. with 1.9 ± 0.5 days, and by Goobie et al. with a median of 1 day, ranging from 1 to 6 days (19,2). Looking at the significantly high rates of incidents, the first 24 h after surgery seem to require delicate care of the patients operated on with open surgical techniques, and they should be admitted to the PICU for close monitoring.

Although scaphocephaly is known as the most common craniosynostosis subtype, the descriptives of this study demonstrated trigonocephaly as the most prominent one (32–34). The incidence of trigonocephaly is increasing, regardless of geography or population size, at a rate of 5%–50% (32,35). Ethnicity plays an additional role, and the decision for surgery depends on cultural aspects. For example, Anderson et al. reported more complex craniosynostosis with lesser sagittal synostosis in the Asian ethnicity and less schedule for surgery in the former subtype in their cohort (36). Families' perception of disease and approval for surgery likely impacts surgery rates. Despite observations on scaphocephaly as the common synostosis, Farzaneh et al. demonstrated fewer schedules for surgery rates and higher family approval for more disfiguring deformities such as unicoronal and metopic subtypes (37). Furthermore, the institutional data of our facility on outpatient referrals confirmed the highest scaphocephaly rates for nonsyndromic infants; however, surgery approvals for those constituting the study population were mostly trigonocephalic infants.

The present study has several limitations. The low surgery rates at our facility, compared to other high-output centers, and the exclusion of infants with syndromic synostosis (due to a more complex, multisuture-involved synostosis type with significant morbidity rates) in order to maintain homogeneity, contributed to the relatively low study population rate and limited the outcomes. However, the annual escalating trend in surgery schedules due to surgeons' experience, positive multidisciplinary team efforts, and family approach towards craniosynostosis surgery will enable more comprehensive future studies on craniosynostosis. Ignoring the long-term outcomes of this surgery, including operational success, aesthetic concerns, and other long-term health issues, was another limitation; however, the aim of the present study was to encompass the short-term PICU outcomes of such children, in search of an answer to 'does every infant need PICU care?' The final limitations of this study were the inability to calculate the intraoperative EBV_{loss} due to missing intraoperative Hct values, as well as another common limitation of retrospective studies: no set intraoperative/postoperative transfusion guidelines. Therefore, our results do not reflect more recent surgical outcomes in patients with craniosynostosis.

In conclusion, despite declining morbidity rates in advance of new surgical approaches or surgeons' experience, resulting in bypassing the ICU stage in a selected group of infants (2,7), close metabolic and hemodynamic monitoring during the first 24 h after surgery at an intensive care unit for facilities with resource-limited settings is essential. Future studies are needed to define the threshold values of several metabolic and hemodynamic markers for risk assessment after cranial vault surgery.

Abbreviations: PICU: pediatric intensive care unit; TXA: tranexamic acid; FOA: fronto-orbital advancement; FFP: fresh frozen plasma; PRBC: packed red blood cell; BE: base excess; EBV_{loss}: estimated blood volume loss; MV: mechanical ventilation; CT: computed tomography; n: frequency; %: percentage; HDU: high dependency unit; ASA: American Society of Anesthesiologists.

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Appendix

Hypotension: *Blood pressure below the 5th percentile or below two standard deviations (SDs) of the mean for age and sex in two consecutive measures, which, necessitating 20 mL/kg of fluid infusion, achieve hemodynamic balance.*[*]
Minor hypotension: *Hypotensive infant that necessitates 20 mL/kg of fluid infusion and achieves hemodynamic balance.*
Severe hypotension: *hypotension requiring inotropic support (dopamine and/or epinephrine infusions), despite sufficient fluid resuscitation.*
Hematocrit $_{initial:}$ *Hematocrits obtained at arrival.*
Hematocrit $_{final:}$ *Hematocrits obtained at 24 h.*
Anemia: Hct_{final} *between 25% and 30%.*
Significant anemia: $Hct_{final} < 24\%$.
Significant bleeding from surgical drains: *Blood loss >30 mL/kg per day.*
PRBC infusion: *10 mL/kg packed red blood cell infusion to patients with anemia in the presence of hemodynamic instability.*
Hypothermia: *Axillary body temperature < 36 °C for two consecutive measurements between 30-min intervals, despite external warming.*
Lactate elevation: *Lactate >2 mmol/L (threshold of our laboratory; n: 0.5–2 mmol/L), obtained from arterial blood gas.*
Significant metabolic acidosis: *pH <7.30 and BE (base excess) < –5 (obtained from blood gas at arrival).*
Hyperglycemia: *blood glucose over 200 mg/dL.*
Infection: *Based on the clinical and biological criteria of the World Health Organization Recommendations on Hospital-Acquired Infections biological criteria.*[**] *Suspicion of infection on clinical follow-up (fever of axillary body temperature >38.5°, purulent material through body fluids or surgical site), along with the laboratory findings (culture positivity, elevated WBC, CRP, and procalsitonin).*

Calculation of EBV_{loss} *(derived from Vamkavas formulation) (9):*

$$EBV_{loss}\,(mL/kg) = \frac{ERCV_{lost}\,(mL)}{Weight_{(kg)} \times Hct_{initial}/100}$$

$$ERCV\,l_{oss} = ERCV_{arrival} + ERCV_{transfused} - ERCV_{24th\ hour}$$

$$ERCV = EBV\ factor \times weight\ (kg)\ \eth\ EBV\ factor\ is\ 75\ mL\ for\ patients < 12\ months$$
$$\eth\ 80\ mL\ for\ patients \geq 12\ months$$

Where $ERCV_{transfused} = 0.7 \times volume\ transfused$
(ERCV: estimates red cell volume; EBV_{loss}*: estimated blood volume loss);* $ERCV_{transfused} = 0.7 \times$ *volume transfused. Average Hct value of transfused PRBC was 70%, according to our blood bank's inventory. Total volume of PRBC transfuse was used for calculation of* $ERCV_{transfused.}$

[*] Kleinman ME, Chameides L, Schexnayder SM, Samson RA, Hazinski MF, Atkins DL, et al. Part 14: pediatric advanced life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2010 ;122(18 suppl 3): S876–908.

[**] World Health Organization. Prevention of Hospital-Acquired Infections: A Practical Guide. 2nd edition. Geneva, Switzerland: WHO, 2012. Available at http://apps.who.int/medicinedocs/documents/ s16355e /s16355e.pdf