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Patient Blood Management in Craniosynostosis Surgery

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Abstract

Background: Craniosynostosis surgery is one of the most hemorrhagic interventions, where transfusion rates vary from 20% to 100% depending on the study. **Objective:** To describe intraoperative and postoperative outcomes in a secondary analysis of children who underwent craniosynostosis surgery included in the initial retrospective study with the aim of proposing intraoperative implementation optimization protocols for postoperative outcome improvement. **Methods:** Secondary analysis. The study was approved by the Ethics Committee. **Results:** There were 69 children with a median age of 10 [0 - 207] months. Eight (11.6%) patients had intraoperative and/or postoperative complications. One patient (1.5%) had intraoperative hemorrhagic shock, and two patients (2.9%) had intraoperative broncholaryngospasm. One patient (1.5%) had postoperative anaphylaxis. One patient (1.5%) had postoperative hemorrhagic shock. One patient (1.5%) had postoperative respiratory failure. Two patients (2.9%) had postoperative neurologic failure. One patient (1.5%) had neuro-meningeal sepsis. One patient (1.5%) had a re-operation. There was no in-hospital mortality. Fourty-eight patients (69.6%) had intraoperative transfusions. **Conclusion:** Transfusion protocols guided with point-of-care tests should be included in patient blood management programs in craniosynostosis surgery.

Keywords

Craniosynostosis, Children, Transfusion, Outcome, Point of Care Viscoelastic Assays, Rotational Thromboelastometry

1. Introduction

Cranial vault remodeling surgery is one of the most hemorrhagic interventions, where transfusion rates vary from 20% to 100% depending on the study [1] [2]

[3]. Depending on the type of craniosynostosis, intraoperative blood loss has been reported to be higher in syndromic cranial vault remodeling, where venous anomalies play a major role in this outcome [4] [5]. Tranexamic acid and higher fibrinogen levels have demonstrated a reduction in transfusion requirements and blood loss in craniosynostosis surgery [6] [7].

It has been reported that transfusion with all types of blood products was one of the independent predictors of adverse postoperative outcome in terms of morbidity and length of hospital stay [8] [9]. Hospitalization costs were increased in transfused patients compared with non-transfused patients [10]. Preoperative, intraoperative and postoperative hemoglobin levels have been correlated with postoperative morbidity, length of hospital stay and length of mechanical ventilation in surgical pediatric patients [11]. Transfusion can be a necessary therapeutic intervention in hemorrhagic settings, and it is important to assess the benefits and risks when deciding to administer blood products in patients. Several physio-pathologic mechanisms underlie adverse outcomes correlated with transfusion [12]. First, transfusion can be related to infectious risks due to transfusion-transmitted viruses, bacterial contamination, vector-borne bacteria, parasites and prions [12]. Second, transfusion can be related to immunological risks that can lead to transfusion-related acute injury known as TRALI; immunological risks can lead to febrile nonhemolytic transfusion reactions, allergic and anaphylactic reactions, hemolytic transfusion reactions, transfusion-related immunomodulation known as TRIM, posttransfusion purpura and transfusion-associated graft versus host disease [12].

Finally, transfusion can be related to noninfectious and nonimmunological risks, which can be due to mis-transfusion and can be expressed as transfusion-associated circulatory overload known as TACO and as coagulopathy complications in massive transfusion [12].

The incidence of transfusion-related acute lung injury in critically ill patients has been reported to be 6.9%. Reported predictors of TRALI were mechanical ventilation, sepsis and high risk of mortality ill score [13]. The hypothesis underlying TRALI is the presence of antibodies or other inflammation mediators in blood products [13].

Transfusion-related immunomodulation is probably due to complex reactions that lead to dual proinflammatory and immunosuppressive responses [14].

Transfused patients are generally critically ill, and critical illness is associated with acute inflammation and immunosuppression.

We described here intraoperative and postoperative outcomes in a secondary analysis of patients who underwent craniosynostosis surgery included in the initial retrospective study [9]. This outcome description in this potential hemorrhagic setting had the objectives of proposing intraoperative implementation optimization protocols for postoperative outcome improvement.

2. Methods and Materials

A secondary analysis of patients who underwent cranial vault remodeling was

performed in the initial retrospective study [9].

The study was approved by the Ethics Committee of Necker Enfants Malades University Hospital under registration number 2017-CK-5-R1 on 21 March 2017.

Patients were retrospectively included from 1 January 2014 to 17 May 2017.

The inclusion criteria were all children included in the initial study who underwent craniosynostosis surgery and were less than 18 years old (see **Figure 1**, inclusion and exclusion criteria flow chart).

The exclusion criteria were patients included in the initial study who did not undergo craniosynostosis surgery and were aged more than 18 years old (see **Figure 1**).

Outcomes included intraoperative and postoperative organ dysfunction, length of hospital stay (LOS), length of intensive care unit stay (LOSICU), total length of hospital stay (TLOS = LOS + LOSICU), length of mechanical ventilation (LMV), and intraoperative blood product requirements.

Organ dysfunction was defined as a state of organ alteration with clinical, laboratory and imaging findings including infection that was not present in the preoperative period or that was present preoperatively with postoperative majoration or increase.

Patients were followed until discharge from hospital.

Statistics were analyzed with XLSTAT 2020.4.1. software. Continuous variables were expressed as medians with ranges or means with standard deviations. Categorial variables were described in proportions.

In our hospital, patients who underwent craniosynostosis surgery were managed intraoperatively according to a defined protocol. All patients were monitored with an arterial and central venous catheter, an indwelling bladder catheter, nasogastric tubing, a high-volume fluid administrating device, a Bair Hugger®, and a core temperature probe. Induction of anesthesia was performed with sevoflurane, sufentanil at a 0.3 - 0.5 μg/kg bolus intravenously (IV) and with a short-acting nondepolarizing muscle relaxant such atracurium at a 0.5 mg/kg bolus IV. Airway was secured with oro-tracheal intubation. Antibiotic prophylaxis

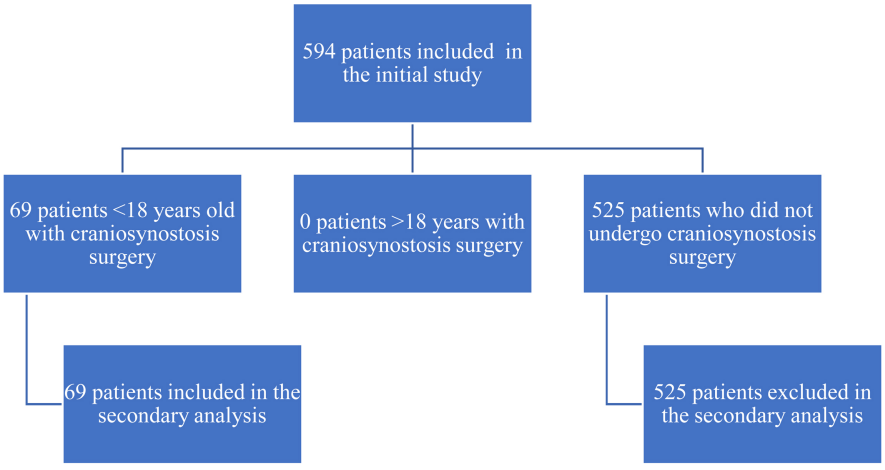

Figure 1. Inclusion and exclusion criteria flow chart.

was performed with cefazolin at a 50 mg/kg bolus IV. Maintenance of anesthesia was realized with sufentanil as an IV infusion of 0.3 - 0.5 µg/kg/h with sevoflurane. All patients received tranexamic acid as a 10 mg/kg IV bolus followed by an IV infusion of 10 mg/kg/h up to 6 hours postoperatively. A maintenance infusion was performed with a crystalloid (isopedia®) at 3 ml/kg/h if the patient weighed less than 10 kg and 5 ml/kg/h if the weight was above 10 kg. Hemoglobin levels were assessed on a regular basis. Fluid therapy was managed by monitoring central venous pressure, arterial blood pressure and pulse pressure variation with colloids (voluven® or plasmion®) administered as a 20 - 30 ml/kg bolus, packed red blood cells (PRBCs) and albumin. Fresh frozen plasma (FFP) at 15 ml/kg and concentrated platelet units at 0.1 - 0.2 UI/kg (CUP) were administered if transfusion requirements were above the total circulating blood volume. The volume of transfused packed red blood cells was determined as followed: PRBC in ml = Target hematocrit levels-Initial hematocrit levels/Weight in kg.

After surgery, the patient was transferred sedated and intubated in the post-anesthesia care unit (PACU) or the pediatric intensive care unit (PICU) for surveillance.

Postoperative analgesia was realized with intravenous morphine and oral morphine, intravenous acetaminophen and intrarectal ibuprofen. Patients could start oral intake feeding 4 hours after extubation. Blood draining systems were removed on postoperative day 2. All patients received intravenously 5 mg/kg iron (venofer®) as an infusion. Patients were discharged from the PICU when hemoglobin levels equaled or were above 12 g/dL.

3. Results

Table 1 illustrates the general characteristics. For more details see Figure S1 in Supplemental files.

There were 69 children with a median age of 10 [0 - 207] months. There were thirty-six (52.2%), sixteen (23.2%), fourteen (20.3%) and three (4.3%) American Society of Anesthesiologists grade one, two, three and four patients, respectively. Four (5.8%) patients had an emergency intervention, and sixty-five (94.2%) had an elective surgery. Eight (11.6%) patients had intraoperative and/or postoperative complications. One patient (1.5%) had intraoperative hemorrhagic shock, and two patients (2.9%) had intraoperative broncholaryngospasm. One patient (1.5%) had postoperative anaphylaxis. One patient (1.5%) had postoperative hemorrhagic shock. One patient (1.5%) had postoperative respiratory failure. Two patients (2.9%) had postoperative neurologic failure. One patient (1.5%) had neuro-meningeal sepsis. One patient (1.5%) had a re-operation.

There was no in-hospital mortality.

Fourty-eight patients (69.6%) had intraoperative transfusion with PRBC, FFP or CUP.

Median PRBC volume was 1 [0 - 4] units. The median FFP volume was 0 [0 - 2] units, and the median CUP volume was 0 [0 - 2] units. The mean preoperative

Table 1. General characteristics.

Characteristic	N = 69
Median age months [range]	10 [0 - 207]
ASA I n (%)	36 (52.2)
ASA II n (%)	16 (23.2)
ASA III n (%)	14 (20.3)
ASA IV n (%)	3 (4.3)
Emergency surgery n (%)	4 (5.8)
Elective surgery n (%)	65 (94.2)
Re-operation n (%)	1 (1.5)
Patients with intra-operative and or postoperative complications (organ failure or sepsis) n (%)	8 (11.6)
Intra-operative hemorrhagic shock n (%)	1 (1.5)
Intra-operative broncho-laryngospasm n (%)	2 (2.9)
Postoperative anaphylaxis n (%)	1 (1.5)
Postoperative hemorrhagic shock n (%)	1 (1.5)
Postoperative respiratory failure n (%)	1 (1.5)
Postoperative neurologic failure n (%)	2 (2.9)
Postoperative neuro-meningeal sepsis n (%)	1 (1.5)
In-hospital mortality n (%)	0 (0)
Transfusion n (%)	48 (69.6)
Median packed red blood cells units [range]	1 [0 - 4]
Median fresh frozen plasma volume units [range]	0 [0 - 2]
Median concentrated platelet units [range]	0 [0 - 2]
Mean preoperative hemoglobin levels ± standard deviation in g/dL	12.0 ± 1.2
Mean postoperative hemoglobin levels ± standard deviation in g/dL	11.6 ± 1.6
Median crystalloid volume in ml [range]	0 [0 - 1000]
Median colloid volume in ml [range]	250 [30 - 2050]
Median length of intensive care unit stay in days [range]	3 [1 - 90]
Median length of hospital stay in days [range]	2 [0 - 8]
Median total length of hospital stay in days [range]	5 [2 - 90]
Median total length of mechanical ventilation in days [range]	0 [0 - 79]

hemoglobin level was 12.0 ± 1.2 g/dL, and the mean postoperative hemoglobin level was 11.6 ± 1.6 g/dL.

Median crystalloid volume was 0 [0 - 1000] ml. Median colloid volume was 250 [30 - 2050] ml.

The median length of intensive care unit stay (LOSICU) was 3 [1 - 90] days. The median length of hospital stay (LOS) was 2 [0 - 8] days. The median total length of hospital stay (LOSICU + LOS = TLOS) was 5 [2 - 90] days. The median length of mechanical ventilation (LMV) was 0 [0 - 79] days.

Table 2 illustrates co-morbidities.

Table 2. Co-morbidities.

Co-morbidity	Number of patients (%)
Saethre-Chotzen syndrome	1 (1.5)
Polymal formation syndrome with congenital heart disease and metabolic disease	1 (1.5)
Apert syndrome	2 (2.9)
Arachnoid cyst	1 (1.5)
Asthma	2 (2.9)
Chiari's malformation	2 (2.9)
Congenital coagulation disorder	1 (1.5)
Congenital heart disease	2 (2.9)
Crouzon syndrome	6 (8.7)
Epilepsy	1 (1.5)
Former pre-term	2 (2.9)
Intracerebral tumor	1 (1.5)
Obstructive apneic syndrome	3 (4.3)
Rachitism	1 (1.5)
Tracheomalacia	1 (1.5)

The most common comorbidity was Crouzon syndrome in six patients (8.7%), followed by obstructive apneic syndrome in three patients (4.3%), Apert syndrome, asthma, Chiari's malformation, congenital heart disease, and former preterm birth in two patients (2.9%).

4. Discussion

The intraoperative transfusion rate in this secondary cohort was 69.6%. Most of the patients received PRBC and/or FFP units. Cranial vault modeling is a potential hemorrhagic surgery, and intraoperative transfusion with point-of-care viscoelastic assays needs to be included in patients who undergo this intervention. It has been proven that point-of-care tests to guide transfusion in hemorrhagic surgery, such as craniosynostosis, reduce transfusion requirements [6] [15] [16]. **Figures 2-4** illustrate algorithms with rotational thromboelastometry (ROTEM) in different age groups. ROTEM parameters in children have been described with ROTEM delta version [17]. These algorithms can be applied in other potential hemorrhagic settings to guide blood product administration [18] [19]. In this secondary cohort, the intraoperative hemorrhagic shock rate was 1.5%. Syndromic craniosynostosis has been reported to be correlated with higher intraoperative blood loss, emphasizing the necessity of integrating point-of-care tests for transfusion optimization in these patients [4]. Cranial vault surgery concerns small infants most of the time, and blood loss in these patients can occur acutely and rapidly; thus, anticipating this situation is mandatory. The rates of intraoperative hemorrhagic shock in children vary according to surgical

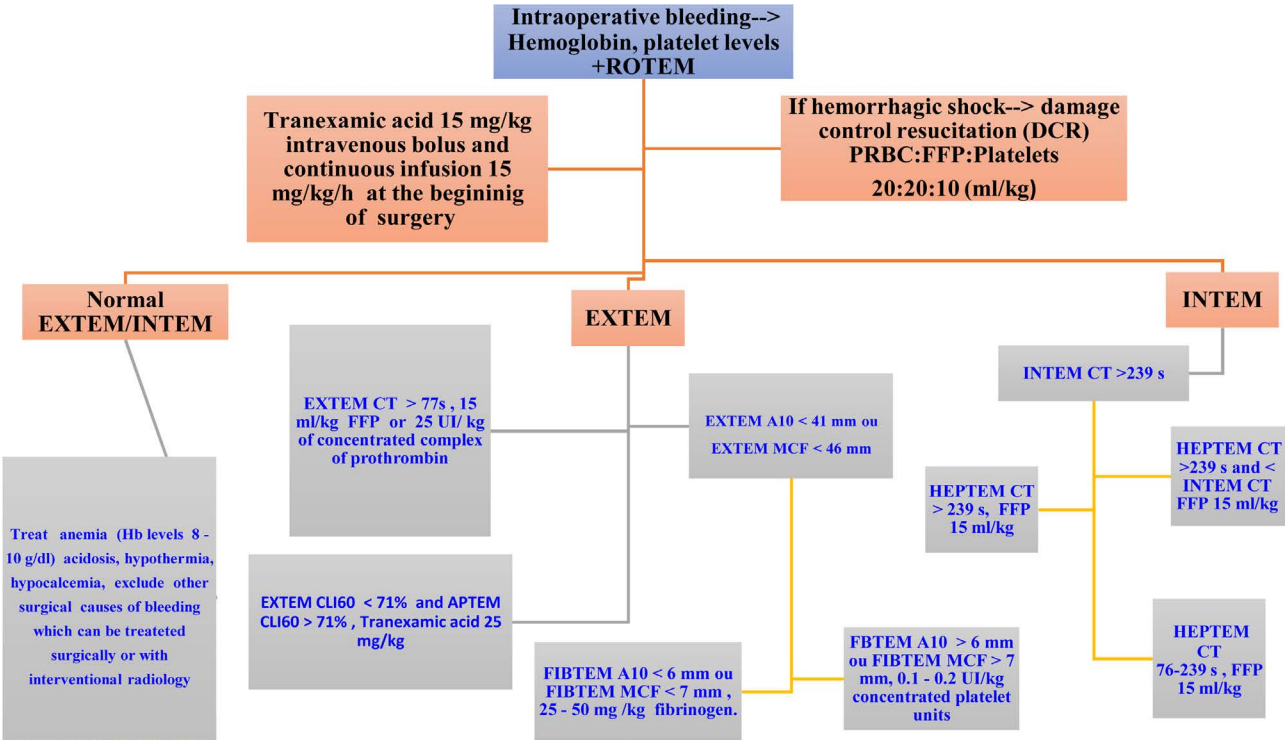

Figure 2. ROTEM algorithm in children between enfant 0 - 24 months. CT = coagulation time in seconds, A10 = clot firmness at 10 minutes, MCF = maximum clot firmness, CLI60 = lysis index in % 60 minutes after CT, ML = maximum lysis in %, FFP = fresh frozen plasma, PRBC = packed red blood cells, Hb = hemoglobin.

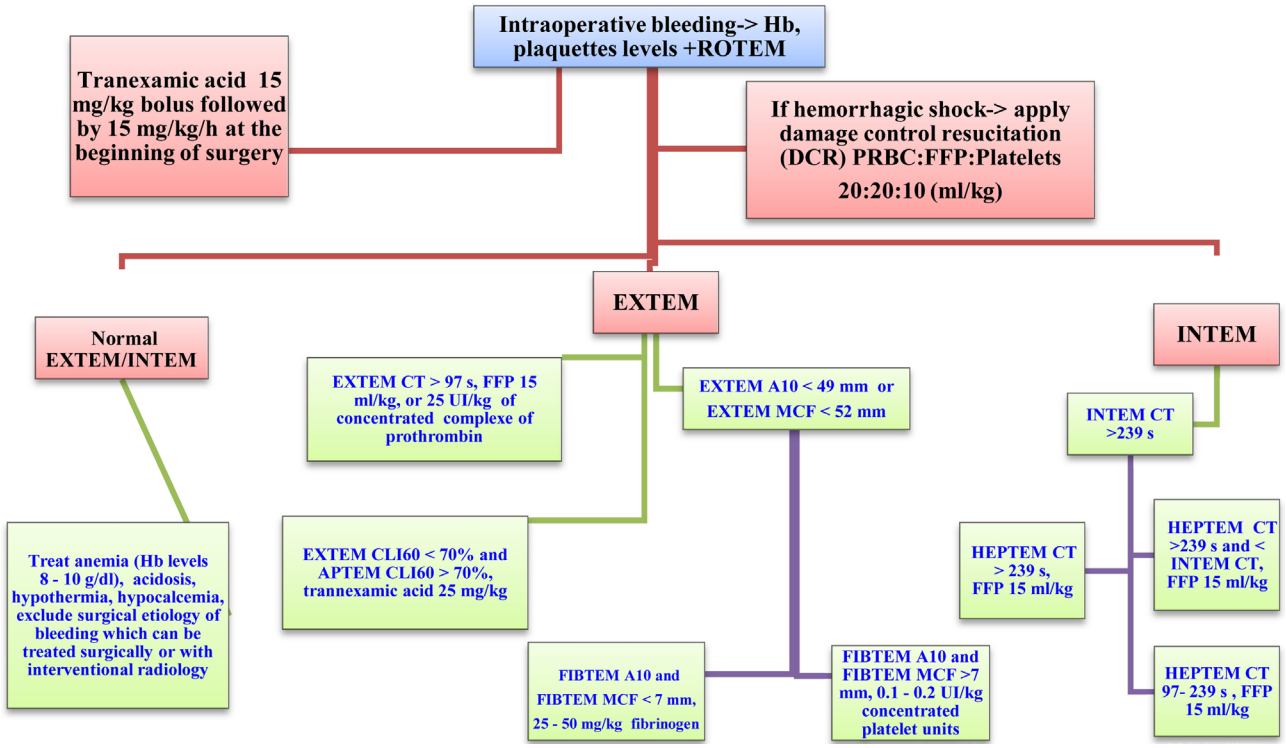

Figure 3. ROTEM algorithm in children 2 - 16 years. CT = coagulation time in seconds, A10 = clot firmness after 10 minutes, MCF = maximum clot firmness, CLI60 = lysis index in % 60 minutes after CT, ML = maximum lysis in %, FFP = fresh frozen plasma, PRBC = packed red blood cells, Hb = hemoglobin.

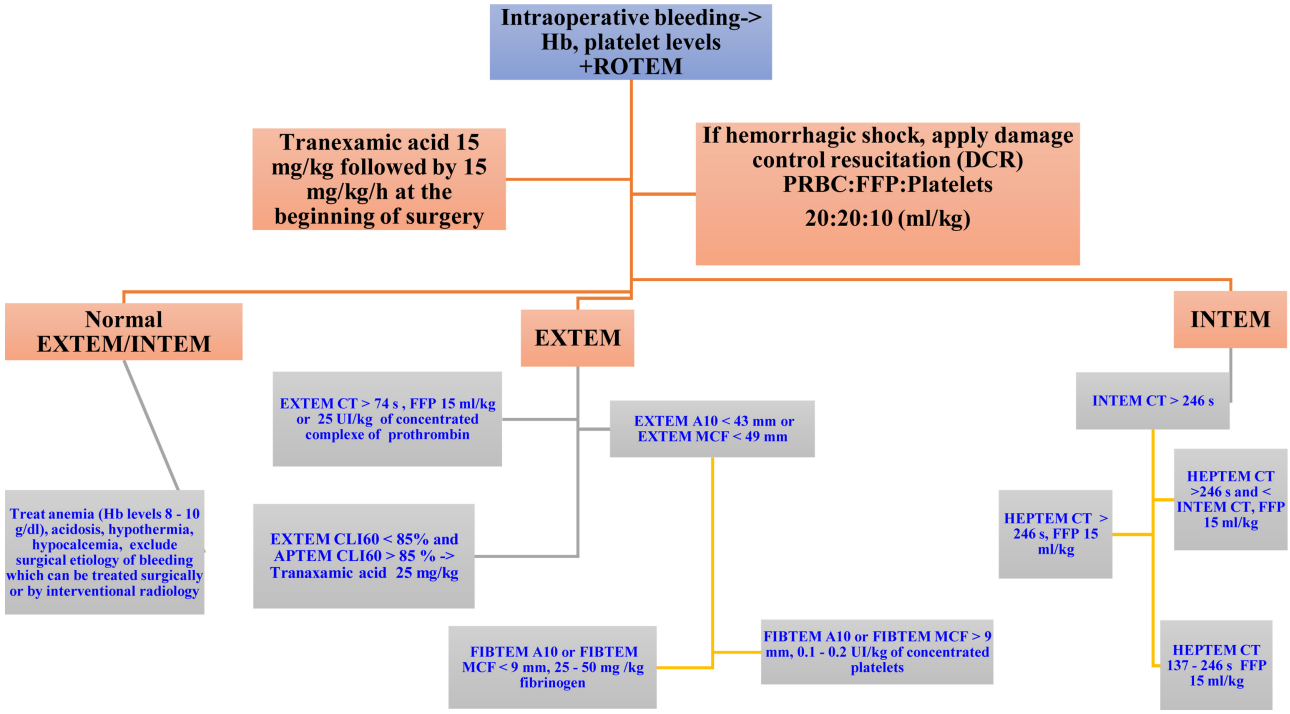

Figure 4. ROTEM Algorithm > 16 years. CT = coagulation time in seconds, A10 = clot firmness at 10 minutes, MCF = maximum clot firmness, CLI60 = lysis index in % 60 minutes after CT, ML = maximum lysis in %, FFP = fresh frozen plasma, PRBC = packed red blood cells, Hb = hemoglobin.

settings and age and have been reported to vary between 0 and 5.6% [20]-[25]. In small children, blood product requirements can rapidly reach total circulating blood volume, and massive transfusion is very likely in potential hemorrhagic situations. Transfusion and massive blood product administration are predictors of adverse postoperative outcomes that must be put into balance with the risk of anemia, which is also a predictor of postoperative unfavorable evolution in surgical children [10] [11] [12] [13] [14] [25] [26] [27] [28]. Preoperative and intraoperative hemoglobin levels have been negatively correlated with postoperative outcome; hemoglobin levels below 6 g/dL and intraoperative hemoglobin levels below 5 g/dL have been related to higher LOS [11]. Postoperative hemoglobin levels have been positively correlated with LMV, with hemoglobin levels higher than 12 g/dL being related to higher LMV. Restrictive transfusion strategies compared to liberal strategies in critically ill patients did not increase adverse outcomes. Maintaining a hemoglobin level target of 12 g/dL or more is not necessary for all patients and should be assessed according to patients global status and co-existing co-morbidities like congenital heart disease, prematurity, sepsis etc.

Preoperative erythropoietin has been reported to reduce blood product transfusion in craniosynostosis surgery, and integrating this molecule with iron supplementation in blood transfusion management protocols in this surgery could contribute to reducing the rate of intraoperative transfusions [29].

Crystalloid and colloid fluid therapy, similar to transfusion, need to be guided

with validated variables and tools in the pediatric population for optimal fluid and hemodynamic management [30] [31] [32] [33]. Non-optimal intraoperative values of cerebral and renal regional oxygen saturation assessed with near-infrared spectroscopy (NIRS), mixed venous oxygen saturation and lactate levels were predictors of adverse postoperative outcome in terms of organ dysfunction and LOS. Monitoring these parameters intraoperatively and optimizing them intraoperatively could improve postoperative outcome in major surgical settings [33]. Intraoperative fluid therapy optimization with validated tools in children could also help improve postoperative outcome in this surgery [32].

5. Conclusion

Transfusion protocols guided with point-of-care tests should be included in patient blood management programs in craniosynostosis surgery. Targeting higher postoperative hemoglobin levels in all patients is not necessary and should be assessed depending on patient comorbidities. Restrictive transfusion strategies are alternatives to liberal practices to reduce transfusion rates. Intraoperative operative fluid optimization with validated tools in children could also help to improve postoperative outcome in this surgery.

Presentation of Preliminary Data

This manuscript has been registered as a preprint on the preprint platform Research Square under the DOI registration number https://doi.org/10.21203/rs.3.rs-774234/v1.

Author Contributions

Claudine Kumba conceptualized and designed the study and drafted the initial manuscript. She designed the data collection instruments, collected data, carried out initial and final analyses.

Ethics Approval

This study received approval from the Ethics Committee of Necker on 21 March 2017 under registration number 2017-CK-5-R1 and waived patient consent.

Conflicts of Interest

The author declared no conflicts of interest.

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Supplemental Files

Patient	Surgery	Co-morbidity	Age in years	Emergency surgery	Re-operation	Intraoperative complications	Postoperative organ failure	Postoperative infection	patient avec complications perop et ou postop	Death	Transfusion	ASA score	LOSICU in days	LOS in days	TLOS in days	LMV in days
1	Craniosynostosis	0	12	0	0	0	0	0	0	0	1	2	5	0	5	0
2	Craniosynostosis	0	0	1	0	0	0	0	0	0	1	2	7	1	8	0
3	Craniosynostosis	0	2	0	0	0	0	0	0	0	1	2	3	1	4	0
4	Craniosynostosis	0	4	0	0	0	0	0	0	0	1	1	1	5	6	0
5	Craniosynostosis	0	3	0	0	0	0	0	0	0	1	1	3	1	4	0
6	Craniosynostosis	Crouzon syndrome	1,5	1	1	0	Neurologic failure	Neuro-meningeal sepsis	1	0	1	4	90	0	90	79
7	Craniosynostosis	0	9	0	0	0	0	0	0	0	1	2	1	1	2	0
8	Craniosynostosis	0	38	0	0	0	0	0	0	0	1	1	2	1	3	0
9	Craniosynostosis	Obstructive apneic syndrome	30	0	0	0	0	0	0	0	1	2	2	1	3	0
10	Craniosynostosis	0	8	0	0	0	0	0	0	0	1	1	2	1	3	0
11	Craniosynostosis	0	7	0	0	0	Hemorrhagic shock		0	1	0	1	3	2	5	0
12	Craniosynostosis	0	6	0	0	0	0	0	0	0	1	1	3	1	4	0
13	Craniosynostosis	0	7	0	0	0	0	0	0	0	1	1	3	5	8	0
14	Craniosynostosis	0	14	1	0	0	0	0	0	0	1	1	3	1	4	0
15	Craniosynostosis	0	4	0	0	0	0	0	0	0	1	1	3	1	4	0
16	Craniosynostosis	Congenital coagulation disorder	5	0	0	0	0	0	0	0	1	3	3	3	6	0
17	Craniosynostosis	Crouzon syndrome	207	0	0	0	0	0	0	0	1	3	11	7	18	4
18	Craniosynostosis	Rachitism	11	0	0	0	0	0	0	0	1	2	2	2	4	0
19	Craniosynostosis	0	11	0	0	0	0	0	0	0	1	1	3	2	5	0
20	Craniosynostosis	0	7	0	0	0	0	0	0	0	1	1	3	3	6	0
21	Craniosynostosis	0	23	0	0	0	0	0	0	0	1	1	3	2	5	0
22	Craniosynostosis	0	3	0	0	0	0	0	0	0	1	1	3	2	5	0
23	Craniosynostosis	Congenital heart disease	12	0	0	0	0	0	0	0	1	3	2	3	5	0
24	Craniosynostosis	Apert syndrome	23	0	0	Broncho-laryngospasm		0	0	1	0	1	3	3	2	5	0
25	Craniosynostosis	0	6	0	0	0	0	0	0	0	1	1	1	2	3	0
26	Craniosynostosis	0	17	0	0	0	0	0	0	0	1	1	2	2	4	0
27	Craniosynostosis	Asthma	52	0	0	0	0	0	0	0	1	2	3	1	4	0
28	Craniosynostosis	0	4	0	0	0	0	0	0	0	1	1	3	2	5	0
29	Craniosynostosis	0	11	0	0	0	0	0	0	0	1	1	4	3	7	0
30	Craniosynostosis	0	8	0	0	0	0	0	0	0	1	1	3	2	5	0
31	Craniosynostosis	0	18	0	0	0	0	0	0	0	1	1	3	1	4	0
31	Craniosynostosis	0	73	0	0	0	0	0	0	0	1	1	3	2	5	0
33	Craniosynostosis	0	15	0	0	0	0	0	0	0	1	1	3	1	4	0
34	Craniosynostosis	0	9	0	0	0	0	0	0	0	1	1	3	1	4	0
35	Craniosynostosis	Tracheomalacia	10	0	0	0	Respiratory failure		0	1	0	1	3	9	2	11	0
36	Craniosynostosis	Crouzon syndrome	67	0	0	0	Anaphylaxis		0	1	0	1	2	8	5	13	7
36	Craniosynostosis	0	7	0	0	0	0	0	0	0	1	1	3	8	11	0
38	Craniosynostosis	0	10	0	0	0	0	0	0	0	1	1	3	1	4	0
39	Craniosynostosis	Congenital heart disease	4	0	0	0	0	0	0	0	1	3	4	1	5	0
40	Craniosynostosis	0	8	0	0	0	0	0	0	0	1	1	3	2	5	0
41	Craniosynostosis	0	42	0	0	0	0	0	0	0	1	2	3	2	5	0
42	Craniosynostosis	0	5	0	0	0	0	0	0	0	1	1	3	1	4	0
43	Craniosynostosis	0	25	0	0	0	0	0	0	0	1	1	4	3	7	0
44	Craniosynostosis	0	4	0	0	0	0	0	0	0	1	1	3	2	5	0
45	Craniosynostosis	Former pre-term	8	0	0	0	0	0	0	0	1	2	3	2	5	0
46	Craniosynostosis	Former pre-term	13	0	0	0	0	0	0	0	1	2	3	4	7	0
47	Craniosynostosis	0	7	0	0	0	0	0	0	0	1	1	2	2	4	0
48	Craniosynostosis	0	6	0	0	0	0	0	0	0	1	1	3	1	4	0
49	Craniosynostosis	Chiari's malformation	192	0	0	0	0	0	0	0	0	3	2	3	5	0
50	Craniosynostosis	Apert syndrome	4	0	0	Broncho-laryngospasm		0	0	1	0	3	3	3	6	0
52	Craniosynostosis	Chiari's malformation	64	0	0	0	0	0	0	0	0	3	2	2	4	0
52	Craniosynostosis	Obstructive apneic syndrome	10	0	0	0	0	0	0	0	0	1	3	1	4	0
53	Craniosynostosis	0	6	0	0	0	0	0	0	0	0	2	3	1	4	0
54	Craniosynostosis	Obstructive apneic syndrome	8	0	0	0	0	0	0	0	0	3	5	2	7	0
55	Craniosynostosis	Epilepsy	200	0	0	0	0	0	0	0	0	2	2	3	5	0
56	Craniosynostosis	0	23	0	0	0	0	0	0	0	0	1	3	1	4	0
57	Craniosynostosis	Saethre-Chotzen syndrome	20	0	0	0	0	0	0	0	0	3	3	1	4	0
58	Craniosynostosis	Arachnoid cyst	96	0	0	0	Neurologic failure		0	1	0	2	3	3	6	1
59	Craniosynostosis	0	4	0	0	0	0	0	0	0	0	1	3	0	3	0
60	Craniosynostosis	0	4	0	0	0	0	0	0	0	0	1	3	1	4	0
61	Craniosynostosis	0	4	0	0	0	0	0	0	0	0	1	3	1	4	0
62	Craniosynostosis	0	35	0	0	0	0	0	0	0	0	2	3	1	4	0
63	Craniosynostosis	Crouzon syndrome	51	0	0	0	0	0	0	0	0	3	2	1	3	0
64	Craniosynostosis	0	4	0	0	Hemorrhagic shock		0	0	1	0	1	3	1	4	0
65	Craniosynostosis	polymalformation syndrome with	29	0	0	0	0	0	0	0	0	4	2	1	3	0
66	Craniosynostosis	Intracerebral tumor	131	0	0	0	0	0	0	0	0	2	1	3	4	0
67	Craniosynostosis	Asthma	180	0	0	0	0	0	0	0	0	3	2	3	5	0
68	Craniosynostosis	Crouzon syndrome	33	1	0	0	0	0	0	0	0	4	2	1	3	0
69	Craniosynostosis	Crouzon syndrome	79	0	0	0	0	0	0	0	0	3	6	1	7	0

Figure S1. Clinical characteristics.