Pediatric Anesthesia

Pediatric Anesthesia ISSN 1155-5645

ORIGINAL ARTICLE

Improvements in patient blood management for pediatric craniosynostosis surgery using a ROTEM®-assisted strategy – feasibility and costs

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Keywords
blood transfusion; blood coagulation disorders; blood coagulation factors; blood coagulation tests; thromboelastometry; hemorrhage

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Section Editor: Andrew Davidson

Accepted 2 December 2013

doi:10.1111/pan.12341

Summary

Background: Moderate to severe intraoperative bleeding and the presence of acquired coagulopathy remain serious problems in the management of major pediatric craniosynostosis surgery. After implementation of a ROTEM®-assisted patient blood management (PBM) strategy, using primarily purified coagulation factor concentrates, feasibility and costs of this new regimen were analyzed.
Methods: Retrospective analysis of all consecutive children who underwent primary elective major craniofacial surgery for craniosynostosis repair was carried out at the Children's University Hospital, Zurich, between 2007 and 2013. Laboratory workup and transfusion requirements were compared.
Results: A total of 47 children (36 in the historic group and 11 after implementation of PBM) were analyzed. Although all patients in this study needed transfusion of red blood cell concentrates, there was a total avoidance of perioperative transfusion of fresh frozen plasma and a reduction in transfused platelets (one of nine children vs nine of 36 children in the historic group) after implementation of the PBM strategy. Based on a predefined ROTEM® threshold in the PBM group (FibTEM MCF <8 mm), administration of fibrinogen concentrate was necessary in all of these children. The mean total costs per patient consisting of transfused allogeneic blood products and coagulation factor concentrates were reduced by 17.1% after implementation of PBM (1071.82 EUR per patient before vs 888.93 EUR after implementation).
Conclusions: The implementation of a ROTEM®-assisted PBM is feasible and is associated with a considerable reduction in intraoperative transfusion requirements and thereby a decrease in transfusion-related direct costs.

Background

Isolated, nonsyndromic craniosynostosis occurs with an incidence of about one in 3000 live births, and surgical repair is usually performed between 4 and 13 months of life. Total calvarial remodeling and fronto-orbital advancement and remodeling represent the cornerstone of surgical treatment for common congenital craniosynostosis (1). Although surgical and anesthesia techniques have been constantly refined over the years, open craniosynostosis surgery is still associated with substantial bleeding, with the need for transfusion of allogeneic blood products in virtually all children who undergo major craniosynostosis repair worldwide (2,3). Although traditional coagulation management, which consisted of transfusion of autologous blood products, offers a fairly acceptable safety profile, there is strong evidence that transfusion-related side effects are associated with increased morbidity and mortality in children (4–7). Furthermore, the avoidance of overtransfusion may decrease these adverse events, particularly transfusion-associated circulatory overload (TACO) and

transfusion-associated acute lung injury (TRALI) (7). In addition, due to emerging recommendations from the World Health Organization focusing on the implementation of a patient blood management (PBM) (8), we have set up a new strategy of transfusion/coagulation management in 2011. This new algorithm was mainly based on timely point-of-care analyses (hemogram, blood gas analysis, and ROTEM® measurements) and the consistent administration of tranexamic acid (TXA) and purified coagulation factors, if necessary. To assess the feasibility and related costs of this new strategy, we conducted a retrospective data analysis of all nonsyndromic major craniofacial surgeries performed between 2007 and 2013 at our hospital.

Methods

Electronic anesthesia records, laboratory records, and medical charts were searched retrospectively for all pediatric patients who underwent primary elective major craniofacial surgery for craniosynostosis repair at the Children's University Hospital, Zurich, between 2007 and 2013. Total calvarial remodeling and fronto-orbital advancement and remodeling were included in this study only to ensure comparable bleeding between groups. Patients with craniofacial syndromes were excluded from analysis as surgical procedures and consecutive blood loss might be considerably different. All surgeries were performed by the same surgical team consisting of one maxillofacial surgeon working always together with a neurosurgeon during the procedure, while different experienced consultant anesthetists performed anesthesia. The study was approved by the Institutional Ethics Committee (KEK-ZH-No 2012-0585).

Anesthesia, surgery, and postoperative care

General anesthesia was induced using either inhalation of sevoflurane or intravenous propofol. Endotracheal intubation was performed after muscle relaxation; anesthesia was maintained using sevoflurane in oxygen/air mixture, and narcotics (fentanyl boluses or continuous alfentanil infusion). Based on our routine fluid management, in the first hour after the start of anesthesia, all children received 20 $ml \cdot kg^{-1}$ of a lactated Ringer's solution with 2% glucose (Ringer Lactate Glucose 2%; Bichsel AG, Interlaken, Switzerland) for compensation of preoperative fasting period and basic fluid administration, followed by continuous infusion of 10 $ml \cdot kg^{-1} \cdot h^{-1}$. At the discretion of the anesthesiologist, intraoperative blood loss was replaced by infusion of lactated Ringer's solution (Ringer Lactate; Sintetica-Bioren SA, Couvet, Switzerland) and/or gelatin solution (Physiogel, B. Braun Medical AG, Sempach, Switzerland). Management of blood product administration pre- and post-PBM strategy implementation is detailed below. Intraoperative blood loss was calculated as described by Kearney for this population (9).

Intraoperative coagulation management

Laboratory assessment

Intraoperative blood samples were obtained as guided by routine clinical care and at discretion of the attending anesthesiologist. For ROTEM® analyses, one 1.4-ml tube containing citrate (0.106 molar solution; S-Monovettes®, Sarstedt, Nuembrecht, Germany) was taken and a second tube for plasmatic coagulation tests (STA Compact coagulation analyzer, Roche Diagnostics [Rotkreuz, Switzerland], ACL Top 500, American Diagnostics [Axon Lab AG, Baden, Switzerland]), while 1 ml EDTA blood sample was used for cell count (Sysmex XE-2100; Sysmex Europe GmbH, Norderstedt, Germany). All samples were immediately sent to the central laboratory. To analyze clot formation, an extrinsically (ExTEM®) and intrinsically (InTEM®) activated assay as well as an extrinsically activated test containing the platelet-blocking substance cytochalasin D (FibTEM®) to separately evaluate functional fibrin polymerization without platelet activity was performed. Technical details of the ROTEM® analyzer have been described elsewhere (10). During the entire study period, the anesthetists had online access to the ROTEM® and (with methodology-related delay) to all laboratory tests.

Transfusion guidelines and blood product administration

To maintain transfusion/coagulation thresholds, red blood cell concentrates were transfused if intraoperative hemoglobin levels dropped below 8 $g \cdot dl^{-1}$. This was performed over the entire study period, although no strict transfusion guidelines were set up before 2011.

Historically, fresh frozen plasma (FFP; Octaplas, Octapharma AG, Lachen, Switzerland) was transfused if relevant ongoing bleeding was observed or laboratory measurements revealed signs of coagulopathy (e.g. prothrombin time [PT] or activated partial thromboplastin time [aPTT] prolonged more than 1.5 times normal). As cryoprecipitate was not available in our country, fibrinogen concentrate (Haemocomplettan®P; CSL Behring GmbH, Bern, Switzerland) was occasionally used instead of or in addition to FFP if plasma fibrinogen concentration dropped below 150 $mg \cdot dl^{-1}$. Platelet concentrates were administered if platelet count was below 50 000 μl^{-1}. During that time, therapy was mainly based on plasma coagulation tests. A ROTEM® device was occasionally but rarely used from 2009 to 2011, but no

strict transfusion thresholds were set up. All other procoagulant factors (e.g. TXA, prothrombin complex concentrates (PCC), factor XIII concentrate) were available during the entire study period, but were used at the discretion of the anesthesia care provider.

In 2011, a PBM strategy was set up by our anesthesia department in collaboration with the leading hematologist in our hospital (Figure 1). This strategy standardized blood management and implemented the following changes for intraoperative management of craniosynostosis surgery patients:

1 Intraoperative prophylactic use of intravenous TXA (Exacyl, Sanofi Aventis, Paris, France) for all patients as initial bolus followed by continuous infusion.
2 Baseline and hourly measurements of blood gas analysis, blood counts, and routine coagulation tests (PT, aPTT/INR, plasma fibrinogen) and ROTEM® measurements (InTEM, ExTEM, FibTEM; ApTEM only if signs of hyperfibrinolysis such as maximum lysis (ML) $>15\%$ were observed).
3 Red blood cells (RBC) were transfused if hemoglobin level was <8 g·dl^{-1} targeting 10 g·dl^{-1} (amount of RBC was calculated by the following relation: the transfusion of 4 ml·kg^{-1}RBC will increase Hb of approximately 1 g·dl^{-1}).
4 Platelet apheresis concentrate (PC) was transfused if platelet count was $<50\,000$ μl^{-1} (dosage: 20 ml·kg^{-1} PC if body weight was <15 kg; otherwise transfuse one unit PC).
5 ROTEM®-based threshold to administer human fibrinogen concentrate if FibTEM was below 8 mm (corresponding to a fibrinogen level of approximately <150 mg·dl^{-1}).
6 Administration of FXIII concentrate (Fibrogammin®P, CSL Behring GmbH) if FXIII concentration was below 60% or no improvements in FibTEM can be established (despite adequate substitution of fibrinogen) and signs of severe bleeding were observed.
7 Fresh frozen plasma transfusion or administration of a four-factor PCC was indicated if severe disturbances of thrombin generation were displayed (ExTEM CT >90s and/or InTEM CT >260s) or ongoing bleeding occurred that did not respond to coagulation therapy.

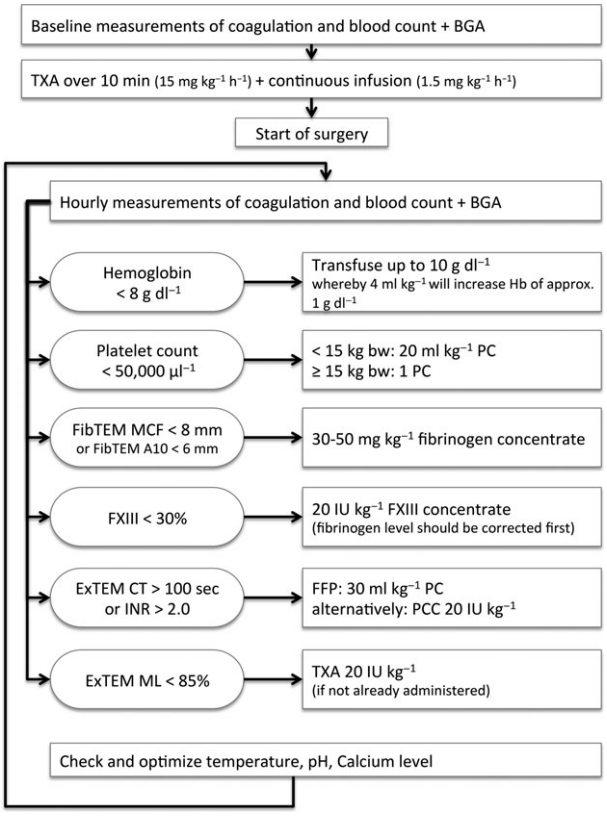

Figure 1 Flow chart of new ROTEM®-assisted patient blood management strategy.

In general, substitution of coagulation factors was performed only if relevant bleeding was observed, but not due to pathologic laboratory results without signs of bleeding.

Following surgery, children were transferred to the pediatric intensive care unit (PICU). Postoperative blood management and transfusion were at the discretion of the critical care team. Internal transfusion protocols at the PICU specified to transfuse RBC if hemoglobin levels dropped below 7 g·dl^{-1} (at a dose of 20 ml·kg^{-1}), to give platelet concentrate if platelet count dropped below 50 000 μl^{-1} (at a dose of 20 ml·kg^{-1}), and to transfuse FFP (at a dose of 15 ml·kg^{-1}) if drainage output was markedly increased or other clinical signs of increased bleeding were observed, in combination with a PT or aPTT >1.5 times normal.

Statistics

To characterize perioperative changes in hemostatic profile, all measured values were descriptively analyzed. Data are presented as median values with 25th and 75th percentiles, if not otherwise indicated. Cost analysis was applied based on the current prices for allogeneic blood products and coagulation factor concentrates at our hospital. As the absolute numbers of surgeries per year are not equally distributed, the mean relative amounts of allogeneic blood products and coagulation factors concentrates were calculated to compare the actual transfusion requirements and costs per patient. Results of blood loss are given as calculated relative amount of estimated total blood volume. The SPSS software package (version

18.0; SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The Kolmogorov–Smirnov test was applied to test for Gaussian distribution of study variables. Data before and after implementation of PBM were analyzed descriptively and using Mann–Whitney test or chi-square test as appropriate, whereby a $P < 0.05$ was defined to show significant differences between both groups.

Results

Forty-seven consecutive ASA 1 or 2 patients who underwent nonsyndromic primary total calvarial remodeling or fronto-orbital advancement and remodeling between 2007 and 2013 in our hospital were included: 36 patients from 2007 to 2011 and 11 patients who were treated after implementation of the new PBM strategy in 2011. Patient characteristics and description of the perioperative course are presented in Table 1. No significant overall differences were observed in terms of age, weight, height, and baseline coagulation tests, except for a mildly prolonged aPTT in the historical group ($P < 0.036$) and lower plasma fibrinogen levels in the group treated with the new strategy ($P < 0.002$). No changes were observed with respect to intraoperative fluid management. Surgical time was marginally longer in the historical group, while no changes in calculated blood loss were observed.

The absolute number of required transfusions and related costs are presented in Table 2. Although all patients in this study needed transfusion of red blood cell concentrates, there was a total avoidance of perioperative transfusion of FFP and a significant reduction in transfused platelets after implementation of the new blood management (Figure 2). Over the time, and specifically with the new management, fibrinogen concentrates were administered more frequently, as finally all patients after change in blood management received fibrinogen. Postoperative transfusion of allogeneic blood products (RBC, FFP, and platelets) was carried out in 25%, while after changing the blood management, only two children (18%) received postoperative transfusion of platelet concentrate due to low levels <50 000 μl^{-1} without any signs of bleeding. None of the patients received coagulation factor concentrates postoperatively in ICU.

Table 1 Patient characteristics and description of the perioperative course before and after implementation of a new patient blood management (PBM) strategy

	Before implementation of PBM strategy (2007–2011) ($n = 36$)	After implementation of PBM strategy (2011–2013) ($n = 11$)
Age (months)	10.0 (8.0–11.0)	13.0 (8.0–16.0)
Weight (kg)	8.8 (7.7–9.9)	10.0 (8.4–10.5)
Height (cm)	72 (69–75)	74 (69–80)
Sex (m/f)	20/16	6/5
Baseline Hb ($mg \cdot dl^{-1}$)	11.5 (11.1–12.3)	10.6 (10.1–11.9)
Baseline platelet count (μl^{-1})	359 (286–435)	330 (252–376)
Baseline-activated partial thromboplastin time (s)*	34 (28–37)	29 (26–31)
Baseline INR	0.97 (0.93–1.06)	0.96 (0.87–1.03)
Baseline fibrinogen ($mg \cdot dl^{-1}$)*	255 (210–280)	200 (150–220)
Surgical time (min)*	189 (164–212)	163 (142–180)
Calculated blood loss (% of calculated total blood volume)	107 (77–143)	71 (58–146)
Total amount of crystalloids ($ml \cdot kg^{-1}$)	72 (49–94)	71 (61–93)
Total amount of colloids ($ml \cdot kg^{-1}$)	56 (37–79)	50 (44–67)
Length of stay in ICU (days)	1 (1–2)	1 (1–1)

Data are expressed as median (interquartile range) or number as appropriate.
*$P < 0.05$ (Mann–Whitney test).

Table 2 Data on coagulation management and related costs

	Before implementation of PBM strategy (2007–2011) ($n = 36$)	After implementation of PBM strategy (2011–2013) ($n = 11$)
Number of intraoperative transfusions of red blood cells	36 (100%)	11 (100%)
Number of intraoperative transfusions of fresh frozen plasma	26 (72%)	0*
Number of intraoperative transfusions of platelet concentrate	9 (25%)	1 (9%)
Number of intraoperative transfusions of fibrinogen concentrate	22 (61%)	11 (100%)*
Number of intraoperative transfusions of FXIII concentrate	0	5 (45%)*
Number of postoperative transfusion on ICU	9 (25%)	2 (18%)
Perioperative administration of tranexamic acid	6 (16%)	11 (100%)
Mean costs of allogeneic blood products per patient[a]	808.73 EUR	416.11 EUR
Mean costs of coagulation factors per patient[a]	263.09 EUR	472.82 EUR
Mean total costs of PBM per patient[a]	1071.82 EUR	888.93 EUR

Data are expressed as absolute number (%).
PBM, patient blood management
[a]Calculated mean costs per patient in Euro.
*$P < 0.05$ (chi-square test).

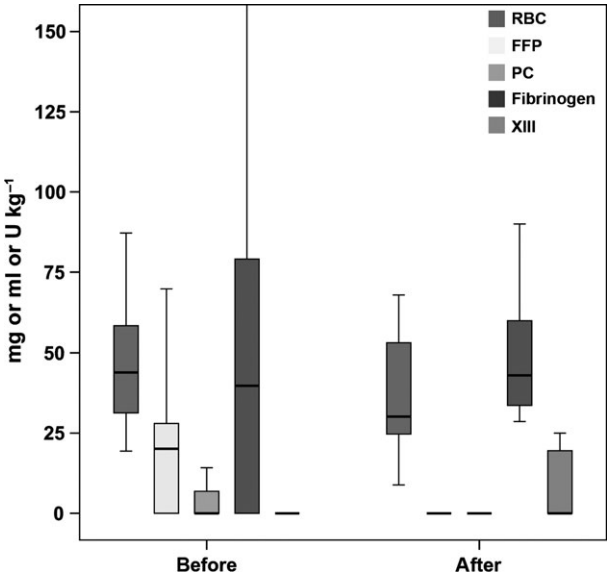

Figure 2 Intraoperative transfusion requirements of allogeneic blood products and coagulation factor concentrates for major craniofacial surgeries before and after implementation of patient blood management. RBC, red blood cell concentrate; FFP, fresh frozen plasma; PC, platelet concentrate; fibrinogen, purified fibrinogen concentrate; FXIII, purified factor XIII concentrate. All data are given in milligrams or milliliters or units (U) per kilogram bodyweight. *Significant difference before and after implementation of new patient blood management ($P < 0.05$).

The mean total costs per patient consisting of costs for transfused allogeneic blood products and costs for coagulation factor concentrates were reduced by 17.1% after implementation of the new PBM (1071.82 EUR per patient before vs 888.93 EUR after implementation). This was mainly triggered by markedly lower mean amounts of transfused platelet concentrates (273.50 EUR per patients before vs 99.50 EUR after implementation) and FFP (125.40 EUR before vs 0 EUR after implementation). No postoperative adverse events (i.e., prolonged time on ventilator until extubation, prolonged hospital stay, signs of thromboembolic events) were recorded in any patient during the hospital stay.

Discussion

This retrospective study demonstrates that the implementation of a comprehensive PBM strategy based on point-of-care testing and the use of purified coagulation factors rather than allogeneic blood products for primary coagulation management were feasible in the daily intraoperative care of craniosynostosis surgical patients at our tertiary care pediatric anesthesia department. In addition, this PBM regime was associated with total avoidance of FFP as well as reduced requirements of platelet concentrate during major craniosynostosis surgery in children. The World Health Organization has identified PBM as important in the care of surgical patients worldwide (8). PBM, as a modern therapeutic concept, relies on the detection and analysis of pre- and intraoperative anemia and, in addition, on an improvement in intraoperative coagulation therapy.

It must be stated that a number of contributors might be responsible for perioperative maintenance of adequate hemostasis, and thus, this has to be discussed separately. First of all, the implementation of a standardized algorithm itself might be a major driver toward more conservative usage of allogeneic blood products (11). The threshold for transfusing RBC intraoperatively in a bleeding child in our department was set at <8 g·dl^{-1} over the entire observation period, which is in accordance with recent recommendations (12). All children in our study still needed to be transfused with RBC, which indicates that a certain procedure-dependent blood loss cannot be avoided. In contrast, maintenance of perioperative hemostatic competence might be depending on a more conservatory therapy that restricts the use of blood products to where it is clearly indicated. One step toward reduction in perioperative blood loss is the systematic usage of TXA as an antifibrinolytic agent. There is evidence based on data published to support a prophylactic use of antifibrinolytics during major pediatric surgery. Two randomized controlled trials have shown that an initial dose of TXA followed by a continuous infusion significantly reduced the amount of transfused RBC during craniosynostosis repair in children (13,14) and it was likewise concluded from a web-based survey (15). In fact, since the implementation of ROTEM® testing and prophylactic administration of TXA at the same time, we have not observed signs of hyperfibrinolysis during craniofacial procedures in our department. Thus, irrespective of the strategy used for the treatment for coagulopathy, it seems to be wise to use adjunct antifibrinolytic therapy in order to reduce perioperative bleeding in children.

For optimal guidance of an intraoperative coagulation therapy, a fast and reliable test should be established. The benefit of using viscoelastic tests such as ROTEM® and TEG® for the treatment for perioperative coagulopathy was mainly shown in adults (16,17), but also in children (18–22). The ROTEM® and TEG® were able to show relevant lysis immediately and thus were stated to be the gold standard in the detection of hyperfibrinolysis. In addition, a timely analysis of especially the fibrin polymerization becomes even more meaningful, as it has been clearly shown that fibrinogen deficiency is typically the first step and cornerstone in developing dilution coagulopathy (17). In terms of

detecting fibrin polymerization disorders, the ROTEM® device might be considerably more helpful in the clinical setting as compared to other methods (23,24). Although the recommended trigger levels for starting fibrinogen therapy increased over the last years, a universally accepted trigger level is still missing, specifically for the use in children. However, we feel it might be justified to set up a FibTEM MCF <8 mm (<150 $mg \cdot dl^{-1}$) as lowest tolerable level in a perioperative bleeding episode; there is emerging evidence that the historically stated thresholds of <100 $mg \cdot dl^{-1}$ could be too low in the setting of hemorrhage (25). The detection of a reduced fibrinogen level can be further accelerated if the amplitude of the FibTEM assay after 10 min (A10) is used to guide fibrinogen substitution (26). To restore intraoperative low fibrinogen levels, a purified fibrinogen concentrate offers a safe and easy way to substitute fibrinogen. Interestingly, a recently published study of transfusion practice in the UK showed that 48% of children and 62% of infants received FFP transfusions in the absence of bleeding: A third of these transfusions were performed in the OR (27), thus underlining the need for an adapted local PBM strategy.

In addition to adequate fibrinogen substitution, we have defined that an intraoperative FXIII level <30% (or <60% in the presence of massive bleeding) should be treated with FXIII concentrate, as FXIII represents an important factor in generating a stable clot and increased resistance to fibrinolysis (17). However, one could argue that more evidence-based data need to be generated to determine an optimal and safe threshold for FXIII substitution. Although we are not able to provide such data with the current study, we have observed that clot firmness assessed by ROTEM® was more likely to be increased by additional factor XIII substitution, especially if fibrinogen concentrate was already given several times.

Notably, prolonged CT times were not observed in our PBM group, which may underline the fact that fibrinogen deficiency mainly occurs in this setting, while all other coagulation factors (necessary to maintain adequate thrombin generation) were still within a sufficient range.

As a drawback of such a PBM, coagulation therapy using purified factor concentrates was frequently scrutinized to be associated with higher costs as compared to transfusion of allogeneic blood products. Interestingly, our study results have shown that implementation of a targeted bleeding management has actually decreased mean costs per patient more than 17%, even with the inclusion of costs for ROTEM®-related reagents. This is in accordance with a recently published study in adults (16).

The present study has several limitations. First, this is a retrospective study conducted for internal quality control and reflects considerably the handling and knowledge of our staff. However, as the realization of a randomized controlled trial becomes more and more difficult in terms of regulatory and financial requirements, especially in children, we think that these data may serve as reasonable basis to improve management also in other centers or may lead to the development of further adequately powered studies. In addition, the reduction in allogeneic blood products in this study cannot be linked to one specific treatment step of our new implemented algorithm; it may be attributed to the concert of all factors, including administration of TXA and the timely ROTEM®-based treatment; especially, the latter one, with its ability to display nearly the entire phase of clot formation, was frequently mentioned as extremely helpful in the management of massive bleeding by our staff. Last but not least, the study was neither designed nor powered to find safe and beneficial thresholds for transfusion and coagulation therapy. This needs to be achieved by future prospective studies.

Conclusion

In conclusion, the implementation of a PBM strategy with nonsyndromic craniosynostosis surgery at our pediatric institution demonstrated a 64% reduction in the number of allogeneic blood product exposures per patient compared to our historical group. This was achieved primarily by a reduction in FFP transfusions. It must be noted that there was no reduction in the RBC exposure rate, which in both groups was 100%. The PBM strategy achieved a 17.1% reduction in the total cost of transfused hematological products per patient. It is of high interest to conduct further studies in this context in order to determine and justify safe and reliable laboratory thresholds and treatment algorithms to further reduce perioperative transfusion requirements.

Disclosure

The study was approved by the Institutional Ethics Committee (KEK-ZH-No 2012-0585).

Funding

This research was carried out without funding.

Conflict of interest

Dr. Haas has received speaker's fee and travel support from CSL Behring GmbH, Octapharma AG, and TEM International. Dr. Haas was employed at CSL Behring from 2007 to 2009 as Medical Director.

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