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

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

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 craniosynostosis surgery 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.
transfusion-associated acute lung injury (TRALI) (7). In addition, due to emerging recommendations 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 anesthesiologists 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·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·kg⁻¹·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-Mono- vettes®, Sarstedt, Nümbrecht, 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 anesthesiologists 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·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·dl⁻¹. Platelet concentrates were administered if platelet count was below 50 000 ul⁻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 craniostenosis 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®, 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.

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

![Figure 1](image-url)
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 \( \mu l^{-1} \) without any signs of bleeding. None of the patients received coagulation factor concentrates postoperatively in ICU.

**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* | 808.73 EUR | 416.11 EUR |
| Mean costs of coagulation factors per patient* | 263.09 EUR | 472.82 EUR |
| Mean total costs of PBM per patient* | 1071.82 EUR | 888.93 EUR |

Data are expressed as absolute number (%). PBM, patient blood management.

*Calculated mean costs per patient in Euro.

* \( P < 0.05 \) (chi-square test).
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 patient 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 conservative 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\(\textsuperscript{\textregistered}\) 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\(\textsuperscript{\textregistered}\) and TEG\(\textsuperscript{\textregistered}\) for the treatment for perioperative coagulopathy was mainly shown in adults (16,17), but also in children (18–22). The ROTEM\(\textsuperscript{\textregistered}\) and TEG\(\textsuperscript{\textregistered}\) 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·dl⁻¹) as lowest
tolerable level in a perioperative bleeding episode; there
is emerging evidence that the historically stated thresh-
holds of <100 mg·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. Inter-
estingly, a recently published study of transfusion prac-
tice 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 pro-
vide 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
coaagulation 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 scruti-
nized 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 dif-
ficult 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 imple-
menced 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 con-
text in order to determine and justify safe and reliable
laboratory thresholds and treatment algorithms to fur-
ther reduce perioperative transfusion requirements.

Disclosure

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

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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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