British Journal of Anaesthesia **114** (1): 91–102 (2015)
Advance Access publication 10 October 2014 · doi:10.1093/bja/aeu339

BJA

PAEDIATRICS

Thromboelastometry-guided intraoperative haemostatic management reduces bleeding and red cell transfusion after paediatric cardiac surgery

Y. Nakayama[1], Y. Nakajima[1]*, K. A. Tanaka[2], D. I. Sessler[3], S. Maeda[1], J. Iida[1], S. Ogawa[1] and T. Mizobe[1]

[1] Department of Anaesthesiology and Intensive Care, Kyoto Prefectural University of Medicine, Kyoto, Japan
[2] Department of Anaesthesiology, University of Pittsburgh, Pittsburgh, PA, USA
[3] Department of Outcomes Research, Cleveland Clinic, Cleveland, OH, USA

* Corresponding author. E-mail: nakajima@koto.kpu-m.ac.jp

Editor's key points

- Haemodilution-induced coagulopathy and postoperative blood loss have greater impact in paediatric than in adult cardiac surgery.
- A thromboelastometry-based algorithm was developed and compared with conventional transfusion management in a single-centre study.
- An algorithm incorporating thromboelastometry led to reduced postoperative bleeding and shorter intensive care unit stay in paediatric cardiac surgical patients.

Background. Thromboelastometric evaluation of coagulation might be useful for prediction and management of bleeding after paediatric cardiac surgery. We tested the hypothesis that the use of a thromboelastometry-guided algorithm for blood product management reduces blood loss and transfusion requirements.

Methods. We studied 78 patients undergoing paediatric cardiac surgery with cardiopulmonary bypass (CPB) for the initial 12 h after operation. Stepwise multiple linear regression was used to develop an algorithm to guide blood product transfusions. Thereafter, we randomly assigned 100 patients to conventional or algorithm-guided blood product management, and assessed bleeding and red cell transfusion requirements.

Results. CPB time, post-bypass rotational thromboelastometry (ROTEM®) EXTEM amplitude at 10 min (A10), and FIBTEM-A10 were independently associated with chest tube drainage volume during the initial 12 h after operation. Discriminative analysis determined cut-off values of 30 mm for EXTEM-A10 and 5 mm for FIBTEM-A10, and estimated optimal intraoperative fresh-frozen plasma and platelet concentrate transfusion volumes. Thromboelastometry-guided post-bypass blood product management significantly reduced postoperative bleeding (9 *vs* 16 ml kg^{-1}, $P<0.001$) and packed red cell transfusion requirement (11 *vs* 23 ml kg^{-1}, $P=0.005$) at 12 h after surgery, and duration of critical care stay (60 *vs* 71 h, $P=0.014$).

Conclusions. Rotational thromboelastometry-guided early haemostatic intervention by rapid intraoperative correction of EXTEM-A10 and FIBTEM-A10 reduced blood loss and red cell transfusion requirements after CPB, and reduced critical care duration in paediatric cardiac surgical patients.

Clinical trial registration. UMIN Clinical Trials Registry UMIN000006832 (December 4, 2011).

Keywords: blood coagulation; blood coagulation tests; blood transfusion; paediatrics

Accepted for publication: 16 July 2014

Haemodilution, hypothermia, antithrombotic agents, exposure to extracorporeal circulation, and inflammatory mediators during cardiopulmonary bypass (CPB) impair platelet function and reduce concentrations of coagulation factors, while platelet dysfunction, reduced clotting factors, and fibrinolysis contribute to perioperative haemorrhage. Patients with paediatric congenital heart disease undergoing cardiac surgery are likely to experience postoperative bleeding.[1] The priming volume of the CPB circuit is often considerably more than that of the circulating blood volume, and circulating coagulation factors are diluted by almost a factor of 2.[2]

Conventional measures of coagulation such as prothrombin time (PT), activated partial thromboplastin time (aPTT), activated clotting time (ACT), plasma fibrinogen, and platelet count do not accurately predict perioperative bleeding.[3–5] Rotational thromboelastometry (ROTEM®; TEM International, Munich, Germany) and thromboelastography (TEG; Haemoscope/Haemonetics, IL, USA) assess whole-blood coagulation profile including interactions between polymerizing fibrin and platelets, and fibrinolysis. Although they are useful in liver transplantation,[6] trauma management,[7] and adult cardiac surgery,[8 9] their usefulness in paediatric

haemostatic management, especially in children undergoing cardiac surgery, is not clear.[10–13]

In this two-phased study, we initially determined predictors of bleeding after paediatric cardiac surgery and designed a blood transfusion algorithm (development phase). In the subsequent validation phase, we tested the primary hypotheses that a thromboelastometry-based blood transfusion algorithm reduces postoperative bleeding and red cell transfusion requirements during the initial 12 h after surgery.

Methods

Our study protocol was approved by the Kyoto Prefecture University of Medicine Institutional Review Board, Kyoto, Japan, and registered at UMIN Clinical Trials Registry as UMIN000006832 (December 4, 2011, Principal Investigator: Y.Nakaj.). Written informed consent was obtained from the parents/guardians of each patient.

From December 2011 to May 2013, children weighing <20 kg were enrolled before elective cardiac surgery with CPB at the Kyoto Prefecture University Hospital. Patients were excluded if they had any known coagulation defect, liver dysfunction, or under anticoagulants or if they required a second run of CPB for additional surgical repair(s) after the initial CPB during surgery. Aspirin, if used, was discontinued 7 days before surgery, and warfarin, if used, was discontinued 5 days before surgery and replaced with heparin. Anaesthesia and CPB anaesthesia was induced using midazolam, fentanyl, and rocuronium bromide; these agents were also added into the CPB circuit, and no antifibrinolytic agents were used. Anaesthesia was maintained with sevoflurane, fentanyl, and rocuronium.

Size-adapted Capiox bypass circuits and membrane oxygenators (TERUMO Corporation, Tokyo, Japan) were used; RX05 and RX15 oxygenators for patients weighing <9 and ≥ 9 kg, respectively, were used. Total priming volume for the bypass circuit was 280–400 ml, consisting of lactated Ringer's solution, mannitol, and sodium bicarbonate. Anticoagulation during CPB was managed with 300 U kg^{-1} porcine heparin (Novo-Heparin, Mochida Pharmaceutical Co., Ltd, Tokyo, Japan) and additional boluses of 50 U kg^{-1}, as needed, to maintain an ACT of at least 400 s. Heparin anticoagulation was antagonized with 3 mg kg^{-1} protamine (Novo-Protamine Sulphate, Mochida Pharmaceutical Co., Ltd).

An intraoperative cell salvage device (Cell Saver 5 Haemonetics; Braintree, MA, USA) was used in all cases. Red blood cell concentrates were transfused to maintain the haematocrit at 25–30% during CPB. Bypass was conducted under mild hypothermia (core temperature, 32–34°C). Intermittent blood cardioplegia was performed for myocardial protection. Modified ultra-filtration was performed 5–15 min before protamine administration, with a target haematocrit of 30–35%.

Blood transfusion after paediatric intensive care unit (PICU) admission was managed without ROTEM® guidance by paediatric cardiac surgeons and intensivists who were blinded to group assignment and intraoperative ROTEM® results. When chest tube drainage exceeded 1.0 ml kg^{-1} h^{-1} with haemodynamic perturbation (decreased arterial pressure, decreased pulse pressure, increased heart rate by 20% from baseline, urine blood volume <1.0 ml kg^{-1} h^{-1}), we performed coagulation tests. Haematocrit values $<30\%$ for red blood cell concentrates, ACT ≥ 150 s for fresh-frozen plasma (FFP), and platelet count $\leq 80\times10^3$ μl^{-1} for platelet concentrates were used as transfusion trigger in PICU. Neither cryoprecipitate nor fibrinogen concentrate was available at this institution.

The decision to discharge patients from the PICU (Supplementary Appendix S1) was based on criteria established by the American Academy of Pediatrics,[14] and clinicians making discharge decisions were blinded to the randomization.

Measurements

We collected data on the following subject characteristics: height (cm); weight (kg); age (months); gender; blood type; presence of cyanosis; Risk Adjustment for Congenital Heart Surgery (RACHS-1) score;[15] duration of the surgical procedure (min); CPB time (min); aortic cross clamp time (min); total amount of blood products transfused intraoperatively (ml kg^{-1}), including red blood cell concentrates, FFP, platelet concentrates, and autotransfusion from the cell salvage device; total amount of blood products transfused after operation up to 12 and 24 h after admission to the PICU (ml kg^{-1}); total amount of chest tube drainage at 12 and 24 h after PICU admission (ml kg^{-1}); lactate concentration in arterial blood gas at the end of surgery and at 12 h after PICU admission (mmol litre^{-1}); mechanical ventilation time in the PICU (h); duration of PICU stay (h); and 28 day survival. Arterial blood was sampled for coagulation testing at four times: (i) baseline, after induction of anaesthesia; (ii) at the end of CPB, 5 min after protamine administration but before administration of any haemostatic product; (iii) at the end of surgery, but before admission to the PICU; and (iv) 24 h after induction of anaesthesia. Blood was collected in 3.2% citrated tubes (Insepack II-W, Sekisui Medical Co., Ltd, Tokyo, Japan).

We conducted thromboelastometry at the bedside using the ROTEM® device. Five assays—EXTEM, INTEM, FIBTEM, APTEM, and HEPTEM—were tested in citrated whole blood (300 μl) after recalcification (20 μl of 0.2 mM $CaCl_2$).[16 17] We sent blood samples to our clinical laboratory for other tests (normal range shown in parentheses). PT (9.4–12.1 s), aPTT (24.2–34.1 s), fibrinogen (150–310 mg dl^{-1}), antithrombin III (93–124%), and plasmin-α_2 plasmin inhibitor complex were measured using STACIA (Mitsubishi Chemical Medience Corporation, Tokyo, Japan) per using manufacturer's kits and directions, with appropriate calibrations. Fibrinogen concentrations were determined using a PT-derived method. Platelet count and haematocrit values were measured by MYTHIC 22OT (J) (A&T Corporation, Kanagawa, Japan).

Development phase

We used univariate and multivariate linear regression analysis, as used in previous studies,[18 19] to determine factors that correlated with total amount of chest tube drainage at 12 h after PICU admission, which was our dependent variable, since clinically important bleeding rarely continues longer.[3] Initially,