BJA

British Journal of Anaesthesia 115 (2): 234–43 (2015)

doi: 10.1093/bja/aev136
Advance Access Publication Date 15 May 2015
Clinical Practice

CLINICAL PRACTICE

Higher fibrinogen concentrations for reduction of transfusion requirements during major paediatric surgery: A prospective randomised controlled trial†

T. Haas[1,*], N. Spielmann[1], T. Restin[2], B. Seifert[3], G. Henze[1], J. Obwegeser[4], K. Min[5], D. Jeszenszky[6], M. Weiss[1] and M. Schmugge[7]

[1]Department of Anaesthesia, University Children's Hospital Zurich, Steinwiesstrasse 75, 8032 Zurich, Switzerland, [2]Department of Anaesthesia, University Hospital Zurich, Zurich, Switzerland, [3]Department of Biostatistics, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland, [4]Department of Oral and Maxillofacial Surgery, University Children's Hospital Zurich, Zurich, Switzerland, [5]Swiss Scoliosis, Centre for Spinal and Scoliosis Surgery, Zurich, Switzerland, [6]Department of Spine Surgery and Neurosurgery, Schulthess Clinic, Zurich, Switzerland, and [7]Department of Haematology, University Children's Hospital Zurich, Zurich, Switzerland

*Corresponding author. E-mail: thorsten.haas@kispi.uzh.ch

Abstract

Background: Hypofibrinogenaemia is one of the main reasons for development of perioperative coagulopathy during major paediatric surgery. The aim of this study was to assess whether prophylactic maintenance of higher fibrinogen concentrations through administration of fibrinogen concentrate would decrease the volume of transfused red blood cell (RBCs).

Methods: In this prospective, randomised, clinical trial, patients aged 6 months to 17 yr undergoing craniosynostosis and scoliosis surgery received fibrinogen concentrate (30 mg kg^{-1}) at two predefined intraoperative fibrinogen concentrations [ROTEM® FIBTEM maximum clot firmness (MCF) of <8 mm (conventional) or <13 mm (early substitution)]. Total volume of transfused RBCs was recorded over 24 h after start of surgery.

Results: Thirty children who underwent craniosynostosis surgery and 19 children who underwent scoliosis surgery were treated per protocol. During craniosynostosis surgery, children in the early substitution group received significantly less RBCs (median, 28 ml kg^{-1}; IQR, 21 to 50 ml kg^{-1}) compared with the conventional fibrinogen trigger of <8 mm (median, 56 ml kg^{-1}; IQR, 28 to 62 ml kg^{-1}) (P=0.03). Calculated blood loss as per cent of estimated total blood volume decreased from a median of 160% (IQR, 110–190%) to a median of 90% (IQR, 78–110%) (P=0.017). No significant changes were observed in the scoliosis surgery population. No bleeding events requiring surgical intervention, postoperative transfusions of RBCs, or treatment-related adverse events were observed.

Conclusions: Intraoperative administration of fibrinogen concentrate using a FIBTEM MCF trigger level of <13 mm can be successfully used to significantly decrease bleeding, and transfusion requirements in the setting of craniosynostosis surgery, but not scoliosis.

Clinical trial registry number: ClinicalTrials.gov NCT01487837.

Key words: blood, coagulation; coagulation; coagulopathy; hemorrhage; pediatrics; thrombelastography; transfusion

† This Article is accompanied by Editorial Aev167.

Accepted: March 22, 2015

Editor's key points

- Hypofibrinogenaemia can lead to acquired coagulopathy after major paediatric surgery.
- The effect of a liberal fibrinogen concentrate treatment strategy on red blood cell transfusion was studied in a single centre randomised study of craniosynostosis and scoliosis surgery patients.
- Thromboelastometry-guided maintenance of high normal fibrinogen concentrations reduced blood loss and transfusion in craniosynostosis surgery.

Major paediatric surgery is frequently associated with extensive blood loss, which increases the risk for morbidity and mortality.[1] The risks associated with transfusion highlight the urgent need for blood conserving strategies, especially in children. These include implementation of patient blood management programs with coagulation management.[2 3] Both major paediatric orthopaedic surgery and craniosynostosis surgery are frequently associated with moderate to severe bleeding.[4–6] The development of hypofibrinogenaemia is a major reason for coagulopathic bleeding during craniosynostosis surgery.[7] A prospective observational trial in adolescents who underwent major spine surgery demonstrated that preoperative fibrinogen concentrations predict mean total perioperative blood loss.[4] Thus, restoration of adequate fibrinogen concentrations plays a major role in maintenance of effective haemostasis.

As in most European countries cryoprecipitate is not available, and fresh frozen plasma (FFP) has demonstrated questionable efficacy in restoring diminished fibrinogen concentrations after perioperative bleeding,[8–10] administration of purified fibrinogen concentrate has become the standard of care in a number of countries, including Switzerland. Fibrinogen concentrate is recommended in the current European guidelines for perioperative bleeding management,[11] although data in children are rare.[7 12] In the previously mentioned studies, targeted fibrinogen administration was successfully implemented using the ROTEM® FIBTEM assay (TEM International, Munich, Germany) to monitor and guide fibrinogen substitution, applying a trigger level of FIBTEM MCF <8 mm.[11]

The aim of this study was to assess if earlier substitution of fibrinogen without waiting for hypofibrinogenaemia, defined as FIBTEM MCF <8 mm, decreases blood loss and consequently transfusion of allogeneic blood products. We hypothesized that maintenance of baseline fibrinogen concentrations for this population[13] (ROTEM® trigger of FIBTEM MCF <13 mm) can reduce the need for transfusion of red blood cells (RBC's) in two types of major paediatric surgery.

Methods

Study design and population

This phase IV, prospective, randomised, single-blinded, parallel-group, stratified clinical trial was conducted at a single children's hospital (University Children's Hospital, Zurich, Switzerland). The study was approved by the local ethics committee (KEK-ZH-No. 2011-0440) and the Swiss Regulatory Medical Authorities (registration No.: 2011 DR 4222), conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, and registered at ClinicalTrials.gov identifier No. NCT01487837.

Eligible male and female patients between 6 months and 17 yr of age who were to have elective craniosynostosis or scoliosis surgery were enrolled between February 2012 and September 2014, if informed consent of one parent was obtained. Craniosynostosis surgery was defined as anterior vault reconstruction with fronto-orbital advancement, and scoliosis surgery as dorsal instrumentation of more than 6 segments. Exclusion criteria encompassed any diagnosed preexisting congenital or acquired coagulation disorder, a medical history consistent with increased bleeding tendency, ongoing anticoagulation therapy or drug intake that could cause bleeding, clinical signs or diagnosis of acute thromboembolism, participation in another clinical trial, and pregnant or lactating women.

A telephone randomisation system was used. Before starting the trial, a randomisation list, stratified by procedure, was prepared by a statistician and sent to dedicated, trained staff members in our hospital pharmacy. After the start of anaesthesia for a consented study patient, the investigator retrieved the randomisation group by calling the pharmacy. Patients were randomised to one of the treatment groups after the start of anaesthesia and stratified by type of surgery (craniosynostosis or scoliosis surgery).

Procedures

All subjects in this study received antifibrinolytic prophylaxis by administration of tranexamic acid (TXA) at an initial dose of 15 mg kg^{-1} followed by continuous infusion of 1.5 mg kg^{-1} h^{-1} until 3 h after transfer to the paediatric intensive care unit (PICU). Laboratory investigation (cell count, blood gas analysis, standard plasmatic coagulation testing, factor XIII, and ROTEM® analysis) was performed after induction of anaesthesia, at the start of surgery, and every 60 min thereafter, or more frequently at the discretion of the anaesthetist in charge, if acute bleeding was present (Fig. 1). Laboratory testing, including ROTEM® analyses, was performed at the hospital's central laboratory with real-time online access to ROTEM® traces from the operating theatre. ROTEM® FIBTEM MCF could usually be obtained within 15 min of blood draw. Fibrinogen concentrate was administered for ROTEM® FIBTEM MCF <8 mm (conventional group) or <13 mm (early substitution group), at any intraoperative measurement, independent of the presence of bleeding. The trigger of <8 mm in the conventional group was established based on the recommendation from a European guideline,[11] and the concentration of <13 mm represents the baseline fibrinogen concentrations for this population.[13] Fibrinogen concentrate (Haemocomplettan P, CSL Behring GmbH, Marburg, Germany) was administered at a dose of 30 mg kg^{-1} if indicated according to the predefined FIBTEM concentrations by pump-controlled i.v. administration over 10 min. This dose and the indication of acquired hypofibrinogenaemia is within the labelling for this drug in Switzerland, and likewise published in a European guideline for perioperative bleeding management in children.[11] FIBTEM was also performed 10 min after the end of fibrinogen administration and fibrinogen concentrate was repeatedly administered if threshold FIBTEM concentrations were not reached.

Body temperature was continuously monitored and all children were kept normothermic during the procedure to ensure physiologic conditions for haemostasis. Red blood cell concentrates (RBCs) were transfused following a strict transfusion protocol for haemoglobin concentrations <8 g dl^{-1} with a 10 g dl^{-1} haemoglobin concentration target. Transfused RBC volume was calculated by approximating that transfusion of 4 ml kg^{-1} RBC increases haemoglobin by 1 g dl^{-1}.[14] If intraoperative blood salvage with a mechanically processed autologous transfusion (MAT) device was performed, the autologous blood concentrate was used