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Paediatrics

Early or late fresh frozen plasma administration in newborns and small infants undergoing cardiac surgery: the APPEAR randomized trial

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Abstract

Background. In newborns and small infants undergoing cardiac surgery with cardiopulmonary bypass (CPB) and blood priming, it is unclear whether there is reduced blood loss if fresh frozen plasma (FFP) is added to the CPB priming volume. This single-centre, randomized trial tested the hypothesis that the administration of FFP after CPB (late FFP group) is superior to FFP priming (early FFP group) in terms of postoperative bleeding and overall red blood cell (RBC) transfusion.

Methods. Seventy-three infants weighing <10 kg were randomly allocated to receive FFP to supplement RBCs in the CPB priming solution (n=36) or immediately after CPB (n=37). The primary endpoint was a difference in postoperative blood loss; secondary endpoints included the amount of RBCs and FFP transfused through the first 48 postoperative hours.

Results. All patients were included in the analysis. Patients in the late FFP arm had greater postoperative mean blood loss than patients in the early FFP arm [33.1 (SD 20.6) *vs* 24.1 (12.9) ml kg^{-1}; P=0.028], but no differences in transfusions were found. The subgroup of cyanotic heart disease patients had comparable results, but with greater use of RBCs in the late FFP group.

Conclusions. In infants undergoing cardiac surgery, FFP in the priming solution appears slightly superior to late administration in terms of postoperative bleeding.

Clinical trial registration: www.ClinicalTrials.gov, NCT02738190.

Key words: blood coagulation disorders; heart defects; congenital; paediatrics

The haemostatic system of newborns and small infants is downregulated, with lower activity of both coagulation factors and native anticoagulants.[1] Cyanosis, which is present in many paediatric cardiac patients, is associated with polycythaemia, low fibrinogen and clotting factors concentration, low platelet count, and increased fibrinolysis.[2] In complex paediatric cardiac surgery, the use of cardiopulmonary bypass (CPB) has repercussions for variations in temperature, activation of the inflammatory

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Editor's key points

- Infants undergoing cardiac surgery typically need blood priming in the bypass circuit to prevent excessive haemodilution.
- Maintenance of colloid oncotic pressure during bypass is typically achieved by adding 5% albumin, fresh frozen plasma, or synthetic colloid to the priming volume.
- This study found that patients receiving early (priming volume) fresh frozen plasma had significantly less postoperative bleeding.
- Early fresh frozen plasma preserved postoperative functional fibrinogen levels.

cascade, and haemodilution. Despite the use of miniaturized circuits,[3] CPB still has a major impact on perioperative bleeding.

In newborns and small infants undergoing cardiac surgery, red blood cells (RBCs) are usually added to the CPB priming volume to prevent excessive haemodilution.[4–6] At the same time, maintenance of a physiologic colloid oncotic pressure during CPB must be preserved to prevent interstitial fluid accumulation;[7 8] this is achieved by adding either 5% albumin, fresh frozen plasma (FFP), or colloids to the priming. At present, few studies have investigated the superiority of FFP or albumin-based priming solutions in newborns and small infants, and the results are conflicting.[9–13] Potential advantages of the use of albumin in the priming solution are avoidance or limitation of exposure to allogeneic blood-derived FFP and prevention of fibrinogen adsorption and platelet adhesion to the CPB circuit and oxygenator foreign surfaces.[14] Conversely, FFP-based priming may retain a slightly higher colloid oncotic pressure and prevent the haemodilution of soluble coagulation factors and fibrinogen.

To address the above-mentioned gap in knowledge, we designed a randomized trial of Albumin vs. Plasma for PaEdiAtric pRiming (APPEAR) in newborns and small (<10 kg) infants. We compared differences in coagulation and postoperative bleeding generated by the administration of FFP at different points in time (in the priming solution or at the end of CPB). Our hypothesis was that later administration of FFP is superior to its addition in the priming volume. This hypothesis was based on the assumption that by diluting soluble coagulation factors, less thrombin is generated during CPB and there is less coagulation factor consumption.

Methods

The study was approved by the local ethics committee of IRCCS San Raffaele Hospital and by the Italian Agency of Drugs. The study was registered at ClinicalTrials.gov (identifier code NCT02738190). The study was funded by research funds from IRCCS Policlinico San Donato, a clinical research hospital partially funded by the Italian Ministry of Health.

Written informed consent to participate in the study was signed by the parents of the patients.

Patient population and randomization

Inclusion criteria were planned cardiac surgery with CPB and blood priming solution and a weight <10 kg. Exclusion criteria were emergency surgery, known congenital coagulopathy, participation in another trial, or refusal to participate. The withdrawal criterion was the need for extracorporeal membrane oxygenation to wean the patient from CPB or to support them within the first 24 h from admission in the intensive care unit (ICU). A randomization code was generated with a computerized system and the patients were assigned to each group by a research doctor. The attending anaesthesiologist and the surgical staff were not blinded; conversely, ICU and ward doctors were blinded, as well as the person in charge of database data entry.

Surgery and CPB

Every subject received our standard surgical care and CPB technique. A total intraoperative dose of 30 mg kg^{-1} of tranexamic acid was administered in all patients. CPB was established after a loading dose of 300 IU kg^{-1} of unfractionated heparin plus additional doses (80 IU kg^{-1}) to reach and maintain a target activated clotting time of ≥450 s. The CPB circuit included a hollow-fibre oxygenator (Sorin KIDS D100 or D101, Livanova, Mirandola, Italy), a roller head pump (Sorin S5 HLM, Livanova), or a centrifugal pump (Bio-Medicus, Medtronic, Minneapolis, MN, USA).

Interventions

Routine laboratory tests were performed the day before surgery, including activated partial thromboplastin time (aPTT; s), prothrombin time international normalized ratio (PT-INR), and fibrinogen levels (mg dl^{-1}), plus basal haematocrit (HCT; %) and platelet count (cells × 1000 μl^{-1}). In the operating room, patients were randomly allocated to the early (bypass prime) FFP or late FFP group. After general anaesthesia induction, an arterial line was positioned and a blood sample was taken (1.3 mL) to perform ROTEM (TEM International, Munich, Germany) tissue factor–activated (EXTEM) and fibrin-based thromboelastometry (FIBTEM) tests. Clotting time (s) at EXTEM and maximum clot firmness (MCF; mm) at the EXTEM and FIBTEM (MCF; mm) were recorded.

CPB priming of patients in the late FFP arm was formulated with albumin 5% plus RBCs. Patients in the early FFP group received a priming solution with FFP plus RBCs. The solution was titrated to reach an 'on pump' HCT of 30%. The amount of RBCs used in the priming solution varied according to the patient's baseline HCT and weight and the priming volume. The 'clear prime volume' (albumin 5% or FFP) was obtained as the difference between the circuit priming volume and the calculated amount of RBCs. An additional 500 IU of unfractionated heparin, 1 mg kg^{-1} dexamethasone, and 5 mEq of sodium bicarbonate were routinely administered in the priming solution of both groups.

The target patient temperature was chosen based on the type of surgical procedure and cardioplegia protocol. Every volume addition needed during CPB was made giving albumin 5% or RBCs according to our HCT target.

Ultrafiltration was a standard of care; conventional or modified ultrafiltration was applied during and after CPB, respectively, according to the surgeon's preference. The ultrafiltrated volume was fixed at 30 ml kg^{-1}. During ultrafiltration, patients in the late FFP arm had half of the volume replaced with FFP (15 ml kg^{-1}). With the same timing, patients in the early FFP group received the same replacement with albumin 5%. Patients in the late FFP arm received an additional dose of 15 ml kg^{-1} of FFP during haemostasis and before transfer to the ICU.