Aprotinin versus tranexamic acid in children undergoing cardiac surgery: an observational study

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Abstract

OBJECTIVES: The upcoming release of aprotinin in paediatric cardiac surgery prompted a re-evaluation of its use in comparison to tranexamic acid (TXA) focusing on their effect on exposure to blood transfusions as well as severe postoperative morbidity or mortality.

METHODS: This retrospective study was conducted in a tertiary children hospital from 2002 to 2015. Patients receiving aprotinin (Aprotinin group: 2002–2007) were compared with those receiving TXA group (2008–2015) using propensity score analysis. Primary outcome measures were ‘exposure to blood products’ and ‘severe postoperative morbidity or mortality’. High-risk subgroups that included neonates, complex (Risk Adjusted Classification for Congenital Heart Surgery-1 ≥ 3) and redo surgery were also analysed.

RESULTS: The study included 2157 patients, 1136 in the Aprotinin group and 1021 in the TXA group. Exposure to blood products was significantly higher in the Aprotinin group (78% vs 60%; \(P < 0.001\)) as well as in the complex and redo surgery subgroups. Incidence of mortality and/or severe morbidity was higher in the Aprotinin group (33% vs 28%; \(P = 0.007\)), as well as in the neonate group. However,
cardiopulmonary bypass priming volume and intraoperative fluid balance were significantly decreased, and the use of modified ultrafiltration significantly increased in the TXA group.

CONCLUSIONS: In our population, children receiving aprotinin were more frequently transfused and were at a higher risk of developing severe postoperative morbidity or mortality than those receiving TXA. Subgroups at high risk of bleeding or inflammation did not seem to benefit from aprotinin. These differences might be explained by a safer profile of TXA, but also attributed to major changes in our patient blood management strategies over years.

Keywords: Paediatric • Cardiac surgery • Antifibrinolytics • Aprotinin • Tranexamic acid • Blood transfusion

INTRODUCTION

Bleeding is a common complication in paediatric cardiac surgery and leads to a high transfusion burden. Multimodal strategies have been progressively implemented, as bleeding and exposure to blood products have been associated with worse outcomes [1, 2]. In particular, antifibrinolytics are commonly used in paediatric cardiac surgery to counteract the deleterious effects of the cardiopulmonary bypass (CPB) on the coagulation system, mainly fibrinolysis activation and platelet dysfunction [3]. Aprotinin is a natural broad-spectrum serine protease inhibitor acting on plasmin, trypsin and kallikrein. It has also demonstrated a preserving effect on platelets and anti-inflammatory properties [4, 5]. Tranexamic acid (TXA) is a synthetic lysine analogue that interferes with the binding of plasminogen to fibrin, which is required for activation of plasminogen into plasmin [3]. TXA appears to have less anti-inflammatory properties than aprotinin [5].

In February 2008, the licence for aprotinin was suspended by the European Commission based on 1 randomized control trial [6] and several observational studies [7–9] showing that aprotinin use was associated with an increased risk of mortality in adult cardiac surgery. However, several limitations were identified in these studies, which prompted a comprehensive review on the use of antifibrinolitics in cardiac surgery by Health Canada and then by the Commission on Human Medicine. These reviews concluded that the benefits of aprotinin outweigh its risks when used in appropriately managed patients undergoing isolated coronary artery bypass graft surgery. Accordingly, the European Medicines Agency (EMA) recommended to the EU that the suspension of the licence for aprotinin in this context be lifted [10].

In children, several studies have suggested that the adverse events associated with aprotinin in adults may not occur [11, 12]. A large observational study including more than 30,000 children undergoing cardiac surgery found no increased mortality or dialysis associated with aprotinin exposure [13]. Furthermore, in a subsequent observational study, the same authors reported improved outcomes associated with TXA compared to aprotinin [14]. Nonetheless, these 2 studies evaluated patients in 2003–2004 and 2004–2008, respectively, and may therefore not reflect the actual situation.

The upcoming release of aprotinin as an antifibrinolytic agent in adult cardiac surgery prompted a re-evaluation of its use in comparison to TXA. The goal of our study is to compare children receiving aprotinin and TXA on bleeding and blood products exposure, as well as severe postoperative morbidity or mortality in the perioperative period of paediatric cardiac surgery. Subgroups of high-risk patients who can benefit from the antifibrinolytic and/or anti-inflammatory effect of aprotinin are also analysed.

MATERIALS AND METHODS

Study design

This retrospective cohort study included all consecutive children, aged 0–16 years, admitted for cardiac surgery with CPB from January 2002 to December 2015. Aside from the whole population, we also analysed the following high-risk subgroups: neonates (age < 30 days); complex surgery [Risk Adjusted Classification for Congenital Heart Surgery (RACHS-1) ≥ 3]; and patients undergoing redo surgery. The local Ethic Committee (Chairperson: Dr J. Grosswasser) approved the study and waived the need for informed consent (CEH No. 11/10) due to the retrospective nature of the study. This manuscript adheres to the applicable STROBE guidelines for observational studies [15].

Clinical practice

Anaesthetic management was standardized during the whole study period. Blood products were transfused in the operating room, as well as in the paediatric intensive care unit (PICU) according to standardized protocols. A detailed overview can be found in the Supplementary Material file.

Antifibrinolytics

Aprotinin was used from January 2002 to December 2007 at a dosage of 1 million IU m⁻² at the induction of anaesthesia and in the CPB prime solution. TXA was used since January 2008 at a dosage of 10 mg kg⁻¹ after the induction of anaesthesia and in the CPB prime solution followed by a continuous infusion of 10 mg kg⁻¹ h⁻¹ until the end of surgery.

Variables

Demographic data, severity scores and intraoperative data were retrieved from the medical chart. The American Society of Anaesthesiology (ASA) score was used to describe the physical status of the patient. Redo surgery was defined as a previous cardiac surgery recorded in the history of patients. Cardiac surgical procedures were categorized according to the RACHS-1 [16]. Intraoperative data included surgery, CPB and aortic cross-clamp duration. The use of aortic cross-clamp (Yes/No) and circulatory arrest (Yes/No) was also noted. The cardiac disease was characterized as cyanotic if the disease included a right-to-left shunt. Preoperative and postoperative haematological data and baseline coagulation tests were noted as well.

The first primary outcome, ‘exposure to blood products’ was defined as any transfusion of red blood cell (RBC), fresh frozen
plasma and/or platelet concentrates up to the fifth postoperative day. The second one was a composite outcome including death during the hospital stay and/or the presence of severe postoperative morbidity as previously described [2]. Briefly, severe postoperative morbidity was defined as the presence of at least 2 of the following events at any time during hospital stay: respiratory failure, prolonged inotropic support or renal failure. Respiratory failure was defined as the need for mechanical ventilation for >89 h at any time from PICU admission to the time of extubation, which included the 75th percentile of our study population. Prolonged inotropic support was defined as continuous vasoactive drug infusion for haemodynamic support for >48 h postoperatively (excluding dopamine or dobutamine <5 µg kg⁻¹ min⁻¹). Renal failure was defined as the worst estimated postoperative creatinine clearance value showing a >75% reduction compared with the preoperative baseline estimated postoperative creatinine clearance [2].

Secondary outcomes included: intraoperative, postoperative and calculated blood loss at postoperative day 3, infection and neurologic event. Duration of mechanical ventilation, PICU and hospital length of stay were also registered. Intraoperative blood loss was obtained by weighting surgical sponges and measuring blood loss in volumetric containers after surgical aspiration. Postoperative blood loss was assessed by measuring chest tube drainage. RBC, fresh frozen plasma and platelet transfusion were registered in the operating room and PICU from admission until postoperative day 5. Infection was defined as the need for antibiotics other than the usual anti-staphylococcal prophylaxis initiated by the attending intensive care physician for a suspected or proven infection caused by any pathogen or for a clinical syndrome associated with a high probability of infection, according to Goldstein et al. [17]. Neurological event was defined as a transient or permanent functional abnormality in a body area because of a reduction in brain function, and also included seizures. Both primary and secondary outcome measures were compared between both groups during the primary hospitalization.

Statistical analysis

Continuous variables were tested with the Shapiro–Wilk normality test and presented as median and interquartile range or mean and standard deviations as appropriate. Categorical variables were presented as frequencies and percentages and compared with the χ² test. Continuous variables were compared using the T-test or Wilcoxon rank sum test as appropriate.

Propensity scores were performed on 2 groups: aprotinin and TXA. Following variables were introduced for matching between groups: age, preoperative weight, ASA score, presence of a cyanotic heart disease (Yes/No), redo surgery (Yes/No), RACHS-1 score and duration of both CPB and aortic cross-clamp. We used a fairly new propensity score algorithm, known as Covariate Balancing Propensity Score (CBPS), that models treatment assignment while optimizing the covariate balance. With CBPS, a single model determines the treatment assignment mechanism and the covariate balancing weights. This method has been proven to be superior to traditional logistic regression approaches and boosted classification and regression trees. The CBPS R package was used to perform the propensity score, estimating an average treatment effect requesting an exact match [18]. An absolute standardized difference of <10–15% was considered to support the assumption of balance between groups. After the propensity score, we used the survey R package to perform logistic regressions for binary outcome variables and linear regressions for continuous outcomes, which include the treatment group effect, the weight resulting from the matching and the variables present in the propensity score in order to obtain a doubly robust estimator. This estimator corrects the last remaining possible imbalance between the covariates and produces an unbiased treatment effect. The survey R package includes the Huber–White-corrected standard errors, which maintains the standard errors unbiased even under heterogeneity of the residuals. The R software (R Core Team, 2016) version 3.2.2 was used to produce the results. Before drawing conclusions on the outcome measures, we applied a Bonferroni correction for multiple comparison purposes. For the primary outcome measures, a P-value of 0.05/2 = 0.025 and for the secondary outcome measures, a P-value of 0.05/18 = 0.003, are considered significant. Confidence intervals (CIs) for the difference in primary (97.5% CI) and secondary (99.7%) outcomes between both groups were also reported.

RESULTS

Patients

Between January 2006 and December 2015, a total of 2222 children underwent cardiac surgery with CPB. Sixty children did not receive antifibrinolytics and were excluded, leaving 2162 patients for analysis; 1020 patients in the TXA and 1142 patients in the Aprotinin group. Demographic data and intraoperative variables are shown in Table 1. Patients in the Aprotinin group were older and heavier and presented a cyanotic disease more frequently. They had higher CPB priming volume and intraoperative fluid balance, and were less frequently ultrafiltrated. RACHS-1 score was significantly higher in the Aprotinin group. Aortic cross-clamp and circulatory arrest were also more frequent in the Aprotinin group.

Preoperative and postoperative haematological data are presented in Table 2. In the Aprotinin group, the preoperative fibrinogen level was higher. Platelet count was lower up to postoperative day 3 compared to the TXA group. Subgroups are also presented in Table 1. Overall, in the Aprotinin group, there were significantly less neonates, complex surgeries and patients undergoing redo surgeries.

Outcomes

Results of the propensity matching are presented in Table 3. The absolute standardized difference was reduced to zero for all the selected variables. Primary outcomes are presented in Table 4. Overall, 59.8% of the patients in the TXA group and 77.5% in the Aprotinin group were exposed to blood products (P < 0.001). There was no difference in transfusion rates between the 2 groups in the neonate population. Complex surgery and redo surgery patients in the Aprotinin group were more frequently transfused than those in the TXA group.

Overall, 287 patients (28.1%) in the TXA group and 375 (32.8%) in the Aprotinin group developed severe postoperative morbidity or died (P = 0.007). In the neonate population, severe postoperative morbidity or mortality was lower in the TXA group compared to the Aprotinin group. There was no difference between both groups for the complex and redo surgery populations.

Secondary outcomes are presented in Table 5. Blood loss was significantly higher in the Aprotinin group. The overall increased exposure to blood products was related to higher RBC and
platelet transfusions. The amount of RBC transfusion was also higher in the Aprotinin group. The increased frequency of postoperative morbidity or mortality was related to an increased number of patients requiring prolonged inotropic support in the Aprotinin group. Postoperative neurologic event and infection episodes were also more frequent in the Aprotinin group. Duration of mechanical ventilation, intensive care and hospital length of stay were similar in both groups.

Table 1: Preoperative characteristics and intraoperative data

| Variables                  | TXA group (N = 1020) | Aprotinin group (N = 1142) | P-value |
|----------------------------|----------------------|-----------------------------|---------|
| Male gender                | 594 (58.2)           | 637 (55.8)                  | 0.250   |
| Age (months)               | 9.6 (3.0–38.7)       | 16.0 (6.0–52.0)             | <0.001  |
| Preoperative weight (kg)   | 6.8 (4.3–13.5)       | 8.0 (5.0–15.0)              | <0.001  |
| Cyanotic heart disease (yes) | 430 (42.2)     | 531 (46.5)                  | 0.043   |
| ASA                        |                      |                             | 0.275   |
| II                         | 85 (8.4)             | 102 (9.0)                   |         |
| III                        | 752 (74.0)           | 851 (74.7)                  |         |
| IV                         | 176 (17.3)           | 187 (16.4)                  |         |
| V                          | 3 (0.3)              | 0 (0.0)                     |         |
| Elective surgery           | 951 (93.2)           | 1118 (97.9)                 | <0.001  |
| Redo surgery               | 247 (24.2)           | 130 (20.7)                  | <0.001  |
| RACHS-1 score              |                      |                             | 0.008   |
| Risk category 1–2          | 488 (47.8)           | 560 (49.0)                  |         |
| Risk category 3–4          | 496 (48.7)           | 550 (48.2)                  |         |
| Risk category 5–6          | 25 (2.5)             | 6 (0.5)                     |         |
| CPB priming volume (ml kg⁻¹) | 45.2 (30.8–58.4)   | 81.4 (57.9–116.4)           | <0.001  |
| Fluid balance (ml kg⁻¹)     | 21.2 (4.2–37.0)      | 35.1 (16.0–54.9)            | <0.001  |
| Surgery time (min)         | 218 (180–262)        | 210.0 (171–253)             |         |
| CPB time (min)             | 109 (78–139)         | 112 (78–142)                | 0.268   |
| Aortic cross-clamp time (min) | 48.0 (30.0–69.0)  | 53.0 (32.0–76.0)            | <0.001  |
| Aortic cross-clamp         | 875 (85.8)           | 1058 (92.7)                 | <0.001  |
| Circulatory arrest         | 64 (6.3)             | 121 (10.6)                  | <0.001  |
| MUF                        | 972 (96.1)           | 1008 (88.5)                 | <0.001  |
| Subgroups                  |                      |                             |         |
| Neonates (N = 236)         | 144 (14.1)           | 92 (8.1)                    | 0.009   |
| Complex surgery (N = 1084) | 524 (51.4)           | 560 (49.0)                  | 0.007   |
| Redo surgery (N = 377)     | 247 (24.2)           | 130 (11.4)                  | <0.001  |

Values represent the n (%) and median (25th–75th quartile) as appropriate.
ASA: American Society of Anaesthesiology; CPB: cardiopulmonary bypass; MUF: modified ultrafiltration; RACHS-1: Risk Adjusted Classification for Congenital Heart Disease; TXA: tranexamic acid.

Table 2: Preoperative and postoperative haematological data

| Variables                  | TXA group (N = 1020) | Aprotinin group (N = 1142) | P-value |
|----------------------------|----------------------|-----------------------------|---------|
| Preoperative               |                      |                             |         |
| Hb (g d⁻¹)                 | 12.9 (11.6–14.9)     | 15.0 (11.6–15.1)            | 0.498   |
| Hct (%)                    | 38.9 (35.1–45.3)     | 39.1 (35.0–46.0)            | 0.489   |
| Platelets (×10³ µl⁻¹)      | 324 (254–415)        | 307 (239–400)               | 0.002   |
| INR                        | 1.0 (1.0–1.1)        | 1.1 (1.0–1.1)               | 0.779   |
| Fibrinogen (mg d⁻¹)        | 271 (227–325)        | 285 (240–335)               | 0.001   |
| POD1                       |                      |                             |         |
| Hb (g d⁻¹)                 | 10.8 (9.9–12.0)      | 10.7 (9.5–12.0)             | 0.059   |
| Hct (%)                    | 32.5 (29.4–36.4)     | 32.2 (28.6–36.4)            | 0.085   |
| Platelets (×10³ µl⁻¹)      | 202 (150–255)        | 178 (134–228)               | <0.001  |
| INR                        | 1.3 (1.2–1.4)        | 1.3 (1.2–1.4)               | 0.220   |
| Fibrinogen (mg d⁻¹)        | 243 (191–302)        | 235 (190–285)               | 0.069   |
| POD3                       |                      |                             |         |
| Hb (g d⁻¹)                 | 10.4 (9.4–11.6)      | 10.4 (9.3–11.6)             | 0.377   |
| Hct (%)                    | 31.4 (28.2–34.8)     | 31.4 (27.9–35.2)            | 0.510   |
| Platelets (×10³ µl⁻¹)      | 200 (147–257)        | 181 (132–232)               | <0.001  |
| POD5                       |                      |                             |         |
| Hb (g d⁻¹)                 | 10.9 (9.8–12.1)      | 11.2 (9.8–12.3)             | 0.196   |
| Hct (%)                    | 33.2 (29.6–37.1)     | 33.3 (29.6–37.3)            | 0.821   |
| Platelets (×10³ µl⁻¹)      | 227 (150–317)        | 229 (147–292)               | 0.359   |

Values represent the median (25th–75th quartile).
Hb: haemoglobin; Hct: haematocrit; INR: International Normalized Ratio; POD: postoperative day; TXA: tranexamic acid.
DISCUSSION

In this observational before-and-after study, implementation of a blood management strategy including the use of TXA after the withdrawal of aprotinin was associated with a lower exposure to blood components transfusion and a lower incidence of postoperative mortality or severe morbidity. Compared to placebo, aprotinin reduces blood loss and transfusion requirements in paediatric cardiac surgery [19]. However, when compared to TXA, aprotinin failed to show any superiority in terms of blood loss reduction or blood transfusion [20]. Moreover, some studies report improved outcomes with TXA compared to aprotinin [14].

Our results on bleeding and transfusion-related outcomes are in line with those of Pasquali et al., while evaluating children operated on more recently. We also reported a higher rate of neurologic events and infection in the Aprotinin group compared to the TXA group. Although an inadequate adjustment of overall confounders cannot be excluded, an association between aprotinin use, neurologic injury and rate of infection has already been reported. Adult cardiac patients receiving aprotinin have a higher rate of late events of ischaemic stroke and neurologic disability [21]. A possible explanation may be the occurrence of microvascular thrombosis due to platelet-fibrin thrombi among multiple vessels, including the cerebral arteries, as seen on post-mortem examination of patients who had received aprotinin [21]. The increased rate of infection observed in the Aprotinin group may be related to the higher transfusion rate observed in this group, as a strong association has been reported between transfusion and the incidence of infection [1, 22].

The study of high-risk subgroups showed an increased exposure in blood products use in complex and redo surgery patients in the Aprotinin group, whereas this difference was not seen in neonates. The absence of a difference in this subgroup could be assigned to our institutional transfusion protocol in neonates who receive blood products in the CPB and during surgery. As seen in Table 4, nearly all neonates were exposed to blood products as a result of what a difference between both groups is difficult to demonstrate. Furthermore, this subgroup was too small to draw any conclusions. Regarding severe postoperative morbidity or mortality, the subgroup of neonates showed a significant difference between both antifibrinolytics. In sum, the analyses of subgroups that could benefit from the antifibrinolytic

| Variables | Before matching | Aprotinin (N = 1142) | ASD (%) | After matching | Aprotinin (N = 1142) | ASD (%) |
|-----------|----------------|----------------------|---------|----------------|----------------------|---------|
| Age (months) | TXA (N = 1020) | 29.86 ± 42.93 | 36.63 ± 44.72 | 15.46 | 33.89 ± 47.28 | 33.89 ± 41.67 | 0.00 |
| Preoperative weight (kg) | | 11.03 ± 11.25 | 11.61 ± 9.99 | 5.46 | 11.68 ± 11.73 | 11.68 ± 11.39 | 0.00 |
| ASA score | | 3.1 ± 0.51 | 3.08 ± 0.5 | 4.12 | 3.08 ± 0.52 | 3.08 ± 0.49 | 0.00 |
| Cyanotic heart disease (yes) | | 42.16 | 46.50 | 8.73 | 43.97 | 43.97 | 0.00 |
| Redo surgery (yes) | | 24.22 | 11.38 | 34.03 | 17.85 | 17.85 | 0.00 |
| CPB time (min) | | 2.61 ± 0.92 | 2.56 ± 0.81 | 6.24 | 2.57 ± 0.92 | 2.57 ± 0.81 | 0.00 |
| Aortic cross-clamp time (min) | | 112.5 ± 45.42 | 114.74 ± 47.16 | 4.84 | 113.86 ± 45.7 | 113.86 ± 49.13 | 0.00 |

Values are presented as mean ± SD or as percentage. The ASDs after matching are all smaller than 10, and the P-values after matching are almost non-significant, indicating that the groups made are equal on these covariates.

ASA: American Society of Anaesthesiologists; ASD: absolute standardized difference; CPB: cardiopulmonary bypass; RACHS-1: Risk Adjusted Classification for Congenital Heart Disease; SD: standard deviation; TXA: tranexamic acid.

Table 4: Primary outcomes in the whole population and high-risk subgroups

| Variables | TXA group (N = 1020) | Aprotinin group (N = 1142) | 97.5% CI* | P-value |
|-----------------|----------------------|---------------------------|-----------|---------|
| Exposure to blood products | Overall | 363 (59.8) | 885 (77.5) | 0.14–0.22 | <0.001 |
| Neocntes (N = 236) | 138 (95.9) | 91 (99.0) | -0.01 to 0.07 | 0.091 |
| Complex surgery (N = 1084) | 346 (66.2) | 445 (79.4) | 0.08–0.19 | <0.001 |
| Redo surgery (N = 377) | 93 (37.8) | 68 (52.1) | 0.03–0.15 | 0.003 |
| Severe postoperative morbidity or mortality | Overall | 287 (28.1) | 375 (32.8) | 0.01–0.09 | 0.007 |
| Neocntes (N = 236) | 87 (60.8) | 72 (77.8) | 0.05–0.30 | 0.002 |
| Complex surgery (N = 1084) | 211 (40.3) | 244 (43.4) | -0.03 to 0.09 | 0.148 |
| Redo surgery (N = 377) | 33 (13.5) | 113 (8.7) | -0.11 to 0.02 | 0.102 |

Values represent the n (%).

*The 97.5% CI includes the 97.5% CI of the mean difference of the primary between the TXA and the Aprotinin groups. CI: confidence interval; TXA: tranexamic acid.
and/or anti-inflammatory properties of aprotinin were not able to show any advantage of aprotinin over TXA.

In 2008, the withdrawal of aprotinin had physicians worried about increased risks of bleeding leading to the development of other perioperative strategies for decreasing blood loss and transfusions requirements. As a result, patient blood management strategies evolved markedly in paediatric cardiac surgery and a possible reintroduction of aprotinin in the actual context should be carefully evaluated. In our population, the CPB priming volume decreased substantially between the 2 study periods. Miniaturizing of the CPB circuits resulted in lower priming volumes, less positive fluid balance and decreased dilution of coagulation factors and haemoglobin. Increased use of modified ultrafiltration techniques possibly led to greater postoperative haemoconcentration and better removing of inflammatory mediators [23]. Increased use of surgical glues, a promising strategy for reducing blood loss and exposure to blood products may also have contributed to our results [24]. Over time, more restrictive transfusion strategies were advocated regarding RBCs [25]. Restrictive transfusion triggers have been used in our study, which were not modified substantially throughout the study period as demonstrated by comparable postoperative haemoglobin concentration in the 2 groups of patients. The extended use of thromboelastometry to guide intraoperative haemostatic management has also been associated with reduced bleeding and transfusion [26]. Rotational thromboelastometry was introduced in our centre in 2014 for observational clinical research purposes [27]. Data obtained with the device were not used for the clinical management of patients included in the present study.

Nevertheless, all the strategies progressively developed in our centre have allowed for a reduction in blood loss and blood transfusion requirements that could have contributed to the observed reduction in the incidence of postoperative morbidity and mortality. It is well known that blood loss is associated with exposure to blood products and worse outcomes and that patient blood management strategies are associated with reduced blood product transfusion [28, 29]. Therefore, strategies aiming at decreasing blood loss and exposure to blood products could contribute to improved outcomes.

Currently, there is no hard evidence that supports the reintroduction of aprotinin in paediatric cardiac surgery. Aside from the controversies in adult studies and the lack of evidence in paediatric ones, aprotinin is only registered by the EMA for high-risk adults undergoing coronary artery bypass graft surgery. Only a large multicentric randomized controlled trial comparing aprotinin and TXA would shed light on this issue. Given the safe and extended use of lysine analogues, is there still enough equipoise to design such a time-consuming and expensive study? Admittedly, antifibrinolytic drugs provide a worthwhile reduction in blood loss and allogeneic RBC transfusions [30]. Administration of antifibrinolytic drugs is one of the strategies that should be integrated in a broader blood management algorithm aimed at reducing blood loss and transfusion of blood products [29].

**Limitations**

Although this study included a large number of patients, it presents some limitations. First, the retrospective and before-

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Table 5: Secondary outcomes in the whole population

| Variables                        | TXA group (N = 1020) | Aprotinin group (N = 1142) | 99.7% CI* | P-value |
|----------------------------------|----------------------|----------------------------|-----------|---------|
| **Bleeding and transfusions**    |                      |                            |           |         |
| Intraoperative blood loss (ml kg⁻¹) | 30.0 ± 27.2          | 48.5 ± 35.8                | 15.0–22.0 | <0.001  |
| PO blood loss (24 h) (ml kg⁻¹)   | 14.9 ± 12.6          | 19.7 ± 19.5                | 2.8–7.0   | <0.001  |
| PO blood loss (total) (ml kg⁻¹)  | 31.9 ± 58.8          | 39.8 ± 57.2                | 0.9–15.1  | <0.001  |
| RBC exposure                     | 583 (57.2)           | 847 (74.2)                 | 0.1–0.2   | <0.001  |
| FFP exposure                     | 179 (17.5)           | 208 (18.2)                 | -0.1 to 0.1 | 0.652   |
| Platelet exposure                | 71 (7.0)             | 123 (10.8)                 | 0.0–0.1   | 0.005   |
| RBC transfusion (ml kg⁻¹)        | 13.9 ± 24.6          | 31.2 ± 35.4                | 13.9–20.8 | <0.001  |
| FFP transfusion (ml kg⁻¹)        | 39.3 ± 29.2          | 34.3 ± 40.6                | -5.4 to 0.1 | 0.503   |
| Platelet transfusion (ml kg⁻¹)   | 28.3 ± 29.5          | 28.3 ± 26.7                | -0.5 to 2.3 | 0.774   |
| **Morbidity and mortality**      |                      |                            |           |         |
| Infection                        | 404 (39.6)           | 518 (45.4)                 | -0.0 to -0.1 | 0.004   |
| Neurologic event                 | 56 (5.5)             | 148 (13.0)                 | 0.1–0.1   | <0.001  |
| Respiratory failure²             | 245 (24.0)           | 290 (25.4)                 | -0.1 to 0.1 | 0.428   |
| Length of MV (h)                 | 78.3 ± 140.8         | 99.5 ± 422.6               | -21.8 to 64.6 | 0.170   |
| PICU LOS (days)                  | 9.9 ± 19.6           | 8.9 ± 21.2                 | -3.7 to 1.7 | 0.206   |
| Hospital LOS (days)              | 21.9 ± 36.4          | 23.2 ± 33.0                | -3.1 to 5.7 | 0.338   |
| Renal failure³                   | 36 (3.5)             | 30 (2.6)                   | -0.0 to 0.0 | 0.278   |
| Prolonged inotropic support⁴     | 32 (41.8)            | 37 (57.7)                  | 0.1–0.2   | <0.001  |
| Mortality (in hospital)          | 32 (3.1)             | 37 (5.3)                   | -0.0 to 0.0 | 0.681   |

Values represent the n (%) and mean ± SD as appropriate.

*The 99.7% CI includes the 99.7% CI of the mean difference of the primary between the TXA and the Aprotinin groups.

²Respiratory failure is defined as the need for MV for >89 h at any time from PICU admission to the time of extubation.

³Renal failure is defined as the worst eCCr value showing a >75% reduction compared with the preoperative baseline eCCr.

⁴Prolonged inotropic support is defined as continuous vasoactive drug infusion for haemodynamic support for >48 h postoperatively (excluding dopamine or dobutamine <5 µg kg⁻¹ min⁻¹).

**CI:** confidence interval; **eCCr:** estimated postoperative creatinine clearance; **FFP:** fresh frozen plasma; **LOS:** length of stay; **MV:** mechanical ventilation; **PICU:** paediatric intensive care unit; **PO:** postoperative; **RBC:** red blood cell; **SD:** standard deviation; **TXA:** tranexamic acid.
and-after design of this observational study cannot exclude the inclusion of unmeasured bias even if a propensity score analysis was conducted to minimize the risk. Second, as mentioned earlier, the influence of evolving practice on the results cannot be excluded. Over time, aprotinin was replaced by TXA, but other strategies aiming at decreasing blood loss were also introduced that could have contributed to explain the difference in outcome between both groups. In this study, the same small group of anaesthesiologists, cardiac surgeons, cardiologists and intensive care paediatricians treated all patients during this period which decreases the impact of some of these biases. Third, platelets count was lower from the preoperative period up to postoperative day 3 in the Aprotinin group compared to the TXA group. Although the observed differences were minimal, we cannot exclude that it might have played a role in the difference in bleeding and transfusion of platelets between the 2 groups. Fourth, ours is a single-centre study, which may affect its generalizability. Indeed, local practice patterns might impede application of our results to other institutions. Finally, it is difficult to compare studies that have evaluated both aprotinin and TXA because studied populations were heterogeneous and dosing schemes were different.

CONCLUSION

In our study, the replacement of aprotinin by TXA in the context of major changes in patient blood management strategies was associated with lower blood loss and transfusion requirements and improved outcomes in children. This study also could not demonstrate any benefit of aprotinin in subpopulations at high risk of bleeding or inflammation. Based on current literature and present study, there is insufficient evidence to reintroduce aprotinin in paediatric cardiac surgery unless we do so within the context of a well-designed study.

SUPPLEMENTARY MATERIAL

Supplementary material is available at EJCTS online.

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