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Aprotinin is safe in pediatric patients undergoing cardiac surgery

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Objective: Aprotinin, a serine protease inhibitor, decreases transfusion requirements and inflammatory response after cardiopulmonary bypass. This study was done to determine whether aprotinin is associated with adverse outcomes, particularly mortality and acute kidney failure, in pediatric patients (<18 years of age) undergoing cardiopulmonary bypass.

Methods: We compared a cohort of all pediatric cardiopulmonary bypass operations from 1994–1999, when aprotinin was not used (n = 1230), with a cohort from 2000–2006, when all patients received high-dose aprotinin (n = 1251). Primary end points were operative and late mortality, acute kidney failure, need for dialysis, and neurologic complications. Association of aprotinin with primary end points was assessed by means of univariate analysis, multivariate logistic regression, and Cox regression analysis, where appropriate.

Results: The aprotinin group was younger (mean age, 3.49 ± 1.84 vs 3.64 ± 4.75 years; $P = .019$) and had a higher Aristotle score (7.8 ± 2.3 vs 7.2 ± 2.6, $P < .001$). Univariate and multivariate analysis showed no significant difference between the no-aprotinin and aprotinin groups for operative mortality (55 [4.5%] vs 47 [3.8%], $P = .508$), acute kidney failure (68 [6.0%] vs 69 [5.7%], $P = .77$), need for temporary dialysis (6 [0.49%] vs 12 [0.96%], $P = .17$), or neurologic complications (14 [1.1%] vs 17 [1.4%], $P = .62$). By means of Cox regression analysis, aprotinin had no influence on late mortality (24 vs 10 deaths, $P = .078$).

Conclusion: In this retrospective cohort study of pediatric patients undergoing cardiopulmonary bypass, there was no association between the use of aprotinin and acute kidney failure, need for dialysis, neurologic complications, and operative or late mortality. We continue to use aprotinin for all pediatric patients undergoing cardiopulmonary bypass.

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Aprotinin (Trasylol; Bayer Pharmaceutical, West Haven, Conn) is an antifibrinolytic serine protease inhibitor purified from bovine lung. Aprotinin was approved by the US Food and Drug Administration to reduce perioperative blood loss in high-risk patients undergoing cardiopulmonary bypass (CPB) for coronary artery bypass grafting in 1993.[1] Aprotinin reduces bleeding by delaying the rapid plasmin-mediated lysis of the fibrin clot. Several randomized, prospective, placebo-controlled, carefully performed trials on aprotinin use have shown that it reduces requirements for blood transfusion in adult cardiac surgery.[2-4] Aprotinin has also been shown to decrease the inflammatory response to CPB.[5,6] After completing an internal study that demonstrated that aprotinin reduced operative closure time and blood product use after pediatric cardiac bypass, our center began routinely using aprotinin in all of our patients undergoing CPB in early 2000.[7] Several other pediatric cardiac surgery centers have shown that the use of aprotinin in pediatric

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Abbreviations and Acronyms
CPB = cardiopulmonary bypass
DHCA = deep hypothermic circulatory arrest

patients undergoing CPB is associated with decreased use of blood products and cost savings from decreased operative time.[8,9]

Recently, the safety of aprotinin use in adult cardiac surgery has been called into question, particularly in 2 separate reports published by Mangano and colleagues.[10,11] They reported that aprotinin use was associated with increased risk of perioperative acute kidney failure, cerebral vascular accidents, and long-term mortality. Both studies have elicited numerous letters to the editor and editorials.[12-14]

The purpose of our study was to determine whether the use of aprotinin was associated with adverse outcomes, particularly mortality and impairment of kidney function, in pediatric patients (<18 years of age) undergoing CPB. We also analyzed the patients with regard to postoperative new-onset neurologic injury. The conduct of this study was facilitated by our change in treatment protocols to include aprotinin in all of our patients undergoing CPB in early 2000. This study was not directed at the efficacy of aprotinin; it was limited to the safety issues recently raised.

Materials and Methods

This was a retrospective, nonrandomized cohort study. The Institutional Review Board at Children's Memorial Hospital, Chicago, Illinois, approved this study and granted a waiver of informed consent on May 4, 2006. We identified patients through the computerized database for cardiac surgical patients at Children's Memorial Hospital, which was established in 1990. We compared all pediatric patients having CPB for the 6-year period before use of aprotinin (1994–1999) with a cohort of patients who all received aprotinin (2000–2006). The aprotinin protocol that we used is shown in Table 1. The primary outcome measures evaluated were operative and late mortality, biochemical acute kidney failure, and the need for temporary dialysis. Operative mortality was defined as death within 30 days of an operation or within the primary hospitalization (Society of Thoracic Surgeons and European Association for Cardiothoracic Surgery definition).[15] Biochemical acute kidney failure was defined as an increase in serum creatinine levels to twice or more than the preoperative level (personal e-mail communication with J. P. Jacobs, Multi-Societal Pediatric and Congenital Cardiac Database Taskforce, 2007). The serum creatinine value selected for analysis was the peak value in the first postoperative 72 hours.[16] The need for temporary dialysis was defined as any patient having placement of an intravenous dialysis catheter or peritoneal dialysis catheter that was used for dialysis at any time during the hospital stay.

TABLE 1. Aprotinin protocol at Children's Memorial Hospital

- 1-mL test dose after arterial line placed
- 171.5 mL/m^2 patient loading and pump prime dose (maximum, 200 mL)
- 40 mL/m^2/h infusion through bypass run and for 1 h postoperatively (maximum, 50 mL/h)
- 1 mL = 10,000 KIU

Demographic and clinical characteristics were summarized by using means and standard deviations for continuous variables and frequencies for categorical variables and compared between the 2 study groups by using t tests and χ^2 tests. All outcomes of interest were as follows: biochemical acute kidney failure, postoperative temporary dialysis, operative mortality, and late mortality are binary. In addition to aprotinin, predictors studied included age, sex, body surface area, operative status (emergency status vs nonemergency status), Aristotle score, deep hypothermic circulatory arrest (DHCA; yes vs no), preoperative ventilator support (yes vs no), prior open cardiothoracic operations (yes vs no), CPB time, aortic crossclamp time, and preoperative serum creatinine level. The data consisted of multiple operations per patient over the study period. The repeated nature of the data was taken into consideration in the regression analyses.

A Cox regression frailty model (Therneau) with a random effect for patient was used to determine predictors of late mortality.[17] Time at risk was defined by using the Anderson–Gill approach. Time at risk for patients with multiple operations was from one surgical date to the next. Follow-up times were censored at April 27, 2007. A generalized linear model for binary outcome (Liang and Zeger) with logit link was used to determine predictors of the other 3 outcomes. Repeated measures were modeled by using compound symmetry structure.[18] The overall strategy was to use results from univariate associations as a data reduction tool to identify candidates for a multiple-predictor model. Univariate models included each predictor one at a time, controlling for aprotinin. A P value of .1 determined inclusion in a multiple-predictor model in addition to predictors that were statistically significantly different between the 2 study groups. In addition, the interaction effect between aprotinin and risk stratification based on the median Aristotle score was explored. Separate models for each level were considered if this effect was statistically significant. Power considerations allowed for multiple-predictor models for biochemical acute kidney failure and operative mortality outcomes. Odds ratios and corresponding 95% confidence intervals are presented for statistically significant categorical predictors. The incidence of neurologic outcomes was low, and hence the χ^2 test was used to test the association between aprotinin and outcome if adverse outcomes were observed in at least 10 operations. The low incidence did not allow for repeated-measures analyses of multiple operations.

Statistical analyses were conducted with SAS statistical software (version 9.1; SAS, Cary, NC) and S-Plus (version 6.2; Insightful Corp, Seattle, Wash). All conclusions were made at the .05 level of significance.