Antifibrinolytic therapy during cardiopulmonary bypass reduces proinflammatory cytokine levels: A randomized, double-blind, placebo-controlled study of ϵ -aminocaproic acid and aprotinin

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Objectives: Aprotinin is a broad-spectrum serine protease inhibitor that has been shown to attenuate the systemic inflammatory response in patients undergoing cardiac surgery with cardiopulmonary bypass. Although ϵ -aminocaproic acid is similar to aprotinin in its ability to inhibit excessive fibrinolysis (ie, plasmin activity and D-dimer formation), its ability to influence proinflammatory cytokine production remains unclear. This study was designed to compare the effects of ϵ -aminocaproic acid and aprotinin on plasma levels of interleukin-6 and interleukin-8 during and after cardiopulmonary bypass.

Methods: Sixty patients were randomized in a double-blind fashion to receive ϵ -aminocaproic acid, aprotinin, or saline (placebo) in similar dosing regimens (loading dose, pump prime, and infusion). Arterial blood samples were collected before, during, and after cardiopulmonary bypass, and plasma levels of D-dimer, interleukin-6, and interleukin-8 were measured. Data were analyzed using repeated measures analysis of variance.

Results: Both ϵ -aminocaproic acid and aprotinin administration resulted in significant ($P < .05$) reductions in D-dimer and interleukin-8 levels compared with saline. These reductions in D-dimer and interleukin-8 levels did not differ between the 2 drug-treated groups. The effect of these two antifibrinolytic agents on interleukin-6 was qualitatively similar to that noted with interleukin-8 but did not reach statistical significance.

Conclusions: When dosed in a similar manner, ϵ -aminocaproic acid seems to be as effective as aprotinin at reducing interleukin-6 and interleukin-8 levels in patients undergoing primary coronary artery bypass graft surgery. These data indicate that suppression of excessive plasmin activity or D-dimer formation or both may play an important role in the generation of proinflammatory cytokines during and after cardiopulmonary bypass.

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Cardiac surgery and cardiopulmonary bypass (CPB) initiate an inflammatory response characterized by the release of proinflammatory cytokines.¹⁻⁴ Exposure of blood to the foreign surfaces of the CPB circuit, endotoxemia, and ischemia-reperfusion injury all contribute to this inflammatory response by activating the complement, coagulation, and fibrinolytic systems.¹⁻⁵ Interleukin (IL)-6 and IL-8 are two well-known proinflammatory cytokines that are significantly increased

during and after cardiac surgery with CPB.⁵⁻⁸ IL-6 and IL-8 are soluble proteins secreted by a variety of cell types, including activated monocytes, tissue macrophages, and endothelial cells.^{1,2} Elevations in IL-6 and IL-8 levels after CPB are associated with an increased risk of organ injury⁹⁻¹² and death.¹³

The full-Hammersmith (high) dose of aprotinin is currently used in patients undergoing cardiac surgery with CPB to reduce blood loss and inflammation. This dosing regimen includes a bolus dose, pump prime, and infusion that is started before CPB and usually continued until the patient's arrival in the intensive care unit. The rationale for using this high-dose regimen is based on the need to maintain sufficient aprotinin levels to inhibit a variety of serine proteases (eg, plasmin, kallikrein, and trypsin) known to contribute to excessive fibrinolysis and the inflammatory response.² Aprotinin inhibits fibrinolysis by directly binding plasmin, the cleavage enzyme responsible for D-dimer formation. Aprotinin has been shown to inhibit not only markers of fibrinolysis such as D-dimer¹⁴ but also a variety of humoral and cellular markers of inflammation,^{1,2} as well as specific inflammatory processes such as the leukocyte extravasation.¹⁵

ϵ -Aminocaproic acid is a lysine analog that is also commonly used to inhibit excessive fibrinolysis and reduce blood loss after cardiac surgery with CPB.^{16,17} ϵ -Aminocaproic acid is most effective when levels are maintained above the therapeutic target during the duration of CPB and in the early post-CPB period.¹⁸ Suboptimal dosing of ϵ -aminocaproic acid, especially in some bolus-only protocols, could lead to incomplete inhibition of fibrinolysis and may explain its variable efficacy when evaluating blood loss reduction.¹⁶⁻¹⁸ In contrast with aprotinin, very little has been reported about the effects of lysine analogs, such as ϵ -aminocaproic acid, on the inflammatory response. Given the limited mode of action (plasmin inhibition only) of this class of antifibrinolytic agents, it seems unlikely that they would be as effective as aprotinin at suppressing the inflammatory response. We performed a prospective, randomized, double-blind, placebo-controlled trial to test the hypothesis that the administration of ϵ -aminocaproic acid to patients undergoing cardiac surgery with CPB will be less effective than aprotinin in reducing circulating levels of IL-6 and IL-8. In addition, we measured D-dimer levels to determine if an equivalent therapeutic effect is achieved when these antifibrinolytic drugs are administered in a similar fashion.

Methods

Patient Selection

After institutional review board approval and written informed consent, 60 patients scheduled for elective, primary coronary artery bypass with CPB were enrolled in this study. Patients were randomly assigned to receive one of the following: (1) full-dose aprotinin (2×10^6 kallikrein inactivation unit [KIU] [load], $2 \times$

10^6 KIU [pump prime], and 5×10^5 KIU/h [infusion]); (2) ϵ -aminocaproic acid (100 mg/kg [load], 5 g [pump prime], and 30 mg $\cdot$ kg $\cdot$ h [infusion]); or (3) saline (200 mL [load], 200 mL [pump prime], and 50 mL/h [infusion]) in a double-blinded fashion. Exclusion criteria were a history of corticosteroid, dipyridamole, or anticoagulant therapy, documented platelet or coagulation abnormalities, or treatment with thrombolytic therapy within 5 days of surgery. In addition, patients were not included if serum creatinine was greater than 2.0 mg/dL, ejection fraction was less than 30%, or there was a history of adverse reaction to aprotinin or ϵ -aminocaproic acid.

Technique of Operation

After induction with etomidate (0.3 mg/kg), fentanyl (5 to 10 mcg/kg), and rocuronium (1 mg/kg), a pulmonary artery catheter was inserted through the right internal jugular vein. Anesthesia was maintained with inhaled isoflurane (0.4%-1.0%) and intravenous fentanyl (25-50 mcg/kg). A propofol infusion (25-50 mcg $\cdot$ kg $\cdot$ min) was started at the beginning of "rewarming" and continued into the postoperative period for sedation.

All the procedures were performed by 1 of 3 surgeons using a standardized technique for coronary revascularization and myocardial protection. CPB was performed using a hollow fiber oxygenator system (Gish, Irvine, Calif) with nonpulsatile flow using a centrifugal pump (Biomedicus, Eden Prairie, Minn). The CPB circuit was primed with 1.8 L of lactated Ringer's solution, 100 cc of 25% albumin, 44.6 mEq of sodium bicarbonate, and 50 g of mannitol. Myocardial protection included moderate hypothermia (28°C-32°C) with antegrade and retrograde sanguineous (4:1, blood:crystalloid) cardioplegia every 10 to 20 minutes. Perfusion flow rates were maintained at 2 L $\cdot$ min $\cdot$ m² during hypothermia and at 2.5 L $\cdot$ min $\cdot$ m² during normothermia.

Anticoagulation was achieved with bovine heparin and monitored to achieve initial kaolin activated clotting time levels of 480 seconds. A Hepcon system (Medtronic, Minneapolis, Minn) was used for heparin and protamine titration. Blood was collected from the surgical field by pump suction during full anticoagulation and returned to the patient intraoperatively. Mediastinal chest drainage was not reinfused. Packed red blood cells were transfused when the hemoglobin level decreased less than 6.0 g/dL during CPB and 8.0 g/dL in the early post-CPB period. Platelet concentrates were transfused if there was evidence of significant microvascular bleeding and a platelet count of less than 70,000/ μ L.

Interleukin and D-Dimer Measurements

Arterial blood samples were collected at (1) baseline (before anesthetic induction), (2) 10 minutes after aortic crossclamp removal, (3) 15 minutes after protamine administration (heparin reversal), (4) 3 hours after separation from CPB, and (5) 18 to 24 hours after CPB. Blood was drawn from an arterial line directly into a polypropylene syringe and transferred into a 3.2% Na-citrate-buffered Vacutainer (Becton Dickinson, Franklin Lakes, NJ). The concentrations of IL-6 and IL-8 in plasma were determined with a sandwich-type enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, Minn). D-dimer levels were determined using a turbidimetric immunoassay (Beckman Coulter, Miami, Fla). All standards and samples were assayed in duplicate.

TABLE 1. Patient demographics

	Saline	Aprotinin	ϵ -Aminocaproic acid
No. of patients	20	20	20
General			
Age (y)	63 $\pm$ 8	64 $\pm$ 9	62 $\pm$ 9
Male sex - no. (%)	20 (100)	20 (100)	20 (100)
Body mass index	29.5 $\pm$ 4.1	29.1 $\pm$ 6.1	30.8 $\pm$ 4.6
Ejection fraction (%)	44 $\pm$ 13	44 $\pm$ 11	51 $\pm$ 13
Cardiovascular risk factors			
Current smoking (<3 mo)	3 (15)	4 (20)	4 (20)
Hypertension	18 (90)	16 (80)	18 (90)
Hypercholesterolemia	15 (75)	18 (90)	16 (80)
Diabetes mellitus	10 (50)	6 (30)	11 (55)
Previous cardiac history			
Myocardial infarction	12 (60)	7 (35)	10 (50)
Canadian Cardiovascular Society score	3.0 $\pm$ 0.7	3.0 $\pm$ 0.6	3.0 $\pm$ 0.9
New York Heart Association classification	1.8 $\pm$ 0.9	1.8 $\pm$ 0.8	1.9 $\pm$ 1.0
Preoperative medications			
Aspirin	20 (100)	20 (100)	20 (100)
Intravenous heparin	3 (15)	2 (10)	5 (25)
Statin therapy	12 (60)	14 (70)	17 (85)
Beta-blockers	18 (90)	17 (85)	16 (80)
Angiotensin-converting enzyme inhibitors	14 (70)	15 (75)	14 (70)

Values are mean $\pm$ SD unless otherwise indicated. Values in parentheses represent percentages of each group. No values were significantly different between groups.

Perioperative Variables

The duration of aortic clamping and CPB, and the number and type of bypass grafts were recorded. Mediastinal chest tube drainage and blood product administration were recorded for the first 24 hours after surgery. The duration of postoperative mechanical ventilation and inotropic support were also documented.

Statistical Analysis

The sample size calculation was based on previous data from Kawamura and colleagues,⁷ who demonstrated CPB-induced increases in IL-6 and IL-8. For a significance level of .05, we calculated that a sample size of 18 per group would have 90% power to detect a 40% treatment effect in either peak IL-6 or IL-8 levels. We further assumed that combined patient dropout or incomplete data sets could have an occurrence rate of up to 10% and therefore determined that enrollment of 60 subjects (20 per group) would be required for this study.

Statistical analysis was performed with SAS statistical software (SAS Institute, Inc, Cary, NC). Differences in dichotomous variables between groups were evaluated by the chi-square test, and differences in continuous variables were analyzed by a 1-way analysis of variance (ANOVA) for normally distributed data and a nonparametric 1-way ANOVA when applicable. The behavior over time of variables measured at multiple time points in each subject of each of the 3 treatment groups was analyzed by repeated-measures ANOVA. Cytokine values at a given time point were compared by a least-squares means test. All values in the figures, tables, and text are expressed as mean $\pm$ SD, unless otherwise stated.

Results

A total of 60 patients were randomized to receive aprotinin, ϵ -aminocaproic acid, or saline (n = 20 for each treatment

group). Patient and surgical demographic data are outlined in Tables 1 and 2, respectively. There were no significant differences between the patient and surgical demographic variables in any of the treatment groups except in 4-hour and 24-hour mediastinal chest tube drainage. Patients in the aprotinin and ϵ -aminocaproic acid groups had significantly less mediastinal chest tube drainage compared with the patients in the saline group ($P < .05$). There was no significant difference in blood loss noted between patients in the aprotinin and ϵ -aminocaproic acid groups.

D-Dimer Levels

The effect of aprotinin and ϵ -aminocaproic acid on perioperative D-dimer formation is illustrated in Figure 1. D-dimer levels in all 3 treatment groups increased significantly ($P < .001$) from baseline during CPB (after aortic crossclamp removal), peaked after protamine administration, and remained significantly elevated 3 hours post-CPB. Both ϵ -aminocaproic acid and aprotinin administration resulted in a significant ($P < .0001$) overall treatment effect on D-dimer levels compared with saline. Furthermore, at each of the 3 time points, D-dimer levels were significantly ($P < .0001$) attenuated by ϵ -aminocaproic acid and aprotinin. There were no differences in the D-dimer levels between patients who received ϵ -aminocaproic acid or aprotinin.

Interleukin Levels

The influence of CPB on IL-6 and IL-8 for each treatment group (saline, aprotinin, and ϵ -aminocaproic acid) is illus-

Figure 1. D-dimer concentrations for saline, aprotinin, and ϵ -aminocaproic acid treatment groups measured before induction, after aortic crossclamp removal, 15 minutes after protamine administration, and 3 hours after separation from *cardiopulmonary bypass* (CPB). The values are expressed as mean $\pm$ SEM (* $P < .05$ for both ϵ -aminocaproic acid and aprotinin compared with saline).

Figure 2. Plasma concentrations of *interleukin* (IL)-6 for saline, aprotinin, and ϵ -aminocaproic acid treatment groups measured before induction, after aortic crossclamp removal, 15 minutes after protamine administration, and 3 hours after separation from CPB. The values are expressed as mean $\pm$ SEM.

TABLE 2. Surgical demographics

	Saline	Aprotinin	ϵ -Aminocaproic acid
Procedure			
CABG only	20 (100)	20 (100)	20 (100)
Single internal thoracic artery use	19 (95)	19 (95)	19 (95)
No. of bypass grafts	3.2 $\pm$ 0.9	3.3 $\pm$ 1.0	3.4 $\pm$ 0.7
Aortic crossclamp time (min)	76 $\pm$ 22	76 $\pm$ 27	71 $\pm$ 17
CPB time (min)	127 $\pm$ 34	128 $\pm$ 36	123 $\pm$ 28
Mean activated clotting times			
10 min after initiation of CPB	721 $\pm$ 172	685 $\pm$ 228	632 $\pm$ 90
45 min after initiation of CPB	714 $\pm$ 174	733 $\pm$ 166	640 $\pm$ 130
During normothermic CPB before separation	655 $\pm$ 155	725 $\pm$ 196	621 $\pm$ 159
Anticoagulation			
Total heparin ($\times 100$ IU)	496 $\pm$ 130	474 $\pm$ 103	437 $\pm$ 103
Total protamine (mg)	335 $\pm$ 114	366 $\pm$ 118	350 $\pm$ 145
Mediastinal chest tube drainage			
First 4 h (mL)	220 (155, 309)	134* (83, 231)	171* (94, 239)
24 h (mL)	707 (532, 867)	418* (343, 627)	475* (371, 671)
Transfusions (units)			
Packed red blood cells (operating room)	0 (0, 0)	0 (0, 0)	0 (0, 0.5)
Platelets (operating room)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Packed red blood cells (intensive care unit)	2 (0, 2)	0 (0, 2)	0.5 (0, 2)
Platelets (intensive care unit)	0 (0, 0.5)	0 (0, 0.5)	0 (0, 0)
Clinical milestones			
Mechanical ventilation (h)	22 (18, 42)	21 (14, 44)	24 (21, 42)
Inotropic support (h)	18 (11, 22)	19 (9, 21)	19 (12, 20)

CABG, Coronary artery bypass graft; CPB, cardiopulmonary bypass. Values are mean $\pm$ SD unless otherwise indicated. Values for mediastinal chest tube drainage, transfusions, and clinical milestones are reported as median with 25th and 75th percentile values in parentheses.

*Values were significantly different from the saline group ($P < .05$).

trated in Figures 2 and 3, respectively. There were no significant differences in preinduction (baseline) levels of IL-6 and IL-8 among treatment groups. IL-6 and IL-8 levels increased significantly during CPB (after aortic crossclamp release) compared with baseline levels and peaked after

CPB (post-protamine) in all 3 treatment groups. Three hours after CPB, proinflammatory cytokine levels decreased from post-protamine levels and continued to decrease 18 hours after CPB, but they remained significantly elevated compared with baseline. The administration of ϵ -aminocaproic

Figure 3. Plasma concentrations of IL-8 for saline, aprotinin, and ϵ -aminocaproic acid treatment groups measured before induction, after aortic crossclamp removal, 15 minutes after protamine administration, and 3 hours after separation from CPB. The values are expressed as mean $\pm$ SEM (* $P < .05$ compared with both ϵ -aminocaproic acid and aprotinin compared with saline).

acid and aprotinin resulted in lower peak IL-6 levels compared with saline but did not reach statistical significance ($P = .097$ and $P = .229$, respectively). Likewise, the overall treatment effect of ϵ -aminocaproic acid ($P = .099$) and aprotinin ($P = .263$) did not reach statistical significance. Peak IL-8 levels were significantly reduced by ϵ -aminocaproic acid ($P = .003$) and aprotinin ($P = .017$) treatment. Furthermore, both ϵ -aminocaproic acid and aprotinin administration resulted in a significant overall treatment effect on IL-8 levels compared with saline ($P = .004$ and $P = .024$, respectively). There were no significant differences between the ϵ -aminocaproic acid and aprotinin groups with respect to IL-6 and IL-8 levels at any time during or after the surgery.

Discussion

Contrary to our hypothesis, this randomized, placebo-controlled study demonstrated that ϵ -aminocaproic acid, administered as described, significantly reduced IL-8 levels in patients undergoing primary CABG surgery to an extent equivalent to that achieved with high-dose aprotinin. ϵ -Aminocaproic acid and aprotinin also had a similar qualitative effect on IL-6, yet the reductions were not statistically significant. Aprotinin's ability to inhibit a variety of serine proteases other than plasmin did not seem to provide any significant advantage in reducing IL-6 and IL-8 during or after CPB. The fact that these two antifibrinolytic agents had an equal impact on D-dimer levels may have had a significant influence on our results. Taken together, our results indicate that aprotinin's effect on these two well-known proinflammatory cytokines may be the result of inhibition of excessive plasmin activity or D-dimer formation or both.

The role of excessive plasmin activity in the generation of proinflammatory cytokines has only recently been explored. The finding that a lysine analog (ϵ -aminocaproic acid) had similar effects on IL-6 and IL-8 release as aprotinin indicates that inhibition of excessive plasmin activity alone may have a greater importance in promoting the inflammatory response than has been previously appreciated. Plasmin has been shown to directly activate complement by cleaving C3 resulting in the production of the anaphylatoxins C3a and C5a, which are known to induce leukocyte activation and proinflammatory cytokine release.^{2,19,20} In addition, Syrovets and colleagues²¹ demonstrated that plasmin can also directly induce proinflammatory cytokine release (IL-1 α , IL-1 β , and TNF- α) by monocytes. Clearly, a better understanding of the mechanisms by which excessive plasmin activity contributes to complement activation and inflammatory cytokines will be required before the full benefits of lysine analogs will be appreciated in the setting of cardiac surgery.

The equivalent reduction in D-dimer formation by ϵ -aminocaproic acid and aprotinin indicate that these two antifibrinolytic agents were equally effective at inhibiting fibrinolysis in patients undergoing primary CABG surgery. Whether this was the result of using similar dosing regimens (loading dose, pump prime, and infusion) or a relatively low-risk patient population remains unclear. Our dosing regimen for ϵ -aminocaproic acid was based on early work by Butterworth and colleagues.¹⁸ According to their model, our dosing regimen would have maintained drug levels well above the therapeutic target (130 $\mu\text{g/mL}$), particularly during the late CPB and early post-CPB period when D-dimer formation is known to peak.^{18,22} It is certainly plausible that suppression of D-dimer formation alone may have contributed to reduction in these proinflammatory cytokines. In vitro studies by several investigators suggest that exposure of D-dimer fragments to monocytes initiates the synthesis and release of IL-6.²³⁻²⁵ Further study will be required to determine if reductions in D-dimer formation has a causal relationship with circulating proinflammatory cytokines in the setting of cardiac surgery.

The limitations of this study are similar to those associated with any clinical trial attempting to evaluate a drug effect under a complex set of pathophysiologic conditions. Although groups appear relatively well matched, there may exist other covariates that might influence the inflammatory response. Furthermore, the inflammatory response involves a myriad of humoral and cellular components other than IL-6 and IL-8 that may be as important to patient outcomes. The size of this study may also be a limitation, especially with regard to IL-6. A nonsignificant trend toward reduction of IL-6 levels was seen in both drug-treated groups. The absence of statistical significance may represent a type 2 error. Similarly, this study is underpowered to identify

important clinical outcomes related to decreases in these inflammatory markers or thrombotic events (eg, graft occlusion and stroke) that may be associated with our antifibrinolytic dosing regimens.

Conclusion

This study found that ϵ -aminocaproic acid is as effective as aprotinin in reducing CPB-induced increases in IL-6 and IL-8 in patients undergoing primary CABG surgery. The use of a similar dosing regimen for aprotinin and ϵ -aminocaproic acid during CPB and in the early post-CPB period may have played a significant role in achieving equivalent reductions in D-dimer levels with both drugs. These data support the notion that excessive fibrinolysis contributes to the inflammatory response in this clinical setting. Future studies will be needed to more fully characterize the effects of inhibiting excessive fibrinolysis on the inflammatory response and clinical outcome.

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