The intraoperative use of Amicar® to reduce bleeding associated with open heart surgery

ANN E. APRILE, CRNA, MSN
Howell, Michigan
TIMOTHY J. PALMER, CRNA, MS
Madison Heights, Michigan

In an effort to reduce morbidity associated with transfusion of blood products, Amicar® is used as a prophylactic inhibitor of hyperfibrinolysis associated with diffuse perioperative bleeding in patients undergoing open heart surgery. Previous studies indicate a significant reduction of intraoperative and postoperative bleeding in patients receiving Amicar during open heart surgery. Fifteen historical controls who did not receive Amicar were compared to 15 nonrandomized, prospective patients who received Amicar and who underwent open heart surgery by the same surgeon. The study found a significant reduction in postoperative chest tube output for the group receiving Amicar, as well as a reduction in perioperative blood product transfusion in patients who received Amicar. One patient in the Amicar group experienced a thrombotic event.

Key words: Amicar® (epsilon-aminocaproic acid), coagulation pathway, fibrinolysis.

Introduction
Anesthesia care providers transfuse more than 50% of the 20 million units of blood and blood components administered throughout the United States each year. While the risk of overall mortality associated with blood transfusion is extremely low, the potential for transmitting infectious agents or producing immunologic complications is present with every unit.

Minimizing blood or blood product transfusion to the patient population should be a standard goal for the anesthesia care provider and can be conceptualized via three distinct mechanisms: reducing intraoperative blood loss, tolerating lower patient hematocrits, or utilizing blood salvaging techniques for autologous transfusion. The importance of maintaining appropriate hemoglobin levels perioperatively cannot be understated, especially in terms of the cardiac surgery candidate.1,2

Coronary artery bypass graft surgery is an accepted modality for revascularization of compromised myocardial tissue. This procedure has significant direct and occult effects upon the hemostatic mechanism. Despite the reversal of heparin anticoagulation with protamine sulfate and adequate hemostasis during operation, excessive bleeding after cardiopulmonary bypass is a serious problem that complicates the recovery of patients undergoing open heart operation. Blood loss during and after cardiopulmonary bypass remains a significant complication of cardiac surgery. Approximately 3-5% of patients undergoing open heart surgery require transfusion of more than 10 units of blood.3,4

Amicar® inhibits the proteolytic activity of plasmin and the subsequent conversion of plasminogen to plasmin via plasminogen activator.5 Amicar
is a synthetic antifibrinolytic agent that is advocated by some investigators as an adjunct therapy for controlling spontaneous hemorrhage associated with the use of an extracorporeal circuit during coronary artery bypass graft surgery. Fibrinolysis is believed to play a major role in perioperative blood loss associated with open heart bypass surgery. By minimizing or interfering with the onset of hyperfibrinolysis, postoperative transfusion of blood products to the patient may be significantly reduced.

This study was designed to determine whether the perioperative administration of Amicar during coronary artery bypass grafting for acquired heart disease was associated with a significant reduction in postoperative bleeding as determined by reduced chest tube bleeding and the subsequent reduction in transfused blood products.

**Methods and materials**

This nonrandomized study compared the impact of Amicar on a prospective recipient sample and a historical control group. Prospective data were collected from October 1993 to January 1994. The sample population for this study was 30 patients isolated to the care of the same primary surgeon and scheduled for surgical correction of acquired heart disease. The patients were divided into a historical control, non-Amicar group (n = 15) and a prospective group (n = 15) which received Amicar. This study was reviewed by institutional representatives, and it was determined that it was of “exempt status” due to the fact that the prospective group was being managed in what amounted to standard clinical management by that surgeon and that no special manipulations (anesthetic or surgical) were required.

The patient eligibility criteria for this study included the following:

- Patients undergoing uncomplicated cardiac surgery (uncomplicated being defined as first-time cardiac surgery patients undergoing routine coronary artery bypass grafting, utilizing saphenous vein grafts and/or left internal mammary artery graft).
- Patients with no history of congenital heart defect.
- Patients with no known valvular disease.
- Patients with no preoperative reliance on cardiac support devices such as an intra-aortic balloon pump.
- Patients with no history of abnormal bleeding disorders.
- Patients with a normal coagulation profile.
- Patients with a negative history for coagulopathy including hypercoagulable states or diseases associated with thrombosis.
- Patients with no long-term heparin or antiplatelet therapy.

Data collection was stratified into three phases: preoperative data, intraoperative data, and postoperative data. Three data collection forms were used to record patient data (preoperative, intraoperative, and postoperative) to be collected on the evening prior, or the morning of the scheduled surgery. Intraoperative data were collected in the surgical suite. Postoperative data were collected in the intensive care unit (ICU) at 6 hours, 12 hours, and 24 hours postoperatively. In the case of the historical control group, all data were retrieved from the patients’ medical chart.

The preoperative assessment data sheet was designed to provide demographic data, such as age, gender, height, weight, and type of operation. Physiological and laboratory data included hematocrit (Hct), hemoglobin (Hgb), platelet count, fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT), activated clotting time (ACT), left ventricular ejection fraction, and Amicar dosing schedule.

The intraoperative assessment data sheet included laboratory and physical data as follows: baseline activated clotting time, postheparinization activated clotting time, postcardiopulmonary bypass activated clotting time, duration of cardiopulmonary bypass, duration of aortic cross-clamping, total number of distal anastomosis, use of the left internal mammary artery, lowest bladder temperature, postcardiopulmonary bypass hematocrit, total heparin administration, total protamine administration, estimated crystalloid volume delivered to the patient, estimated blood loss, and blood product administration.

The postoperative assessment data sheet summarized 24-hour chest tube output, crystalloid and blood product infusion, as well as delineating the following laboratory values at 6, 12, and 24 hours postoperatively: Hct, Hgb, platelets, PT, PTT, and fibrinogen.

Upon arrival of the patient into the operating room, a baseline arterial blood-gas and ACT sample was drawn from an arterial line that was established in the preoperative holding area. Two milliliters of blood were required for the ACT sample, which was analyzed using the Hemochron™ ACT counter. The patient was induced utilizing a general anesthetic technique. Five grams of Amicar was administered postinduction (prior to skin incision) to the patient through the central venous line, and 5 g was added to the priming solution for the
extracorporeal circuit. The extracorporeal circuit utilized was the Maxima™ (Medtronic) hollow-fiber membrane oxygenator, a Cobe™ roller pump delivery system, and Cobe™ tubing components. The prime solution for the extracorporeal circuit consisted of 2,000 mL of Plasmalyte “A,” 5,000 U of heparin, 50 mEq of sodium bicarbonate, 25 g of mannitol, 25 g of albumin, and 5 g of Amicar. The heparin dose was calculated at 300 U/kg, and 5 minutes after administration, an ACT sample was drawn. An ACT of 480+ seconds was the end point (to establish a safe level of anticoagulation) for this institution.

Upon initiation of cardiopulmonary bypass, the patient was rapidly cooled and the aorta cross-clamped upon spontaneous fibrillation of the heart. Multidose blood cardioplegia (4:1 blood to crystalloid ratio) and systemic hypothermia of 28-32°C were instituted in all cases. Perfusion flow was nonpulsatile and maintained at 2.0-3.0 L/min/m². Mean arterial pressure was maintained between 60 and 80 mmHg. Upon termination of bypass, residual heparinization was reversed with protamine sulfate dosed at approximately 1-1.3 mg per 100 U of heparin. The final dose of Amicar (5 g) was administered to the patient at this time.

Analysis of data was performed using The Statistica™ (StatSoft) and Microsoft Excel™ computer statistical analysis software. Descriptive statistics were used to render sample mean, standard deviation, and variance of the control group, and the group of patients receiving Amicar. The Students t-test was used to compare the means between the groups of 38 variables measured during the study. The alpha limit was established as *P* ≤ 0.01. The repeated measures ANOVA test was used to assess within-group and between-group differences of repeated test values measured in the study.

There were 38 variables compared between the control group and the group receiving Amicar. Selection of these variables was based on a review of literature as well as institutional limitations. Additional discussion with the surgeon and perfusion team allowed for a more concise decision of which variables were to be measured. The variables were categorized into three separate groups defined as preoperative conditions, intraoperative conditions, and postoperative conditions. This was felt necessary in order to isolate variables having a potentially causal effect on the patient’s postoperative parameters. Table I provides a variable to variable comparison of the two groups. The degree of significance was established at *P* ≤ 0.01. All subsequent findings discussed will associate the term “not significant” to the value of “*P*” being greater than or equal to 0.01.

Results

- **Preoperative conditions.** The age range between the groups did not differ significantly with the mean age of the control group being 65.6 years and the mean age for the Amicar group being 56.1. Weight distributions between the two groups were relatively similar and not statistically different (Table I).

  The preoperative platelet count and the baseline ACT did not vary significantly between the two groups. Preoperative baseline laboratory measurements of PT, PTT, Hgb, and Hct demonstrated no significant differences between the control group and the group receiving Amicar. Baseline measurement of fibrinogen was eliminated as a source for comparison due to the fact that only one result was recorded for the group receiving Amicar, and only eight results were recorded for the control group.

- **Intraoperative conditions.** The cardiopulmonary bypass times between the two groups did not vary significantly with the control group having shorter durations (X = 83 minutes) than the group receiving Amicar (X = 95 minutes). This is further reflected in aortic cross-clamp times measured between the two groups with a lower duration for the control group (X = 69 minutes) in comparison to the group receiving Amicar (X = 82 minutes).

  The number of anastomoses differed (no statistical significance) between the two groups with the control group requiring fewer grafts (X = 2.93) than the Amicar group (X = 3.46). The lowest core temperature between the groups was significantly higher (P ≤ 0.01) with the control group (X = 31.07°C) than the Amicar group (X = 30°C). The control group received higher doses of protamine for heparin reversal (X = 545 mg) than did the Amicar group (X = 486 mg). Heparin doses between the two groups were not significantly different, and while protamine treatment did reflect differences in dosing between the two groups, they were not statistically different. The postoperative ACT varied significantly (P ≤ 0.01) between the two groups. The control group times were returned close to baseline (X = 133 seconds), whereas the postoperative ACT for the group receiving Amicar dropped below preoperative baseline values (X = 115 seconds).

  The amount of blood given on bypass was higher for the control group (X = 420 mL) in comparison to the group receiving Amicar (X = 140 mL). This difference was not statistically significant. Crystalloid administration (while on bypass) represented no significant difference between the two groups.

- **Postoperative conditions.** Postoperative platelet counts between the two groups did not differ
significantly when measured at 6, 12, and 24 hours respectively. Postoperative measurement of PT, PTT, Hct at 12 and 24 hours, Hgb at 12 and 24 hours, blood administration in the ICU, and platelets given in ICU, were not significantly different between the two groups.

Hemoglobin measurements taken at 6 hours postoperatively were significantly different ($P \leq 0.01$) between the two groups. The control group had higher levels ($X = 9.76 \text{ g/dL}$) than the group receiving Amicar ($X = 8.98 \text{ g/dL}$). A similar relationship is borne out with comparison of the measured values of the postoperative Hct at 6 hours ($P \leq 0.01$) with the control Hct being higher ($X = 28.7\%$) than the group receiving Amicar ($X = 26.8\%$).

Chest tube output measured at 12 hours and 24 hours postoperatively was not significantly different between the two groups; however, when measured at 6 hours ($P \leq 0.01$), and the sum of the three measurements totaled, the group receiving Amicar demonstrated significantly less blood loss ($P \leq 0.01$). At 6 hours the control group lost $470 \pm 362 \text{ mL}$ compared to $219 \pm 94 \text{ mL}$ for the group receiving Amicar. At 12 hours the control group lost $262 \pm 182 \text{ mL}$ compared to $245 \pm 185 \text{ mL}$ for the group receiving Amicar. At 24 hours the control group lost $305 \pm 179 \text{ mL}$ versus a $172 \pm 101 \text{ mL}$
blood loss for the group receiving Amicar. The total chest tube output for the first 24 hours postoperation was $1037 \pm 532$ mL for the control group in comparison to $637 \pm 293$ mL for the group receiving Amicar.

The total blood administration to the patients from the time of skin incision until 24 hours postoperatively was significantly lower ($P < 0.01$) for the group receiving Amicar ($257 \pm 309$ mL) when compared to the control group ($741 \pm 528$ mL). The amount of Hespan* administered to patients postoperatively was not significantly different between the two groups. The control group received more Hespan ($800 \pm 702$ mL) when compared to the Amicar group ($333 \pm 361$ mL).

None of the patients in either group were returned to the operating room for excessive postoperative bleeding. One patient in the Amicar group was diagnosed as having suffered from a postoperative stroke attributed to an embolic event. One patient in the control group was administered 10 g of Amicar during the postoperative period. No patients in either group were treated with additional protamine.

Discussion

When reviewing the results of data for variables that directly address the impact of Amicar on reducing chest tube output and subsequent blood product transfusion, initial conclusions advocating the use of Amicar can be assumed to be valid.

On the basis of postoperative chest tube output being used as a determinant of postoperative blood loss, this study implies that the prophylactic use of Amicar for patients undergoing open heart surgery does reduce perioperative bleeding in patients presenting with acquired heart disease. A relevant question at this point is whether or not increased blood product transfusion is the result of bleeding due to inhibition of the hemostatic mechanism. The most obvious concern would involve adequate reversal of patient heparinization with protamine sulfate. As was discussed previously, there were no significant differences between the two groups in this area.

Although not rendered statistically significant, of interest is the stratification of protamine administration between the two groups. The control group received higher doses of protamine than did the Amicar group. This has particular relevance when examining a frequency distribution of protamine administration. The protocol for protamine administration at this institution is based on a fixed dose regimen (in the majority of cases) regardless of the amount of heparin administered. This can be demonstrated by the Amicar group which dosed patients with 400 mg two times (13.33%) and 500 mg 13 times (86.67%). In contrast the control group demonstrated much greater variability in their dosing schedule. One patient received 480 mg (6.67%), five patients received 500 mg (46.67%), three patients received doses between 520 and 580 mg (20%), three patients received 600 mg (20%), and one patient received 750 mg (6.67%). Approximately 47% (7 of 15) of the control group patients were treated with protamine doses greater than the largest amount of protamine administered in the Amicar group. The most common reason for additional protamine administration is continued bleeding during the period of surgical closure (after initial heparin reversal).

Comparison of the two groups for total blood product transfusion supports that the prophylactic use of Amicar for patients undergoing open heart surgery results in a reduction of transfused blood products for patients with acquired heart disease.

There were significant differences between the two groups ($P \leq 0.01$) for total blood product administration (Figure 1). The difference between the two groups in terms of total blood administration cannot be associated with differences between the

![Figure 1](image-url)
two groups in regard to baseline Hgb, Hct platelet count, PT, PTT, cardiopulmonary bypass time, aortic cross-clamp time, crystalloid administration, or heparin administration. Intraoperative blood product transfusion may represent a plausible explanation for the postoperative differences (at 6 hours) in Hgb and Hct levels between the two groups. The mode for transfusion (whether by anesthesia or via extracorporeal circuit) was undetermined. The point at which transfusion was begun was also left undetermined. Intraoperative crystalloid administration fails to account for the drop in hematocrit relative to the fact that the amount of crystalloid administered to the Amicar group was not significantly different from the amount received by the control group. The control group required more blood intraoperatively than did the Amicar group despite having shorter bypass times. Surgical blood loss was a measured variable assigned to the study. Too few results, however, were obtained to utilize the data for statistical analysis. It is reasonable to assume that higher blood loss associated with the control group would result in larger volumes of blood product administration. Tables II and III demonstrate the significant differences between the two groups ($P \leq 0.01$) for total blood product administration.

<table>
<thead>
<tr>
<th>Table II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood administration for control group</td>
</tr>
<tr>
<td>Category</td>
</tr>
<tr>
<td>0.00</td>
</tr>
<tr>
<td>350.00</td>
</tr>
<tr>
<td>410.00</td>
</tr>
<tr>
<td>700.00</td>
</tr>
<tr>
<td>1050.00</td>
</tr>
<tr>
<td>1250.00</td>
</tr>
<tr>
<td>1400.00</td>
</tr>
<tr>
<td>1750.00</td>
</tr>
</tbody>
</table>

Utilizing D-dimer, fibrin degradation products, fibrin split products, thromboelastograph, and sonoclot to test patient values prior to receiving Amicar and prior to initiating cardiopulmonary bypass would allow for a baseline frame of reference from which to compare postoperative/postbypass changes in the hemostatic mechanism. These values should be tested to develop a consistent picture of the role Amicar is capable of in attenuating postoperative bleeding diatheses. Greater precision in regard to the measurement of blood loss is suggested. This applies not only to quantity but also to administration in open heart surgical patients was reached. This study rejects the null hypothesis that states there would be no differences between the two groups in regard to differences in blood loss and blood product administration. Significant differences were measured between the groups relative to the variables examined. These could be explained with a rationale implying the efficacy of Amicar.

The overall conclusion from this study is that Amicar reduced perioperative bleeding in a population consisting of patients undergoing open heart surgery requiring cardiopulmonary bypass. The effect most likely contributes to a significant reduction of blood products administered. The mechanism for this action, on the basis of this study, remains undetermined. It can be postulated that it is due to a favorable impact of Amicar on the patient's hemostatic mechanism, but more conclusive testing of this hypothesis is suggested.

Certainly the limitations of using a historical sample group could be avoided by utilizing a carefully controlled prospective design. Recommendations for future research should involve a more aggressive investigation of the impact of Amicar on the hemostatic mechanism by including data and laboratory results that would yield a more comprehensive picture of the patient's coagulation profile. Utilizing D-dimer, fibrin degradation products, fibrin split products, thromboelastograph, and sonoclot to test patient values prior to receiving Amicar and prior to initiating cardiopulmonary bypass would allow for a baseline frame of reference from which to compare postoperative/postbypass changes in the hemostatic mechanism. These values should be tested to develop a consistent picture of the role Amicar is capable of in attenuating postoperative bleeding diatheses. Greater precision in regard to the measurement of blood loss is suggested. This applies not only to quantity but also to
determine when and where the blood loss is likely to be encountered. Development of criteria for transfusion of blood products when using prophylactic Amicar could generate valuable research in the application of antifibrinolytic agents in general.

REFERENCES


AUTHORS

Ann E. Apriole, CRNA, MSN, is a graduate of the Oakland University Graduate Program of Nurse Anesthesia. She is employed at William Beaumont Hospital in Royal Oak, Michigan, and she is currently enrolled in the DNSc Program at Rush University, Chicago, Illinois. Timothy J. Palmer, CRNA, MS, is a graduate of the Henry Ford Hospital - University of Detroit Mercy Graduate Program of Nurse Anesthesiology. He is currently a staff anesthetist at William Beaumont Hospital in Royal Oak, Michigan, and at Henry Ford Hospital in Detroit, Michigan. He is also clinical and didactic faculty in the William Beaumont Hospital - Oakland University Graduate Program in Nurse Anesthesia.