The Use of Epsilon-aminocaproic Acid to Reduce Bleeding during Cardiac Bypass in Children with Congenital Heart Disease

P. D. McClure, M.D., F.R.C.P. (C),* and J. Izsak, M.D.†

Many patients with congenital heart disease bleed excessively during surgical correction. While there are many reasons for this, activation of the fibrinolytic system may be responsible in some patients.1–5

Although normally quiescent, the fibrinolytic system can be activated by physical or emotional stress, hemorrhage, release of adrenaline into the circulation, and diffuse intravascular coagulation. Activation leads to conversions of plasminogen to plasmin. Plasmin attacks both fibrin and other clotting factors, and hence may contribute to bleeding produced by other mechanisms. Several amino-acid compounds have been found to inhibit the fibrinolytic system. One of these, epsilon-aminocaproic acid† (EACA) inhibits both activation of plasminogen and plasminogen activator.

The purpose of the present study was to see whether EACA would reduce bleeding during cardiac bypass operations in children with congenital heart disease. With the exception of euglobulin lysis time, systematic clotting studies were not done in all cases and are therefore not reported.

METHODS AND MATERIALS

The double-blind experiment included 71 consecutive patients more than 2 years of age undergoing open-heart surgery at The Hospital for Sick Children. Patients, whether cyanotic or acyanotic, were randomly selected to receive EACA or placebo in the intra-

* Associate Professor of Pediatrics, University of Toronto; Chief, Division of Hematology, The Hospital for Sick Children, Toronto, Ontario, Canada.
† Associate Resident, Pediatrics, The Hospital for Sick Children.

Send reprint requests to Dr. McClure, Division of Hematology, The Hospital for Sick Children, Toronto, Ontario, Canada.
† Amicar, Lederle Products Dept., Cyanamid of Canada Ltd., Montreal, P.Q., Canada.

venous fluid administered during and after operation.

The test solution, made up by the Blood Bank technologists, consisted of EACA, 3 g in 100 ml of intravenous solution (one third physiologic saline solution, two thirds 5 per cent glucose). The placebo was simply the intravenous solution. Both test and placebo solutions were identically marked so as not to identify the contents. The solutions were dispensed from the Blood Bank with the blood for the patient, so that the surgeons, anaesthetists and hematologists did not know whether the patient received EACA or placebo.

Intravenous infusion commenced when the chest was opened and continued for 24 hours. It was calculated to deliver 75 mg of EACA/kg body weight in the first hour and 15 mg/kg/hr thereafter. Also, 17 ml of solution containing either EACA or placebo were added to each unit of blood used in the cardiopulmonary bypass pump. When severe bleeding developed, patients were treated by the surgeons with measures which they deemed appropriate, including fibrinogen, factor VIII concentrates, heparin neutralization, platelet transfusion and vitamin K. Suggestions for treatment were not made by the authors, but where “conventional methods” failed the patient was taken off the double-blind schedule and given EACA.

Blood loss was recorded for two periods, Period 1, from cessation of cardiac bypass to the end of the operation, and Period 2, for 24 hours from the end of operation. We estimated blood losses by weighing sponges and measuring aspirates and drainage; we noted whether drainage was serosanguineous or frank blood.

Euglobulin lysis times (ELT), which roughly indicate the activity of the fibrinolytic system, were measured by the method of Biggs and MacFarlane* at the beginning of the operation and again when the chest was closed.

Downloaded From: http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jas
TABLE 1. Infusion with Placebo and EACA in 56 Patients, Distribution by Diagnosis

<table>
<thead>
<tr>
<th>Group</th>
<th>Type of Heart Disease</th>
<th>Infusion with Placebo</th>
<th>Infusion with EACA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanotic</td>
<td>Tetralogy of Fallot</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Transposition of great vessels</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td><strong>TOTAL</strong></td>
<td><strong>18</strong></td>
<td><strong>12</strong></td>
</tr>
<tr>
<td>Acyanotic</td>
<td>Ventricular septal defect</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Aortic or pulmonary stenosis</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><strong>TOTAL</strong></td>
<td><strong>13</strong></td>
<td><strong>13</strong></td>
</tr>
</tbody>
</table>

TABLE 2. Average Blood Loss in Patients Receiving Either EACA or Placebo

<table>
<thead>
<tr>
<th>Group</th>
<th>Infusion</th>
<th>Number of Patients</th>
<th>Mean Time on Bypass (Min)</th>
<th>Mean Blood Loss, ml/kg Body Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Period 1</td>
<td>Period 2</td>
</tr>
<tr>
<td>Cyanotic</td>
<td>Placebo</td>
<td>18</td>
<td>71.2</td>
<td>42.8</td>
</tr>
<tr>
<td></td>
<td>EACA</td>
<td>12</td>
<td>68.4</td>
<td>23.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>N.S.</strong></td>
<td><strong>P &lt; .01</strong></td>
</tr>
<tr>
<td>Acyanotic</td>
<td>Placebo</td>
<td>13</td>
<td>37.3</td>
<td>17.3</td>
</tr>
<tr>
<td></td>
<td>EACA</td>
<td>13</td>
<td>36.6</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>N.S.</strong></td>
<td><strong>P &lt; .05</strong></td>
</tr>
</tbody>
</table>

* N.S., not significant.

RESULTS

Studies could not be completed in 12 of the patients because either the test substance was not given in proper dosage or relevant information was not recorded. In addition, three patients died during operation, two while receiving the placebo and one while receiving EACA. The latter died of left heart failure, with no evidence of intravascular coagulation which has been attributed to EACA. Of the remainder (56), 25 received EACA and 31 placebo; 30 were cyanotic and 26 were acyanotic (table 1).

Although bleeding was more profuse in the cyanotic than in the acyanotic patients, blood losses in both groups were significantly decreased by EACA (table 2). This was most striking in the cyanotic group, where blood loss was decreased 42 per cent. We found that blood loss in Period 1 was directly related to the length of time the patient was on cardiac bypass in both cyanotic and acyanotic patients who received the placebo (fig. 1). However, in patients who received EACA, blood loss in Period 1 appeared to be unrelated to the duration of cardiac bypass (fig. 2). Blood losses during the 24 hour postoperative period (Period 2) were the same in the treated and untreated groups (table 2).

About half the patients had short euglobulin lysis times at onset of operation, but by the end of operation most patients had normal values whether EACA or placebo was given (table 3).

Two of the 56 patients subsequently died. One, who had received EACA, had severe renal failure, a not uncommon complication of cardiac surgery. There was no indication of excess intravascular coagulation, and we have no evidence that EACA contributed to death. The second death was due to a mechanical problem with the repair procedure. Hemothorax occurred in four patients,
one of whom had been given EACA. Eight patients were removed from the study at some point and given EACA for excess bleeding. All of these had been on placebo. This study includes their data up to the time of EACA administration.

**DISCUSSION**

Reports indicate that fibrinolysis is usually active during open-heart surgery. Whether this contributes significantly to bleeding in these patients is a contentious point. Some investigators have felt there is little correlation between fibrinolysis and bleeding. Others have attributed excessive bleeding to fibrinolysis and, in fact, have used fibrinolytic inhibitors with apparent success. In a control study of 20 patients, Gans and Kravit showed that in patients undergoing open-heart surgery, pretreatment with EACA effectively inhibited fibrinolytic activity during cardiac bypass; but they did not compare blood losses in the treated and control groups. In a large group of 240 patients treated with EACA either during or after cardiac bypass, Stermans and Lillehei found a significant decrease in the average blood loss compared with that in 100 patients not so treated. Ambrus et al. were unable to show a reduction in blood loss in patients given EACA, but did show a reduction when Trasylol, another fibrinolytic agent, was used. Gomes and McGoon found no reduction in blood loss in patients who received EACA.

In the present double-blind experiment, we compared the blood loss in patients receiving EACA during and for a 24-hour period after cardiac bypass with that in untreated patients, we found a significant decrease in the treated patients. The decrease was most obvious in the cyanotic and in those who were subjected to prolonged bypass procedures. The time intervals for which blood losses were estimated did not include the periods before and during cardiac bypass, because bleeding during this period is often related to the surgical procedure and is difficult to measure accurately. Instead, we concentrated on bleeding that occurred after cessation of cardiac bypass. Reduced bleeding in treated patients was found in the immediate post-bypass period (Period 1) but not in the subsequent 24 hours (Period 2).

Because of the small number of subjects, we cannot tell whether the excessive bleeding was due to prolonged bypass or to the type of heart disease. Both are probably important, although our results suggest that the prolonged
bypass procedure is the more important factor. This was the conclusion of Marin also. He suggested that excessive bleeding was related not only to long cardiopulmonary bypass but also to excessive fibrinolytic activity.

About half the patients had short ELT's at the onset of operation (table 2). A higher percentage of positive tests would be expected if the test had been done just after opening the chest.13 In most of our patients ELT's had returned to normal at the end of operation, a finding which is also similar to that of Gralnick and Fischer.13 This suggests that the most active period of fibrinolysis occurs after the chest is open and during cardiac bypass. It could also account for the decrease in bleeding in the treated patients during the immediate post-bypass period.

Marin also suggested that because of the technical problem of obtaining rapid laboratory control of fibrinolysis, EACA could logically be given routinely to patients undergoing cardiac bypass. Others have warned against this approach.14,15 Our experience of the absence of complications with this drug in patients on cardiac bypass, and that of Sterns and Lillehei16 and Midell et al.,17 would support Marin's view. We feel that the drug should be used in patients with cyanotic congenital heart disease who are expected to be on cardiac bypass for more than an hour. We agree with Abildgaard18 that comprehensive investigation of the hemostatic mechanism should be undertaken in the bleeding patient. Sometimes, however, decisions about therapy, especially in the case of fibrinolysis, have to be made before laboratory tests can be completed.

In summary, blood losses during open-heart surgery in children with congenital heart disease given epsilon-aminocaproic acid were compared with those in an untreated control group by means of a double-blind study. Bleeding was significantly less in the treated group. The decrease in bleeding was most marked in the period immediately after cessation of cardiac bypass in those patients who had cyanotic heart disease and in those subjected to prolonged cardiac bypass. No complication was encountered. It is suggested that EACA should be considered for use in patients with cyanotic congenital heart disease who are expected to have long periods of cardiopulmonary bypass.

The authors thank Dr. Jeremy Sloan and Dr. Margaret Blackwood and other members of the Anesthesia Department for their assistance in this project. Dr. William Mustard and Dr. George Trusler very kindly allowed us to study their patients.

REFERENCES

Table 3. Distribution of Abnormal ELT Values in Patients Undergoing Cardiac Bypass

<table>
<thead>
<tr>
<th>Timing of ELT Test</th>
<th>Placebo</th>
<th>EACA</th>
</tr>
</thead>
<tbody>
<tr>
<td>At onset of operation</td>
<td>16/31</td>
<td>14/24</td>
</tr>
<tr>
<td>At end of operation</td>
<td>4/29</td>
<td>5/23</td>
</tr>
</tbody>
</table>

* Number abnormal/total tested.


Obstetrics

FIBRINOLYSIS AND CESAREAN SECTION Changes in serum plasminogen activator and fibrin split products during and after elective cesarean section were studied in ten healthy pregnant women and compared with the changes observed in ten age-matched nonpregnant women undergoing hysterectomy or salpingectomy. The cesarean section patients showed a highly significant reduction in plasminogen activator response during operation. No significant difference was observed in the serum fibrin split products. These results suggest that depressed mobilization of plasminogen activator can occur in the later months of normal pregnancy. Despite a lowered plasminogen activator content, there is still sufficient fibrinolytic potential either systemically or locally to deal with the modest demands of normal daily wear and tear. However, in the presence of clinically significant disseminated intravascular coagulation (DIC), microcirculatory blockade with ensuing tissue damage may occur. (Woodfield, D.G., and others: Systemic Fibrinolysis during and following Elective Cesarean Section and Gynecological Operation. J Obstet Gynecol Br Commonw 79: 538–543, 1972.)

GLUCOSE INSULIN AND GROWTH HORMONE IN MOTHER AND NEONATE Measurements of blood glucose, insulin, and growth hormone (HGH) were made in maternal venous blood, umbilical artery and vein blood, and amniotic fluid samples from 270 pregnant women. The umbilical vein (UV) glucose level (95.9 ± 3.9 mg/100 ml) correlated significantly with the maternal (MV) level (118.4 ± 5.3 mg/100 ml) and was significantly higher than the umbilical artery concentration (73.9 ± 2.9 mg/100 ml). Blood insulin levels were highest in the maternal samples (45.3 ± 6.2 units/ml). The umbilical artery (UA) insulin level (15.2 ± 2.5 μunits/ml) was greater, thought not significantly, than the UV level (14.5 ± 2.6 μunits/ml). Fetal insulin levels increased with increasing fetal size. Fetal HGH levels were high (UV 56.8 ± 3.4 μg/ml; UA 63.6 ± 4.9 μg/ml). No relationship between fetal HGH levels and either fetal or placental weight was seen. Amniotic fluid (AF) glucose levels reflected maternal blood glucose levels and decreased with increasing gestational age. AF glucose levels were higher in pregnancies complicated by diabetes mellitus than in normal pregnancies. The study demonstrated significant relationships between gestational age and AF insulin content and between infant birth weight and AF insulin content. (Spellacy, W.N., and others: Maternal, Fetal and Amniotic Fluid Levels of Glucose, Insulin and Growth Hormone. Obstet Gynecol 41: 323–331, 1973.)