Efficacy of aprotinin in children undergoing craniofacial surgery

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Object. This prospective, randomized, placebo-controlled, double-blind trial was undertaken to assess the efficacy of aprotinin in reducing the need for blood transfusions in 39 children undergoing reconstructive craniofacial surgery.

Methods. Two demographically similar groups—a total of 39 patients with a mean age of 1.2 ± 1.2 years—were studied. The efficacy of aprotinin (240 mg/m² administered intravenously over 20 minutes, followed by infusions of 56 mg/m²/hr) was compared with that of an equal infusion of 0.9% saline (placebo).

Patients in the aprotinin group received less blood per kilogram of body weight than patients in the placebo group (32 ± 25 ml/kg compared with 52 ± 34 ml/kg, respectively, p = 0.04). Those patients in whom aprotinin was administered experienced less change in their hematocrit levels during surgery (aprotinin −33 ± 13% compared with placebo −44 ± 9%, p = 0.01). Each patient underwent a transfusion as per study protocol, and there was no significant change in hematocrit levels from the beginning to the end of surgery. The surgical faculty judged blood loss in patients in the aprotinin group to be significantly less than usual (p = 0.03). The use of aprotinin was also associated with reduced blood transfusion requirements during the first 3 postoperative days (p = 0.03). There was no adverse event reported in either the aprotinin or placebo group.

Conclusions. Aprotinin decreased blood transfusion requirements in pediatric patients undergoing craniofacial reconstruction, thereby reducing the risks associated with exposure to banked blood components.

Key Words • pediatric neurosurgery • plastic surgery • anesthesia • blood transfusion • children

Aprotinin, a serine protease inhibitor, was isolated in 1930 and has been used in numerous clinical settings, including acute pancreatitis, adult respiratory distress syndrome, trauma, and septic shock. It has been studied in cardiac surgery in both adult and pediatric patients and has become the drug of choice for minimizing blood loss following cardiopulmonary bypass.1,3,16,17

More recently, aprotinin has been studied for use in several procedures that have potential for large blood loss, for example, orthotopic liver transplants in adult and pediatric populations, total hip arthroplasty, spinal fusion, and nonbypass thoracic cases. Craniofacial surgery in infants has become more extensive, and complete cranial vault reshaping has a high risk of excessive blood loss. Given the success of aprotinin in pediatric patients having cardiac surgeries,1,4 we hypothesized that its administration in children undergoing reconstructive craniofacial surgery would reduce perioperative blood loss and the need for blood transfusion, compared with placebo.

Clinical Material and Methods

The study protocol was approved by the University of Michigan Health System’s Institutional Review Board. Informed consent was obtained from the parents or legal guardian of each patient. Between March 1999 and July 2001, 39 patients admitted to the C. S. Mott Children’s Hospital for craniofacial surgery were recruited into the study. Pediatric patients younger than 12 years of age undergoing craniofacial reconstruction for cranial vault reshaping or frontal orbital advancement were eligible to participate in the study. Patients were excluded from the study for the following reasons: age younger than 1 month, evidence of renal insufficiency or failure (preoperative serum creatinine levels > 0.8 mg/dl), preexisting coagulation abnormality, history of aprotinin allergy, or previous craniofacial surgery. The patients were randomized to receive either aprotinin (240 mg/m² intravenous bolus over 20 minutes, followed by infusions of 56 mg/m²/hr) or an equal volume of 0.9% saline as a placebo. Patients were assigned to either group based on a computer-generated list of random numbers. The same surgical team performed all operative procedures.

Anesthesia was induced by the inhalation of sevoflurane, and a combination of fentanyl, midazolam, pancuronium, and isoflurane were used for maintenance. After induction of anesthesia and the insertion of intravenous and intraarticular cannulas, a 1-ml test dose of the study drug was given. The patients were observed for 10 minutes for an allergic reaction (hives, hypotension, or bronchospasm). If there
was no allergic reaction, a loading dose of 240 mg/m² (171.5 ml/m²) was infused over 20 minutes and followed by continuous infusions of 56 mg/m²/hr (40 ml/m²/hr) for the duration of the surgery. The study drug (placebo or aprotinin) was prepared by the pharmacy and administered in a double-blind fashion. One 3-ml syringe (containing the 1-ml test dose) and five 60-ml syringes of solution (aprotinin or placebo) were all labeled as the study drug by the pharmacy personnel for each case. Only the pharmacist who kept a record of the patient’s identification number and the randomization list could identify which study drug was used in case of an emergency.

Serial hematocrit and arterial blood gas levels were measured hourly for the duration of the surgical procedure or more frequently following large or unexpected blood loss. Prothrombin time, partial thromboplastin time, fibrinogen, and platelets were measured intra- and postoperatively based on clinical judgment in the event of continued blood loss. Standard criteria for the transfusion of banked blood and blood components were used in the operating room, intensive care unit, and patient wards. This included a hematocrit level less than 20% or hemodynamic instability intraoperatively and a hematocrit level less than 25% postoperatively. The target hematocrit level for patients following transfusion was 35 to 40%. Platelets were transfused for counts less than 10⁹/mm³, fresh frozen plasma for prothrombin times longer than 15 seconds and partial thromboplastin times longer than 40 seconds, and cryoprecipitate was given for a fibrinogen level less than 120 mg/dl. The surgeons, who were blinded to the treatment, assessed the appearance of the operative field during the neurosurgical and plastic surgery portions of the procedure. The field was characterized as drier than expected, as expected, or wetter than expected. The circulating nurse in the operating room estimated the blood loss from suction canisters and by weighing surgical sponges. The patients were followed up for 3 days, during which time laboratory tests performed included complete blood count, BUN, and serum creatinine. The total amount of blood products received and any complications were noted.

Using data from a pilot study and previous open heart surgeries in pediatric patients, we estimated that the sample size required for an 80% probability of detecting a 25% reduction in the amount of blood transfused, assuming a Type I error rate of 5%, was 18 patients per group. Data are expressed as the means ± standard deviation unless otherwise noted. Comparisons between the aprotinin and placebo groups for continuous data, such as the amount of blood transfused and the change in hematocrit levels, were performed using the unpaired t-test. Chi-square and continuity-corrected Fisher exact tests were used to compare the surgeons’ assessments of the surgical field and complication rates. All tests were considered significant at a probability value of less than 0.05.

### Results

Demographic data for the study population are summarized in Table 1. The operations performed included cranial vault reshaping or frontal orbit advancement for numerous types of craniosynostoses. There was no significant difference between groups with respect to duration of surgery. Two patients in the aprotinin group had been taking nonsteroidal antiinflammatory agents preoperatively. Three of the patients in the placebo group and one in the aprotinin group had craniofacial anomalies associated with a congenital syndrome. The placebo group included two patients with Saethre–Chotzen syndrome and one patient with Crouzon syndrome. One patient in the aprotinin group had Apert syndrome. (Note that patients with Apert syndrome often have more complex bone involvement.)

The amount of blood transfused during the operation was significantly less in the aprotinin group compared with that in the placebo group (32 ± 25 ml/kg compared with 52 ± 34 ml/kg, respectively; p = 0.04). During the course of surgery, the hematocrit level dropped significantly lower in patients in the placebo group (placebo −44 ± 9% compared with aprotinin −33 ± 13%, p = 0.01). There was no significant difference in the change from the preoperative hematocrit level to that at the completion of surgery (aprotinin −14 ± 21% compared with placebo −5 ± 23%, p = 0.21). Although the estimated loss of blood per kilogram of body weight was less in patients in the aprotinin group than in those in the placebo group (28 ± 21 ml/kg compared with 39 ± 25 ml/kg, respectively; p = 0.14), the difference did not reach statistical significance.

### Table 1

Demographic summary of 39 patients who underwent craniofacial surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aprotinin</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>18</td>
<td>21</td>
<td>39</td>
</tr>
<tr>
<td>median age (yrs)</td>
<td>1.4 ± 1.1</td>
<td>0.76 ± 0.5†</td>
<td>1.2 ± 1.2</td>
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<tr>
<td>sex (% M/F)</td>
<td>64/36</td>
<td>61/39</td>
<td>64/36</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>10.3 ± 3.2</td>
<td>11.2 ± 15.2</td>
<td>10.9 ± 1.4</td>
</tr>
<tr>
<td>ASA classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>hematocrit level (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preop</td>
<td>33.2 ± 3.9</td>
<td>33.2 ± 3.1</td>
<td>33.2 ± 3.4</td>
</tr>
<tr>
<td>lowest</td>
<td>22.3 ± 4.8</td>
<td>18.5 ± 2.7†</td>
<td>20.3 ± 4.3</td>
</tr>
<tr>
<td>postop</td>
<td>28.2 ± 5.9</td>
<td>31.4 ± 7.3</td>
<td>30.0 ± 6.8</td>
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<tr>
<td>duration of surgery (min)</td>
<td>480 ± 84</td>
<td>463 ± 77</td>
<td>471 ± 80</td>
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<tr>
<td>surgical procedure</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>cranial vault reshaping</td>
<td>6</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>frontal orbital advancement</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>combined</td>
<td>9</td>
<td>9</td>
<td>18</td>
</tr>
</tbody>
</table>

†p < 0.05.

ASA = American Society of Anesthesiologists physical status classification.

### Table 2

Surgeons’ assessments of the operative field in 39 patients who underwent craniofacial surgery

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Aprotinin</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>18</td>
<td>21</td>
<td>39</td>
</tr>
<tr>
<td>drier than expected</td>
<td></td>
<td>69*</td>
<td>26</td>
</tr>
<tr>
<td>as expected or wetter than</td>
<td></td>
<td>31</td>
<td>74</td>
</tr>
</tbody>
</table>

*p < 0.05.
Aprotinin in craniofacial surgery in pediatric patients

One patient in the aprotinin group received a unit of platelets. Seven patients received fresh frozen plasma; five in the placebo group and two in the aprotinin group. No patient in the study received cryoprecipitate. There was no statistical significance to this data. The surgeons judged the appearance of the operative field (Table 2) to be drier than expected more frequently among patients in the aprotinin group (69%) compared with those in the placebo group (26%; p = 0.03).

During the first 3 postoperative days, patients in the aprotinin group received fewer packed red blood cells than those in the placebo group (33 ± 24 ml/kg compared with 57 ± 38 ml/kg, respectively; p = 0.03). The BUN and creatinine levels remained within normal limits for both groups of patients. There were no complications, including neurological sequelae from the surgery, or deaths in either group.

Discussion

Data from the present study indicate that the use of aprotinin in children undergoing reconstructive craniofacial surgery is associated with a decrease in blood transfusion requirements. These results are supported by the finding that the hematocrit in patients in the placebo group dropped to a lower level prior to transfusion during surgery. Both groups received standard transfusion therapy for anemia during surgery and left the operating room with a target hematocrit level in the range of 35 to 40%. The total amount of blood transfused among patients in the aprotinin group remained significantly lower for 3 postoperative days. Although subjective, the surgeons were often able to identify the patients who had received aprotinin based on the reduced bleeding in the surgical field.

With recent advances in complex pediatric surgery, many children can undergo surgical procedures at a younger age but are nonetheless exposed to the risk of significant blood loss. Exposure to banked donor units of blood and blood components is associated with an increased risk of infection with hepatitis B and C and possibly the human immunodeficiency virus. Repeated exposure to multiple donor units also increases the likelihood of the formation of abnormal antibodies, making accurate cross-matching more difficult and time-consuming. Thus, even from the narrow perspective of conserving banked blood components, efforts to minimize their administration to children would be advantageous.

The role of aprotinin in noncardiac cases is controversial. Given the differences in aprotinin dosage regimens and the variety of patient populations studied, the usefulness of aprotinin is difficult to assess. Garcia-Huete, et al., found that aprotinin was not effective in reducing blood loss during liver transplantation, yet Marcel, et al., assert that aprotinin reduces fibrinolysis during such surgeries. Because these procedures are performed in patients at a young age, the risk of hypotension and the need for multiple transfusions is increased. The benefit of aprotinin in reducing blood loss was originally thought to be related to its ability to inhibit plasmin-induced complement activation, thus decreasing fibrinolysis. Data from several studies in pediatric patients have shown a decrease in fibrin split products. Further, it has been shown that platelets remain inactivated during cardiopulmonary bypass, thereby maintaining the viability of the platelet population. This may be an important mechanism for decreasing blood loss in noncardiac surgery.

Although the estimated volume of blood loss per kilogram of body weight was not significantly different, the patients who had received aprotinin required significantly less blood during the first 3 postoperative days. Two mechanisms may explain this apparent discrepancy. First, the possibility exists that aprotinin may contribute to enhanced hemodynamic stability in the postoperative period by attenuating the intensity of the inflammatory response to surgery. As a kallikrein inhibitor, aprotinin inhibits the conversion of kinogen to kinin, thus preventing accompanying decreases in total peripheral vascular resistance. Aprotinin may attenuate the increased peripheral vascular permeability and fibrinolysis that occurs as a result of surgery, thus contributing to greater overall hemodynamic stability in the postoperative period. Second, the amount of blood transfused may be a more sensitive indicator of the severity of bleeding than the amount estimated by the circulating nurse in the operating room.

The results of the present study indicate a decrease in the amount of blood transfused and increased surgeon satisfaction with the quality of the surgical field with the use of aprotinin. Although the number of patients in the present study was too small to draw conclusions about the safety of aprotinin, there was no indication that aprotinin use was associated with any adverse effect. Allergic reactions are rare (1.2%), although patients are at greater risk on reexposure to aprotinin. No patient in this study had prior exposure to aprotinin and no allergic reaction was observed. There has been some concern that aprotinin may be associated with postoperative renal dysfunction in children undergoing cardiac surgery. This concern is in contrast to data demonstrating the improvement of BUN and serum creatinine in pediatric patients, however. Adverse renal effects were not noted in this study.

Conclusions

In this era of managed health care with limited medical resources, cost-effective patient care modalities will likely succeed. In our institution, aprotinin is used primarily in children undergoing repeated open heart surgery. Aprotinin has been shown to decrease blood loss in infants undergoing reconstructive craniofacial surgery and thus has become part of our standard of care for these patients. Although earlier information would tend to discourage the use of aprotinin in noncardiac cases, our data indicate that for a specific group of children, namely those undergoing cranial vault reshaping or frontal orbital advancement, aprotinin can provide a means of limiting banked blood unit transfusions, thereby decreasing the risks that accompany exposure to multiple blood components. This decrease in blood loss enables physicians to perform more extensive and complete cranial vault reshaping with less risk to the patient.

References


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