

ORIGINAL ARTICLE

Aprotinin and transfusion requirements in pediatric craniofacial surgery

Zulfiqar Ahmed¹, Lori Stricker², Arlene Rozzelle³ & Maria Zestos²

1 Anesthesia Associates of Ann Arbor, Oakwood Hospital, Dearborn, MI, USA

2 Department of Anesthesia, Children's Hospital of Michigan, Detroit, MI, USA

3 Department of Plastic Surgery, Children's Hospital of Michigan, Detroit, MI, USA

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Correspondence

Dr Zulfiqar Ahmed, Anesthesia Associates
of Ann Arbor, Oakwood Hospital and
Medical Center, 10181 Oakwood Boulevard,
Dearborn, MI 48124, USA
Email: zahmedz@yahoo.com

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Summary

Objective: To evaluate transfusion requirements in children receiving aprotinin during craniofacial surgery.

Background: Pediatric craniofacial procedures may involve massive blood loss. Aprotinin may decrease perioperative blood loss and transfusion requirements.

Methods: Patients (aged 1 month to 3 years) who had major reconstructive craniofacial surgery received intraoperative aprotinin (13 patients) or placebo (13 patients). Administered colloids and blood products were recorded.

Results: Patients in the aprotinin and placebo groups had similar mean age, body weight, body surface area, operative time, and length of hospital stay. Mean volumes of total colloids (aprotinin group: 70 ± 40 ml; and placebo group: 120 ± 80 ml; $P \leq 0.05$) and packed red blood cells (aprotinin group: 380 ± 90 ml; and placebo group: 550 ± 200 ml; $P \leq 0.004$) were less in the aprotinin group than in the placebo group. Mean urine output during surgery was greater in the aprotinin group than in the placebo group (320 ± 200 ml vs 150 ± 70 ml, respectively; $P \leq 0.003$). Mean blood urea nitrogen and serum creatinine values after surgery were similar between the groups. Complications of aprotinin included anaphylaxis (one patient) and rash (one patient); no deaths occurred.

Conclusions: Aprotinin was associated with decreased packed red blood cell transfusion requirements in children undergoing craniofacial surgery, with no renal toxicity or death. Aprotinin is no longer available for clinical use in the USA because of adverse effects in adults; re-evaluation of aprotinin is warranted for children scheduled to undergo surgery involving potentially high blood loss.

Introduction

Aprotinin is a serine protease inhibitor that inhibits fibrinolysis and may decrease intraoperative blood requirements and duration of postoperative ventilation, intensive care unit stay, and hospital stay for surgical procedures involving major blood loss (1). Although aprotinin may decrease postoperative blood loss and transfusion requirements via its known actions on the coagulation cascade, its detailed mechanism of action may involve a reduction in inflammatory 'cross-talk' (2). Aprotinin has been used for pediatric cardiac surgery

(3), spinal fusion (4,5), pediatric lung transplant (6), and adult cardiac surgery (7–9). However, aprotinin has been associated with an increased risk of death after cardiac surgery compared with other lysine analogue drugs and was removed from clinical use in 2007 (10–13).

Craniofacial procedures in children have the potential for large blood loss. These procedures may involve wide flap dissection, multiple osteotomies, and/or dilutional coagulopathy, with depletion of soluble coagulation factors (14,15). A previous study showed that aprotinin may decrease the need for blood transfusion in patients undergoing craniofacial surgery (16).

We performed this study before aprotinin was removed from the market in the USA to determine whether aprotinin decreases intraoperative transfusion requirements in pediatric patients undergoing craniofacial surgery. Specifically, the aim of this study was to evaluate transfusion requirements for packed red blood cells (PRBCs) in children receiving aprotinin during craniofacial surgery.

Methods

Subjects

During the period September 2003 through July 2006, patients (aged 1 month to 3 years) scheduled for major reconstructive craniofacial surgery at a tertiary care children's hospital were recruited for this prospective, randomized, placebo-controlled study. Patients were evaluated with respect to history and physical examination. Patients were excluded from the study if there was a history of (i) trauma that required craniofacial reconstruction; (ii) major systemic disease, renal impairment, or bleeding disorder; (iii) allergy to aprotinin; or (iv) exposure to aprotinin within the prior 6 months. Written informed consent was obtained from all parents or legally authorized representatives of the study patients. The study protocol was approved by the Institutional Review Board of Wayne State University (Detroit, MI, USA). The study was not registered at any registry due to unknowing of their existence.

Intervention

The 26 patients in this study were prospectively randomized to either the aprotinin or placebo (normal saline) group (13 patients in each group). Drug and placebo were prepared and labeled in a double-blind fashion by a staff anesthesiologist who was not involved in the clinical care of the patients. After inhalational induction of anesthesia, intravenous cannulas were inserted, vecuronium ($0.1 \text{ mg}\cdot\text{kg}^{-1}$) and fentanyl ($1\text{--}2 \text{ }\mu\text{g}\cdot\text{kg}^{-1}$) were administered, the trachea was intubated, and an arterial line was inserted.

Each patient received either aprotinin or placebo (normal saline) once the intravenous and arterial lines were placed. Dose delivery of aprotinin was as described for pediatric cardiac surgical procedures (3). A test dose of aprotinin (1.4 mg in 1 ml , intravenous) was administered; if there was no evidence of allergic reaction after 3 min, a loading dose of aprotinin was administered ($240 \text{ mg}\cdot\text{m}^{-2} = 171.5 \text{ ml}\cdot\text{m}^{-2}$, intravenous) over a period of 30 min, followed by the maintenance infusion of aprotinin ($56 \text{ mg}\cdot\text{m}^{-2}\cdot\text{h}^{-1} = 40 \text{ ml}\cdot\text{m}^{-2}\cdot\text{h}^{-1}$, intravenous;

maximum, $50 \text{ ml}\cdot\text{h}^{-1}$). Anesthesia was maintained with isoflurane, air, oxygen, and fentanyl ($1\text{--}3 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$, intravenous) titrated to the desired anesthetic level. Arterial blood gases were analyzed every hour for the duration of surgery. At the completion of surgery, all patients were extubated and admitted to the intensive care unit.

Crystalloid and colloid administration during surgery was based on the clinical discretion of the anesthesiologist. Patients were transfused according to blood loss and clinical assessment, as routine. Serial measurements of hematocrit (Hct), coagulation parameters, and blood gases were taken hourly or as needed during and after surgery. Transfusions of PRBCs were administered when there was a clinical and laboratory evidence of hemodynamic instability, $\text{Hct} < 20\%$, or ongoing blood loss. Postoperative Hct was maintained at $\geq 28\%$. Other blood products were transfused based on clinical judgment and hematologic parameters. Platelets were transfused when platelet count was $\leq 10^5 \mu\text{l}^{-1}$, and fresh frozen plasma (FFP) was transfused when prothrombin time was $> 15 \text{ s}$ and partial thromboplastin time was $> 40 \text{ s}$. Cryoprecipitate was administered when the fibrinogen level was $< 120 \text{ mg}\cdot\text{dl}^{-1}$. Urine output during the intraoperative period was recorded. All patients had a drain placed at the operative site for postoperative drainage; drainage volume was recorded daily until the drain was removed, typically on the second day after surgery. Patients were followed until discharge from the hospital.

Data analysis

Data analysis was performed with statistical software (SPSS 14; IBM SPSS Statistics, Armonk, NY, USA). Power analysis was based on a retrospective review of similar cases previously admitted at our hospital; a sample size of 13 patients was required for 80% probability of detecting a 30% decrease in the amount of blood transfused. Power was calculated based on an independent sample *t*-test using a sample of patients (SAMPLE POWER 2.0; IBM Inc., Chicago, IL, USA). Data are expressed as mean $\pm$ standard deviation (SD) unless otherwise indicated. Demographic and hematologic data for the aprotinin and placebo groups were compared using *t*-test. Statistical significance was defined as $P \leq 0.05$.

Results

The aprotinin and placebo groups were similar with respect to mean age, body weight, body surface area, operative time, and length of hospital stay (Table 1). Mean volumes of total colloids received and PRBCs

Table 1 Relation between aprotinin and placebo and operative and postoperative parameters in children undergoing craniofacial surgery^a

Parameter	Aprotinin	Placebo	<i>P</i> ≤ †
Number of patients	13	13	
Age (months)	10 ± 7	11 ± 8	NS
Body weight (kg)	10 ± 2	9 ± 3	NS
Body surface area (m ²)	0.46 ± 0.14	0.41 ± 0.08	NS
Operative time (min)	350 ± 60	310 ± 80	NS
Hospital stay (days)	4 ± 1	4 ± 1	NS
Intraoperative volumes			
Crystalloid (ml)	760 ± 440	700 ± 300	NS
Crystalloid (ml·kg ⁻¹)	80 ± 40	70 ± 20	NS
Albumin (ml)	110 ± 100	120 ± 100	NS
Total colloids (ml·kg ⁻¹) ^b	70 ± 40	120 ± 80	0.05
FFP (ml)	100 ± 150	220 ± 200	NS
FFP (ml·kg ⁻¹)	10 ± 20	20 ± 20	NS
PRBCs (ml)	380 ± 90	550 ± 200	0.004
PRBCs (ml·kg ⁻¹)	40 ± 10	60 ± 20	0.05
Urine output (ml)	320 ± 200	150 ± 70	0.003
Urine output (ml·kg ⁻¹)	30 ± 10	16 ± 7	0.01
Hematocrit (%)			
Start	34 ± 3	34 ± 4	NS
Lowest	27 ± 2	25 ± 5	NS
Final	40 ± 6	38 ± 4	NS
Drain output (ml)			
Day 1	60	103	NS
Day 2	100	99	NS
Average (days 1 and 2)	80 ± 30	101 ± 3	NS
No. of patients who received FFP	5 (38)	9 (69)	NS
No. of patients who received postoperative transfusion ^c	2 (15)	3 (20)	NS
Blood urea nitrogen (mg·dl ⁻¹)			
Day 0	7 ± 3	7 ± 1	NS
Day 1	9 ± 3	8 ± 2	NS
Serum creatinine (mg·dl ⁻¹)			
Day 0	0.28 ± 0.05	0.28 ± 0.06	NS
Day 1	0.31 ± 0.06	0.3 ± 0.60	NS

FFP, fresh frozen plasma; PRBCs, packed red blood cells.

^aData are reported as mean ± sd or number (%). Day of surgery was defined as day 0.^bTotal colloids = albumin + FFP + platelets + PRBC.^cPostoperative transfusions: aprotinin group, one patient received platelets in the postanesthesia care unit, and one patient received PRBCs in the intensive care unit; placebo group, one patient received PRBCs in the postanesthesia care unit, and two patients received PRBCs (with or without FFP) in the intensive care unit during the first 24 h after surgery.†NS, not significant (*P* > 0.05).

transfused during operation were significantly less in the aprotinin group than in the placebo group. Mean urine output during surgery was significantly greater in the aprotinin group than in the placebo group;

however, mean blood urea nitrogen and serum creatinine after surgery were similar between the groups. The number of patients who received postoperative transfusion (indications: PRBCs for hemoglobin <10 mg·dl⁻¹; platelets for decreased platelet count with continued bleeding) was similar between the groups. Mean postoperative drain output was also similar between the groups.

Among the 26 study patients, three developed signs of allergic reaction (Table 2). One patient developed an anaphylactic reaction, including hypotension and bronchoconstriction, when the loading dose of aprotinin was given; the patient was treated successfully with fluid resuscitation and antihistamines, and the surgical procedure was canceled. One patient in the aprotinin group developed a skin rash, which resolved with diphenhydramine treatment; the patient remained in the study. One patient in the placebo group developed a skin rash and was withdrawn from the trial. Other complications were noted (Table 2). Follow-up at 30 days after operation showed no deaths, thrombotic complications, or renal insufficiency.

Discussion

Results of the present study showed that aprotinin significantly decreased mean PRBCs and total colloids administered during pediatric craniofacial surgery. The lowest mean intraoperative Hct was similar between the aprotinin and placebo groups, in contrast with a previous report that the lowest intraoperative Hct was lower in the placebo group than in the aprotinin group (16). In the present study, there were no deaths associated with aprotinin use. The decrease in blood transfusion

Table 2 Complications in children undergoing craniofacial surgery^aAprotinin group (complications in 1 of 13 [8%] patients)^b

Mild rash (resolved with diphenhydramine, intraoperative)

Placebo group (complications in 6 of 13 [46%] patients)

Subdural hemorrhage, fever, seizures, scrotal edema, re-intubation (single patient, no residual effect)

Cerebrospinal fluid leak at 2 months after surgery (surgically repaired)

Mild rash (patient removed from study)

Operative site drain broke (required re-operation for removal)

Jerky movements (brief postoperative myoclonus with no residual effects)

Scalp abscess

^a*N* = 26 patients (aprotinin, 13 patients; and placebo, 13 patients). Each complication listed occurred in one patient.^bAnaphylaxis, including hypotension and bronchoconstriction (patient stabilized and operation canceled, patient excluded).

requirements may benefit patients by decreasing the risk of blood borne infection, transfusion reactions, errors, and cost.

Despite the decreased amount of PRBCs and total colloids administered in the aprotinin group, mean urine output was significantly greater in the aprotinin group than in the placebo group. This could be attributed, in part, to microvascular vasodilation and improved renal function, protecting the kidneys from ischemic changes (17,18). The decreased urine output in the placebo group compared with the aprotinin group might have been associated with the greater mean amount of PRBCs transfused in the placebo group; transfusion of stored PRBCs may cause decreased renal perfusion and decreased oxygenation of the microvasculature (19), and vasoactive agents in stored blood, such as kinins, may have affected the renal microvascular circulation. Based on the above-noted outcomes, it is plausible that patients in the aprotinin group who received less stored blood might have had greater glomerular capillary perfusion, glomerular filtration, and urine output than patients in the placebo group. Perioperative mean blood urea nitrogen and creatinine were similar between the groups, and there was no renal dysfunction in any patient.

We did not determine estimated intraoperative blood loss because this parameter can be difficult to measure accurately. Potential sources of error in this parameter may occur because of dilution with saline irrigation and unmeasured blood loss from drips on the floor, surgical gowns, and gloves.

In the present study, one patient had a major allergic reaction to aprotinin that resulted in cancellation of surgery, and one patient developed a rash after receiving aprotinin. The incidence of aprotinin-related allergic reactions is reported to range from 1.2% to 7.7% (20).

The removal of aprotinin from clinical use was based on concerns of adverse outcomes in the adult population. In high-risk adults undergoing coronary artery bypass graft surgery, aprotinin has been associated with renal failure (10,21,22). However, the present study showed no increased risk of renal injury in children receiving aprotinin. Furthermore, in neonates undergoing cardiopulmonary bypass for congenital heart disease, aprotinin is associated with reduced transfusion requirements, shorter surgical closure time, less use of blood products,

and less postoperative renal dysfunction than lysine analogue drugs (tranexamic acid and ϵ -aminocaproic acid) (23). Therefore, it may be beneficial to re-evaluate the use of aprotinin in children because of the potential benefit of decreased transfusion requirements without the renal morbidity observed in adults (23). In response to criticism of the trial that resulted in the removal of aprotinin from the market, it has recently been reintroduced in the Canadian (2011) and European (2012) markets (24). Although aprotinin cannot be re-instituted for use in children until it is proven to have acceptable safety, further studies are warranted to evaluate this issue.

Limitations of the present study include small sample size, absence of long-term follow-up data, lack of a well-defined blood transfusion or fluid management protocol, and limitations in the ability to calculate blood loss accurately. The delay from completion of this study (shortly before aprotinin was removed from clinical use by the United States Food and Drug Administration) and submission for publication was a result of a change in practice of the authors (ZA, LS, MZ).

In summary, this study showed a decreased PRBC transfusion requirement in children receiving aprotinin during craniofacial surgery, without any renal toxicity or death (3,4,6). Although aprotinin is no longer available for clinical use in the USA because of adverse effects noted in adults, further study is warranted to re-evaluate the use of aprotinin in children scheduled for surgery involving potentially high blood loss.

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Conflict of interest

No conflicts of interest declared.

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