Aprotinin in pediatric neuromuscular scoliosis surgery

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Abstract Reduction of blood transfusions in patients with neuromuscular scoliosis can decrease potential complications such as immune suppression, infection, hemolytic reaction and viral transmission. Aprotinin (Trasylol[®], Bayer), an antifibrinolytic, has proven to be effective in reducing blood loss in cardiac and liver surgery, but little data exists in patients undergoing spinal fusion for neuromuscular scoliosis. The purpose of this study was to evaluate the safety and efficacy of aprotinin in pediatric neuromuscular scoliosis patients undergoing spinal fusion. The medical records of all patients undergoing initial spinal fusions for neuromuscular scoliosis between January 1999 and March 2003 were reviewed to determine demographic data, perioperative data, wound drainage and number of transfusion required. Cases were compared to a matched group of historical controls. We had 14 patients in the aprotinin group and 17 in the control group. Total blood loss in the aprotinin group was significantly lower compared to the control group (715 vs. 2,110 ml; $P = 0.007$). Significantly less blood loss occurred in the aprotinin group when blood loss per kilogram was evaluated as well (23 vs. 60 ml/kg, respectively; $P = 0.002$). Intra-operative packed red blood cell (PRBC) transfusions were also significantly lower in the aprotinin group (1.25 vs. 3.16 units; $P = 0.001$). No clinical evidence of anaphylaxis, deep vein thrombosis (DVT) or renal failure was observed in the aprotinin group. After considering the price of drug therapy, operating room time, and the cost of blood products, the use of aprotinin saved an

average of \$8,577 per patient. In our series, the use of aprotinin resulted in decreased blood loss and a decreased rate of transfusions in children with neuromuscular scoliosis undergoing extensive spinal fusion. At our institution, the use of aprotinin is safe and cost effective for patients with neuromuscular scoliosis.

Keywords Aprotinin · Antifibrinolytics · Blood loss · Neuromuscular scoliosis · Spinal fusion

Introduction

Corrective surgery for children with neuromuscular scoliosis is associated with extensive blood loss [4]. Multiple blood product transfusions may expose patients to potential complications, including immune suppression, dilutional coagulopathy, bacterial infection, viral disease transmission, anaphylaxis, systemic inflammatory response syndrome (SIRS), and pulmonary edema [14].

Several intra-operative approaches may be utilized to reduce blood loss and transfusion requirements. Proper positioning with the abdomen hanging free to minimize inferior vena cava compression, autologous blood donation, red cell scavenging devices, controlled hypotension, as well as hyperventilation have been used to decrease bleeding [1, 14]. Despite multiple efforts to decrease blood loss, neuromuscular scoliosis surgery continues to be associated with large amounts of blood loss. This may, in part, be attributed to coagulation changes observed in this population of patients [6, 12].

Aprotinin (Trasylol[®], Bayer), an antifibrinolytic, has proven to be very effective in reducing preoperative blood loss in major orthopaedic procedures, thereby minimizing the need for blood products [5, 8, 14]. Although its exact

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mechanism of action has not been completely understood, it modulates coagulation factors by inhibiting plasmin and kallikrein activity [11, 15]. In addition, it has been shown to stabilize platelet membrane receptors, thus improving platelet adherence and function [13].

Aprotinin has been extensively used in cardiothoracic surgery [2, 13] and recently in orthopaedic surgery [4, 5, 8, 12, 14]. However, despite the expanding role of aprotinin in orthopaedic surgical cases, there is limited data evaluating the role of this antifibrinolytic in scoliosis surgery in children with neuromuscular disease.

The objective of this study was to determine the effect of aprotinin on peri-operative blood loss and transfusion requirements in neuromuscular scoliosis patients undergoing extensive spinal surgery.

Materials and methods

After receiving approval from our institutional review board, the medical records of all patients who underwent scoliosis surgery between January 1999 and March 2003 were reviewed. Inclusion criteria were a neuromuscular diagnosis, first time scoliosis correctional surgery with posterior spinal instrumentation of a minimum of 11 vertebral levels, and anesthesia with controlled hypotension. Exclusion criteria were weight greater than 70 kg, underlying coagulopathy, and use of platelet modifying agents (e.g., aspirin or plavix) pre-operatively. Fourteen patients that met criteria received aprotinin. A historical control group of 17 patients with similar demographic information was identified for comparison.

Clinical data including the patient's age, weight, gender, initial Cobb angle, etiology of scoliosis, and number of segments fused were determined from chart review. Dosage of aprotinin, intra-operative blood loss, duration of surgery, prothrombin time (PT), activated partial thromboplastin time (aPTT), hematocrit and platelet counts were acquired from peri-operative records. Drain outputs were obtained until post-operative day 2. Finally, the amount of blood products transfused throughout their hospitalization for scoliosis surgery was recorded (including intra-operative transfusions). The criteria for transfusing blood products for neuromuscular patients at our institution include a hematocrit of $\leq 24\%$ or clinical signs of hemodynamic instability evidenced by hypotension, tachycardia or diminished peripheral perfusion with a hematocrit of $\leq 30\%$. Any adverse events associated with drug therapy, such as renal failure and thromboembolism, were noted.

All primary surgeons had extensive experience in neuromuscular scoliosis surgery. The patients were positioned prone with their abdomen hanging free. Anesthesia was induced intravenously and maintained with propofol

infusion and an intrathecal opioid (Duramorph® or sufentanil). Aprotinin is normally supplied as a solution which contains 10,000 KIU/ml which is equivalent to 1.4 mg/ml. In our study, the aprotinin group received 50,000 kallikrein inhibitor units (KIU) as a test dose at least half hour prior to incision. Once it was determined that there were no adverse reactions to aprotinin, patients were loaded with 20,000 KIU/kg and then a maintenance dose of 5,000 KIU kg⁻¹ h⁻¹ was administered during the operation. The mean arterial blood pressure was maintained at 55–60 mm Hg. All patients underwent normovolemic hemodilution.

Data was compared to a group of 17 historical controls which were matched based on demographic data and number of levels fused. Student's *t* tests were used to compare the two sets of data.

A cost analysis of aprotinin use was performed based on best available cost estimates of drug and blood products. At our institution, the price for each 200 ml bottle of aprotinin is \$491 (a 100 ml bottle costs \$267.50). The cost for 1 unit of PRBC is \$400, for 1 unit of platelets is \$600, and for 1 unit of fresh frozen plasma (FFP) is \$40. At our hospital, the cost for the first hour of operating room time for a spinal fusion is \$4,526. Each additional 15 min of operating room time costs \$962. These charges are based on estimates by our perioperative services financial analyst, independent of surgeon and anesthesia charges.

Results

There were 14 patients in the aprotinin group and 17 controls. The average age of the patients in the aprotinin group was 12.4 versus 14.8 years in the control group. The most common diagnoses were cerebral palsy and muscular dystrophy in both groups. The average weight, number of levels fused, pre-operative hemoglobins and platelet counts were similar in both groups (Table 1). The mean length of surgery was 314 min in the aprotinin group versus 420 min in the control group ($P = 0.019$). On average, the aprotinin group received 1,539,746 KIU

Table 1 Preoperative demographic information

Mean values	Aprotinin (<i>n</i> = 14)	Control (<i>n</i> = 17)	<i>P</i> value
Weight (kg)	35.8	38.3	0.7
Number of levels fused	14.4	15.3	0.06
Hemoglobin (g/dl)	14.4	14.0	0.4
Platelets ($\times 10^3/\mu\text{l}$)	278	268	0.7

of drug (range 4,400,000–3,936,208 KIU). This equates to an average dose of 154 ml (range 44–394 ml).

The aprotinin group had significantly less intra-operative blood loss compared to controls (715 vs. 2,110 ml, $P = 0.007$) (Fig. 1). Normalized for the length of surgery, the aprotinin group had less blood loss per min than the control group (2.24 vs. 5.15 ml/min, $P = 0.025$). The difference in blood loss per kilogram in the aprotinin group was also significantly lower (23.3 vs. 60.2 ml/kg, $P = 0.002$) (Fig. 2). The aprotinin group required less intra-operative transfusions receiving 1.25 units of PRBCs versus 3.16 units for the control group ($P = 0.001$), 0.81 units of FFP versus 2.8 units ($P = 0.001$) and zero platelet transfusions versus 1.65 units ($P = 0.05$), respectively (Fig. 3). The number of post-operative blood transfusions was lower in the aprotinin group as well (0.19 units of PRBCs versus 1.28 units, $P = 0.0003$). Drain outputs (for the first two post-operative days) for the aprotinin group was 232 versus 524 ml in the control group ($P = 0.005$).

There was no clinical evidence of anaphylaxis, deep vein thrombosis (DVT), renal failure or myocardial ischemia in either group. One patient in the control group had a post-operative wound infection and underwent surgical debridement and subsequent antibiotic treatment.

After considering both the price of drug therapy and the cost of blood products, the use of aprotinin saved an average of \$1,778.60 per patient (Table 2). If one factors in the additional cost of prolonged surgical time, the average savings was \$8,576.74 per patient.

Discussion

Spinal deformity correction in neuromuscular patients can lead to significant blood loss and need for blood transfusion. Meert et al. reported that neuromuscular scoliosis

Fig. 1 Total blood loss

Fig. 2 Blood loss adjusted for weight of the patient

patients undergoing spinal surgery are more likely to have excessive blood loss requiring blood transfusion due to lower body weight, greater number of instrumented levels and decreased ability to donate autologous blood before surgery [6, 12]. Despite modern methods of minimizing blood loss, excessive blood loss in neuromuscular scoliosis is still a concern.

The complete mechanism of action of aprotinin has yet to be elucidated. However, it is believed that aprotinin inhibits several serine proteases, specifically trypsin, chymotrypsin and plasmin at a plasma concentration of about 125 KIU/ml (low dose), thus slowing fibrinolysis [11]. At plasma concentrations greater than 300 KIU/ml (high dose), aprotinin also becomes an inhibitor of kallikrein, and therefore inhibits the formation of factor XIIa [7]. As a result, at high dose both the intrinsic coagulation cascade and fibrinolysis are inhibited.

Several studies have previously shown that aprotinin is effective in decreasing surgical blood loss in various fields of orthopaedic surgery [1, 14]. A report by Cole et al. [1] demonstrated a favorable outcome in pediatric spinal surgery with the use of aprotinin: on average, the aprotinin group required only 1.1 versus 2.2 units of blood for the placebo group. Urban et al. [14] compared blood loss in adult spinal reconstruction patients receiving either aprotinin or Amicar to a control group. These investigators found that although both groups of patients had decreased surgical blood loss, the aprotinin group had significantly less blood loss than the Amicar and the control group ($P < 0.05$). Our study supports the results of these previous studies: intra-operative blood loss, post-operative blood loss, and rate of blood transfusions were all significantly less in our patients receiving aprotinin compared to our controls.

Concerns exist about the safety of aprotinin since the drug has been associated with an increased risk of renal failure and cardiovascular events in patients undergoing

Fig. 3 Peri-operative blood products transfused **Table 2** Cost analysis of aprotinin use

Mean values	Aprotinin (<i>n</i> = 14)	Aprotinin costs	Control (<i>n</i> = 17)	Control costs
Intraop PRBCs (units)	1.25	\$500	3.16	\$1,264
Postop PRBCs (units)	0.19	\$76	1.28	\$512
Platelets (6 units)	0	\$0	1.65	\$990
FFP (units)	0.81	\$32.40	2.80	\$112
Drug (ml)	154	\$491	0	\$0
OR time (min)	314	\$20,815.86	420	\$27,614.00
Total cost (not incl OR time)		\$1,099.40		\$2,878.00
Total cost (incl OR time)		\$21,915.26		\$30,492.00

cardiac surgery [10]. In fact, distribution of aprotinin was temporarily suspended in the United States by the Food and Drug Administration (FDA) on November 5, 2007 based on preliminary safety results from a Canadian heart study [3]. In a systematic review of orthopaedic clinical trials (spine, joint replacement and musculoskeletal oncology) with aprotinin, Kokoszka et al. [9] evaluated 15 randomized prospective studies with level-I and -II evidence. His review demonstrated that the use of aprotinin decreased blood loss significantly and did not increase the risk for renal failure or DVT. Additional reports have not demonstrated an increase in DVT formation in patients receiving aprotinin during spinal surgery, although the numbers are too small to prove that a difference is not present [1, 14]. According to Cole et al. [1] venous duplex studies of the lower limbs of pediatric neuromuscular scoliosis patients, revealed no thrombus formation in aprotinin treated patients and 13% in the control group, although this was

not statistically significant. In our investigation, no patient in either group developed signs of DVT, pulmonary embolus, myocardial ischemia or renal failure. The use of aprotinin may be safer in children compared to adult cardiac patients, however, more research needs to be done to support this hypothesis.

Since aprotinin is a polypeptide procured from bovine lung, it carries an inherent risk of an allergic reaction [2]. The risk of allergic reaction is higher with prior sensitization. According to Dietrich et al. [2], patients undergoing cardiac surgery, who received aprotinin twice within 6 months had 5% risk of anaphylaxis. The risk was significantly attenuated if the second exposure was greater than 6 months after the first. Therefore, the current recommendation is to deliver a test dose half-hour prior to the start of the surgery. Although we had no allergic or anaphylactic reactions in our series, we believe that multiple exposures to aprotinin should be avoided. Since

neuromuscular scoliosis patients may have to undergo multiple operations during their lifetime, the use of aprotinin should be utilized during the procedure that carries the highest risk of bleeding.

A potential confounding variable in our study was the duration of surgery: the mean length of surgery in our aprotinin group was significantly shorter than the surgical time of our control group. One could argue that our differences in intraoperative blood loss may be explained by the increased operative time in the control group. Alternatively, one could argue that the use of aprotinin resulted in less blood loss, improved visualization, and faster surgical times since the number of levels fused in both groups was not significantly different (Table 1). To resolve this, we normalized for surgical time by comparing EBL/min between the two groups: the mean blood loss per min in the aprotinin group (2.24 ml/min) was significantly less than that in the control group (5.15 ml/min) ($P = 0.025$). Therefore, we believe that the decreased blood loss from aprotinin use is a cause rather than a result of the shorter operative times.

The cost of aprotinin has been a concern for hospital administrators. After considering both the price of drug therapy and the cost of blood products at our institution, the use of aprotinin saved an average of \$1,778.60 per patient. If one considers the additional cost incurred by increased surgical time, the savings reached nearly \$8,577 per patient. Stated differently, for aprotinin to be cost-effective at our institution, we need only avoid transfusing 1.25 units of blood or save 7.7 min of surgical time per 200 ml vial of aprotinin used. Our results more than exceeded this break-even point.

Based on our study, the use of aprotinin resulted in decreased blood loss and a decreased rate of transfusions in children with neuromuscular scoliosis undergoing extensive spinal fusion. In spite of recent safety concerns, we had no cases of DVT, pulmonary embolus, myocardial ischemia or renal failure in our treatment group. At our institution, the use of aprotinin is cost effective for patients with neuromuscular scoliosis.

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