Pro-Con Debate:
Aprotinin Should Routinely be Used in Infants and Children Undergoing Complex Open Heart Surgery
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Introduction

Aprotinin is a nonspecific serine proteinase inhibitor which is isolated from the bovine lung. It was first introduced into clinical use in 1953 as a treatment of acute pancreatitis. (1) In 1983, Kirklin (2) postulated that the contact of blood with the foreign surface of the oxygenator on the cardiopulmonary bypass (CPB) circuit initiated a cascade of events triggering an inflammatory response leading to "post perfusion syndrome". With knowledge of aprotinin's ability to inhibit plasmin kallikrein he further postulated that aprotinin would block the inflammatory response after CPB. Uncontrolled pilot studies on patients who received aprotinin undergoing coronary artery bypass grafts on CPB revealed one striking feature; the patients did not bleed post bypass. This led to further investigation evaluating the use of aprotinin as a measure to decrease post CPB transfusion requirements. CPB can lead to postoperative bleeding by several mechanisms. In addition to the effects of hemodilution and hypothermia, CPB activates coagulation, fibrinolytic and inflammatory pathways and impairs platelet function. (3)In neonates, the potential for bleeding is further increased in by the large ratio of pump prime volume to the patient's blood volume, causing greater hemodilution. Aprotinin is believed to prevent bleeding during and after bypass by three different mechanisms. Upon contact with the CPB circuit, tissue and plasma kallikrein is split to kinin. Kinin transforms plasminogen to plasmin and plasmin activates neutrophils. Aprotinin inhibits contact activation by inhibiting tissue and plasma kallikrein release. (4) Secondly, aprotinin demonstrates antifibrinolytic

activity by increasing plasma fibrinogen and inhibiting fibrinolysis secondary to thrombin induced intravascular coagulation. (5) Finally, aprotinin has been shown to decreases platelet dysfunction and platelet aggregation after CPB.(6)

Pediatric Usage

Post-operative bleeding in a child undergoing complex congenital heart repair has long been a challenge to the pediatric cardiac anesthesiologist. Children with complex congenital heart defects often require multiple surgical repairs with the need for repeated sternotomies. Additionally, excessive hemodilution of clotting factors in the neonate, long CPB duration required for many complex pediatric cardiac surgical procedures, and/or institution of deep hypothermic circulatory arrest, all contribute to bleeding post bypass. Long suture lines along the great vessels in operations such as the Norwood procedure or the Arterial Switch may also contribute to post bypass bleeding. In 1987, Roysten et.al. (7) conducted the first randomized prospective study, comparing two groups of adults undergoing repeat median sternotomy for open-heart surgery. The authors reported an eightfold reduction of red blood cell (RBC) transfusions in the group receiving aprotinin when compared to a placebo.

In a randomized double blind study, D'Errico et.al.(8) compared the efficacy of large dose aprotinin, small dose aprotinin and placebo in reducing transfusion requirements in children undergoing repeat open heart surgery. The authors concluded that the use of aprotinin decreased the number of units of banked blood components transfused in the first 24 hours post operatively. In addition, time spent in the operating room was shorter in both aprotinin groups due to decreased time to chest wall closure. The cost savings resulting from the reduction of blood transfused shorter OR time significantly reduced overall patient charges in both aprotinin groups. In a similar study, Miller et.al. (9) found aprotinin was effective in decreasing blood product exposure, shortened skin closer times, shortened durations in the intensive care unit and overall hospital stay, with subsequent reduction in hospital charges. Finally, in 2006, Arnold and colleagues (10) performed a meta-analysis of randomized controlled trials of aprotinin involving children undergoing corrective or palliative cardiac surgery with CPB. This meta- analysis revealed aprotinin reduced the proportion of children who received RBC or whole blood transfusions during cardiac surgery by 33%. However, aprotinin had no significant effect on the volume of blood transfused or post-operative chest tube drainage.

Aprotinin is one of several antifibrinolytic drugs shown to diminish post CPB bleeding. The lysine analogs aminocaproic acid and tranexamic acid have also shown to be effective. Lysine analogs inhibit plasminogen activation to plasmin, thereby inhibiting contact activation during CPB and fibrinolysis. A study in 2005 by Bulutcu, et.al.(11) compared four groups of children undergoing cardiac surgery on CPB for cyanotic heart disease. The study sample received aprotinin alone, tranexamic acid alone, or a combination of aprotinin and tranexamic acid. The placebo group had significantly greater blood loss, with more RBC and fresh frozen plasma (FFP) transfused when compared to the other three groups. There was no difference between the aprotinin and tranexamic acid groups, alone or in combination. Although studies have shown that these lysine analogs can be as effective as aprotinin in preventing post cardiopulmonary bypass bleeding in both adults and children, aprotinin may have advantages lysine analogs do not exhibit. Aprotinin may contribute to enhance hemodynamic stability in the postoperative period by attenuating the intensity of the inflammatory response to CPB. It may also attenuate the increased peripheral vascular permeability and fibrinolysis which occurs as a result of CPB, and contribute to postoperative hemodynamic stability.(12)

McDonough et.al. reviewed the use of aprotinin in children undergoing cardiopulmonary bypass for congenital cardiac surgery from 1993 to 2000(13). The authors concluded that there was some evidence that aprotinin attenuated the inflammatory response in neonates, which led to a reduction in ventilator support and earlier extubation. A meta-analysis by Murkinin in 2001 (14) of prospective randomized placebo controlled clinical trials in North America of adults undergoing CABG surgery found that aprotinin may have anti-inflammatory effects similar to that of methylprednisolone in decreasing systemic inflammatory responses. In addition, Murkinin noted a significant decrease in the incidence of stroke in adults who receive full dose aprotinin versus placebo, leading the author to conclude that aprotinin may have a cerebroprotective effect.

Aprotinin is also noted to be relatively safe when administered in the pediatric population. Jaquiss et.al. (15) noted an overall incidence of allergic reactions to aprotinin during pediatric cardiac surgery to be 1.6%. First time exposure risk was 0.7%, with the risk increasing with the number of exposures. Patients who developed reactions in this study showed no signs of hemodynamic, respiratory, renal or neurologic complications attributed to an aprotinin reaction.

With its ability to decrease blood loss and transfusions after CPB, decreasing OR time, ICU and hospital stays, hospital costs, and potential reduction in ventilator support and earlier extubation, reduction of neurologic deficits with a low incidence of allergic reactions, aprotinin seemed to be the ideal drug for children with complex congential heart disease undergoing CPB.

The Controversy

In 2006, Mangano et.al. (16) published an observational study involving 4374 adults undergoing CABG on CPB, comparing outcomes of patients receiving placebo, aprotinin, aminocaproic acid and tranexamic acid individually. The authors concluded patients who received aprotinin were not only at twice the risk of renal failure requiring dialysis, they carried a 55% increased risk of myocardial infarction or heart failure and a 181% increased of the risk of stroke when compared to the placebo or lysine analogs. The authors noted that all antifibrinolytic agents reduced blood loss to the same extent. Around the same time, another observational study was published by Karkouti et.al. (17) using propensity scoring to compare tranexamic acid with aprotinin in adults undergoing cardiac surgery requiring CPB. The results of this study demonstrated a higher prevalence of renal dysfunction post bypass in the aprotinin group compared to the tranexamic acid group. Renal failure became even more pronounced when pre-existing renal disease was present. Again, the authors noted no difference in post operative bleeding between the two groups of patients. These two studies led the FDA to release a public health advisory, recommending careful monitoring of patients who receive aprotinin for renal, cardiac and central nervous system toxicity(18). The advisory further suggested that aprotinin be limited to patients "where the clinical benefit of reduced blood loss is essential to medical management of the patient and outweighs potential risk." The FDA however did note that both studies were observational, and limited by non-randomized assignment of patients where the treatment was chosen by their physician as part of standard medical care. The FDA concluded that the patients who had received aprotinin "may have been at a higher risk to begin with for these serious adverse events compared to patients receiving no treatment or treatment with another drug intended to decrease bleeding."

In an editorial, in December 2006, (19) Body et.al. noted that while Mangano and Karkouti had intensified discussions regarding the safety of aprotinin, their conclusions should be questioned because the studies were observational with uncontrolled decisions about which

antifibrinolytic agent was used. The authors referenced conflicting data presented in 2004 by Sedrakyan et.al. (20) with regards to the effect of aprotinin on clinical outcomes following CABG . Sedrakyan performed a meta-analysis of 35 randomized clinical trials from 1988-2001 in patients undergoing CABG who received aprotinin or placebo control. Data from this meta-analysis confirmed aprotinin reduced transfusion requirements relative to placebo but patients in both groups showed no differences in mortality, myocardial infraction or renal failure. In addition, there was an associated reduced risk of stroke in the patients who received aprotinin. To date, no association of poor clinical outcomes following aprotinin administration in children has been reported.

Summary

There is a large amount of evidence in the literature that demonstrates the benefits of aprotinin in children undergoing repeat median sternotomy for open-heart surgery. These benefits include a decrease in the amount of blood lost and transfused, shorter OR, ICU and hospital stays, and decreased cost. Furthermore, there is evidence that suggests that decrease the inflammatory response to surgery and CPB leasing to improved outcomes including more cardiovascular stability, requirement for fewer inotropes, reduction in ventilator support, earlier extubation, and reduction of neurologic deficits. While the lysine analogs may be as effective at decreasing blood loss after CPB, they do not demonstrate the additional beneficial anti-inflammatory effects of aprotinin. Further study on this high risk pediatric population with regards to the use of aprotinin is warranted and encouraged. Prospective randomized studies evaluating outcomes of the various antifibrinolytic therapies available will allow us to rationally decide the cost effectiveness of these drugs and their impact on patient outcomes. Until such data become available, the continued use of aprotinin for repeat or complex open heart surgery in children is well supported by existing evidence.

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