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The Use of Aprotinin in Pediatric Patients: A Review

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Abstract: This literature review includes all reports from 1993 to 2000 concerning the use of aprotinin in children undergoing cardiopulmonary bypass (CPB) for congenital cardiac surgery. This review examined a nonhomogeneous pediatric patient population ranging from neonates to children up to 18 years of age, presenting many challenges. There have been publications advocating its use and those that have found no significant difference between the control group and those receiving aprotinin. The literature suggests that there is improvement in post-operative blood loss in pediatric patients undergoing redo cardiac surgery, but no significant difference in blood loss in those undergoing primary surgical repair. There is some evidence in the neonatal study groups that with high-dose aprotinin the inflammatory response is attenuated, leading to a reduction in inotropic support, earlier extubation, a tendency toward reduced post- operative blood loss and a reduced hospital stay. In most of the studies, the actual dose of aprotinin has varied with "high-dose aprotinin" demonstrating the most significant differences. To achieve an adequate dose of aprotinin, the dose must be calculated on either the patient's weight or their body surface area, and must include an appropriate dose in the prime of the cardiopulmonary bypass circuit, to achieve a plasma concentration between 200 KIU/mL to 400 KIU/mL. The incidence of anaphylactic reactions reported in the literature range from 0.3 to 0.6%. To date, there is no evidence to indicate any contraindication related to the use of aprotinin in the pediatric population. **Keywords:** pediatric, aprotinin, cardiopulmonary bypass, hemostasis, inflammatory system. *JECT. 2003;35:346–349*

The pediatric population undergoing cardiopulmonary bypass (CPB) is a very diverse group, ranging from neonates to children up to 18 years of age who may have repeated surgical interventions over their lifetimes, for palliative and/or corrective surgery. Over half the children undergoing CPB in North America are younger than 1 year of age, with neonates comprising approximately 36% of this group (1). The clotting mechanisms are incompletely developed in infants, which is exacerbated with hemodilution and long CPB times, leading to an increased inflammatory reaction and capillary leak syndrome. Children undergoing repeated cardiac procedures are exposed to more blood products and are at greater risk of post-operative blood loss caused by the friability of tissues, long suture lines, synthetic materials, and prolonged CPB times. Aprotinin has been studied by various groups measuring the efficacy of the drug in the pediatric population to determine reduction in post-operative bleeding, reduce exposures to blood products, and the inflammatory response.

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CLINICAL STUDIES

The first pediatric study was reported by Herynkopf and associates in 1994 (2). In this double-blind controlled study, a low-dose aprotinin regimen was shown to reduce post-operative transfusion requirements and increased the number of patients requiring no blood transfusion. The patients included in this study ranged in weight from 5 to 60 kg, with no information about priming volume or surgical procedures.

In 1995 Penkoske and associates (3) reported a study of 80 patients with a historical control group of 55, that a high-dose aprotinin regimen reduced chest drainage, closure time, and blood unit exposure. D'Errico and coworkers in 1996 (4) performed a randomized controlled trial (RCT) comparing the effects of high and low aprotinin doses and placebo in selected patients undergoing re-operative open-heart surgical procedures. Results demonstrated that aprotinin reduced blood transfusion requirements, decreased operating room time, reduced hospital stay, and hospital charges. The study (designed to include 80 patients) was prematurely terminated after 61 patients because of a significant reduction in blood transfusions with the use of aprotinin. In this study, the surgeon's subjective assessment of the dryness of the surgical field was considered an important factor, although it is difficult to subject to statistical analysis.

Davies and colleagues in 1997 (5) reported on an RCT of 42 patients. They found that high-dose aprotinin decreased fibrinolytic platelet activation, but had no influence on chest drainage, hemoglobin loss, or transfusion requirements. This study also included the surgeon's assessment of the surgical field.

Tweddell and colleagues (6) found that aprotinin decreased thoracic drainage in single ventricle palliation. A later report, published as an abstract, on a retrospective study also found that aprotinin improved arterial saturation in patients undergoing the Fontan operation, decreased the transpulmonary gradient reflecting on the effect of the inflammatory response, rather than that of hemostasis.

An RCT in 34 infants by Wipperman and associates (7) demonstrated that the high- dose aprotinin group required less inotropic support in the 48 hours following CPB, suggesting a superior recovery of myocardial function. In this study, there was no mention of hemostasis or blood loss in either group.

APROTININ DOSAGE REGIMENS

A decrease in blood loss may be related to the fact that platelets remain unstimulated, thus maintaining their viability during CPB, with an adequate dose of aprotinin. Aprotinin, a protease inhibitor, has shown its capacity to block fibrinolysis in low doses and to attenuate contact activation in higher doses; that is, plasma levels >200 kallikrein inhibiting units (KIU).

A prospective randomized study by Dietrich et al. studied 60 children weighing less than 10 kg undergoing cardiac surgery. They were assigned to one of three groups; low-dose, high-dose, and control (8). Samples that were taken 60 minutes on CPB, showed fibrinolysis levels that were significantly lower in the two aprotinin groups, the lowest concentrations in the high-dose aprotinin group; however, there was only a tendency toward reduction in coagulation activation. The lack of effect on coagulation may be caused by the lower plasma concentrations of aprotinin measured in this pediatric study. Neither group had concentrations greater than 100 KIU/mL, half that reached with high- dose aprotinin treatment in adults (a level suggested as necessary to inhibit kallikrein and contact-phase activation). This is most likely because of the dilution effect created by the large ratio of pump prime to the patient's circulating volume. The dose of aprotinin administered to pediatric patients must take into consideration this larger ratio of circuit prime to the patient's circulating blood volume, so that the aprotinin dose should be calculated to include the volume of the prime. The dose calculation for pediatrics as reported by Mossinger and Dietrich (9) uses the patient's weight and the priming volume of the CPB circuit. This study consists of three groups. The high-dose group received 30,000 KIU/kg (4.2 mg/kg) of aprotinin after induction of anesthesia and an additional bolus of 30,000 KIU/kg (4.2 mg/kg) into the pump prime. In their low-dose group, both the initial bolus and the pump prime dose of aprotinin were halved to 15,000 KIU/kg (2.1 mg/kg). Group three received the high dose with an additional bolus of aprotinin to the pump prime, a total of 500,000 KIU/kg (70 mg/kg) in the prime. No continuous infusion was given during the procedure. The plasma levels of aprotinin in groups one and two were lower than 200 KIU/mL (0.03 mg/mL) a value usually reached in adults with high- dose aprotinin. Group three patients had levels greater than 200 KIU/mL (0.03 mg/mL) throughout the procedure. These findings lead to a second study in patients under 10kg, who were given the high-dose bolus before CPB, but with a total of at least 500,000 KIU (70 mg) added to the prime. This dose was based on the dilution effect of their pump prime volume of at least 500 mL that produced peak plasma concentrations greater than 400 KIU/mL (0.06 mg/mL), and the levels remained elevated above those found in adults throughout the operation. Analysis showed a significant reduction in thrombin generation with the higher dose, as compared to the initial three groups, and the suppression of fibrinolysis demonstrated a dose-related effect, with further attenuation at the highest dose.

A second dosing regime as described by Davies et al.utilized body surface area for their calculations (10). Children with a body surface area of $1.16m^2$ or less were administered aprotinin after induction of anesthesia. A loading dose of 140/KIU/m^2 was given as an intravenous bolus over 20 min, with a pump priming dose of 240 KIU/m^2 and a continuous central venous infusion of 56 KIU/m^2/h from the onset of surgery until skin closure. For children with a body surface area of more than $1.16m^2$, aprotinin was administered as a loading dose of 250 KIU/m^2 given as an intravenous bolus over 20 min, with a pump priming dose of 280 KIU/m^2, and a continuous central venous infusion of 70 KIU/m^2/h from the onset of surgery to skin closure. This study showed no beneficial clinical effects of the use of aprotinin in routine pediatric cardiac operations; however, when blood loss was assessed, a clinically significant reduction was seen in those patients receiving aprotinin.

Mossinger et al. (11) noted that a comparison between the actual amounts of aprotinin calculated either from the child's surface area or from weight are very dependent on the age of the child, the discrepancy being highest in the youngest patients. The ratio of the surface area dose/weight dose being 2.4 to 1 in the newborn; this discrepancy does not become insignificant until adolescence. The use of a weight-based dose is acceptable, provided the concentration of aprotinin in the pump prime remains high.

A test dose is administered before administration of the loading dose. The loading dose was calculated on the basis

of body surface area 240 mg/m^2 and given intravenously. The same dose was added to the CPB prime. A continual infusion 56 mg/m^{2}h was administered throughout surgery. The low-dose regimen was 50% that of the high dose.

These are two examples of varying dose regimens that demonstrate little consistency in current clinical practice. Aprotinin plasma concentration levels should be measured to assess adequate circulating levels in the pediatric patient.

ADVERSE REACTIONS

There is an incidence of anaphylactic reactions that are more likely to be seen with high-dose regimens and in patients with previous exposures. Weipert and colleagues reported that in 50% of patients with high-dose aprotinin treatment (1 g) G antibodies to aprotinin developed within 3 months after operation. Two years following exposure, 50% of all patients still showed measurable levels of immunoglobulin (1 g) G antibodies against aprotinin (12). These antibodies against aprotinin are responsible for the immediate type allergic reaction that has been described. To date, a clinically useful reliable and predictable test system does not exist. Dietrich et al. report a drug reaction in pediatric patients of 2.8% (7 of 248) on re-exposure in less than 180 days (59% were children) (13). This number differs from those of other reports: Schulze and associates reported an incidence of 5.8% for allergic reactions after re-exposure (14). Diefenbach and associates reported an incidence of 6% (15). Dietrich recommends giving all patients a test dose (10,000 KIU) delaying the bolus injection until just before initiation of bypass, using H_1/H_2 (clemastine 0.03 mg/kg, cimetidine 5 mg/kg) blockade with all repeat exposures and avoiding re-exposure within 6 months of the previous drug administration.

There is controversy as to when to give the initial aprotinin test dose. Should it be given as soon as the patient is anesthetized before the incision to attenuate the inflammatory response, or to wait until the patient has been cannulated so that CPB can be initiated if there was an anaphylactic reaction? As suggested by Dietrich et al., a test dose must be given befoe any aprotinin infusion (13).

Inflammatory Response

With an adequate dose of aprotinin, platelet function is preserved and, in turn, reduces post-operative blood loss. Aprotinin seems to have a significant neutralizing effect on the inflammatory reaction to CPB in children, which may be more important. Wippermann et al. (16) in an RCT of 34 infants studied a high-dose aprotinin regime. The control group required more post-operative transfusion and larger volumes of fluids and colloids than the aprotinin group; however, this was not significantly different. Of interest, the high-dose aprotinin patients required less inotropic support in the first 48 h following CPB.

Tweddell et al. (6) demonstrated that there was a decrease in pulmonary vascular resistance and an increase in systemic arterial saturation in patients undergoing staged repair for hypoplastic left heart syndrome. More studies must be done in this area to understand the potential anti-inflammatory properties of aprotinin.

ULTRAFILTRATION

In most pediatric cardiac centers, hemofiltration and modified ultrafiltration is utilized during and following CPB. There has been some discussion as to whether aprotinin is removed by ultrafiltration. Earlier reports suggested that the drug was removed, based on its sieving coefficient of 1.0 (17). A study by Gail and associates demonstrated that hemofiltration during CPB did not significantly alter serum aprotinin levels in patients receiving aprotinin. The study randomized patients to half-Hammersmith or full-Hammersmith dosing regimens, hemofiltration versus no hemofiltration.(18). Plasma levels of aprotininin fell during CPB in all patients, but there was no significant difference between filtered and nonfiltered patients in similar dosing groups. This study suggests that hemofiltration does not remove significant amounts of aprotinin during CPB. One measurement that was taken of the ultrafiltrate showed that the serum plasma concentration of aprotinin was slightly less than that found in the ultrafiltrate.

CONCLUSION

This literature review includes includes reports from 1993 to 2000 concerning the use of aprotinin in children undergoing CPB for cardiac surgery. These clinical studies are difficult to interperatate because of the nonhomogeneous patient population, variations in surgical procedures, dose regimens, age, techniques, and patient management. As well, there are few randomized control trials that include significant study subjects with standard measured outcomes.

The ability of aprotinin to inhibit fibrinolysis, reduce contact activation, and thrombin generation while preserving hemostasis has been achieved with adequate dosing. High-dose aprotinin has been associated with a significant reduction in blood loss and transfusion requirements in neonates undergoing complex cardiac surgery. Carrel noted that reoperations in the pediatric population have shown to reduce post-operative blood loss, blood product donor exposures, and patient charges when compared to the control group (19). The study by Miller et al. demonstrated a reduction in patient charges in the pedi-

atric groups undergoing reoperation, because of a reduction of coagulation product transfusions, OR time, postoperative ICU, and over-all hospital stay with high-dose aprotinin (20).

Boldt et al., in their comparison study of children over 10 kg undergoing primary surgical repair with high-dose aprotinin, in two studies, could find no difference between the groups, therefore not recommending routine aprotinin use for children older than 1 year undergoing primary cardiac surgery (21, 22).

The incidence of anaphylaxis has been reported in 2.8 to 6% in various re-exposed patient study groups. If adequate precautions are taken (i.e., a test dose and the CPB circuit ready for use), there is no contraindication for the use of aprotinin in the pediatric population.

Royston suggests that aprotinin (as well as other serine protease inhibitors) could reduce both cellular and immune inflammatory reactions (23). Aprotinin has been shown to be beneficial for neonates and children undergoing redo cardiac surgery with minimal adverse effects. A moderate reduction in blood loss and blood product transfusions was demonstrated in most studies and was statistically significant in those studies with larger patient groups.

There is a need for further studies in the pediatric population to establish an adequate dosage regime and to investigate aprotinin's role in attenuating the inflammatory response. Most of these reviewed publications indicate that a high-dose protocol is required for optimizing hemostasis and attenuating the inflammatory system.

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