Heparin Reversal in Children Following Cardiopulmonary Bypass

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Abstract

Inadequate or excessive doses of heparin and protamine during cardiopulmonary bypass (CPB) are associated with both theoretical and well-documented real complications. A simple and safe method of determining optimal doses of heparin and protamine has its place in pediatric cardiac surgery.

Use of a heparin dose-activated clotting time (ACT) response curve method was compared to an older arbitrarily fixed dose method of anticoagulation management for CPB in 85 infants and children. All patients were initially heparinized with 3 mg/kg heparin. In group 1, a two point dose-response curve, generated prior to CPB, was used to determine doses of incremental heparin during CPB and protamine following CPB. In group 2, fixed doses of incremental heparin (1.5 mg/kg each hr of CPB) and protamine (2:1 ratio of protamine to initial heparin dose) were administered.

Age, weight, and duration of CPB were similar in each group. Adequate maintenance of anticoagulation with heparin and its reversal with protamine were demonstrated by ACTs in each patient. Group 1 patients required 28% less heparin ($P < 0.01$) and 39% less protamine ($P < 0.01$) than did group 2 patients. The authors conclude that the dose-response curve provides a simple and reliable method to optimize anticoagulation management during CPB in pediatric patients.

Materials and Methods

Eighty-five infants and children requiring CPB for repair of a variety of congenital heart defects were prospectively studied. Their ages and weights are displayed in the Table.

The Hemochron• was used to monitor ACT in all patients using 2.0 ml whole blood samples obtained through radial artery catheters. In all patients, control ACT was determined. Then 3 mg/kg of beef lung was administered through a central venous catheter. Five minutes later, ACT was repeated prior to CPB. 2500 units of heparin per unit of blood were added to the extracorporeal priming volume.

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a International Technidyne, Edison, NJ 08818
b LyphoMed, Inc., Melrose Park, IL 60101
Table 1
Anticoagulation Management During Pediatric Cardiopulmonary Bypass Using a Heparin Dose-ACT Response Curve (Group 1) and an Arbitrary Dose Protocol (Group 2)

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>44</td>
<td>41</td>
</tr>
<tr>
<td>Age (mo)</td>
<td>36 ± 39</td>
<td>46 ± 40</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>13 ± 11</td>
<td>14 ± 8</td>
</tr>
<tr>
<td>Control ACT (sec)*</td>
<td>113 ± 14</td>
<td>121 ± 12</td>
</tr>
<tr>
<td>Initial post-heparin ACT (sec)</td>
<td>537 ± 164</td>
<td>653 ± 177</td>
</tr>
<tr>
<td>Duration of CPB (min)</td>
<td>79 ± 46</td>
<td>91 ± 61</td>
</tr>
<tr>
<td>Total heparin dose (mg/kg)*</td>
<td>7.5 ± 1.7</td>
<td>10.4 ± 4.6</td>
</tr>
<tr>
<td>ACT pre-protamine (sec)*</td>
<td>478 ± 131</td>
<td>817 ± 498</td>
</tr>
<tr>
<td>Protamine dose (mg/kg)*</td>
<td>3.7 ± 1.5</td>
<td>6.1 ± 1.1</td>
</tr>
<tr>
<td>ACT post-protamine (sec)*</td>
<td>111 ± 10</td>
<td>125 ± 14</td>
</tr>
<tr>
<td>ACT post-protamine (%)</td>
<td>98 ± 14</td>
<td>104 ± 18</td>
</tr>
</tbody>
</table>

Values are means S.D.
ACT = activated clotting time
CPB = cardiopulmonary bypass
*Groups are significantly different from each other (P<0.01)

In Group 1 (44 patients), a heparin dose-ACT response curve was then constructed. ACT was monitored frequently throughout CPB. When ACT decreased below 480 sec, an incremental dose of heparin, calculated as described by Cohen1 from the dose-response curve, was administered. Following cessation of CPB, the protamine dose was calculated as described by Bull2 using the dose-response curve: the protamine dose in mg/kg is 1.3 times the indicated heparin level in mg/kg. ACT was again determined 10 min following protamine administration.

In Group 2 (41 patients), ACT was monitored throughout CPB, but a dose-response curve was not constructed. An incremental heparin dose of 1.5 mg/kg was administered every 60 min. or when ACT decreased below 480 sec. during CPB. Following cessation of CPB, 6 mg/kg of protamine was administered (i.e., a protamine: initial heparin dose ratio of 2:1). ACT was again determined 10 min following protamine administration.

The following data from each group was subjected to statistical analysis by unpaired t-test: age, weight, control ACT, ACT 5 min following initial heparin, duration of CPB, total heparin dose, ACT prior to protamine, protamine dose, and ACT 10 min following protamine. P less than 0.05 was considered statistically significant.

Discussion

Use of heparin dose-ACT response curves during CPB has been shown to optimize heparin and protamine therapy for each patient.2,3 Such individual management has real benefits: the disastrous complications of clot formation during CPB due to inadequate heparin dosage can be avoided, as can the theoretical complications of heparin overdosage, such as difficult reversal or heparin rebound. A decrease in total heparin dose during CPB has been demonstrated with ACT use.1

Likewise, individualization of protamine dose leads to adequate heparin reversal and avoids excessive protamine administration. Thus, the recognized complications and side effects associated with protamine, including systemic vasodilation,4 pulmonary vasoconstriction,5 myocardial depression,6 hypersensitivity,7 and platelet dysfunction,8-9 may be minimized. Experience with ACT monitoring in children indicates that both heparin and protamine requirements are higher than in adults,10 underscoring the need for individualized therapy.

Our experience indicates that the use of the pre-CPB dose-response curve is easily applied to children. The technique described by Cohen1 is simple, does not require reconstruction of the curve during CPB, and provides valid information for calculation of doses of incremental heparin and protamine.

Our results demonstrate that the advantages of using the dose-response method can be realized in infants and children. As has been observed in adults,1 a wide range of ACT was observed following initial heparinization of our patients, indicating the importance of individualized therapy guided by the dose-response curve.

Using the dose-response curve, adequate anticoagulation was maintained throughout CPB with a total dose of heparin that was significantly lower than that used with the older protocol. Prior to reversal with protamine, patients in the dose-response group had a significantly lower, but still safe, ACT than did patients in the old protocol group.

Adequate reversal of heparin with protamine was achieved in both groups. However, significantly less protamine was used in the dose-response group. This may be advantageous in view of the known complications associated with protamine.4-9

We conclude that use of a two point heparin dose-ACT response curve generated prior to CPB provides optimal management of heparin and protamine therapy in infants and children.

Questions from the Audience

**Question—Sandra Pfefferkorn:** I believe Richard said earlier that you use membrane oxygenators on all of your pediatric patients. Do all of these, in this protocol, use membranes?

**Answer:** No. This study was over a three year period and some of these patients reflect a membrane oxygenator and some reflect a bubbler oxygenator. Group 2, the protocol method, or the old method, reflects the majority of bubbler oxygenators.

**Question—Sandra Pfefferkorn:** Some people across the country have reported, maybe not in the literature, that there is some increase in the need for heparin, or larger doses of heparin in patients using membrane oxygenators, as well as the use of a hemoconcentrator with hollow fibers. I was just wondering if that could have affected your study in any way.

**Answer—Hydrick:** No, we really haven’t seen that. We’re using the same heparin management that we did with the bubbler oxygenator and with the membrane oxygenator, and the safe coagulation times. There seems to be no change using the hollow fiber membrane versus the bubbler oxygenator.

**Question—Roger Hineman:** You alluded to protamine substitute medications. Would you elaborate a little on what those are and how they are used?

**Answer:** The only one I’m familiar with is hexadamenthrom. I think that’s the pronounciation. It’s a synthetic protamine, not used frequently, because it has the same side effects as protamine, as we know it. That’s the only one I’m familiar with. The alternative method was omitting the protamine administration entirely, and this was done in several patients at several different hospitals. The problem in those cases was that they had a lot of post-operative bleeding. It was hard to control in some patients and took a lot of blood and extra time in the operating room.

**Question—Bobby Merson:** Do you have any heparin in your prime? If you do, what kind of ACTs do you get once you go on bypass and then start cooling?

**Answer:** We prime our pump with 2,500 units of heparin per unit of blood and that produces an activated clotting time greater than 1,000 seconds. So we have seen activated clotting times in the 350 range before bypass. We really don’t treat that because we feel or know that anticoagulation in the cardiopulmonary bypass circuit is very high.

**Question—Bobbie Merson:** When you were following your older protocol and just giving your heparin every hour, you just continued to give it, even if it was over 1,000 seconds?

**Answer:** Yes, we monitored the ACTs just as an arbitrary measurement. We didn’t really do anything. If we saw the ACT being 480 seconds, we just gave additional heparin according to the length of bypass. If we did notice the ACT was low before the time to give more heparin, we would give heparin then.