Heparin Use in Pediatric Bypass—Empirical Regimen (ACT) vs. Heparin Concentration: A Multicenter Trial

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ABSTRACT

There are two common approaches to heparin administration for pediatric bypass: one involves the empirical dosing of heparin based on the activated clotting time (ACT), and the other on heparin concentration. It has been observed that heparin requirements are substantially greater when maintaining a concentration as opposed to an ACT. This study gathered heparin administration data from five pediatric centers, two using an empirical regimen and ACT technique and three using heparin concentration as measured by the Heparin Management System (HMS).

All patients less than or equal to 20 kg were evaluated and grouped by technique. There were 49 patients in the HMS group and 46 in the ACT group.

There was no significant difference between groups for patient weight, bypass time, post-heparin ACT, bypass ACT, protamine dose, or 24-h blood loss (mL/kg/24). There was a significant difference \( p < .01 \) for prime heparin (4.7 ± 1.3 units/cc HMS vs. 1.9 ± 0.4 units/cc ACT), heparin loading dose (476.5 ± 175.3 units/kg HMS vs. 384.6 ± 54.3 units/kg ACT), and total heparin (16.6 ± 6.7 units/kg/min HMS vs. 9.5 ± 5.9 units/kg/min ACT). The use of the HMS for heparin management in pediatric bypass required more heparin but no difference in protamine use or 24-h blood loss.

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INTRODUCTION

Use of activated clotting time (ACT) as a bedside monitoring tool was first described by Hattersley in 1966 (1). Since this time, the ACT has been used to monitor the anticoagulant effect to guide heparin administration during cardiopulmonary bypass. Optimal heparin technique and anticoagulation management has been shown to be difficult to manage with the ACT alone because of variability in patient response (2). This led to the development, by Bull et al., of a technique to individualize heparin administration known as the heparin dose response curve (HDR) (3).

Bull’s original technique involved the administration of two separate doses of heparin prebypass. Each dose was followed by measurement of the ACT and plotting of a line to determine the patient’s response to heparin. Today many centers administer heparin based on an empirical protocol or one dose for all patients. If the ACT exceeds a predetermined amount, bypass is initiated and additional heparin is given based on the amount of time on bypass or the ACT falling below a minimal value. Because it has been shown that hemodilution and temperature both affect ACT (4, 5), and these may be extreme in pediatrics, it is not uncommon for the ACT to be affected during pediatric cardiopulmonary bypass.

There are two common approaches to heparin administration for pediatric bypass. One involves the empirical dosing of heparin based on ACT and the other on an automated HDR and whole blood heparin concentration measurement. It has been observed that heparin requirements seem to be substantially greater in pediatric cardiopulmonary bypass (CPB) when maintaining a concentration as opposed to an ACT. The purpose of this study was to evaluate the differences in heparin and protamine administration data between centers using empirical heparin administration and ACT and heparin concentration.

METHODS AND MATERIALS

Eight centers performing pediatric cardiopulmonary bypass were selected at random from a list of pediatric open-heart centers and contacted regarding participation in the study. The data needed, and follow-up, were to be gathered by the contact at each center. Five centers agreed and participated in the study.* These centers were then interviewed by telephone regarding heparin management. Two centers used the ACT technique, measured with the Hemochron,a and three used the heparin concentration and HDR as measured with the Medtronic Heparin Management System (HMS).bHeparin management techniques were described by means of telephone interview with each institution. Data forms were mailed to all centers and included: date of surgery; sex; height; weight; ACT (baseline, postheparin, bypass, postprotamine); heparin loading dose, prime dose, and bypass heparin; heparin dose response (HMS users); prime volume; protamine dose; bypass time. All centers using the HMS obtain at least one ACT on bypass but administer heparin based on the heparin concentration and not the ACT. Center specific technique is described in Table 1.

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b Medtronic-Hemotec, Parker, CO
All patients less than or equal to 20 kg were evaluated and grouped by heparin management technique. All ACT results were limited to 1000 sec to avoid variances in numbers caused by the different endpoint of the two ACT devices used by the different centers. Statistical analysis included the Student’s t-test and were performed using Microsoft Excel.  

### RESULTS

There were 49 patients in the HMS group and 46 in the ACT group. Table 2 shows the mean, standard deviation, and statistical results of the measured parameters. There was no significant difference between groups for patient weight, bypass time, postheparin ACT, bypass ACT, protamine dose, or 24-h blood loss (mL/kg/24). There were significant differences ($p < .01$) for prime heparin, heparin loading dose, additional heparin on CPB and total heparin.

### DISCUSSION

The authors acknowledge that this was not a controlled study, and the intention was to compare and contrast heparin and protamine management in pediatric centers using ACT management versus maintaining heparin concentrations.

It is interesting to note that although the HMS technique used significantly more total heparin (16.6 vs. 9.5 mg/kg/min) there was not significantly more protamine use (7.0 vs. 5.5 mg/kg) or blood loss (30.5 vs. 32.3 ml/kg/24 hours). Using the HMS resulted in prime heparin being over twice as much as the ACT group. Additional heparin on CPB was over ten times greater in the HMS group. These differences would result in larger total heparin doses over the course of a bypass run. Several studies have shown that the heparin concentration after initiation of bypass falls toward the concentration of heparin in the prime (6, 7). Because studies have shown that the ACT is extended because of hypothermia and/or hemodilution (4, 5), both of which tend to be exaggerated in pediatric CPB, the ACT would be expected to be extended just because of initiation of bypass. Does an extended ACT imply adequate anticoagulation?

Total heparin dose, additional heparin on CPB, heparin loading dose, and prime heparin in the HMS were all significantly greater than the ACT group. There was also a significant difference in standard deviations for heparin loading dose and prime heparin for the HMS group, implying a dosing regimen more specific to the individual patients’ needs. Horkay (8) has shown that the biological half-life of heparin was 35 min in pediatric patients and that the heparin concentration declines more rapidly in children than in adults, possibly because of the higher blood volume to body weight and increased metabolism of children. So an extended ACT caused by hemodilution may not provide adequate subclinical anticoagulation.

One argument against greater heparin administration is greater bleeding. Although total heparin was over one and one-half times that of the ACT group, there was not a significant difference in 24-h blood loss indexed to patient weight. Gravlee found increased blood loss in five adult patients with a heparin management technique that used lower heparin levels than those observed in the HMS group in this study (9). In a repeat study with 33 adult patients Gravlee found no significant difference in postoperative blood loss (10). Turner-Gromes found no significant difference in postoperative blood loss in a group of 48 children using heparin concentrations observed in the HMS group of this study (11).

Although there was more total heparin given in the HMS users, there was not a greater need for protamine. This may be attributed to the fact that the HMS reverses heparin according the patient’s circulating blood volume as opposed to total heparin.

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**Table 2: Variables evaluated, Mean ± SD (statistical significance for $p < .01$)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HMS</th>
<th>ACT</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>7.8 ± 4.2</td>
<td>8.5 ± 5.6</td>
<td>0.5</td>
</tr>
<tr>
<td>CPB (min)</td>
<td>103.8 ± 51.3</td>
<td>93.8 ± 49.6</td>
<td>0.31</td>
</tr>
<tr>
<td>Prime volume (ml)</td>
<td>719.6 ± 146.5</td>
<td>850.8 ± 165.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Prime heparin (ml)</td>
<td>4.7 ± 1.3</td>
<td>1.9 ± 0.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heparin loading dose (µ/kg)</td>
<td>476.5 ± 175.3</td>
<td>384.6 ± 54.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Additional heparin on CPB (units)</td>
<td>3003.1 ± 1804.0</td>
<td>245.7 ± 765.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total heparin (units/kg/min)</td>
<td>16.6 ± 6.7</td>
<td>9.5 ± 5.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ACT-baseline</td>
<td>140.3 ± 16.9</td>
<td>129.8 ± 16.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ACT-postheparin</td>
<td>786.8 ± 239.2</td>
<td>813.2 ± 212.2</td>
<td>0.57</td>
</tr>
<tr>
<td>ACT-CPB</td>
<td>950.9 ± 104.4</td>
<td>947.0 ± 134.5</td>
<td>0.97</td>
</tr>
<tr>
<td>ACT-postprotamine</td>
<td>141.9 ± 31.9</td>
<td>142.1 ± 37.1</td>
<td>0.98</td>
</tr>
<tr>
<td>Protamine (mg/kg)</td>
<td>7.0 ± 3.8</td>
<td>5.5 ± 5.5</td>
<td>0.11</td>
</tr>
<tr>
<td>Postop bleeding (ml/kg/24 h)</td>
<td>30.5 ± 34.4</td>
<td>32.3 ± 29.4</td>
<td>0.81</td>
</tr>
</tbody>
</table>

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Microsoft Corp, Redmond, WA
arin given. Figure 1 shows that although there was no statistical significance between techniques in postprotamine ACTs, the ACT averaged almost 12 sec higher postprotamine in the empirical dosing group. Dauchot also reported this where postprotamine ACT exceeded baseline by 21 sec in ten infants (12).

CONCLUSION

Although this was not a controlled study, one could still conclude that the HMS technique uses more heparin, there is more variability in the heparin amounts using the HMS, which is a more individualized approach, and although there is more heparin given using the HMS, there is no difference in protamine administration. Controlled studies need to be done to evaluate the difference in techniques in pediatrics with regard to subclinical coagulation and outcomes.

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REFERENCES