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A Randomized, Controlled Trial of Heparin Versus Placebo Infusion to Prolong the Usability of Peripherally Placed Percutaneous Central Venous Catheters (PCVCs) in Neonates: The HIP (Heparin Infusion for PCVC) Study

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ABSTRACT

BACKGROUND. Mechanical and infectious complications shorten the effective duration of peripherally inserted central venous catheters. Heparin use to prevent such complications and prolong the usability of peripherally inserted central venous catheters is inconclusive.

OBJECTIVE. Our goal was to evaluate the effectiveness of heparin in prolonging the usability of peripherally inserted central venous catheters in neonates.

DESIGN/METHODS. We performed a multicenter, randomized, controlled trial of heparin infusion (0.5 U/kg per hour) versus placebo for peripherally inserted central venous catheters in neonates. The primary outcome was duration of catheter use. Secondary outcomes were occlusion, catheter-related sepsis, thrombosis, and adverse effects of heparin. To detect a 168-hour (1-week) difference in the duration of catheter use, 192 patients were needed. Kaplan-Meier and Cox regression analyses were performed.

RESULTS. A total of 201 neonates were enrolled (heparin group: n = 100; control group: n = 101). Baseline demographics were similar between the groups. Duration of catheter use was longer in the infants in the heparin versus the placebo group. Study center, gender, birth weight, and type and position of the catheter were not predictors of duration of catheter use. For those in the heparin versus the placebo group, the incidence of elective catheter removal (therapy completed) was 63% vs 42%, of occlusion was 6% vs 31%, of thrombosis was 20% vs 21%, and...
of catheter-related sepsis was 10% vs 6%, respectively. No adverse events were noted.

CONCLUSIONS. Heparin infusion prolonged the duration of peripherally inserted central venous catheter usability, which permitted a higher percentage of neonates to complete therapy without increasing adverse effects.

PROLONGED VASCULAR ACCESS is vital for critically ill and preterm neonates. Peripherally placed percutaneous central venous catheters (PCVCs) provide long-term access necessary for the administration of total parenteral nutrition (TPN) and medications and reduce the need for venipuncture and extended use of umbilical catheters.1–4 PCVCs are associated with complications.5–9 Mechanical complications include occlusion, extravasation, dislodgment, and thrombosis in 10% to 78% of inserted PCVCs.1–4,10 Although they vary among units, rates of bacterial/fungal sepsis have been reported in up to 45% of PCVCs.6–11

Using heparin flushes,12 heparin infusion,1,13 or heparin-bonded catheters,14,15 having a designated team to place PCVCs,12 using Silastic catheters,16 having a mandatory minimum infusion rate,1 using an aseptic technique, making frequent tube changes,1 and administering no blood product through the catheter have been attempted to reduce complications. The most commonly used intervention is continuous infusion of heparin (attached as a separate infusion or added to the TPN).

Systematic reviews of heparin use have reported beneficial effects with arterial catheters7,18; however, it is either ineffective or of uncertain benefit for venous catheters.17,19 Two small studies have evaluated heparin infusion for PCVCs.20,21 A systematic review of heparin use for PCVCs identified the need for additional well-designed studies.22 The benefits of heparin should be weighed against major risks associated with its use, such as aggravation or causation of hemorrhage.23 Our objective for this study was to evaluate the effectiveness of heparin in prolonging the duration of catheter usability and its impact on adverse events.

METHODS
We performed a prospective, randomized, double-masked, placebo-controlled pragmatic clinical trial of heparin versus placebo for PCVCs in neonates. The study was conducted at 4 tertiary care NICUs in Ontario, Canada. Research ethics boards approved the study at each site, and the use of heparin was approved by Health Canada.

Study Population
Neonates requiring PCVC access as judged by the clinical team were eligible to participate. Neonates who had grade 3/4 intraventricular hemorrhage,24 recent onset of presumed or confirmed sepsis (within 48 hours of initiation of antimicrobial therapy), bleeding diathesis, disseminated intravascular coagulation, thrombocytopenia (most recent platelet count of <100 000/mL), arrhythmia, or preexisting liver disease were excluded.

Randomization and Blinding
Neonates were randomly assigned to either heparin or placebo by using a computer-generated random-number table (created by an independent statistician) in blocks of 4 and stratified according to center and gestational age at birth (<30 and ≥30 weeks). Randomization tables were held in the pharmacies and could be accessed by clinical personnel for emergencies (eg, life-threatening hemorrhages). Parental consent was obtained by site investigators/delegates before catheter-insertion attempts. If the attempt was unsuccessful or the placement of the catheter tip was not in the optimal position, the patient was not randomly assigned. If the team elected to use the catheter for clinical purposes, the patient was only randomly assigned if she or he required another catheter and the new catheter was in optimal position. Pharmacists at each institution performed the randomization. The neonatal team, parents, and investigators were blinded to group allocation. Blinding was preserved by dispensing drug and placebo in identical, indistinguishable containers.

Maneuvers
For pragmatic purposes, centers were asked to use the type of catheters with which they were familiar. Four different types of catheters were used (V-Cath [HDC Corporation, Tacoma WA], Neo-PICC [Klein-Baker Medical Inc, San Antonio, TX], L-Cath [BD, Franklin Lakes, NJ], and Per-Q-Cath [Baird Access Systems, Salt Lake City, UT]). The use of a 24- or 27-gauge catheter was left to the discretion of the person inserting the catheter. All PCVCs were placed by using sterile technique as per similar standards in each NICU. The person placing the catheter identified a suitable vein in either the limbs or scalp and measured the desired length for the catheter tip to lie in one of the central veins. Catheters were flushed by normal saline before insertion, and the extension tubing was connected to the PCVC hub. Catheters were secured by transparent occlusive dressing (Tegaderm; 3M, St Paul, MN) that was not changed unless it was soiled or loose. The catheter tip position was confirmed by radiography (anteroposterior and lateral views). The tip of catheters inserted in the upper half of the body were required to be approximately in the superior vena cava or at/near the junction of the subclavian and jugular vein, and catheters placed in the lower half were required to be in the inferior vena cava. If the catheter was inserted deeper than the required length, an adjustment was made and confirmed on ra-
Neonates received study medication in the form of either heparin (10% or 5% dextrose with heparin added) or placebo (10% or 5% dextrose depending on the plasma glucose level). This solution was infused at a rate of 1 mL/hour (for neonates ≥30 weeks’ gestation) or 0.5 mL/hour (for neonates <30 weeks’ gestation) by connecting to the simultaneously running infusion. Although the infusion rate for neonates <30 weeks’ gestation was lower to not compromise their nutrition (amount of fluid was included in the daily requirement), the dose of heparin was the same (0.5 U/kg per hour) for all neonates. When a neonate reached close to full enteral feeds, the infusion was mandated to run at least 1 mL/hour through the catheter (0.5 mL/hour study medication and 0.5 mL/hour TPN or 10% dextrose for neonates ≤30 weeks’ gestation and 1 mL/hour of study medication for neonates >30 weeks’ gestation) until a decision to remove the catheter was made. The heparin dose was adjusted if the infant’s weight changed >10% from baseline. The rate of infusion was left unchanged for neonates <30 weeks’ gestational age even when they crossed 30 weeks’ corrected gestational age.

The nursing staff and pharmacists ensured compatibility of heparin with other infusions. The infusion was stopped temporarily during vancomycin infusion in 5 neonates because of lack of compatibility data. Blood withdrawal or infusion of blood products through the catheter was not allowed. Catheter rewiring was not permitted. Each subject was enrolled only once if more than 1 catheter was inserted. Decisions regarding removal of the catheter were made by the clinical team. Because anticoagulants were rarely used for therapeutic purposes in the NICU, contamination was not an issue, although it was strictly monitored. Contamination may have occurred from simultaneously placed peripheral or umbilical arterial catheters running heparin, but this was expected to be rare and similar in both groups of infants. Co-intervention was unlikely, because heparin-bonded catheters or heparin flushes were not used in any of the NICUs.

**Outcomes and Their Assessment**

**Primary Outcome**

Duration of catheter use was defined as the time between insertion and removal (elective or because of complications) of the catheter in hours.

**Secondary Outcomes**

These outcomes included nonelective reasons for catheter removal and adverse effects. Anticipated complications that may have lead to catheter removal and may have been affected by heparin were tracked:

1. Catheter occlusion was defined as inability to infuse fluid. This was confirmed by a nurse and a physician who attempted to push 1 mL of normal saline via a 5-mL syringe. Use of heparin, urokinase, or tissue plasminogen activator for removal of blockade was not permitted.

2. Catheter-related sepsis was defined as symptoms and signs suggestive of sepsis with a positive blood culture obtained from catheter fluid and a normally sterile site (blood, urine, or cerebrospinal fluid) for the same organism. If an infant met the criteria for catheter-related sepsis, the outcome was ascertained and the study intervention (heparin or placebo) was discontinued. Clinicians were permitted to use clinical judgment regarding removal of catheter for high suspicion of catheter-related sepsis in the presence of persistent identification of an organism from peripheral blood culture without identification of organisms from the PCVC when accompanied by other clinical or laboratory evidence of sepsis, in the interest of the patient’s benefit.

3. Thrombosis was defined as the detection of a thrombus along the catheter path. Thrombosis was diagnosed by ultrasonography and Doppler examination within 72 hours after catheter removal and/or when clinically indicated (distal swelling and persistent thrombocytopenia) by detecting absence of color Doppler signal or gray-scale thrombus visualization along the path of the catheter within the chest or abdomen. All studies were performed by using 7- to 12.5-MHz transducers and were reported at the respective centers.

4. Other causes of catheter removal (although not likely related to heparin use) such as accidental dislodgment, leakage, extravasation, or breakage of the catheter were recorded.

**Adverse Events**

Each infant was monitored for hemorrhage from >2 noncontiguous sites and heparin-induced thrombocytopenia (HIT), defined as a platelet count of <50 000/mL after exclusion of other causes of thrombocytopenia and a positive HIT antibody test.

**Safety**

A safety committee monitored all potential adverse events including deaths and had the power to stop the trial or open the randomization code.

**Sample Size**

The primary outcome was duration of catheter use. Review of the literature and previous year’s data from Mount Sinai Hospital showed a median catheter life span of 14 days (without the use of heparin). A difference of 168 hours (1 week) in the median duration was consid-
ered a clinically important increase (according to a survey of 6 neonatologists and taking the mean value). On the basis of a type 1 error of 0.05, a type 2 error of 0.2 (power 0.8), and follow-up of the last subject until catheter removal, 96 infants were needed (on the basis of survival analysis) in each group (total of 192 infants).

**Statistical Analysis**

Intention-to-treat analyses were performed by using the statistical package SPSS 12 (SPSS Inc, Chicago, IL). χ² and Student’s t tests were used to compare demographics. Duration profiles of the 2 groups were depicted by using a Kaplan-Meier curve and were compared by using the log-rank test. A P value of <.05 was considered significant. “Survival analysis” was used so that information from the catheters that were removed electively was not ignored. Multivariable analysis (Cox’s proportional-hazard model) was performed with variables with a significance level of P < .20 in univariable analyses to assess the effect of potential confounders, and hazard-rate ratios were calculated.

**RESULTS**

**Recruitment**

Two randomization envelopes were opened by mistake (one each for the heparin and the placebo groups) for patients who did not have PCVCs in place. A total of 201 patients were recruited at 4 centers between November 2002 and November 2005 (Fig 1).

**Baseline Characteristics and Status at Randomization**

Baseline characteristics (Table 1) were similar between groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Heparin (n = 100)</th>
<th>Placebo (n = 101)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, mean ± SD, wk</td>
<td>28 ± 3</td>
<td>28 ± 4</td>
<td>.255</td>
</tr>
<tr>
<td>Gestational age, &lt;30/≥30 wk</td>
<td>78.22</td>
<td>82.19</td>
<td></td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>1011 ± 467</td>
<td>1095 ± 565</td>
<td>.432</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>67/33</td>
<td>61/40</td>
<td>.380</td>
</tr>
<tr>
<td>Vaginal delivery, %</td>
<td>41</td>
<td>42</td>
<td>.593</td>
</tr>
<tr>
<td>Apgar score at 1 min, median (range)</td>
<td>6 (0–9)</td>
<td>6 (1–9)</td>
<td>.357</td>
</tr>
<tr>
<td>Apgar score at 5 min, median (range)</td>
<td>8 (0–10)</td>
<td>9 (0–10)</td>
<td>.663</td>
</tr>
<tr>
<td>Maternal chorioamnionitis, %</td>
<td>8</td>
<td>7</td>
<td>.795</td>
</tr>
<tr>
<td>Age at catheter insertion, mean ± SD, d</td>
<td>9 ± 5</td>
<td>8 ± 6</td>
<td>.636</td>
</tr>
<tr>
<td>Weight at catheter insertion, mean ± SD, g</td>
<td>962 ± 410</td>
<td>1064 ± 600</td>
<td>.166</td>
</tr>
<tr>
<td>Pre–catheter-insertion hemoglobin, mean ± SD, g/L</td>
<td>133 ± 25</td>
<td>130 ± 24</td>
<td>.296</td>
</tr>
<tr>
<td>Pre–catheter-insertion platelet count, mL</td>
<td>254 ± 104</td>
<td>236 ± 91</td>
<td>.183</td>
</tr>
<tr>
<td>Pre–catheter-insertion intracranial hemorrhage, no hemorrhage/grade 1/grade 2</td>
<td>5925/6</td>
<td>69166/6</td>
<td>.253</td>
</tr>
</tbody>
</table>

**Type of catheter, n**

<table>
<thead>
<tr>
<th></th>
<th>Heparin</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neo-PICC</td>
<td>25</td>
<td>25</td>
<td>.838</td>
</tr>
<tr>
<td>L-Cath</td>
<td>28</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>V-Cath</td>
<td>40</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Per-Q-Cath</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

**Attempts at catheter placement, median (range), n**

<table>
<thead>
<tr>
<th></th>
<th>Heparin</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (1–5)</td>
<td>1 (1–5)</td>
<td>1 (1–5)</td>
<td>.814</td>
</tr>
</tbody>
</table>

**Site of catheter insertion, n**

<table>
<thead>
<tr>
<th></th>
<th>Heparin</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left arm</td>
<td>44</td>
<td>40</td>
<td>.543</td>
</tr>
<tr>
<td>Right arm</td>
<td>43</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Left leg</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Right leg</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Scalp</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**Position of the tip of catheter, n**

<table>
<thead>
<tr>
<th></th>
<th>Heparin</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior vena cava</td>
<td>77</td>
<td>74</td>
<td>.715</td>
</tr>
<tr>
<td>Subclavian jugular junction</td>
<td>11</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Inferior vena cava</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

**Primary Outcome**

There was a statistically significant increase in the duration of catheter usability (Fig 2) in the infants in the heparin compared with the placebo group (P < .005; hazard ratio: 0.53 [95% confidence interval (CI): 0.35 to 0.81]) assessed by Cox proportional-hazard analyses. This indicates that as the treatment group altered from placebo to heparin, the hazard of complication decreased by 47% (95% CI: 19%–65%). Data on the mean, median, range, and SD of the duration of catheter use are reported in Table 2 for comparison.

**Secondary Outcomes**

Elective catheter removal (after completion of therapy) was statistically significantly more common in the infants in the heparin versus placebo group (P = .002; relative risk: 1.5 [95% CI: 1.2 to 2.0]; risk difference:
The incidence of catheter occlusion was statistically significantly lower in those in the heparin versus placebo group ($P < 0.001$; relative risk: 0.20 [95% CI: 0.09 to 0.42]; risk difference: 0.25 [95% CI: 0.15 to 0.31]; number needed to treat: 4 [95% CI: 3 to 7]). There were no statistically significant differences in the incidences of catheter-related sepsis, suspected catheter-related sepsis, thrombosis, or leaking (Table 2).

Ultrasonography was not performed in 24 (12%) infants (9 in the heparin group and 15 in the placebo group) because of transfer of infants to level 2 nurseries or nonavailability of machines and/or technicians. All thrombi were detected by ultrasonography in the area where the tip of the catheter was noted on radiograph. None of the patients had occlusive thrombosis.

Multivariable analyses (Cox proportional-hazard model) revealed that center, gender, type of catheter, and position of the catheter tip were not statistically significant independent predictors of the duration of catheter use (Table 3).

**Safety**

No infant developed a new or aggravated intraventricular hemorrhage, and no other adverse effect attributable to heparin was identified. No patients required discontinuation of study medication because of bleeding from >2 noncontiguous sites. One patient developed thrombocytopenia after starting the study medication but had a negative antibody test. However, we acknowledge that the prevalence of HIT in the general population is very low.

**DISCUSSION**

In this pragmatic trial, heparin in the dose of 0.5 U/kg per hour was effective in prolonging the duration of PCVC usability in neonates without increasing adverse events. The likelihood of elective catheter removal after completion of therapy was higher among patients in the heparin than the placebo group. The incidence of catheter occlusion was lower in those in the heparin group; however, there were no statistically significant differences in the incidence of thrombosis and catheter-related sepsis between groups.

Previous randomized trials have shown that heparin was ineffective in prolonging duration of PCVC use. Betremieux et al showed no difference in the incidence of catheter occlusion (7 of 27 vs 3 of 19 catheters in patients in the heparin and placebo groups, respectively). Theirs was a small study with methodologic limitations in the form of multiple catheters in 4 patients and randomization at the time of umbilical catheter placement (and to continue that allocation for PCVCs), and the results were reported as per number of catheter and not per infant. Kamala et al studied 66 patients (35 in the heparin group and 31 in the control group) using heparin 1 U/mL of TPN solution and found no difference in the duration of catheter use. Similar to our results, they reported that elective catheter removal was higher in those in the heparin group (63% vs 48%; $P = .3$). The incidence of catheter occlusion was higher in the patients in the placebo group (23% vs 14%; $P = .4$). Catheter-related sepsis (confirmed and suspected), duration of catheter patency, or adverse effects of heparin were not statistically significantly different between groups. The results of our study are similar to those of Kamala et al; however, our study had greater power to detect differences. In addition, we used a very low heparin dose. The dose was smaller compared with the practice at several units of adding heparin to the TPN solution, which leads to higher heparin administration than necessary and may expose infants to adverse effects. The mean total heparin dose received by infants through TPN in these previous reports was ~1000 U/kg; in our study, infants received a median total dose of 108 U/kg (12 U/kg per day for a median duration of 9 days). We elected to use this dose on the basis of the findings of Moclair and Bates, who reported that the effect of heparin in prolonging the duration of catheter patency was static at 0.5 U per dose, and there was no incremental advantage with a higher dose.

Venography is the gold standard for detection of a thrombus, but it is an invasive procedure with associated risks. Ultrasonography has been widely used for thrombus detection in adults but has not been validated.
in infants. The reported sensitivity varied between 83% and 92% and specificity between 87% and 100% for the lower abdominal system.\textsuperscript{27–29} We performed ultrasound examination within 72 hours of withdrawal of the catheter or at the time of a complicating event, because it was difficult to standardize several routine examinations at specified intervals.

The result of no difference in the incidence of thrombosis but higher occlusion rate with placebo is intriguing. We speculate this to be a result of development of a fibrin sleeve\textsuperscript{14} at the catheter, resulting in occlusion, but not large enough to result in thrombus. Nakamura et al\textsuperscript{10} reported that on electron microscopy of the catheter tips, 33% had complete occlusion and 33% had partial occlusion. There is a possibility that the clot was dislodged at the time of catheter removal.

In a systematic review, heparin was found to be effective in thrombus prevention in arterial lines but not in venous catheters.\textsuperscript{17} Heparin was effective in improving umbilical arterial catheter patency.\textsuperscript{18} Shah et al\textsuperscript{19} reported inconclusive evidence for heparin use for intravenous catheters in neonates: 2 studies reported benefit, 1 study reported harm, and 2 studies reported no difference. Studies were not synthesized because of heterogeneity. Thus, effectiveness of heparin for venous catheters had not been proven, possibly because of inherent characteristics of the venous system or low-flow states. Our report is encouraging in that even a small dose seems to be effective.

The incidence of catheter-related sepsis was low. A statistically insignificant increase in the incidence of sepsis in patients in the heparin group could be a result of prolonged duration of catheter use; however, we did not have adequate power to prove this hypothesis. Prolonged duration, colonization with staphylococcus epidermidis, and low birth weight have been identified risk factors of catheter-related sepsis.\textsuperscript{1} Thrombosis of the line can also act as a nidus for infection. Surface heparinization of central venous catheters with heparin has shown to reduce microbial colonization,\textsuperscript{30} although we did not find a statistically significant difference in the incidence of catheter-related sepsis between groups.

We believe that our results are generalizable, because these 4 NICUs care for a variety of neonatal conditions. The clinical teams determined the indication for place-

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Outcomes} & \textbf{Heparin (n = 100)} & \textbf{Placebo (n = 101)} & \textbf{P} \\
\hline
\textbf{Duration of catheter patency, h} & & & \\
Mean (SD) & 267 ± 196 & 233 ± 194 & .220 \\
Median (range) & 218 (6–1095) & 188 (3–1176) & — \\
\textbf{Reasons for removal of catheter, %} & & & \\
Elective & 63 & 42 & .002\textsuperscript{*} \\
Nonelective & 37 & 59 & \\
\textbf{Reasons for nonelective removal of catheter, %} & & & \\
Occlusion & 6 & 31 & .001\textsuperscript{*} \\
Catheter-related sepsis & 5 & 2 & .243 \\
Suspected catheter-related sepsis & 5 & 4 & .722 \\
Extravasation & 8 & 14 & .183 \\
Leakage & 6 & 2 & 1.45 \\
Others & 7 & 6 & .760 \\
\textbf{Duration of catheter patency, h} & & & \\
Among patients who had elective removal, mean (SD) & 290 ± 192 & 319 ± 161 & .422 \\
Among patients who had removal because of complication, mean (SD) & 229 ± 198 & 172 ± 194 & .161 \\
\textbf{Results of ultrasonography, n} & & & \\
Normal & 73 & 68 & \\
Nonocclusive thrombus\textsuperscript{b} & 18 & 18 & \\
\textbf{Univariate analyses} & & & \\
Heparin vs placebo & 0.55 & 0.36 to 0.83 & < .01\textsuperscript{*} \\
Center & 0.87 & 0.75 to 1.01 & .06\textsuperscript{*} \\
Birth weight & 1.00 & 0.999 to 1.00 & .56 \\
Gender & 0.74 & 0.48 to 1.13 & .17\textsuperscript{*} \\
Type of catheter & 1.17 & 0.93 to 1.46 & .17\textsuperscript{*} \\
Position of catheter tip & & & \\
Inferior vena cava vs superior vena cava & 1.05 & 0.55 to 1.99 & .88 \\
Subclavian-jugular vs superior vena cava & 1.75 & 0.995 to 3.07 & .05\textsuperscript{*} \\
\textbf{Multivariate analyses} & & & \\
Heparin vs placebo & 0.53 & 0.35 to 0.81 & < .01 \\
Center & 0.91 & 0.72 to 1.14 & .39 \\
Gender & 0.71 & 0.45 to 1.10 & .12 \\
Type of catheter & 1.06 & 0.75 to 1.49 & .76 \\
Position of catheter tip & & & \\
Inferior vena cava vs superior vena cava & 0.98 & 0.51 to 1.90 & .96 \\
Subclavian-jugular vs superior vena cava & 1.49 & 0.84 to 2.65 & .18 \\
\hline
\end{tabular}
\caption{Outcomes}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
\textbf{Variables} & \textbf{Hazard Ratio} & \textbf{95\% CI for Odds Ratio} \\
\hline
\textbf{Univariate analyses} & & \\
Heparin vs placebo & 0.55 & 0.36 to 0.83 \\
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Position of catheter tip & & \\
Inferior vena cava vs superior vena cava & 0.98 & 0.51 to 1.90 \\
Subclavian-jugular vs superior vena cava & 1.49 & 0.84 to 2.65 \\
\hline
\end{tabular}
\caption{Cox Proportional-Hazard Model}
\end{table}

\textsuperscript{*}Variables with P < .2 were entered in multivariate analyses.

\textsuperscript{b}Thrombus was considered nonocclusive if color Doppler flow was identified around the thrombus.
ment of PCVCs, which may have introduced bias but, at the same time, improved the generalizability. We believe that adverse effects were not observed in our study probably because of the small dose of heparin used.

CONCLUSIONS

The use of heparin in the dose of 0.5 U/kg per hour as a continuous infusion is effective in prolonging the duration of usability of PCVCs without increasing adverse effects. It is effective in reducing catheter-occlusion rates, thus allowing completion of therapy.

ACKNOWLEDGMENTS

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The following investigators participated in the HIP (heparin infusion for PCVc) study: Mount Sinai Hospital, Toronto, Ontario, Canada (80 patients): Dr P. S. Shah, Dr V. Shah, Dr A. Orlsson, and Dr S. Salem; Hamilton Health Sciences Centre, Hamilton, Ontario, Canada (81 patients): A. Kaly; Sunnybrook and Women’s College Health Sciences Centre, Toronto, Ontario, Canada (26 patients): Dr M. S. Dunn and Dr P. Glanc; and the Hospital for Sick Children, Toronto, Ontario, Canada (14 patients): Dr B. Parvez and Dr A. Daneman. The steering committee included Dr P. S. Shah, Dr V. Shah, Dr M. S. Dunn, and Dr A. Orlsson, and the safety committee included Dr E. Kelly (staff neonatologist, Mount Sinai Hospital) and M. Heffer (pharmacist, Mount Sinai Hospital). The data-coordinating center was Mount Sinai Hospital.

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Prakesh S. Shah, Angela Kalyn, Prakash Satodia, Michael S. Dunn, Boriana Parvez, Alan Daneman, Shia Salem, Phyllis Glanc, Arne Ohlsson and Vibhuti Shah

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