Low-Dose Heparin Use and the Patency of Peripheral IV Catheters in Children: A Systematic Review

abstract

objective: To assess evidence from randomized controlled trials (RCTs) on the efficacy of low-dose heparin for prolonging patency of peripheral intravenous (PIV) catheters in the pediatric population.

methods: We searched Medline, Embase, CINAHL, and Cochrane Central Register of Controlled Trials to identify studies up to June 6, 2012. Additional citations were retrieved from the bibliography of selected articles. The eligible studies were RCTs of low-dose heparin used in PIV catheters as compared with control and measured any one of the following outcomes: duration of catheter patency, infusion failure rates, or phlebitis. Data were extracted by 1 reviewer by using a standardized form and checked for accuracy by a second reviewer. Discrepancies were resolved by consensus.

results: Thirteen RCTs were identified (3 RCTs of continuous infusion and 10 RCTs of intermittent flush). Catheters using heparin had longer patency (mean difference [95% confidence interval]: 26.51 hours [2.37 to 50.65], \( P < .001 \), for the infusion studies and 2.82 hours [−0.04 to 5.67], \( P = .05 \), for intermittent flush studies). Heparin usage also resulted in a lower rate of infusion failure (rate ratio [95% confidence interval]: 0.78 [0.62 to 0.99], \( P = .04 \), for the infusion studies and 0.88 [0.72 to 1.09], \( P = .25 \), for intermittent flush studies). Lower phlebitis rates were also observed with heparin usage; however, the results did not reach significance. There was no increase in heparin-related side effects noted.

conclusions: Low-dose heparin as continuous infusion in PIV catheters resulted in clinically significant benefits in terms of catheter patency and fewer episodes of infusion failures. Heparin’s use in intermittent flush solutions showed minimal benefits. Pediatrics 2013;131:e864–e872

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key words

heparin, patency, infusion failure, phlebitis, systematic review

abbreviations

CI—confidence interval
HIT—heparin-induced thrombocytopenia
MD—mean difference
PIV—peripheral intravenous
RCT—randomized controlled trial
OR—odds ratio

Dr Kumar contributed to all stages of the review, wrote the first draft of the manuscript, and approved the final manuscript as submitted; Mr Vandermeer provided statistical support to the project, helped with data analysis, and approved the final manuscript as submitted; Dr Bassler was involved with the planning of this study from the initial stages, helped with risk of bias assessments, and approved the final manuscript as submitted; and Dr Mansoor helped with search selection and data abstraction, reviewed drafts of the manuscript, and approved the final manuscript as submitted.

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Heparin solutions are widely used in central venous and arterial lines for maintaining catheter patency and have become the standard of practice both in adult and pediatric patients. The benefits observed include reduction in catheter occlusions and catheter-related venous thrombosis and likely reduction in catheter-related bacterial infections.\(^1\)–\(^3\) However, the use of heparin in peripheral intravenous (PIV) catheters is debated. A systematic review of randomized controlled trials (RCTs) conducted more than a decade ago revealed that, although intermittent heparin flushes had no added benefits compared with normal saline, low-dose heparin infusions may have benefits in terms of lesser incidence of phlebitis or longer duration of catheter patency.\(^4\)

Since the publication of this review, several new trials have been conducted. Another systematic review, restricted to a neonatal population, reported significant variations in benefits noted in studies from heparin usage in PIV catheters.\(^5\) The authors did not conduct a meta-analysis due to heterogeneity concerns. However, this review included the results from several non-randomized studies (trials with comparison groups but that enrolled subjects not randomly allocated) and did not separately analyze the effects of heparin used in continuous infusion and intermittent flush modes, as indicated from the previously described review.

Our objective was to conduct an updated systematic review in the pediatric population according to defined methodologic standards. Our intent was to synthesize the evidence from RCTs on the efficacy of low-dose heparin for maintaining patency of commonly used non-metallic PIV catheters.

**METHODS**

**Search Strategy**

The research librarian in collaboration with the research team conducted structured searches in the following electronic databases: Medline (1946–2012), Embase (1980–2012), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Central Register of Controlled Trials (CENTRAL). (The original search was conducted in July 2010 and was updated on June 6, 2012, to screen for additional studies.) The following combination of subject headings and text words were used: (infusions, intravenous/OR [infusion* or intravenous]) adj2 [infusion* or drip or catheter] OR Catheterization, Peripheral/ OR [peripheral adj2 (catheter* or intravenous!)] AND (heparin/ OR [heparin or heparin* or α-heparin or liquamin]). Search results were not limited by language, and a date restriction was not applied. Additional citations were retrieved from the bibliography of the selected articles if they appeared to answer the research question. We did not include studies published as abstracts only.

**Study Selection**

Studies were included in the review if they met the following criteria: randomized sequence generation, compared low-dose heparin added to the intravenous fluid through PIV catheter versus no heparin added to the similar base fluid in a pediatric population, and measured any one of the outcomes of duration of catheter patency, occlusion rates, or local site reactions such as thrombophlebitis. Two reviewers independently assessed all citations, and any discrepancies regarding inclusion were resolved, as per the predefined selection criteria, through discussion among the review team.

We did not include RCTs where the stated purpose of initiating a PIV catheter was to obtain a short-duration vascular access such as in emergency department settings. Other exclusions were cluster-randomized designs and studies in which subjects in both groups received systemic heparin from alternate routes for other indications.

**Data Extraction**

Data were extracted by 1 reviewer with the use of a standardized form. All forms were checked for accuracy by a second reviewer, and discrepancies were resolved by discussion between the 2 reviewers. We extracted the following information: characteristics of the study (eg, language of publication, year of publication), characteristics of the study population and of the catheter (eg, age range, reasons for receiving intravenous fluids, catheter size, and material), description of the intervention and comparisons (eg, heparin dose and method of administration), outcome measures and measurements tools, and results.

Our primary outcome of interest was the duration of catheter patency. The secondary outcomes included infusion failure (defined as any reason that resulted in premature removal of the catheter), catheter-related phlebitis (defined as \(\geq 1\) of the following reported in the manuscript: pain, erythema, induration, local tenderness, or palpable cord), and any other major adverse effects reported.

**Assessment of Bias**

We addressed methodologic quality as per the Cochrane risk of bias tool,\(^6\) which includes items for adequacy of random sequence generation, allocation concealment, blinding, loss to follow-up, selective reporting, or other biases. Discrepancies were resolved by discussion and consensus.

**Data Analysis**

The effects of low-dose heparin from infusion and intermittent flush studies were analyzed as separate subgroups, for the reasons cited above. Studies were pooled by using DerSimonian and Laird random-effects model.
studies had more catheters than patients, and thus rate ratios were used to pool some outcomes (ie, infusion failure, phlebitis) with SEs being estimated through Poisson rates, which take into account the multiple catheters. Some studies had >1 heparin group to evaluate various concentrations of heparin. For our main analyses, the data from heparin groups in these studies were combined as a single group for comparison with the control group. Data were analyzed by using RevMan, version 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011. Copenhagen, Denmark).

A priori sensitivity analyses were planned for population characteristics, study quality (as per risk of bias assessments), and method of handling data from electively withdrawn catheters across studies. We also planned to separately evaluate effect size from studies that provided data for one catheter use per enrolled subject, to avoid concerns that result from dependency of data when the same subject is included more than once in a trial.

Assessment of Heterogeneity
An I² statistic was calculated for each analysis to quantify heterogeneity across studies. If substantial (I² >50%) heterogeneity was detected, the potential causes for its existence were explored and further sensitivity analyses undertaken.

RESULTS
Figure 1 shows the flow of the studies through the selection process. We identified 13 RCTs in pediatric populations that answered the review questions, 3 studies evaluating low-dose heparin as a continuous infusion7–9 and 10 studies evaluating heparin as intermittent flush.10–18

The Supplemental Information shows studies that were screened as RCTs but considered ineligible for inclusion upon full-text review.

A brief description and salient characteristics of the included trials are presented in Table 1 (studies listed by the first author’s name and year of publication).

Studies of Heparin Infusion (3 Studies)
All 3 infusion trials were in premature neonates receiving parenteral nutrition that allowed multiple catheter insertions in each study subject. The largest of these trials, by Klenner et al.,8 also reported data for the outcome of the first catheter use. The unit of randomization was the patient for each of the included studies; that is, if PIV needed to be restarted in an enrolled patient, he or she was given the same intervention as per the original allocation. One study8 compared 4 different concentrations of heparin with the control.

Studies of Intermittent Flush (10 Studies)
Five of these trials were restricted to a neonatal population,10,12,13,15,19 whereas the others included patients from pediatric medicine and surgical wards. Three trials evaluated multiple catheter insertions in each study patient.12,15,18 The unit of randomization was the patient for each of these studies. Two studies13,17 compared 2 separate concentrations of heparin with the placebo.

Risk of Bias Assessments
Table 2 shows the risk of bias assessment of the included studies. Seven studies did not adequately describe the method that was used to generate the random sequence for participants. All studies described adequate allocation concealment, and in the majority, the interventions were satisfactorily masked from the caregivers and assessors.
## TABLE 1 Characteristics of Included RCTs Evaluating the Efficacy of Heparin

<table>
<thead>
<tr>
<th>Study</th>
<th>Population, Setting, Catheter Size, and Material</th>
<th>Heparin Group</th>
<th>Control Group</th>
<th>Outcomes Reported</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infusion studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpan 1984&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Premature neonates receiving PN, NICU</td>
<td>13 patients/105 catheters</td>
<td>13 patients/122 catheters</td>
<td>Patency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Catheter: 22G, Teflon</td>
<td>Dose: 1 U/mL</td>
<td>Saline placebo</td>
<td>Infusion failure, phlebitis</td>
<td>Majority 26G in both groups</td>
</tr>
<tr>
<td>Klenner 2003&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Premature neonates receiving PN, NICU</td>
<td>145 patients/565 catheters</td>
<td>151 patients/692 catheters</td>
<td>Patency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Catheter: 26G, polyurethane; 24G, Teflon</td>
<td>Dose: 0.5 U/mL</td>
<td>Saline placebo</td>
<td>Infusion failure, phlebitis</td>
<td></td>
</tr>
<tr>
<td>Moclair 1995&lt;sup&gt;9&lt;/sup&gt; (5 groups)</td>
<td>Premature neonates on PN, NICU</td>
<td>0.1 U/mL (15 patients/35 catheters)</td>
<td>20 patients/72 catheters</td>
<td>Patency</td>
<td>Data from 4 heparin groups combined for primary analysis; observations censored where infusion was no longer required or accidentally removed</td>
</tr>
<tr>
<td></td>
<td>Catheter: 24G, Teflon</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>0.25 U/mL (16 patients/47 catheters)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>0.5 U/mL (23 patients/61 catheters)</td>
<td>PN without heparin</td>
<td></td>
<td>Infusion failure</td>
<td></td>
</tr>
<tr>
<td>Intermittent flush studies</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Arnts 2011&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Neonates, NICU</td>
<td>48 patients/46 catheters</td>
<td>44 patients/44 catheters</td>
<td>Patency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Catheter: 24G, Teflon</td>
<td>Dose: 10 U/mL</td>
<td>Saline placebo</td>
<td>Infusion failure, phlebitis</td>
<td></td>
</tr>
<tr>
<td>Beecroft 1997&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Term neonates and children, most from pediatric wards</td>
<td>238 patients/238 catheters</td>
<td>213 patients/213 catheters</td>
<td>Patency</td>
<td>Multicenter trial; all catheters electively removed at 72 h; positive-pressure flush&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Catheter: 22–24G, majority Teflon</td>
<td>Dose: 10 U/mL&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Saline placebo</td>
<td>Infusion failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Freq: q 8 h&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown 1999&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Neonates, NICU</td>
<td>93 patients/181 catheters, q 6 h</td>
<td>93 patients/150 catheters</td>
<td>Patency</td>
<td>Each neonate could be enrolled once again to the same group</td>
</tr>
<tr>
<td></td>
<td>Catheter: 24G, Teflon</td>
<td>Dose: 5 U/mL</td>
<td>Saline placebo</td>
<td>Infusion failure, phlebitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Freq: q 6 h&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heilskov 1998&lt;sup&gt;13&lt;/sup&gt; (3 groups)</td>
<td>Neonates, NICU or newborn wards</td>
<td>63 patients/63 catheters</td>
<td>27 patients/27 catheters</td>
<td>Patency</td>
<td>Data from 2 heparin groups combined for primary analysis; positive-pressure flush&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Catheter: G not stated, Teflon</td>
<td>Dose: 2 U/mL (28), 10 U/mL (35)</td>
<td>Saline placebo</td>
<td>Infusion failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Freq: q 6 h&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kleiber 1993&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Infants (excluding neonates)/children, pediatric wards</td>
<td>56 patients/56 catheters</td>
<td>68 patients/88 catheters</td>
<td>Patency</td>
<td>Positive-pressure flush&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Catheter: 18–24G, Teflon</td>
<td>Dose: 10 U/mL</td>
<td>Saline placebo</td>
<td>Infusion failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Freq: q 4 h&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kotter 1996&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Neonates, NICU</td>
<td>24 patients/43 catheters</td>
<td>27 patients/75 catheters</td>
<td>Patency</td>
<td>Data presented only for catheters that developed infusion failure/complications</td>
</tr>
<tr>
<td></td>
<td>Catheter: 24G, Teflon</td>
<td>Dose: 10 U/mL</td>
<td>Saline placebo</td>
<td>Infusion failure, phlebitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Freq: q 8 h&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McMullen 1993&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Infants/children, pediatric wards</td>
<td>68 patients/88 catheters</td>
<td>74 patients/74 catheters</td>
<td>Patency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Catheter: 18–24G, material unknown</td>
<td>Dose: 10 U/mL, Freq: not stated</td>
<td>Saline placebo</td>
<td>Infusion failure</td>
<td></td>
</tr>
<tr>
<td>Mok 2007&lt;sup&gt;17&lt;/sup&gt; (3 groups)</td>
<td>Children (age 1–10 y), pediatric wards</td>
<td>82 patients/82 catheters</td>
<td>41 patients/41 catheters</td>
<td>Patency</td>
<td>Data from 2 heparin groups combined for primary analysis; positive-pressure flush&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Catheter: 22–24G, material unknown</td>
<td>Dose: 1 U/mL (41), 10 U/mL (41)</td>
<td>Saline placebo</td>
<td>Infusion failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Freq: q 6–8 h&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelson 1998&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Neonates and infants, pediatrics wards or NICU</td>
<td>26 patients/28 catheters</td>
<td>32 patients/46 catheters</td>
<td>Patency</td>
<td>Lockout of catheters initiated several hours after randomization</td>
</tr>
<tr>
<td></td>
<td>Catheter: 24G, Teflon</td>
<td>Dose: 10 U/mL</td>
<td>Saline placebo</td>
<td>Infusion failure, phlebitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Freq: q 8 h&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schultz 2002&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Neonates, NICU</td>
<td>20 patients/20 catheters</td>
<td>28 patients/29 catheters</td>
<td>Patency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Catheter: 24G, Teflon</td>
<td>Dose: 2 U/mL</td>
<td>Saline placebo</td>
<td>Infusion failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Freq: q 3 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Freq, frequency; G, Gauge; PN, parenteral nutrition; q, every.
<sup>a</sup> Or flushed after administration of any scheduled medications.
<sup>b</sup> One site (of 9) used 100 U/mL heparin solution.
<sup>c</sup> Positive-pressure technique for clamping intravenous locks.
Most studies were classified as “unclear” for the criterion of free of selective reporting, because it was difficult to make this judgment in the absence of availability of trial protocols. Two studies\textsuperscript{15,16} excluded a large number of participants after randomization for reasons of incomplete participant data and change in treatment plans (discontinuation of PIV and/or early discharge from hospital), which, in 1 study,\textsuperscript{15} led to a significant imbalance in the number of participants in the intervention groups that were finally assessed.

**Outcome of Patency**

The studies used variable measures to describe patency outcomes (mean ± SD, median duration, and/or patency at fixed time points). The studies also varied in terms of how they handled data from the proportion of catheters that were removed electively (ie, without development of any complication) when they were no longer needed. Some studies presented data separately for catheters that were removed electively and those discontinued due to complications,\textsuperscript{17} whereas other studies presented combined data with\textsuperscript{6,7,11} censoring for outcome at the point of elective withdrawal. One study presented duration of patency only for catheters that were discontinued due to complications.\textsuperscript{15}

Figure 2 shows the outcome of patency. The use of the heparin as continuous infusion in PIV catheters resulted in significantly longer duration of catheter patency (mean difference [MD]: 26.51 hours; 95% confidence interval [CI]: 2.37–50.65 hours; \( P < .001, I^2 = 43\% \)) as compared with placebo. There was significant heterogeneity in the pooled estimate (\( I^2 = 98\% \)), which mainly resulted from the study by Klenner et al\textsuperscript{8} that used much smaller bore catheters of 26 G for the majority of their subjects (MD without inclusion of this study: 37.20 hours; 95% CI: 30.11–44.30 hours; \( P < .001, I^2 = 43\% \)). Klenner et al also reported comparison of patency outcome for the first catheter data in each subject, showing somewhat greater effect size for first catheters (MD: 11.90 hours; 95% CI: 6.54–17.26 hours) as compared with data from all catheters (MD: 7.40 hours; 95% CI: 5.14–9.66 hours). This study also reported patency at various fixed time points after the start of catheters and showed that catheters using heparin infusion were more likely to be patent at 24 hours (odds ratio [OR]: 1.72; 95% CI: 1.37–2.15), 48 hours (OR: 2.67; 95% CI: 1.93–3.68), and 72 hours (OR: 4.64; 95% CI: 2.28–9.44) as compared with control.

For heparin usage as an intermittent flush solution, the pooled estimate from the available RCTs showed a smaller benefit (MD: 2.82 hours; 95% CI: \( -0.04 \text{ to } 5.48 \text{ hours} \)).

**TABLE 2 Risk of Bias Assessments of the Included Studies**

<table>
<thead>
<tr>
<th>Infusion studies</th>
<th>Adequate Sequence Generation</th>
<th>Allocation Concealment</th>
<th>Blinding of Caregivers and Assessors</th>
<th>Incomplete Outcome Data Addressed</th>
<th>Free of Selective Reporting</th>
<th>Free of Other Bias</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpan 1984</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>A complete list of reasons for catheter removal not provided</td>
</tr>
<tr>
<td>Klenner 2003</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Statistical methods incompletely described</td>
</tr>
<tr>
<td>Moclair 1995</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Method of blinding likely to be at risk for detection; postrandomization exclusions (2 subjects)</td>
</tr>
<tr>
<td>Intermittent flush studies Arnts 2011</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Postrandomization exclusions (14 subjects)</td>
</tr>
<tr>
<td>Beecroft 1997</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Trial stopped early</td>
</tr>
<tr>
<td>Brown 1999</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Postrandomization exclusions (109 catheters) for elective withdrawal of catheters with significant imbalance in intervention groups</td>
</tr>
<tr>
<td>Heilskov 1998</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Postrandomization exclusions (128 subjects) for incomplete data</td>
</tr>
<tr>
<td>Kleiber 1998</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Postrandomization exclusions (8 catheters) for incomplete data</td>
</tr>
<tr>
<td>Kotter 1996</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Postrandomization exclusions (4 subjects) with no explanation</td>
</tr>
<tr>
<td>McMullen 1993</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Postrandomization exclusions (128 subjects) for incomplete data</td>
</tr>
<tr>
<td>Mok 2007</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Postrandomization exclusions (8 catheters) for incomplete data</td>
</tr>
<tr>
<td>Nelson 1998</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Postrandomization exclusions (4 subjects) with no explanation</td>
</tr>
<tr>
<td>Schultz 2002</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Postrandomization exclusions (128 subjects) for incomplete data</td>
</tr>
</tbody>
</table>
to 5.67; \( P = .05 \), with no significant difference in effect size noted between the studies restricted to the neonatal population and the other studies. There was no significant heterogeneity noted in the estimates from these trials.

In a sensitivity analysis, the size of the treatment effects was comparable between the studies that adequately reported random-sequence generation and the studies in which it was unclear (Supplemental Fig 5). Similarly, the treatment effects were not statistically different between the studies that censored for the outcome for elective catheter withdrawal (or provided separately the data for failed catheters) and the studies that provided data for all catheters without censoring for elective withdrawal.

We were unable to identify a dose-response relationship for the patency outcome across the identified studies; however, a few multigroup studies analyzed for dose-response within their study design. Among the infusion studies, Moclair and Bates\(^9\) showed that the infusion of 0.1 unit/mL of heparin was no more effective than control (median patency: 31 vs 25 hours); however, the infusion of 0.25, 0.5, and 1 unit/mL significantly prolonged catheter life (median patency: 49, 69, and 72 hours, respectively) but with no significant additional benefit with more than the dose of 0.5 unit/mL. For heparin as an intermittent flush, the most common dose used in studies was 10 units/mL, although there was minimal additional benefit observed when this dosage was compared with the lower dosage, within-study design of 2 multigroup studies.\(^{13,17}\)

**Infusion Failure**

All included studies reported this outcome (Fig 3). The use of heparin as continuous infusion resulted in a 22% lower rate of infusion failure (rate ratio: 0.78; 95% CI: 0.62–0.99; \( P = .04 \)), whereas the difference was not statistically significant when heparin was used in intermittent flush solutions (rate ratio: 0.88; 95% CI: 0.72–1.09; \( P = .25 \)) compared with the placebo.

In a sensitivity analysis, the size of the treatment effect was not statistically different for intermittent flush studies that adequately reported random-sequence generation versus where it was unclear (Supplemental Fig 6). However, among the infusion studies, greater effect size was noted for the study that adequately reported random-sequence generation\(^7\) as compared with the remaining studies (\( P \) for subgroup differences = .04). Another sensitivity analysis showed that the risk of infusion failure was similar for studies that provided data for 1 catheter per subject and multiple catheters per subject.

**Phlebitis**

A meta-analysis was conducted for 6 of the included studies that reported phlebitis as a distinct outcome (Fig 4). The use of the heparin showed lower rates of phlebitis, both in infusion studies (rate ratio: 0.55; 95% CI: 0.19–1.60; \( P = .27 \)) and in the intermittent flush studies (rate ratio: 0.81; 95% CI: 0.47–1.41; \( P = .46 \)); however, the differences were not statistically significant. The pooled effect size was statistically significant for the studies that provided data for multiple catheters per subject.

**FIGURE 2**

Heparin versus control. Meta-analysis of data for catheter patency. IV, inverse variance.
subject7,8,12,15,18 (5 studies; rate ratio: 0.61; 95% CI: 0.38–0.98; \(P = .04\)). In a sensitivity analysis, the effect size was noted to be greater for studies that adequately reported random-sequence generation compared with studies in which it was unclear (Supplemental Fig 7).

Assessment of Adverse Effects

Only a handful of studies planned to systematically look for treatment-related adverse events. The largest of the included studies,8 which enrolled premature neonates, systematically screened all subjects for intracranial bleeding by a prespecified protocol for head ultrasound. There were 10 such episodes recorded, 3 in the heparin group and 7 in the control group (\(P = .37\)). The authors also screened for occurrence of heparin-induced thrombocytopenia (HIT) and found no difference among the groups for the incidence of isolated thrombocytopenia (platelet count <100 000/mL, 13 episodes in the heparin group versus 10 episodes in the control group; \(P = .55\)) or HIT antibodies (213 subjects who received infusion for >5 days were tested and none were found to be positive). Another study12 reported no new episode of intracranial bleeding after initiation of heparin treatment in the subset of premature neonates who received a head ultrasound screening as a unit policy. There was no increased risk of sepsis noted from the use of heparin in any study.

DISCUSSION

We have presented an updated systematic review of the RCTs in the pediatric population evaluating the effects of low-dose heparin in PIV catheters. The review included several RCTs8,11,12,17–19 published after the meta-analysis by Randolph et al.4 The results reveal that heparin use in PIV catheters prolongs the duration of catheter patency with lower rates of infusion failure. Lower rates for the outcome of phlebitis were also observed with heparin usage; however, the results did not reach statistical significance because of the small number of studies reporting phlebitis distinct from all causes of infusion failure. The effect size noted was larger for studies using heparin as a continuous infusion for each of the outcomes studied.

We explored the difference in effect size noted between the 2 modes of heparin use: that is, continuous infusion and intermittent flush. The difference was not accounted for by using a higher concentration of heparin (\(10 \text{ U/mL}\)) as a flush solution, more frequent (\(\geq 4\) hours) flushing, and flush technique (positive flush).

Contrary to Shah et al.,5 we conducted meta-analyses to arrive at the pooled estimates of outcomes of interest, separately analyzing the effects of heparin used in an intermittent and continuous fashion, and explored potential reasons for heterogeneity where identified. This
approach is consistent with the current literature in systematic review methodology. Our analysis did not show any significant heterogeneity in meta-analyses for the data from intermittent flush studies. However, we noted heterogeneity in estimates from infusion studies, with lesser effect size for prolongation of catheter patency seen in 1 study. It is reassuring that the nature of heterogeneity observed was quantitative (ie, studies varied in terms of magnitude of effect size but not in the direction of effect) with each of the infusion trials individually showing significant benefits for the outcome of patency.

What Are the Implications to Practice?

It is likely that clinicians would be more inclined to accept the use of heparin in continuous infusions because of the clinically significant benefits revealed, as compared with the relatively small benefits noted in the studies of intermittent flush solutions. From the dose-comparison data presented in one of the infusion studies, it seems that the optimal dose for heparin in infusion fluids would be 0.5 unit/mL. Other considerations may also play a part in application of the findings of this systematic review in clinical practice. For example, obtaining a PIV access is technically more difficult in neonates (or in infants); prolonging patency of catheter in these subgroups by use of heparin may be more desirable to clinicians than in older children.

Our review is not without limitations. First, some of the studies included in this review preceded advances in the area of intravenous fluid therapy over the period of time, such as use of in-line filters, newer catheter materials with lesser incidence of thrombophlebitis, and the practice of regular change of intravenous tubing sets. However, we did not notice a clear trend for effect size with the year of publication. Second, for our analysis, we made certain assumptions where appropriate data were not available; for example, for 1 study, mean patency duration was imputed from median values provided as suggested by the Cochrane handbook, and for a few other studies where average catheter duration (mean) was provided without estimates of the SD, we estimated SD from the P values provided. We believe that these assumptions were conservative and that their impact is more likely to bias results toward a null effect. Third, some of the sensitivity analyses were unlikely to have adequate statistical power to detect differences even if they existed because of the small number of studies that were eligible for this review. For example, we were unable to detect differences in effect size of the outcome studies between the studies that censored data for elective catheter withdrawal and those without censoring. However, 2 studies that compared data for all catheters and for catheters withdrawn due to complications within their study design showed greater effect size for patency duration for the latter group. Fourth, we could not apply a formal test for publication bias due to a small number of included studies. However, the funnel plot for the 10 included intermittent flush studies did not reveal any asymmetry. Fifth, not all studies systematically screened for heparin-related side effects. However, 2 large studies
that enrolled premature infants at risk of intracranial bleeding systematically screened for these side effects and reported no increased risk of major bleeding.8,12 Similarly, there was no added risk of HIT noted in the largest of the RCTs.8 Last, 2 studies reported a large number of postrandomization exclusions,15,16 a potential source of bias. The results of the meta-analysis remained unchanged for each of the outcomes presented despite excluding data from these studies.

CONCLUSIONS

The results of this updated systematic review of RCTs reveal that the use of low-dose heparin in PIV catheters prolongs catheter life, with a significant reduction in infusion failure rates when used as continuous infusion. These effects are aligned with beneficial effects of low-dose heparin seen when used in central lines or in peripherally inserted central catheters. The benefits observed when used as an intermittent flushing solution were minimal. There was no increase in heparin-related side effects reported from the dosages used in the trials included in this review.

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Low-Dose Heparin Use and the Patency of Peripheral IV Catheters in Children: A Systematic Review
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