Benefit of Heparin in Central Venous and Pulmonary Artery Catheters*

A Meta-analysis of Randomized Controlled Trials

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Objective: To evaluate the effect of heparin on thrombus formation and infection associated with use of central venous and pulmonary artery catheters.

Data sources: We used MEDLINE, EMBASE, citation review of relevant primary and review articles, personal files, and contact with expert informants.

Study selection: Fourteen randomized controlled trials evaluating prophylactic doses of heparin or heparin bonding were included.

Data extraction: In duplicate, independently, we abstracted data on the population, intervention, outcome, and methodologic quality.

Data synthesis: Prophylactic heparin decreases catheter-related venous thrombosis (relative risk [RR], 0.43; 95% confidence interval [CI], 0.23, 0.78) and bacterial colonization (RR, 0.18; 95% CI, 0.06, 0.60) of central venous catheters and may decrease catheter-related bacteremia (RR, 0.26; 95% CI, 0.07, 1.03). Heparin bonding decreases the risk of pulmonary artery catheter clot formation within 24 h (RR, 0.08; 95% CI, 0.02, 0.37).

Conclusions: Heparin administration effectively reduces thrombus formation and may reduce catheter-related infections in patients who have central venous and pulmonary artery catheters in place. Cost-effectiveness comparisons of unfractionated heparin, low molecular weight heparin, and warfarin are needed.

(CHEST 1998; 113:165-71)

Key words: central venous catheter; heparin; infection; thrombosis; thrombus

Abbreviations: CI = confidence interval; RR = relative risk; TPN = total parenteral nutrition

Many hospitalized patients require a central venous catheter to provide access for pharmacotherapy, fluid administration, and parenteral nutrition. In addition, many critically ill patients require central venous or pulmonary arterial catheterization for hemodynamic monitoring and blood sampling. Vascular thrombosis and systemic infection are complications associated with this instrumentation. Thrombus forms on these catheters in the first few hours1 and thrombosis of large vessels occurs after long-term catheterization in 35 to 67% of patients.2-6 An association has been demonstrated between thrombus formation and catheter-related sepsis,7 pulmonary emboli, and septic thrombi.2,3 The anticoagulant properties of heparin led clinicians to use heparin flushes to fill the lumens of central venous catheters locked between use in an attempt to prevent thrombus formation and to prolong the duration of catheter patency. The efficacy of this practice is unproven. Despite its beneficial antithrombotic effects, decreasing unnecessary exposure to heparin is important to minimize the complications resulting from prior sensitization. Autoimmune-mediated heparin-induced thrombocytopenia occurs in 2.7% of patients exposed to unfractionated heparin, which greatly increases the risk of thrombotic events.8 Other risks of heparin use include allergic reactions and the potential for bleeding complications after multiple, unmonitored heparin flushes.9

Individual trials of heparin in central venous catheters are contradictory, and to our knowledge, there

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Manuscript received February 5, 1997; revision accepted July 28.
are no systematic reviews assessing the benefit. Therefore, we conducted this systematic review to resolve and synthesize the conflicting literature, and to address the potential problem of type II error in interpreting individual studies. Herein, we critically appraise the clinical trials evaluating use of infused and bonded heparin on thrombus formation and infection risk in central venous and pulmonary arterial catheters.

**Materials and Methods**

**Study Identification**

Trials included in this review were identified from a larger subset of all identified randomized trials of central venous and pulmonary artery catheter-related complications. This larger pool of trials was identified by cross-referencing the following MeSH terms using MEDLINE from 1966 to October 1995—catheterization, central venous and catheterization, Swan-Ganz, and catheters, indwelling—with the following MeSH terms—randomization, random allocation, randomized controlled trial(s), randomized response technique, and (controlled) clinical trials, randomized. In addition, every citation for catheterization, central venous, and catheterization, Swan-Ganz from January 1985 to November 1996 was examined and the abstracts of potentially relevant citations were reviewed on line. EMBASE was searched for the years 1988 through 1996 using the terms heparin, catheter, and venous or arterial. After examining the full articles of all abstracts deemed potentially relevant, we reviewed the reference lists of each retrieved article and obtained the article of any reference considered to be a randomized controlled trial. Package inserts from catheter kits were searched for references regarding published and unpublished data. We also contacted companies manufacturing heparin-bonded catheters regarding other unpublished and published randomized controlled trials. In addition, we searched proceedings of the 1994 and 1995 Infectious Disease Society of America, and the American Society for Microbiology Interscience Conference on Antimicrobial Agents and Chemotherapy annual meetings from 1986 to 1996.

**Study Selection**

The following selection criteria were used to identify studies for inclusion in this analysis.

**Study Design:** Randomized controlled clinical trial with randomization by individual patient.

**Population:** Adult or pediatric patients.

**Intervention:** Prophylactic heparin infused through the catheter, given subcutaneously or bonded to the catheter.

**Outcomes:** Catheter patency, catheter thrombus or catheter-related vessel thrombosis, catheter colonization, catheter-related bacteremia, or septicemia.

**Excluded Studies:** Studies with >40% of patients excluded from analysis postrandomization.

**Data Abstraction**

Data abstraction was conducted by two investigators; disagreement was resolved by consensus. Data on the number of catheters and/or the numbers of patients were abstracted the way they were reported. Catheters were the unit of analysis when data were pooled. We asked the primary investigators to provide further information when the data necessary for critical appraisal and/or analysis were missing or unclear.

**A Priori Definitions**

**Duration of Catheter Patency:** The number of hours the catheters were in place.

**Catheter Thrombus:** Clot adherent to or occluding the catheter or a fibrin sleeve in the vessel around the catheter.

**Catheter-Related Vessel Thrombosis:** Partial or total occlusion of blood flow through the vessel.

**Catheter Colonization:** At least 15 cfu cultured from the catheter tip using the semiquantitative method of Maki et al.10

**Catheter-Related Sepsis or Bacteremia:** Catheter colonization as defined above with the same organism cultured from a peripheral blood culture.

**Assessment of Methodologic Quality**

Two investigators independently assessed the methodologic quality according to criteria in Table 1. To evaluate agreement, we calculated a quadratic weighted kappa for each quality item. Disagreements between two reviewers were resolved by a third reviewer.

**Data Analysis**

We combined data to estimate the relative risk (RR) and associated 95% confidence limits across studies using the DerSimonian and Laird random effects model.10a *A priori,* we decided that when the p value was >0.05, differences in RR ≥20% would represent a trend, and differences in RR of <20% would represent no difference between strategies.

We tested for heterogeneity (major differences in the apparent effect of the interventions across studies) using the method proposed by Fleiss.11 Using the null hypothesis that the RRs were the same across studies, a p value of >0.05 for the test of homogeneity is consistent with the fact that the difference in study results are due to the play of chance.

Because heparin bonding is only on the outside of some catheters and lasts from 30 min to 48 h depending on the type of bonding used (personal communications, technical support staff, Cook, Arrow, Medcomp, Abbott, and Baxter catheter manufacturing companies), we analyzed the data including heparin bonding and infused heparin and then excluding heparin bonding.

**Results**

**Study Identification and Selection**

Fifteen trials of central venous catheters were identified and 12 were included.12-23 Two trials of pulmonary artery catheters were identified and included.1,24 We excluded one central venous catheter trial with a dropout rate of >50% prior to assessment of thrombosis.25 One trial that used a heparin drip of 5 U/mL in both the treatment and control arms of a study comparing heparin bonded to nonbonded catheters26 was also excluded. Another article that added together the data from two randomized controlled trials reporting the effects of heparinized infuse on thrombotic complications to secondarily
Table 1—Study Design of Randomized Trials of Heparin Infusion and Bonding*

<table>
<thead>
<tr>
<th>Author, Year, Reference</th>
<th>Heparin Dose</th>
<th>Population</th>
<th>Quality Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central venous catheters</td>
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<tr>
<td>Fassolt et al, 1979^{20}</td>
<td>5,000 U q12h</td>
<td>Adults, medical and surgical</td>
<td>R UB No PRE</td>
</tr>
<tr>
<td>Fabri et al, 1982^{21}</td>
<td>3 U/mL TPN</td>
<td>Adults, surgical</td>
<td>R UB 3/49 PRE</td>
</tr>
<tr>
<td>Brismar et al, 1982^{12}</td>
<td>5,000 U q6h</td>
<td>Adults, gastroenterology</td>
<td>R UB 4/53 PRE</td>
</tr>
<tr>
<td>Ruggero et al, 1983^{22}</td>
<td>1 U/mL TPN</td>
<td>Adults, medical and surgical</td>
<td>R DB No PRE</td>
</tr>
<tr>
<td>Macoviak et al, 1984^{15}</td>
<td>1 U/mL TPN</td>
<td>Adults, medical</td>
<td>R DB No PRE</td>
</tr>
<tr>
<td>Fabri et al, 1984^{14}</td>
<td>3 U/mL TPN</td>
<td>Adults, medical</td>
<td>R UB No PRE</td>
</tr>
<tr>
<td>Efsing et al, 1983^{24}</td>
<td>Heparin bonded</td>
<td>Adults, surgical</td>
<td>R UB 46/159 PRE</td>
</tr>
<tr>
<td>Smith et al, 1991^{14}</td>
<td>50 U q12h</td>
<td>Children, oncology</td>
<td>RCO UB No PRE</td>
</tr>
<tr>
<td>Bailey, 1979^{16}</td>
<td>1 U/mL TPN</td>
<td>Adults, medical and surgical</td>
<td>R DB No PRE</td>
</tr>
<tr>
<td>Appelgren et al, 1996^{17}</td>
<td>Heparin bonded</td>
<td>Adults, medical and surgical</td>
<td>R DB 23/35 PRE</td>
</tr>
<tr>
<td>Monreal et al, 1996^{12}</td>
<td>2,500 U SQ q d</td>
<td>Adults, oncology, Port-a-Cath catheter (Sims Deltec; St. Paul)</td>
<td>R UB 3/32 PRE</td>
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<tr>
<th>Pulmonary artery catheters</th>
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<tr>
<td>Hoar et al, 1981^{1}</td>
<td>Heparin bonded</td>
<td>Adults, CABG surgery</td>
<td>R UB No PRE</td>
</tr>
<tr>
<td>Mangan, 1982^{24}</td>
<td>Heparin bonded</td>
<td>Adults, CABG surgery</td>
<td>R DB No PRE</td>
</tr>
</tbody>
</table>

*CABG=coronary artery bypass graft; SQ=subcutaneous

1Methodologic quality features: R=random; RCO= randomized crossover; DB= double blind; UB= unblinded; PRE= patients excluded po randonization

2Low molecular weight heparin.

examine infectious complications was excluded because the primary data were not abstractable.

The populations, interventions, number of catheters and number of patients, catheter types, and catheter management strategies of the studies included in the final analysis are described in Table 1. Many of these studies were performed prior to the development of standardized definitions of catheter-related infections, and thus we included outcomes that did not strictly adhere to our a priori definitions. Bailey^{16} reported any positive culture from the catheter tip without quantification. Brismar et al^{12} counted one catheter tip culture with <15 cfu as catheter colonization with bacteremia; however, since the same organism grew from the bloodstream, we included this under colonization and bacteremia. Appelgren et al^{17} did not report the minimum number of colony forming units used to define colonization. Huraib et al^{23} compared overall bacteremia rates in patients.

When possible, we excluded patients from the analysis if they were receiving nonheparin antithrombotic agents. However, in one included study by Efsing et al^{21} 66 of 99 patients—a similar number in each group—received dextran 70 as prophylaxis against thromboembolism (1 L on the day of operation, then 500 mL on the first and third postoperative days).

**Methodologic Quality Assessment**

Design features and methodologic quality of the studies included in this review are described in Table 1. Agreement regarding quality rating was good (quadratic weighted kappas of 0.74 to 1.00).

**Meta-analyses**

We combined data from trials using various doses of prophylactic heparin, including unfractionated heparin dosing regimens of 1 U/mL, 3 U/mL, 50 U q12 h, 5,000 U intermittently, and 2,500 U daily of subcutaneous low molecular weight heparin, and we also included heparin bonded catheters (Figs 1 and 2). Pooling the data from four trials, an assessment of the impact of heparin on the formation of a clot on or inside of the catheter or the formation of a fibrin sleeve around the catheter (Fig 1) reveals that heparin is associated with a strong trend for reducing catheter thrombus (RR, 0.66; 95% confidence interval [CI], 0.42, 1.05). The test for heterogeneity of variance was nonsignificant (p=0.681).

Seven trials assessed the impact of heparin on partial or total occlusion of vascular flow (Fig 1). Prophylactic heparin significantly decreases central venous catheter-related venous thrombosis by 57% (RR, 0.43; 95% CI, 0.23, 0.78). The test for heterogeneity of variance was nonsignificant (p=0.526). Significant reduction of deep venous thrombosis was still present after excluding the Efsing et al^{21} trial of heparin bonded catheters (RR, 0.44; 95% CI, 0.22, 0.87).

Three trials assessed the effect of heparin on central venous catheter colonization (Fig 2). Heparin significantly decreases bacterial colonization of the catheter (RR, 0.18; 95% CI, 0.06, 0.60). The test of homogeneity was nonsignificant (p=0.719). The sig-
significant benefit for heparin remained after the Appelgren et al. heparin bonded catheter trial was excluded (RR, 0.19; 95% CI, 0.04, 0.86). Four trials assessed the effect of heparin on central venous catheter-related bacteremia (Fig 2). There was a strong trend for a reduction in catheter-related bacteremia with use of heparin (RR, 0.26; 95% CI, 0.07, 1.03). The test for heterogeneity of variance was nonsignificant (p=0.859). This trend decreased when the Appelgren et al. heparin bonded study was excluded (RR, 0.33; 95% CI, 0.07, 1.56).

One study, not included in the meta-analyses of central venous catheters, compared two prophylactic heparin regimens for dialysis patients.23 Having trained nurses flush subclavian catheters with heparin 1 mL of 2,500 U in each lumen only after dialysis (three times per week) and changing the dressing once per week resulted in a significantly lower bacteremia rate (5% bacteremia rate) than having the hospital IV team flush the catheters with heparin 500 U in 5 mL normal saline solution in each catheter port three times per day and changing the dressing three times per week (15% bacteremia rate).

Two trials were included in the meta-analysis of pulmonary artery catheters. In catheters evaluated by visual inspection in cardiac surgery patients 55 to 155 min after placement, Hoar et al.1 found clot on 10 of 10 nonheparin bonded catheters vs 0 of 10 heparin bonded catheters. In catheters left in place for 18 to 26 h, Mangano24 found clot on 10 of 10 nonheparin bonded catheters whereas only 1 of 10 heparin bonded catheters had clot. Combining both trials, heparin bonding reduced the risk of catheter thrombus forming within the first 24 h by 92% (RR, 0.08; 95% CI, 0.02, 0.37).

**Discussion**

Use of heparin as an antithrombotic agent in catheters has been widespread for more than 20

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**Figure 1.** Effect of heparin on central venous catheter-related thrombotic complications.
years. Although it is clear that indwelling central venous and pulmonary artery catheters are thrombogenic, use of prophylactic anticoagulants is variable. In this systematic review, we found that prophylactic use of heparin significantly decreases central venous catheter-related thrombosis, decreases bacterial colonization of the catheter, and may decrease catheter-related bacteremia. Use of heparin bonding on pulmonary artery catheters reduces the risk of clot formation within the first 24 h of catheter placement.

Central venous catheter-related vessel thrombosis and catheter-related bacteremia are serious causes of morbidity. The methods used to diagnose thrombosis in these studies (line-o-grams and ultrasounds) are less sensitive than venography and the diagnosis of large-vessel thrombosis might have been underestimated. We combined all trials using varying prophylactic doses of heparin and prophylactic heparin, but it is clear from Figure 1 that trials using heparin at doses of 3 U/mL total parenteral nutrition (TPN), 5,000 U q 6 or 12 h, or 2,500 U of subcutaneous low molecular weight heparin every day decreased the risk of major vessel thrombosis and that lower doses may not be effective. Although we also found a significantly decreased risk of bacterial colonization of the catheter and an associated reduction in catheter-related bacteremia with use of heparin, these studies used variable definitions of catheter-related infections, and require confirmation by trials adhering to current stricter definitions.

Heparin, when bonded to the catheter surface, can decrease clot formation on pulmonary artery catheters for at least 24 h after insertion. Commercially available benzalkonium-heparin bonded pulmonary artery catheters lose the bonded heparin in a few hours (personal communications, technical support staff, Baxter and Abbott Corporations) and the in vitro antimicrobial activity within a few days. The newer heparin bonding method called Carmeda Bioactive Surface has been shown to last >4 months and was used by Appelgren et al. Further studies are needed to test whether this new technology decreases the risk of vascular thrombosis associated with prolonged use of pulmonary artery and central venous catheters.

Very low doses of warfarin have also been shown to be effective in reducing catheter-related thrombosis. Bern et al randomized 82 patients with solid tumors to receive or not receive 1 mg of warfarin beginning 3 days prior to catheter insertion and continuing for 90 days. The rates of venogram-proved thrombosis were 4 of 42 in the treatment

**Figure 2. Effect of heparin on central venous catheter-related infectious complications.**
group vs 15 of 40 in the control group with 15 having symptomatic thromboses. Unfortunately, warfarin therapy had to be discontinued in 10% of patients due to prolongation of the prothrombin time.

Prophylactic anticoagulation of central venous catheters decreases the risk of deep venous thrombosis. However, the best agent to use is still controversial. Warfarin, even in low doses, can excessively prolong coagulation parameters. Unfractionated heparin is associated with complications, including autoimmune thrombocytopenia that occurs much less frequently with low molecular weight heparin. Low molecular weight heparin has other benefits such as 99% bioavailability and no requirement for monitoring of coagulation parameters or blood levels once the appropriate prophylactic dose is established. To our knowledge, there is no drug known to interfere with the action of low molecular weight heparin, unlike warfarin. Administration of low molecular weight heparin at once-daily subcutaneous dosing is effective in preventing deep venous thrombosis. The incidence of bleeding associated with low molecular weight heparin prophylaxis in adult trauma patients at high risk is not increased over patients not receiving prophylaxis (1.7%). Unfortunately, the drug cost of low molecular weight heparin is much higher than unfractionated heparin.

Prophylactic heparin is beneficial in reducing catheter-related complications including deep venous thrombosis and bacterial colonization. However, various doses of subcutaneous and IV unfractionated and low molecular weight heparin and new methods of heparin bonding need further comparison to determine the most cost-effective strategy for reducing catheter-related thrombus and thrombosis.

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