Benefit of heparin in central venous and pulmonary artery catheters: a meta-analysis of randomized controlled trials

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

Searching
MEDLINE was searched from 1966 to October 1995 by cross-referencing the MeSH terms 'catheterization', 'central venous and catheterization', 'Swan-Ganz' and 'catheters, indwelling' with the following: 'randomization', 'random allocation', 'randomized controlled trial(s)', 'randomized response technique', and '(controlled) clinical trials, randomized'. Every citation for 'catheterisation', 'central venous and catheterization', and 'Swan-Ganz' from January 1985 to November 1996 was examined, and relevant abstracts were reviewed online. EMBASE was searched from 1988 to 1996 using the terms 'heparin', 'catheter', and 'venous' or 'arterial'. The reference lists from the retrieved articles were also reviewed. The package inserts from catheter kits were scrutinised and companies manufacturing bonded catheters were contacted. Searches were made of the annual meetings of the Infectious Disease Society for America (1994 and 1995) and the American Society for Microbiology's Interscience Conference on Antimicrobial Agents and Chemotherapy (1986 to 1996).

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of central venous and pulmonary artery catheter-related complications were included if the individual adult or paediatric patients were randomised. Studies with greater than 40% of patients excluded from analysis post-randomisation were excluded. Three retrieved trials were excluded for the following reasons: a drop-out rate of greater than 50%; a heparin drip was used in both treatment arms; and the primary data were not extractable.

Specific interventions included in the review
Prophylactic heparin delivered in the following ways:

- infusion through central venous and pulmonary artery catheters in doses ranging from 50 to 5,000 units every 12 hours;
- added to total parenteral nutrition in doses ranging from 1 to 3 units/mL;
- subcutaneous administration in doses of 2,500 units, four times per day; and
- bonded to the catheter.

Participants included in the review
Adults or paediatric patients whose treatment included the insertion of central venous catheters and pulmonary artery catheters. The studies included children and adults receiving oncology treatment, and adults with medical, surgical (including coronary artery bypass graft) and gastroenterological illness.

Outcomes assessed in the review
The following outcomes were assessed: catheter thrombus or fibrin sheath formation; catheter-related deep vein thrombosis; catheter colonisation; and catheter-related bacteraemia and sepsis. The following a priori definitions were formulated:

duration of catheter patency, defined as the number of hours the catheters were in place;
catheter thrombosis, defined as clot adhering to or occluding the catheter or a fibrin sleeve in the vessel around the catheter;

catheter-related vessel thrombosis, defined as partial or total occlusion of blood flow through the vessel;

catheter colonisation, defined as at least 15 cfu cultured from catheter tip using the semi-quantitative method of Maki et al. (see Other Publications of Related Interest no.1).

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
Validity was assessed on the basis of random allocation, the degree of blinding, and the percentage of patients excluded post-randomisation. Two investigators independently assessed validity, with any disagreements being resolved by a third reviewer.

Data extraction
The data were extracted by two investigators, and any disagreements were resolved by consensus. The following data were extracted: the number of catheters and/or the number of patients, heparin dose, and study population. Missing data were sought from the primary investigators.

Methods of synthesis
How were the studies combined?
The relative risk (RR) and 95% confidence intervals (CIs) were calculated using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
Heterogeneity was tested using the method proposed by Fleiss (see Other Publications of Related Interest no.3). The data were analysed for heparin bonding and infused heparin, and then analysed excluding heparin bonding.

Results of the review
Twelve RCTs of central venous catheters and 2 RCTs of pulmonary artery catheters were included. Both used bonded heparin.

Many of the studies were conducted prior to the development of standardised definitions of catheter-related infections. Thus, outcomes were included that did not adhere strictly to the a priori definitions. The agreement relating to quality rating was estimated as a quadratic weighted kappa of 0.74 to 1.00. Central venous catheters.

Catheter thrombus or fibrin sheath (4 RCTs): the RR was 0.66 (95% CI: 0.42, 1.05) and the heterogeneity (P) was 0.681.

Catheter-related deep vein thrombosis (7 RCTs): the RR was 0.43 (95% CI: 0.23, 0.78) and the heterogeneity (P) was 0.526. After excluding the trial of bonded heparin, the RR was 0.44 (95% CI: 0.22, 0.87).

Catheter colonisation (3 RCTs): the RR was 0.18 (95% CI: 0.06, 0.60) and the heterogeneity (P) was 0.719. After excluding the trial of bonded heparin, the RR was 0.19 (95% CI: 0.04, 0.86).

Catheter-related bacteraemia and sepsis (4 RCTs): the RR was 0.26 (95% CI: 0.07, 1.03) and the heterogeneity (P) was 0.859. After excluding the trial of bonded heparin, the RR was 0.33 (95% CI: 0.07, 1.56).

Pulmonary artery catheters: catheter thrombosis within first 24 hours: the RR was 0.08 (95% CI: 0.02, 0.37).
Authors' conclusions
Heparin administration effectively reduced 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.

CRD commentary
The aim and the inclusion criteria were clearly stated. A number of sources were searched for relevant studies. The outcomes were defined. Details of the methods used to assess validity and to extract the data were given. Heterogeneity was assessed statistically. A meta-analysis was appropriate in the absence of significant statistical heterogeneity. The results were clearly displayed. The discussion included consideration of the following limitations of the review: the methods used to diagnose thrombosis in the studies (line-o-grams and ultrasound) were less sensitive than venography and may have underestimated the diagnosis of large vessel thrombosis; and studies used variable definitions of catheter-related infections.

It was not stated whether any language restrictions were applied to include the studies. More comprehensive details of the included studies, such as sample size, would have been welcome. It was unclear whether the analysis was undertaken on an intention to treat basis. The 95% CIs were wide for some outcomes, presumably reflecting the small sample size. In addition, they did not exclude a result of no effect of heparin used with central venous catheters on catheter thrombus and catheter-related bacteraemia and sepsis.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors consider that further trials that adhere to stricter current definitions of catheter-related infections are required. Investigation of a newer heparin bonding method is also required.

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Other publications of related interest

This additional published commentary may also be of interest. Kruse JA. Review: heparin reduces central venous and pulmonary artery catheter clots. Evid Based Med 1998;3:111.
Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Anticoagulants /administration & dosage /therapeutic use; Catheterization, Central Venous /instrumentation; Catheterization, Swan-Ganz /instrumentation; Child; Heparin /administration & dosage /therapeutic use; Humans; Infusions, Intravenous; MEDLINE; Randomized Controlled Trials as Topic; Retrospective Studies; Risk Factors; Thrombophlebitis /etiology /prevention & control; Treatment Outcome; United States

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.