Thrombosis prophylaxis in patient populations with a central venous catheter
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CRD summary
This review assessed the effectiveness of antithrombotic agents in preventing central venous catheter-related thrombosis. The authors concluded that the limited evidence suggested that heparin did not significantly reduce thrombosis in patients receiving parenteral nutrition, but that warfarin and dalteparin did significantly reduce thrombosis in cancer patients. The small number of studies and the lack of a validity assessment limit the evidence presented.

Authors' objectives
To assess the effects of antithrombotic agents on symptomatic and asymptomatic thrombosis related to central venous catheters (CVCs) in patients receiving parenteral nutrition (PN), patients with cancer and patients in intensive care units (ICUs).

Searching
MEDLINE (from 1966 to May 2002) and EMBASE (from 1988 to May 2002) were searched; the search terms were listed. The reference lists in identified studies were also checked.

Study selection
Study designs of evaluations included in the review
Prospective trials were eligible for inclusion if at least 60% of patients had an imaging study performed that could be included in the analysis. The included studies were randomised controlled trials (RCTs) and cohort studies. Where stated, the duration of follow-up in the included studies ranged from 5 days to about 2.5 years.

Specific interventions included in the review
The included studies were of thromboprophylaxis and no thromboprophylaxis. Studies that used heparin flushes or antithrombotic agents in therapeutic or prophylactic doses had to report the amount of drugs given. The included studies used heparin, warfarin, or low molecular weight heparin (dalteparin) for thromboprophylaxis.

Participants included in the review
Studies of specific populations (patients receiving PN, patients with cancer and critically-ill patients in ICUs) of adult or paediatric patients with a CVC in the subclavian, jugular or femoral vein were eligible for inclusion. Studies in which CVCs were inserted at other sites had to report the incidence for thrombosis for that site. Studies of patients undergoing stem cell transplantation were excluded. The included studies involved participants with CVCs inserted in the subclavian, jugular or femoral vein. In the review, catheters were subdivided into three groups: totally implanted subcutaneous catheters, tunneled catheters, and catheters that were not tunneled but went directly into the vein.

Outcomes assessed in the review
Studies that assessed thrombosis (partial or total) in blood vessels in which a CVC was present, or had been present in the previous month, were eligible for inclusion. Thrombosis had to be confirmed by regular imaging techniques (ultrasound or (contrast) venography) or radionuclide venography. Studies using mixed groups had to report thrombosis rates separately for each type of patient and for each different type of CVC regimen. The review assessed asymptomatic and symptomatic thrombosis and bleeding.

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

Assessment of study quality
Validity was not fully assessed. The authors did, however, grade studies using a hierarchy of study design: level 1 studies were RCTs that compared antithrombotic agents with each other, placebo or no treatment; level 2 studies were prospective cohort studies or RCTs randomised for possible prognostic factors and not for antithrombotic treatment. Level 2 studies were subdivided into cohorts receiving no anticoagulation (this category included heparin locks), cohorts receiving heparin flushing, and cohorts receiving another antithrombotic treatment (this category included heparin-bonded catheters). Studies using different catheter regimens, or both heparin-bonded and standard catheters, were treated as separate cohorts. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

Data extraction

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The extracted data included: study design; type of patients and catheters; the number of cases (patients or catheters); the use of anticoagulants and/or heparin flush and dosage; the duration of the observation; the imaging method used to detect thrombosis; and results. Data were extracted for the incidence of asymptomatic or symptomatic thrombosis, as well as symptomatic thrombosis alone. The relative risk (RR) and 95% confidence interval (CI) was calculated for each study.

Methods of synthesis

How were the studies combined?

The studies were grouped according to the patient population (PN, cancer, or ICU) and by study design (level 1 or 2). Level 1 studies that used similar anticoagulant treatments were combined using a meta-analysis. The pooled RR and 95% CI were calculated using a random-effects model (DerSimonian and Laird).

How were differences between studies investigated?

The meta-analysis in patients receiving PN was repeated after excluding the RCT that used additional heparin flushes in both treatment groups. Differences in rates of thrombosis for cohort studies in patients with cancer were discussed in relation to the duration of observation.

Results of the review

Twenty-one studies were included. There were 5 RCTs (204 patients) and one cohort study (30 patients) in patients receiving PN; 2 RCTs (n=150 reported in text, 111 according to tables) and 10 cohort studies (2,015 patients) in patients with cancer; and 4 cohort studies (233 patients) in ICU patients.

Patients receiving PN.

Level 1 studies (5 RCTs, 206 cases from 204 adult patients): the meta-analysis showed a non statistically significant trend towards a reduction in thrombosis (as seen on imaging) with heparin added to PN, compared with control. The RR was 0.77 (95% CI: 0.11, 5.48). After excluding the RCT that used additional heparin flushes in both treatment groups, there was no longer a trend towards reduced thrombosis with heparin; however, statistically significant heterogeneity was detected (P=0.026). The RR was 1.00 (95% CI: 0.06, 17.09).

Level 2 studies: the results for one level 2 study (30 patients) were also reported.

Bleeding: 3 RCTs reported no bleeding complications in patients who received heparin, while one RCT reported three minor bleeding episodes in two patients with underlying bowel disease.

Patients with cancer.

Level 1 studies (2 RCTs, 150 adult patients): the studies used different treatments and the results were not pooled. Both studies found that thromboprophylaxis significantly reduced thrombosis (asymptomatic plus symptomatic) compared with standard catheter care by heparin flushing; one RCT (121 patients) found that 1 mg/day of warfarin significantly reduced thrombosis (RR 0.25, 95% CI: 0.09, 0.70), while the other (29 patients) found that 2,500 IU/day dalteparin significantly reduced thrombosis (RR 0.10, 95% CI: 0.01, 0.71).
Level 2 studies: the results of these (7 cohorts used no anticoagulant, 2 cohorts used heparin flushing, 2 cohorts used low-dose warfarin and 1 cohort used heparin infusion) were also reported.

Bleeding: bleeding did not occur in patients in the 2 RCTs. One level 2 study reported no bleeding in any patients; the other level 2 studies did not assess bleeding.

Patients in ICUs.

No level 1 studies were identified.

Level 2 studies: one study (70 adults without anticoagulation) found thrombosis in 8.5% of femoral veins after femoral vein catheter removal. Three studies in children found variable rates of thrombosis; one non randomised study (50 children) found thrombosis (asymptomatic plus symptomatic and symptomatic alone) in 8% children with heparin-bonded and 44% with standard catheters; one study (93 children) found thrombosis (asymptomatic plus symptomatic) in 18.3% of children with heparin flushing; one study (20 children) found thrombosis (asymptomatic plus symptomatic) in 35% of children with heparin-bonded catheters.

Bleeding: none of the studies reported on bleeding.

Authors' conclusions
The findings from a small number of studies showed that the addition of heparin to PN did not significantly reduce CVC-related thrombosis, while warfarin and dalteparin did significantly reduce thrombosis in cancer patients with CVC. Few studies examined CVCs in intensive care patients. The authors also concluded that prophylactic anticoagulation did not appear to increase bleeding in patients with CVCs.

CRD commentary
The review addressed a clear question in terms of the participants, study design and outcomes. Inclusion criteria for the interventions were not explicitly stated. Only two databases were searched and this might have resulted in the omission of other relevant studies. It was unclear whether any language limitations were applied and no attempts were made to minimise publication bias. The methods used to select the studies and extract the data were not described, so it is not known whether any efforts were made to reduce errors and bias. Validity was not systematically assessed.

The studies were appropriately grouped according to the type of patient and study design. Only studies with similar treatment regimes were combined in a meta-analysis. The methods used to assess heterogeneity were not reported, and heterogeneity was not consistently reported for all meta-analyses. When heterogeneity was significant, no attempts were made to explore potential causes for it. The conclusions regarding dalteparin were based on one small study (29 patients). The evidence was limited by the small number of studies and the lack of a validity assessment.

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

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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.