Intravenous heparin in combination with antibiotics for the treatment of deep vein septic thrombophlebitis: a systematic review
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CRD summary
This review examined the effects of heparin for the treatment of deep vein septic thrombosis. The authors tentatively concluded that the timely use of heparin with appropriate antibiotics may be beneficial. The overall reliability of this conclusion is uncertain, given the lack of controlled evidence and methodological weaknesses in the review process.

Authors' objectives
To examine the effects of heparin for the treatment of deep vein septic thrombosis.

Searching
PubMed, Current Contents and the Cochrane CENTRAL Register were searched for eligible studies; the search terms were reported. Search dates were reported only for PubMed (1950 to 2005). The reference lists of retrieved articles were also examined. Only articles in English or French were reviewed.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), comparative trials and case series were eligible for inclusion. Case reports and series with fewer than 5 participants were excluded.

Specific interventions included in the review
Studies of heparin in addition to proper antibiotic use as therapy for septic thrombophlebitis were eligible for inclusion. The included studies used standard or low molecular weight heparin, administered intravenously for septic thrombophlebitis in pelvic veins or subcutaneously for veins at other body sites. Where stated, heparin was added to the antimicrobial treatment regimen either on clinical suspicion of thrombophlebitis or a few days later when antibiotic therapy alone was deemed to have failed. A wide range of antibiotics was used, all given intravenously. The commonly used antibiotics were cephalothin, oxacillin, combination of ampicillin/gentamycin/clindamycin, and vancomycin.

Participants included in the review
Studies of patients with deep vein septic thrombophlebitis were eligible for inclusion. Studies of patients with thrombophlebitis of superficial veins were excluded. The participants in the included studies had a wide range of disorders and included women who were postpartum or post gynaecological surgery, children with otitis media or undisclosed disorders, intravenous drug users and patients with infections of the head and neck. The range of affected body sites included pelvic, internal jugular, femoral, iliac, cerebral and subclavian veins, and the inferior vena cava. A minority of studies confirmed the diagnosis by radiological investigation in all participants.

Outcomes assessed in the review
Studies that reported the effectiveness and toxicity of heparin and/or mortality rates were eligible for inclusion. The outcomes reported were mortality, time to defervescence (abatement of fever), need for surgical intervention and adverse effects.

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

Assessment of study quality
The authors did not state that they assessed validity.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on the mortality rate, the mean or median and range of time to defervescence after the initiation of antibiotic treatment and/or after the introduction of heparin, and the rate and nature of reported adverse effects.

**Methods of synthesis**
**How were the studies combined?**
The data were summarised in a brief narrative synthesis, grouped by treatment location (pelvic veins or other body sites).

**How were differences between studies investigated?**
Major differences between the studies in terms of design and/or clinical characteristics were highlighted in the body of the text and summary tables.

**Results of the review**
Fourteen studies (n=216) were included: 1 RCT (n=15) and 13 case series (n=201)

Study quality was not reported in the review, except to emphasise that the sole RCT (n=15) was the only comparative study; all the other studies were case series.

**Mortality.**
Mortality was reported in 11 studies (n=115). Two patients died after treatment with heparin: one of septic shock and one of polymicrobial infection and renal tubular necrosis.

**Time to defervescence.**
Values for the time to defervescence were reported in 11 studies (n=184). Estimates were reported as mean or median values, and varied widely from a mean of 37 hours (standard deviation 37) to a median of 15 days (range: 10 to 50). This was partly attributed to clinical heterogeneity in the timing of the addition of heparin to the treatment regimen. No conclusive estimates of the time to defervescence could be obtained. The only comparative data (from the RCT) showed no statistically significant difference in total time to defervescence in postpartum women with septic thrombosis of ovarian veins between those on antibiotics alone and those who (after 5 days of fever) were given heparin in addition.

**Need for surgical intervention.**
Overall, 14 patients required surgical intervention in addition to antibiotics and heparin; this comprised either drainage of abscesses (12 women) or thrombectomy/ligation of the affected vein (2 women). The authors did not state how many studies reported this outcome.

**Adverse events.**
Seven studies (n=118) reported on the adverse effects of heparin. Three of the 118 women experienced such events, which comprised subcutaneous haemorrhage (n=1) or unspecified adverse events (n=2).

**Authors’ conclusions**
The timely use of heparin with appropriate antibiotics may be beneficial for treating patients with septic thrombophlebitis, but the lack of controlled evidence precludes any certainty.
CRD commentary
The review question and inclusion criteria were clear and sufficient information was given about the indications for intervention, medication regimens and findings of the primary studies. The search was adequate, though potentially limited by language restrictions and the failure to seek unpublished studies. It was not clear whether appropriate procedures for the study selection, quality assessment and data extraction processes were undertaken, thus the potential for reviewer bias and error cannot be determined. There was minimal detail about the study design and no evidence of a systematic evaluation of the validity of the included studies; this makes it difficult to assess the reliability of the findings.

The narrative synthesis of the results was appropriate, though the results of the sole RCT were not highlighted. The authors' conclusions tentatively favour the use of heparin. However, given the uncertain quality of the included studies, the lack of controlled evidence and the inconclusive findings of the sole RCT, the overall reliability of their conclusions is uncertain. The authors appropriately highlight the need for controlled studies in this area.

Implications of the review for practice and research
Practice: The authors stated that the administration of heparin, in combination with antibiotics, should be considered early in the treatment of patients with septic thrombophlebitis. However, no good-quality evidence was presented in the review to support this recommendation.

Research: The authors stated that comparative trials are needed to determine the effectiveness, safety and appropriate timing of heparin in the treatment of patients with septic thrombophlebitis.

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the reliability of the review and the conclusions drawn.