A comparison of observational studies and controlled trials of heparin in ulcerative colitis

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CRD summary
This review assessed the effects of heparin in ulcerative colitis and compared findings from observational and controlled studies. The authors concluded that although findings from controlled and observational studies differed, randomised controlled trials provided no evidence of a benefit with heparin. The limited search and limited evidence from a few small studies make it difficult to assess the reliability of the authors' conclusions.

Authors' objectives
To assess the effects of heparin in patients with ulcerative colitis and to compare findings from observational and controlled studies.

Searching
Studies were identified through a search of MEDLINE, a manual search of Index Medicus and checks of reference lists of published reports up to July 2003. The search terms were reported. All available English and non-English abstracts were considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and observational studies were eligible for inclusion. Case reports and case series were excluded.

Specific interventions included in the review
Studies of low molecular weight heparin (LMWH) or unfractionated heparin (UFH) were eligible for inclusion. The included controlled trials compared UFH (0.75 to 1 mg/kg per day) with methylprednisolone (0.75 mg/kg per day) for 10 days, or compared UFH (25 to 40,000 U/day intravenously) with hydrocortisone (200 mg intravenously four times daily, followed by 40 mg oral prednisolone) for 21 days. Observational studies used mainly LMWHs (nadroparine calcium, enoxaparin, dalteparin) in conjunction with glucocorticoids or mesalamine. Other observational studies used UFH in conjunction with either sulfasalazine or glucocorticoids. The observational studies lasted between 56 and 84 days.

Participants included in the review
Studies of patients with ulcerative colitis were eligible for inclusion.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not specified. The primary review outcome was clinical improvement and/or remission.

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
The RCTs appear to have been assessed using criteria described by Chalmers et al. that included assessor blinding; no further details were reported.

The authors did not fully state how the validity assessment was performed.
Data extraction
Two reviewers independently extracted the data and resolved any disagreements through consensus. The numbers of patients with the outcomes of interest were extracted from each study.

Methods of synthesis
How were the studies combined?
Observational studies and RCTs were pooled separately. For observational studies, the mean percentage of patients achieving remission was calculated. For RCTs, pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using both fixed-effect (Mantel-Haenszel) and random-effects (DerSimonian and Laird) models.

How were differences between studies investigated?
For the meta-analyses of the RCTs, statistical heterogeneity was assessed; forest plots were presented for both the fixed-effect and random-effects meta-analyses. Differences between observational and controlled studies were discussed with respect to interventions, cointerventions and study duration.

Results of the review
Two RCTs (n=45) and 5 observational studies (n=70) were included.

In terms of study quality, both RCTs used blinded outcome assessment.

The RCTs showed no statistically significant differences between heparin and glucocorticoids using either the random-effects model (OR 0.34, 95% CI: 0.08, 1.49) or the fixed-effect model (OR 0.21, 95% CI: 0.06, 1.38). No significant heterogeneity was found.

The observational studies gave a pooled cure rate of 87.7% (range: 80 to 100).

Authors' conclusions
The RCTs showed no evidence of a beneficial effect of heparin in the treatment of ulcerative colitis. The results from the controlled trials differed from those of the observational studies.

CRD commentary
The review addressed a clear question that was broadly defined in terms of the participants, intervention and study design; inclusion criteria for the outcomes were not explicitly reported but the primary review outcome was stated clearly. Few sources were searched and the search was limited to published studies, thus the authors might have missed some relevant studies. The search was not restricted by language but no attempts were made to minimise publication bias. Methods were used to minimise reviewer errors and bias in the extraction of data, but it was unclear whether similar steps were taken at the study selection stage. Validity appears to have been assessed using an established checklist. However, it seems that only RCTs were assessed and, even then, insufficient details were provided for the reader to judge the quality of the included studies.

There was inadequate information on the included studies: the definitions used for ulcerative colitis and for clinical improvement or remission, as well as the characteristics of the patients, were not reported. As such, clinical heterogeneity amongst the studies and the generalisability of results could not be assessed. Furthermore, it was not clear whether the RCTs were sufficiently similar for a meta-analysis to be appropriate. The findings were based on a small number of patients in a small number of studies, which suggests a potential lack of statistical power of the meta-analyses to detect a difference between treatment groups. It is difficult to assess the reliability of the authors' conclusions given the limited search and lack of complete reporting of review methods.

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