Meta-analysis: the utility and safety of heparin in the treatment of active ulcerative colitis

Shen J, Ran Z H, Tong J L, Xiao S D

CRD summary
The review concluded that the administration of heparin in participants with ulcerative colitis is safe, but there is no additional benefit over conventional therapy. Although the authors’ conclusions appear to follow from the data presented, clinical differences between the studies, particularly with regard to the specific treatment used, may affect their reliability.

Authors' objectives
To assess the efficacy and safety of heparin as a supplemental therapy, in comparison with conventional therapy, in patients with ulcerative colitis (UC).

Searching
MEDLINE (1966 to January 2007), EMBASE (1980 to January 2007), the Cochrane Controlled Trials Register (Issue 1, 2007), databases on Ovid (1950 to January 2007), BIOSIS Previews (1996 to December 2006) and the Chinese Biomedical Database (1981 to December 2006) were searched; the search terms were reported. In additional, the reference lists of review articles and original studies were screened for additional studies. Abstracts of major gastroenterological meetings, such as Digestive Disease Week of the American Gastroenterological Association and the World Congress of Gastroenterology, were handsearched. Authors were also contacted for additional unpublished studies. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Abstracts and meeting reports were also included. Studies that did not provide details on patient selection, allocation, study design, outcome and measurement methods were excluded.

Specific interventions included in the review
Studies evaluating heparin in comparison with conventional therapy or placebo were eligible for inclusion. Conventional therapy included aminosalicylates, steroids or/and azathioprine with or without placebo. Heparin included unfractionated heparin (UFH), low molecular weight heparin (LMWH), or heparin plus conventional treatment. The exact dosage, regimen and type of heparin or conventional therapy varied between the studies.

Participants included in the review
Studies evaluating adult patients undergoing treatment for active UC were eligible for inclusion. The degree of UC varied between the studies and included mild, moderate or severe. Subgroups of patients with Crohn’s disease were excluded from the analyses.

Outcomes assessed in the review
Studies that assessed the response rate, complete response (CR), partial response (PR), clinical disease activity index, endoscopic assessment, histologic assessment and adverse events were eligible for inclusion.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies from full papers and resolved any disagreements on inclusion through discussion with a third author.

Assessment of study quality
Validity was assessed and scored using the Jadad scale, which considers the reporting and handling of randomisation, double-blinding, and description of withdrawals and drop-outs. The maximum possible score was 5 points. Studies scoring less than 3 were deemed to be of a low quality. Two reviewers independently assessed validity and resolved any disagreements through discussion with a third reviewer.
Data extraction
The data were extracted onto a standardised form. The authors did not state how many reviewers performed the data extraction. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported using intention-to-treat data.

Methods of synthesis
How were the studies combined?
Pooled ORs and 95% CIs were calculated using a fixed-effect model (DerSimonian and Laird), except in the event of significant heterogeneity (0.10 or less) where a random-effects model was used instead. Subanalyses were conducted separately for trials evaluating UFH and LMWH. Sensitivity analyses examined the effects of removing one or more studies from the analysis. Publication bias was assessed using funnel plots.

How were differences between studies investigated?
Heterogeneity was assessed using the chi-squared and I-squared tests. Sensitivity analyses were conducted by estimating the OR in the absence of one or more studies.

Results of the review
Eight RCTs (n=454) were included. Six studies (n=343) were included in the meta-analysis.

Five studies scored a maximum of 5 points for methodological quality and three scored 3 points. There was some evidence of publication bias.

There were no statistically significant differences between heparin supplementation and conventional therapy (OR 0.78, 95% CI: 0.50, 1.21) in response rates. Sensitivity analyses showed similar effects. There were no significant differences for clinical, endoscopic, histologic or serologic evaluations between either heparin or conventional groups.

Treatment with UFH was significantly more effective than conventional therapy (OR 0.26, 95% CI: 0.07, 0.93). There was no significant difference between groups receiving LMWH compared with conventional therapy (OR 0.92, 95% CI: 0.57, 1.47). There were also no significant differences between heparin and placebo (3 studies) or between heparin and conventional therapy (3 studies).

There was no evidence of significant heterogeneity in any of these analyses.

There were no significant differences between heparin and conventional treatment for clinical score (6 out of 7 studies), endoscopic score (6 out of 7 studies), histologic score (all 4 studies) and C-reactive protein (all 3 studies). One of the 2 studies of erythrocyte sedimentation reported a significant reduction, but only in the conventional treatment group and not the heparin group.

There were no significant differences in adverse events between groups in any trials. Serious adverse events included rectal bleeding and nausea.

Authors' conclusions
The results suggest that the administration of heparin in participants with UC is safe, but there are no additional benefits over conventional therapy.

CRD commentary
The review question was clear and supported by detailed inclusion and exclusion criteria. Several relevant sources were searched and attempts were made to locate unpublished studies, although a formal assessment provided some evidence of publication bias. Methods were used to minimise reviewer error and bias in the study selection and validity assessment processes, but it is not clear whether similar steps were employed for the data extraction. Validity was assessed using an established checklist, although only the composite score was presented; this makes it difficult for the reader to judge the validity of the studies for themselves. Clinical heterogeneity was evident, with variations in the degree of UC, heparin type and dose, and conventional treatment type and dose. The authors acknowledged that the various types of LMWH included in the studies differ significantly in their biologic properties, and this may lead to different effects. Therefore, although the authors’ conclusions appear to follow from the data presented, clinical
differences between the studies, particularly with regard to the specific treatment used, may affect their reliability.

**Implications of the review for practice and research**

Practice: The authors stated that adjuvant heparin administration offers no added benefit to patients with UC.

Research: The authors did not state any implications for research.

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