

Is low-molecular-weight heparin more effective than unfractionated heparin for haemofiltration?

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SUMMARY STATEMENT:

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REQUEST:

Is low-molecular-weight heparin more effective than unfractionated heparin for haemofiltration?

REQUESTED BY:

Angela O'Brien, Registered Nurse, Intensive Care Unit, Monash Medical Centre, Clayton.

METHODOLOGY

Search Strategy

The Centre for Clinical Effectiveness defined the 'best available evidence' as that research we can identify that is least susceptible to bias. We determine this according to pre-defined NHMRC criteria (see Appendix).

First we search for systematic reviews, evidence-based clinical practice guidelines, or health technology assessments, and randomised controlled trials. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalisable, or have other methodologic difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, and narrative reviews and consensus statements, in our reports we do not critically appraise them. Some studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

Details of Evidence Request:

Patients	Patients requiring haemofiltration
Interventions	Low molecular weight heparin
Comparisons	Unfractionated heparin
Outcomes	All relevant

Search terms:

Field of focus	Search term
Patient-related	Hemofilt/er/rate/ration/ering/ed, Haemofilt/er/rate/ration/ering/ed
Intervention/Comparison-related	Heparin, low molecular weight heparin, LMW heparin, clexane, enoxaparin, tedelparin, nadroparin, fragmin, dalteparin, fraxiparin.

Resources Searched

We searched the following databases and Internet websites:

- Cochrane Library CD-ROM- Issue 1, 2001
- Best Evidence (OVID)- 1991 to February 2001
- Medline (OVID)- 1966 to Dec Week 4, 2000
- CINAHL (OVID)- 1982 to January 2001
- Current Contents (OVID)- 1993 Week 26 to 2001 Week 09
- PreMedline (OVID)- February 16, 2001
- Journals@ Ovid Full Text- February 22, 2001
- National Guidelines Clearinghouse- February 23, 2001
- Australasian Medical Index- February 23, 2001
- Turning Research into Practice (TRIP) database- February 23, 2001

Refinements, Searching & Reporting Constraints:

We included items of evidence that were available to us on 23 February 2001. We only included articles published in the last 10 years. Critical appraisal was performed on the subset of studies published in English. We included studies that concentrated on haemofiltration and excluded studies concentrating on haemodialysis.

RESULTS:

From our sources we identified 1 articles suitable for critical appraisal which we categorised as follows:

Study Design	Number included
Systematic reviews or meta-analyses	0
Evidence-based clinical practice guidelines	0
Randomised controlled trials	1

Articles were excluded for the following reasons:

Reason for exclusion	Number
Level III evidence	2
Narrative Reviews or Opinion	3
Non-English	2
Haemodialysis	5
Did not include both types of heparin	8
Published prior to 1990	2
Total	22

We are reasonably confident these articles represent the most important findings published to date based on our refinements, searching and reporting constraints.

EVIDENCE SUMMARIES

Format

Evidence summaries are in the form of spreadsheets reproduced at the end of this report. Each spreadsheet contains the article citation, the study design, patient description, scientific validity of the article, results, and pertinent remarks from the authors and Centre for Clinical Effectiveness reviewer.

REFERENCES

1. National Health and Medical Research Council. A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines. Canberra: Commonwealth of Australia, 1999.

ARTICLES CRITICALLY APPRAISED FOR THIS REPORT

Reeves, J. H., B. N. Cumming, et al. (1999). "A controlled trial of low-molecular-weight heparin (dalteparin) versus unfractionated heparin as anticoagulant during continuous venovenous hemodialysis with filtration." Critical Care Medicine October 27(10): 2224-2228.

ARTICLES NOT CRITICALLY APPRAISED

Level III evidence

Schrader, J., W. Stibbe, et al. (1990). "Low molecular weight heparin versus standard heparin. A long-term study in hemodialysis and hemofiltration patients." ASAIO Transactions 36(1): 28-32.

Schrader, J., R. Valentin, et al. (1985). "Low molecular weight heparin in hemodialysis and hemofiltration patients." Kidney International 28(5): 823-9.

Narrative Review or Opinion

Renaud, H., P. Moriniere, et al. (1985). "Low molecular weight heparin in haemodialysis and haemofiltration--comparison with unfractionated heparin." Proceedings of the European Dialysis & Transplant Association - European Renal Association 21: 276-80.

Schrader, J., M. Kandt, et al. (1986). "Comparison of unfractionated heparin and low molecular weight heparin during long-term use in chronic haemodialysis and haemofiltration patients." Haemostasis 16(Suppl 2): 48-58.

Spiegel, D. M. M. D. and R. J. M. D. Anderson (1999). "Is low-molecular-weight heparin useful for venovenous hemofiltration in the intensive care unit? [Editorial]." Critical Care Medicine October 27(10): 2316-2317.

Non-English

Journois, D., D. Safran, et al. (1990). "[Comparison of the antithrombotic effects of heparin, enoxaparin and prostacycline in continuous hemofiltration]." Annales Francaises d Anesthesie et de Reanimation 9(4): 331-7.

Schrader, J., J. Rieger, et al. (1985). "[Use of low molecular-weight heparin in hemodialysis patients]." Klinische Wochenschrift 63: 49-55.

Haemodialysis

- Abramson, S. and J. L. Niles (1999). "Anticoagulation in continuous renal replacement therapy." Current Opinion in Nephrology & Hypertension **8**(6): 701-7.
- Camici, M., R. Giordani, et al. (1998). "Safety and efficacy anticoagulation in extracorporeal hemodialysis by simultaneous administration of low-dose prostacyclin and low molecular weight heparin." Minerva Medica **89**(11-12): 405-9.
- National Kidney Foundation. (1997). "Clinical practice guidelines for hemodialysis adequacy." American Journal of Kidney Disease **30**(3 Suppl 2): S15-S66.
- Janssen, M. J. F. M., J. K. Deegens, et al. (1996). "Citrate compared to low molecular weight heparin anticoagulation in chronic hemodialysis patients." Kidney International March **49**(3): 806-813.
- Sagedal, S., A. Hartmann, et al. (1999). "A single dose of dalteparin effectively prevents clotting during haemodialysis." Nephrology, Dialysis, Transplantation **14**(8): 1943-1947.

Did not include both types of heparin

- de Pont, A.-C. J. M. M. D., H. M. M. D. P. Oudemans-van Straaten, et al. (2000). "Nadroparin versus dalteparin anticoagulation in high-volume, continuous venovenous hemofiltration: A double-blind, randomized, crossover study." Critical Care Medicine February **28**(2): 421-425.
- Gretz, N., M. Quintel, et al. (1995). "Low-dose heparinization for anticoagulation in intensive care patients on continuous hemofiltration." Contributions to Nephrology **116**: 130-5.
- Kozeklangenecker, S. A., S. C. Kettner, et al. (1998). "Anticoagulation with prostaglandin e-1 and unfractionated heparin during continuous venovenous hemofiltration." Critical Care Medicine **26**(7): 1208-1212.
- Langenecker, S. A., M. Felfernig, et al. (1994). "Anticoagulation with prostacyclin and heparin during continuous venovenous hemofiltration." Critical Care Medicine **22**(11): 1774-81.
- Leslie, G. D., I. G. Jacobs, et al. (1996). "Proximally delivered dilute heparin does not improve circuit life in continuous venovenous haemodiafiltration." Intensive Care Medicine **22**(11): 1261-4.
- Lorenzini, J. L., M. Freysz, et al. (1991). "Continuous hemofiltration with a low molecular weight heparin, enoxaparine: report on two cases." International Journal of Clinical Pharmacology, Therapy, & Toxicology **29**(3): 89-91.
- Martin, P. Y., J. C. Chevrolet, et al. (1994). "Anticoagulation in patients treated by continuous venovenous hemofiltration - a retrospective study." American Journal of Kidney Diseases **24**(5): 806-812.

van de Wetering, J., R. G. Westendorp, et al. (1996). "Heparin use in continuous renal replacement procedures: the struggle between filter coagulation and patient hemorrhage." Journal of the American Society of Nephrology **7**(1): 145-50.

Published prior to 1990

Schrader, J., M. Kandt, et al. (1987). "Low molecular weight heparin vs standard heparin in haemodialysis/haemofiltration patients: Results of a multicentre long-term study." Thrombosis Research **Suppl VII**: 25.

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APPENDIX

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Levels Of Evidence

As Defined By "A Guide To The Development, Implementation And Evaluation Of Clinical Practice Guidelines" (National Health & Medical Research Council, Canberra, 2000):

Level I		Evidence obtained from a systematic review or meta-analysis of all relevant randomised controlled trials.
Level II		Evidence obtained from at least one randomised controlled trials.
Level III	-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
	-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies or interrupted time series with a control group.
	-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.
Level IV		Evidence obtained from case series (either post-test or pre-test and post-test), descriptive studies, or case studies.

<p>Evidence Summary Therapy</p> <p>Low molecular-weight heparin for haemofiltration.</p>	<p style="text-align: center;">Study 1</p> <p>Reeves JH, Cumming AR, Gallagher L et al. (1999) A controlled trial of low-molecular-weight heparin (dalteparin) versus unfractionated heparin as anticoagulant during continuous venovenous hemodialysis with filtration. <u>Critical Care Medicine</u> 27(10):2224-8</p>
<p>STUDY DESIGN & NHMRC LEVELS OF EVIDENCE</p>	<p>Level II Randomised Controlled Trial</p>
<p>DESCRIPTION: Subjects, Interventions, Comparisons, Outcomes, Inclusion & Exclusion Criteria</p>	<p>Patients: Patients requiring continuous haemofiltration for acute renal failure or systemic inflammatory response syndrome (SIRS). Intervention: Low molecular weight heparin (dalteparin) Comparison: Unfractionated heparin Outcome: Time to failure of the haemofilter. Incl & Excl Criteria: Patients were included if requiring unfractionated heparin for acute renal failure or as an adjunctive therapy in systemic inflammatory response syndrome. Excluded patients with pre-existing severe coagulopathy, disseminated intravascular coagulation, or known sensitivity to heparin or dalteparin.</p>
<p>VALIDITY: Methodology, rigour, selection, opportunity for bias</p>	<p>Randomisation: Yes, using a computer-generated randomisation sequence. All patients accounted for: Patients who dropped out (e.g. death) were not analysed in the groups to which they were randomised. Patients treated equally: Two different pump systems were used during the study (manual and automatic). An "adjusted-dose" protocol was used for the unfractionated heparin group whereas a "fixed-dose" protocol was used for the dalteparin group. Similar groups: Demographic data is not presented Potential for bias: The main outcome measure is not consistent (e.g. both elective discontinuation and spontaneous failure). Sample size did not provide enough power to detect a difference between groups.</p>
<p>RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p>The overall mean (SE) duration of haemofiltration per patient was 63 (12.1) hours for the unfractionated heparin group and 56 (10.9) hours for the dalteparin group ($p=0.65$). Forty-five of the total 82 haemofilters were discontinued electively. The time to failure for both the manual and automatic systems was identical ($p=0.63$). There was no significant difference in the time to failure for haemofilters anticoagulated with unfractionated heparin compared to dalteparin ($p=0.75$). For unfractionated heparin the mean (SE) time to failure was 51.7 (7.51) hours compared to 46.8 (5.03) hours for the dalteparin group. There were no significant differences between the groups for platelet count ($p=0.57$), bleeding ($p=0.53$), haemorrhages, haemoglobin concentration ($p=0.75$), or amount of blood transfused (0.90). The manual system with unfractionated heparin cost an average of \$196 per day compared to \$222 with dalteparin. The automatic system cost \$237 per day for unfractionated heparin, compared with \$263 for dalteparin.</p>
<p>AUTHORS COMMENTS: Risk/benefit, limitations</p>	<p>"Fixed-dose dalteparin (low molecular-weight heparin) provided identical filter life, comparable safety, but increased total daily cost compared with adjusted dose heparin (unfractionated). Unfractionated heparin remains our anticoagulant of choice for continuous hemofiltration in intensive care."</p>
<p>REVIEWER'S COMMENTS: Risk/benefit, methodology, conclusions</p>	<p>Strengths:</p> <ul style="list-style-type: none"> • Groups were truly randomised • Clear inclusion and exclusion criteria <p>Weaknesses:</p> <ul style="list-style-type: none"> • The study did not have a sufficiently large sample size to detect a difference between the two groups. The study was "under-powered". • The local ethics committee did not require informed consent from participants. • The main outcome measure was time to either elective discontinuation or spontaneous failure. There was no differentiation made between the two in the analysis. • The groups may not have been similar at the beginning of the trial • Patients who dropped out of the study may have differed significantly from those who remained in the trial. No intention to treat analyses were performed.