Venous thrombosis after acute spinal cord injury: cost analysis of prophylaxis guidelines

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of either adjusted-dose unfractionated heparin (ADH) or enoxaparin, a low molecular weight heparin (LMWH), as prophylaxis for deep vein thrombosis (DVT) in patients with acute spinal injury.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with acute spinal cord injury.

Setting
The setting was secondary care. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness data were collected from four studies published in 1988, 1990, 1994 and 1996. The resource data related to two studies published in 1993 and 1996. The price year was 1999.

Source of effectiveness data
The effectiveness data were derived from a review of completed studies.

Outcomes assessed in the review
The main health outcomes considered in the review were the incidences of total DVT, proximal DVT, nonfatal pulmonary embolism (PE) and major bleeding episodes.

Study designs and other criteria for inclusion in the review
The authors stated that, for inclusion in the review, studies had to be prospective, randomised trials published in English from 1962 to the present (date of the review). However, of the two studies selected, that concerning enoxaparin was a retrospective uncontrolled study. All the studies evaluated ADH, and/or a low molecular weight heparin, as prophylaxis for DVT and/or PE in patients with acute spinal cord injury. In fact, no single study was shown to compare both ADH and enoxaparin. Also, for study inclusion, the preferred method for investigating DVT was bilateral ascending contrast venography. Although presented in the paper, those relating to low-dose unfractionated heparin were rejected because "it is not recommended" and those relating to logiparin were not considered because it "is not currently available in the United States".
Sources searched to identify primary studies
MEDLINE was searched.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Two studies that met the authors' inclusion criteria were included in the review (see Other Publications of Related Interest nos.1-2).

Methods of combining primary studies
Not applicable since the results of the studies were not pooled. The results for one treatment arm, ADH, from one study were compared to the results of the observational study on enoxaparin.

Investigation of differences between primary studies
Neither of the studies selected used the authors' preferred method of investigation, bilateral ascending contrast venography and the methods they did use were not the same. Also, the definitions of major bleeding were different. In the ADH study, this was defined as ,excessive oozing from wounds, melena, haemorrhage, and/or an acute decline in haematocrit values' whilst, in the enoxaparin study, it was defined as ,a decrease in haemoglobin values of 2g/dl or more'.

Results of the review
For ADH administered every 12 hours:

the incidence of total DVT was 6.9% (2 out of 29 patients);
the incidence of proximal DVT was 0%;
the incidence of nonfatal PE was 0%; and
the incidence of major bleeding episodes was 24.1% (7 out of 29 patients).

For enoxaparin, 30 mg administered every 12 hours:

the incidence of total DVT was 0%;
the incidence of proximal DVT was 0%;
the incidence of nonfatal PE was 0%; and
the incidence of major bleeding episodes was 2.9% (3 out of 105 patients).

Measure of benefits used in the economic analysis
The authors stated that ,the efficacy of these two regimens are essentially equivalent', thus implying that a cost-minimisation analysis was conducted.
**Direct costs**
The direct costs associated with the hospital were considered in the analysis. These included the costs for the drugs, daily tests for activated partial thromboplastin time (ADH group), and for the diagnosis and treatment of major bleeding complications. The cost analyses were performed for a population of 1,000 patients, over a 12-week period, and thus did not require discounting. The average wholesale prices (1999) were used as proxy for the drug costs. The costs of treating major bleeding complications were derived from published studies. The direct costs of Mamdani et al. (see Other Publications of Related Interest no.3) were calculated using institution-direct medical costs and Medicare diagnosis-related group cost data. The costs calculated by Anderson et al. (see Other Publications of Related Interest no.4) were specific to their hospital. The costs from these two studies were adjusted to 1999 dollars at a rate of 5% per year, and were then presented as average per patient. The costs of diagnosing and treating proximal DVT and nonfatal PE were not included in the cost calculation, as the studies considered in this review did not detect these complications. Resource quantities and unit costs were not presented separately.

**Statistical analysis of costs**
No statistical analysis was performed.

**Indirect Costs**
Indirect costs were not considered in the analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
Threshold analysis was performed to find the daily cost of enoxaparin that would make it cost saving overall.

**Estimated benefits used in the economic analysis**
In accordance with a cost-minimisation analysis, benefits were assumed to be equal. See the 'Effectiveness Results' section.

**Cost results**
The total average costs per patient over a 12-week period were:

- for 13,200 units ADH every 12 hours, $785.89;
- for 10,000 units ADH every 8 hours, $822.85;
- for 15,000 units ADH every 12 hours, $914.41; and
- for 30 mg enoxaparin every 12 hours, $2,888.41. Threshold analysis revealed that, at a daily cost of $9.00, enoxaparin would become cost saving overall.

**Synthesis of costs and benefits**
Not applicable due to the cost-minimisation analysis carried out.

**Authors' conclusions**
Adjusted-dose unfractionated heparin (ADH) produced cost-savings when compared with a 30 mg dose of enoxaparin.
administered every 12 hours. The authors stated "Although the current study demonstrates that adjusted dose heparin is the most cost-effective pharmacoprophylaxis for patients with spinal cord injury and paralysis, the bleeding rate associated with the regimen might be considered unacceptably high by some clinicians".

CRD COMMENTARY - Selection of comparators
The choice of technologies was not entirely clear in that the authors set out to compare ADH with LMWH, but then used only one type of LMWH, enoxaparin. It may have been that no studies of other suitable technologies were available, but the enoxaparin study used did not meet the authors' stated search criteria, hence casting doubt on their methods of selection of technologies. You, as a user of this database, should consider whether enoxaparin and ADH are appropriate technologies in your setting.

Validity of estimate of measure of effectiveness
The search of the literature was poorly reported, but most problematic was the eventual inclusion of a study that could not have been located by the stated inclusion criteria (ie, only prospective, randomised, controlled trials). A serious flaw to the internal validity was the comparison of the results from one arm of a trial with those from another, the latter also being retrospective. The authors also made no mention of the lack of comparability of the studies in terms of methods of measuring outcome. They did mention the small sample size in the enoxaparin study. Indeed there is serious doubt as to the suitability of the samples to represent the study population given a stated overall incidence of non-fatal PEs for this population of 3.6-9.3% as opposed to 0% in the included studies. The authors stated that enoxaparin and ADH were "essentially equivalent" in effectiveness. However, enoxaparin appeared superior in terms of overall DVT rate and also for bleeding. Moreover, this was based on a comparison of one arm of an RCT with an uncontrolled retrospective study in which the comparability of the two groups was unclear, as was the power of this comparison to find meaningful differences. The lead author has stated in recent correspondence that it was only the rate of proximal DVT that was clinically relevant.

Validity of estimate of measure of benefit
Since the authors assumed equal effectiveness, please refer to the commentary on effectiveness above. However, as the authors identified, the benefit of the technology should not only be judged by the narrow measure of effectiveness used, but should include the effect of bleeding complication.

Validity of estimate of costs
The costs of diagnosing and treating proximal DVT and nonfatal PE were not included in the analysis, as no such complications were reported in the studies considered. The costs were extracted from published studies, and wholesale drug prices were used as proxy for the drug costs. In addition, given the lack of cost data in the effectiveness studies, the cost data were taken from different studies, with no explicit justification for one of the sources and costs from the other being specific to the authors’ institution. There was also a lack of transparency in that no breakdown to quantities and unit costs was provided. The sensitivity analysis was extremely limited and was carried out on a rather narrow basis.

The authors claim that ADH is "the most cost-effective". However, cost-effectiveness is defined as the amount of cost for a given amount of effectiveness. Although the authors show evidence of equal effectiveness in terms of rate of proximal DVT, enoxaparin was clearly less harmful, as the authors stated. One might take the narrow view that the effectiveness component of cost-effectiveness excludes the rate of complications. However, this is highly misleading when attempting to value any resource savings in terms of any loss in quality of life or survival. Finally, since the costing relied on the rates of DVT and complications from the two studies, much of the criticism on effectiveness also applies here.

Other issues
The authors made appropriate comparisons of their findings with the results from other studies. The issue of generalisability to other settings was not addressed. The results were reported selectively, with no cost breakdown. The authors' conclusions refer to the spinal cord injured population, but their selected studies seem not to be representative.
of that population.

**Implications of the study**
The authors stated, clearly, there is a need for large, randomised, prospective trials evaluating the use of adjusted-dose heparin vs. the various LMWHs as DVT and PE prophylaxis for patients with spinal cord injury and paralysis. In fact, the serious limitations in their study in terms of study identification, study design, suitability to reflect the study population, comparability between studies, outcome measurement and costing transparency cast much doubt on their conclusions.

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None stated.

**Bibliographic details**

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**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Anticoagulants /economics /therapeutic use; Cost-Benefit Analysis; Drug Costs; Enoxaparin /therapeutic use; Heparin /economics /therapeutic use; Humans; Pulmonary Embolism /etiology /prevention & control; Spinal Cord Injuries /complications /drug therapy; Venous Thrombosis /economics /etiology /prevention & control

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