A randomized trial to compare the efficacy, safety, cost and platelet aggregation effects of enoxaparin and unfractionated heparin (the ESCAPEU trial)


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 enoxaparin, a low molecular weight heparin, in combination with aspirin in patients with unstable angina. The dose of enoxaparin was 1 mg/kg body weight, administered subcutaneously every 12 hours.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult male and female patients with recent onset of rest angina lasting at least 10 minutes, with ischaemic events associated with severe, frequent (at least 3 episodes/day) or accelerated anginal symptoms occurring within the last 72 hours. The patients also had to have at least one of several electrocardiographic criteria. More specifically, a new ST segment depression of at least 0.1 mV, a transient ST segment elevation, or T wave changes in at least two contiguous leads without pathological Q waves in the ischaemic leads. The exclusion criteria included the presence of a left bundle-branch block or pacemaker, persistent ST segment elevation, elevated cardiac enzymes and angina with an established precipitating cause (e.g. heart failure, arrhythmia). Patients with contraindication to anticoagulation or a creatinine clearance of less than 30 mL/minute were also excluded.

Setting
The setting was likely to have been secondary care. The economic study was carried out at the Medical Emergency Department of the Nehru Hospital in Chandigarh, India.

Dates to which data relate
The effectiveness and resource use data were gathered from August 1998 to September 1999. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness analysis.

Study sample
Power calculations were carried out in the preliminary phase of the study. These assumed that the incidence of the primary health outcome would be 40% in the UFH group and 20% in the enoxaparin group. Accordingly, the sample size calculations suggested that 92 patients would be needed to detect the above-mentioned difference of 20% with 70% power and a 5% level of significance. Of the 217 patients initially identified at the study hospital during the enrolment period, 119 were not eligible and 5 did not receive the study treatment. This left a final sample of 93 patients, 42 in the UFH group and 51 in the enoxaparin group. The UFH group comprised 67% men and the mean age was 61 (+/- 6) years (age range: 40 - 79). The enoxaparin group comprised 64% men and the mean age was 59 (+/- 7) years (age range: 41 - 78).

Study design
This was an open, prospective randomised trial, which was carried out in a single centre (the Nehru Hospital. The method of randomisation was not reported, nor was the actual length of follow-up. However, the patients were generally followed until hospital discharge, which occurred on day 5 to 7 unless earlier end points were achieved. The loss to follow-up was not stated. The trial was open since both the patients and physicians were aware of the therapy that the patients received. However, it was stated that the outcome assessment was blind.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. The primary health outcome was the composite end point of cardiac death, myocardial infarction (MI), revascularisation, or recurrent angina within the first 7 days. The secondary outcomes were the single components of the composite end point, major and minor bleeding episodes, adverse events, and platelet aggregation data. Platelet aggregation was analysed in a sub-group of 20 randomly selected patients from each group, using three reagents (epinephrine, adenosine diphosphate and collagen). The study groups were comparable at baseline in terms of their demographic and clinical characteristics.

Effectiveness results
The frequency of the composite end point was 62% in the UFH group and 37% in the enoxaparin group, (p=0.04).

No deaths occurred.

In the UFH group, the frequency of recurrent angina was 48%, acute MI 9%, and revascularisations 5%. The corresponding values in the enoxaparin group were 33% (recurrent angina), 2% (acute MI), and 2% (revascularisations), respectively. None of these differences reached statistical significance.

Adverse events and bleeding episodes were not statistically different across the groups.

Maximum platelet aggregation was achieved with collagen, followed by adenosine diphosphate. UFH was found to be a more potent inhibitor of platelet aggregation than enoxaparin.

Clinical conclusions
The combination of enoxaparin with aspirin was associated with a lower frequency of the composite end point than the combination of standard UFH and aspirin. The safety profile of the two therapies was comparable.

Measure of benefits used in the economic analysis
No summary benefit measure was used in the economic evaluation. In effect, a cost-consequences analysis was conducted.

Direct costs
Discounting was not relevant because the costs per patient were incurred during a short time. The unit costs and the quantities of resources used were not presented separately. The health services included in the economic evaluation
were drugs, coronary care unit stay, ward stay, activated partial thromboplastin time monitoring, thrombolysis and interventions. The cost/resource boundary adopted in the study appears to have been that of the hospital. The resource use data were estimated using actual data derived from the sample of patients that was included in the effectiveness study. The source of the cost data was not reported, but it was likely to have been the hospital where the study took place. The price year was not provided.

Statistical analysis of costs
The costs were presented as mean and median values along with standard deviations. Statistical tests were also carried out to test the statistical significance of differences in the costs.

Indirect Costs
The indirect costs were not considered.

Currency
The costs were estimated in Indian rupees and then converted into US dollars ($). The conversion rate was $1 = 44 rupees.

Sensitivity analysis
Sensitivity analyses were not performed.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The total mean costs per patient were $271.5 (+/- 97.5) (median: $235.9) in the UFH group and $257.7 (+/- 99.5) (median: $226.9) in the enoxaparin group. The difference failed to reach statistical significance, (p=0.12), despite significantly higher initial drug acquisition costs in the enoxaparin group. The drug acquisition costs were $103.4 (+/- 19.7) versus $21.8 (+/- 2.4) in the UFH group, (p<0.001).

Synthesis of costs and benefits
The costs and benefits were not combined.

Authors' conclusions
Enoxaparin proved to be a safe and effective treatment for patients with unstable angina and was likely to be superior to standard unfractionated heparin (UFH). The costs between the groups were comparable, despite the higher initial acquisition costs of enoxaparin.

CRD COMMENTARY - Selection of comparators
The authors stated that UFH was selected as the basic comparator since it is generally considered the treatment of choice in patients with unstable angina. You should decide whether it represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used a randomised trial, which was appropriate for the study question. The study groups were comparable at baseline and power calculations were performed. The method of sample selection was described and the reasons why patients were excluded were reported. The outcome assessment was blinded although the patients
were aware of the treatment they received. The analysis of the clinical study was conducted on an intention to treat. These issues increase the internal validity of the analysis. The study sample was accurately selected and appears to have been representative of the study population. However, the study was performed in a single centre and it reflected treatment and disease patterns observed at the study hospital. Therefore, caution is required when extrapolating the effectiveness results to other groups of patients.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis. In effect, a cost-consequences analysis was conducted.

Validity of estimate of costs
The perspective adopted in the study reflected that of the hospital. It appears that all the relevant categories of costs have been included in the analysis. The authors discussed their reasons for excluding labour costs. However, details on the unit costs and the quantities of resources used were not presented separately and the price year was not given. This makes reflation and replication exercises in other settings difficult. The costs were treated stochastically, but the estimates were specific to the study setting. Sensitivity analyses were not carried out to deal with the issue of variability in data across centres. Discounting was not performed due to the short time horizon of the analysis. The authors stated that the inclusion of the indirect costs would have favoured the enoxaparin group due to fewer hospitalisation days.

Other issues
The authors compared their findings with those from other studies that showed the superiority of enoxaparin over UFH. They also discussed the reasons why some other studies did not achieve similar conclusions. However, the issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were not carried out. This limited the external validity of the study. The article referred to patients with stable angina and this was reflected in the conclusions of the analysis.

Implications of the study
The study results suggested that, even in developing countries, low molecular weight heparin was more effective than standard UFH for the treatment of patients with unstable angina. The intervention also proved to have been cost-neutral. The issue of whether the observed greater inhibition of platelet aggregation could result in more bleeding remained unanswered.

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