Monitoring unfractionated heparin therapy with antifactor Xa activity results in fewer monitoring tests and dosage changes than monitoring with the activated partial thromboplastin time

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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 antifactor Xa heparin activity (HA) and activated partial thromboplastin time (aPTT) to monitor unfractionated heparin (UFH) therapy.

Type of intervention
Drug response monitoring.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients receiving UFH therapy for a broad range of conditions.

Setting
The setting was secondary care. The economic analysis was conducted in Minneapolis, Minnesota, USA.

Dates to which data relate
The effectiveness and resource data were collected between May and August 1996 inclusive. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The cost data were collected prospectively using the same population sample as that used in the effectiveness analysis.

Study sample
Power calculations were not used to determine the sample size. All of the patients who met the study criteria, and who were treated on seven hospital medical-surgical stations during the study period, were entered into the study. The patients were not informed that they were taking part in a study, as both protocols were considered to be standard care. The author considered that the initial study sample was broadly representative of the general patient population who received UFH therapy in many hospitals.

Of the 694 patients who initially began UHF therapy, only 268 patients (39%) were included in the study. There were
137 patients in the HA group and 131 in the aPTT group. Of the 426 patients (61%) who were excluded from the initial sample, 4 had no charts (lost), 19 had missing data, 393 received UHF therapy for less than 10 hours, and a further 10 only used the approved protocol for a portion of the time that they received UHF therapy. HA and aPTT monitoring was performed for all patients, but only the results from the groups to which the patients had been randomised were used to determine UFH dosage adjustments.

The study population was 52% male. The median age of the patients was 69 years in the HA group and 70 years in the aPTT group. Seventy-one per cent of the patients had unstable angina or acute myocardial infarction, 4% cerebrovascular disease, 2% peripheral heart disease, 3% atrial fibrillation, 3% severe heart failure, 4% an artificial heart valve, and 13% venous thrombosis. Patients were excluded from the study if they received UFH therapy for less than 24 hours, if they received less than the full UFH treatment because of a high risk of bleeding, or if their UFH treatment was interrupted for more than 10 hours.

**Study design**
This was a prospective, unblinded, randomised controlled trial, which was carried out in a single centre. The patients were randomised between the HA and the aPTT groups, depending on whether they had odd or even social security numbers. The duration of follow-up was 96 hours after starting the UHF treatment. There was no loss to follow-up.

**Analysis of effectiveness**
The analysis of effectiveness was conducted on an intention to treat basis. The principle clinical outcomes reported in the analysis were the average therapeutic HA and aPTT levels. These were then used to determine whether any UFH dosage adjustments were required for the patients, to ensure their heparin plasma activity was appropriate. The accuracy of monitoring was also assessed, based on the number of monitoring tests and subsequent dosage adjustments required in each of the two groups. Generally, both groups were shown to be comparable at baseline analysis in terms of their clinical and demographic characteristics. The exception was gender, where 55% of the patients were male in the HA group, compared with 42% in the aPTT group. An adjustment was made to take account of this gender imbalance.

**Effectiveness results**
No significant differences were observed between the average HA or aPTT levels in the two groups.

The median HA levels were 0.51 U/mL (inter-quartile range, I-Q: 0.40 - 0.62) in the HA group and 0.50 U/mL (I-Q: 0.40 - 0.60) in the aPTT group, (p=0.47).

The median aPTT levels were 82 seconds (I-Q: 61 - 103) in the HA group and 81 seconds (I-Q: 64 - 98) in the aPTT group, (p=0.25).

The need for monitoring tests was significantly lower in the HA group (median, 1.46 tests per 24 hours; I-Q: 1.25 - 1.68) than in the aPTT group (median, 1.68 tests per 24 hours; I-Q: 1.39 - 1.97), (p<0.0001).

The number of dosage changes were significantly lower in the HA group (median, 0.46 per 24 hours; I-Q: 0.19 - 0.72) than in the aPTT group (median, 0.84 per 24 hours; I-Q: 0.53 - 1.15), (p<0.0001).

**Clinical conclusions**
No strong clinical conclusions were drawn, as it was noted that a large-scale trial would be required to assess whether monitoring UFH therapy with HA would lead to improved clinical outcomes. The average HA and aPTT levels were similar between the two groups. However, the significantly lower level of monitoring and dose change in the HA group was consistent with the view that aPTT monitoring has a greater error rate and is subject to more variability.

**Measure of benefits used in the economic analysis**
No final health outcome measure was used since the clinical study was too small to detect any difference in outcomes.
and, in effect, the economic analysis reported in this paper was based on the difference in the costs only. However, the author did note that a reduction in the number of monitoring tests and dosage changes would reduce the opportunities for adverse events to occur, which can harm either the patient or the health care professional.

**Direct costs**
The resource quantities and the unit costs were reported separately. The hospital costs directly related to monitoring and implementing dosage changes for patients over a 96-hour period were included in the analysis. The time taken to perform aPTT and HA assays in the study laboratory was estimated by observation and by interview. The time taken to change dosages was estimated by interviewing the nursing staff to identify each task required. The personnel time costs were valued using the average total compensation costs for nursing and laboratory staff at the study hospital. The costs of the reagents and materials for each aPTT and HA assay were also included, although the source of the cost data does not appear to have been reported. The number of monitoring tests and dosage changes were recorded. Discounting was not applied to the costs, which was appropriate given the very short duration of the study. The average and incremental costs were reported. The quantities of resources were measured during the study period, May to August 1996. The price year does not appear to have been reported.

**Indirect Costs**
No indirect costs were included.

**Currency**
US dollars ($).

**Sensitivity analysis**
No sensitivity analysis was conducted.

**Estimated benefits used in the economic analysis**
It was acknowledged that HA monitoring has the potential for reducing the number of adverse events, but these events do not appear to have been reported in this analysis. See also the 'Effectiveness Results' section.

**Cost results**
The total costs per patient for monitoring and dosage change over a 96-hour period were estimated to be $31.46 in the HA group, compared with $27.10 in the aPTT group.

The incremental costs associated with HA monitoring were $4.37.

The costs of adverse events were not reported, although it was acknowledged that adverse events may be relevant to the choice of intervention.

**Synthesis of costs and benefits**
Not relevant.

**Authors' conclusions**
The use of a heparin activity (HA) assay to monitor patients receiving unfractionated heparin (UFH) therapy was modestly more costly than using activated partial thromboplastin time (aPTT). However, most of the additional costs of the HA assay were negated by a significantly reduced level of monitoring and dosage change in comparison with the aPTT assay, given that this intervention is less accurate. HA monitoring may be clinically beneficial for some patients when compared with aPTT monitoring, but a large multicentre study is still required to assess this. It may, however, be
possible for a hospital to justify switching to HA monitoring if all costs associated with UFH therapy monitoring, rather than just the limited costs considered here, are included in a future analysis. Further, switching to HA may reduce the chances of adverse events given the lower level of monitoring and dosage change required; there is a potential for an adverse event to occur every time such an adjustment is required, which could affect either the patient or hospital.

**CRD COMMENTARY - Selection of comparators**
The comparator, aPTT assay monitoring, was justified on the grounds that it is a commonly used protocol for patients receiving UFH therapy in the United States.

**Validity of estimate of measure of effectiveness**
A randomised controlled trial was used in the analysis, which was appropriate for the study question. The study sample appears to have been representative of the study population, and both groups were generally comparable at analysis. The exception was gender, for which an adjustment was made.

**Validity of estimate of measure of benefit**
The clinical study did not seek to determine whether the intervention was more effective that the comparator. The author acknowledged that a large-scale multicentre trial would probably be required for this. In this analysis, the intervention was only shown to be at least as effective as the comparator; the economic analysis focused on the resource and cost-consequences of each approach instead, i.e. the number of monitoring tests and dosage changes required. However, the author acknowledged that potential adverse events might also be avoided through a reduction in the need for monitoring and dosage adjustments.

**Validity of estimate of costs**
The author did not state the perspective from which the economic analysis was conducted. Only the specific direct hospital costs associated with assay tests and UFH dosage change were reported. The author acknowledged that there would be a need to include broader relevant hospital costs in order to ascertain whether the HA intervention may, in fact, be associated with lower costs than aPTT. The author also referred briefly to adverse events that may be associated with monitoring and dosage change, the cost of which could be included in a future analysis. The costs and the quantities in this limited analysis were reported separately. The price year(s) used and the source of the unit costs were not explicitly stated.

**Other issues**
The author did not report whether similar analyses had been published elsewhere in the literature, although it was stated that uncertainty still surrounds the clinical effectiveness of the intervention. The author acknowledged that the generalisability of the findings may be limited to the study population, although this was believed to be indicative of the broad patient population that may receive UFH therapy. The results in this analysis were not presented selectively. The author highlights in the discussion that there is a need in future economic and clinical analyses to determine whether the intervention does indeed represent a cost-effective alternative to aPTT monitoring. While in effect this study is a cost-minimisation analysis, this is because both the clinical and cost parameters chosen are not sufficiently broad to determine the cost-effectiveness, rather than because the intervention and the comparator are clinically equivalent.

**Implications of the study**
The author recommends the use of HA monitoring for patients receiving UFH therapy in large-scale hospitals. The author also suggests indirectly that there is a need to collect additional cost data associated with the two monitoring approaches, and acknowledges that a large-scale clinical trial is still required to demonstrate the clinical benefits of HA monitoring.

**Source of funding**

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