Comparison between tinzaparin and standard heparin for chronic haemodialysis in a Canadian center

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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
Two forms of heparin were used for haemodialysis. The first was unfractionated or standard heparin, with an average molecular weight of 15,000 Da. The second was low molecular weight heparin, with molecular weights varying between 1,000 and 10,000 Da, such as tinzaparin. Standard heparin was administered as an initial bolus of 50 to 75 units/kg (dry weight) followed by an infusion to maintain an activated clotting time (ACTESTER) between 150 and 200 seconds. The standard heparin infusion was discontinued 30 to 45 minutes before the end of dialysis. The initial dose of tinzaparin was 40 to 50% of the standard heparin dose. This was injected as a bolus in the arterial line at the beginning of haemodialysis.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised chronic adult haemodialysis patients. Patients with central venous catheters with a bleeding diathesis recorded as a significant episode of bleeding in the preceding 3 months were excluded. Also excluded were patients with thrombocytopenia (less than 150 x 10^9/L), patients with hepatic failure, and those receiving an oral anticoagulation regimen (mainly warfarin). However, patients taking an antiplatelet agent were not excluded.

Setting
The setting was a dialysis unit. The economic study was carried out at the Maisonneuve-Rosemont Hospital, Montreal, Canada.

Dates to which data relate
No dates or price year were reported.

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

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness analysis.
Study sample
Power calculations to determine the sample size were not performed. A sample of 32 eligible patients, who were selected at the study hospital, was included in the analysis. Sixteen patients with a mean age of 66.2 (+/- 17) years, of which 7 were men, were included in group 1. These received tinzaparin over a 4-week period followed by standard heparin, also over a 4-week period. Sixteen patients with a mean age of 65.1 (+/- 12.8) years, of which 10 were men, were included in group 2. These were initially treated with standard heparin over 4 weeks followed by tinzaparin for 4 weeks. Two patients were removed from the initial sample, one because of an allergic reaction to tinzaparin and the other because they received the wrong drug dose.

Study design
This was a prospective, randomised crossover trial, which was carried out in a single centre (the Maisonneuve-Rosemont Hospital). The method of randomisation was not reported. The patients were followed for 8 weeks and 2 patients were lost to follow-up.

Analysis of effectiveness
The analysis of the effectiveness was limited to those patients who completed the study (30 out of 32 in the initial sample). The primary health outcomes were:

visual aspects of the tubing of the extracorporeal circuit and of the dialyser;

time to compression of the vascular access at the end of the haemodialysis session;

episodes of clotting;

reuse of filters;

the number of dialysers;

complications;

the level of satisfaction of the patients and nurses, measured using a questionnaire; and

the time spent for anticoagulation during the session.

The patient groups were shown to be comparable at baseline in terms of their demographics and dialysis treatment. The analysis included a between-groups factor to assess for a potential "order" effect associated with the crossover design.

Effectiveness results
Six patients did not require any adjustment in their dose of tinzaparin. The remaining 26 patients required adjustments, of which 20 required increments and 6 required reductions.

The visual aspects of the tubing of the extracorporeal circuit and of the dialyser were similar in the two study groups. In the majority of cases this was recorded as either 0, indicating no clotting or very clean, or 1, indicating pink but clean and no clotting.

The time to compression of the vascular access at the end of the haemodialysis session was not different in the two groups. For the entire group, this was 9.5 (+/- 3) minutes (range: 6 - 16) with tinzaparin and 9.5 (+/- 1.8) minutes (range: 5.8 - 16.1) with heparin.

Clotting was observed more frequently with tinzaparin than with standard heparin, although there was a tendency for it to decrease over time. Clots were observed in the arterial and venous bubble traps in 18% (+/- 12%) and 10% (+/- 6%), respectively, of the sessions with tinzaparin, and in 3% (+/- 4%) and 2% (+/- 4%) of the sessions with standard heparin, (p<0.005).
There was no statistically significant difference in the reuse of filters. This was 2.2 with tinzaparin and 3.5 with standard heparin. The maximum reuse numbers achieved were 3.8 with tinzaparin and 5.0 with standard heparin.

However, the total number of dialysers utilised for each period of 4 weeks was 4.7 (+/- 4.2) with tinzaparin and 5.6 (+/- 3.7) with standard heparin, (p<0.005).

In terms of complications, 2 patients in the tinzaparin group and 8 patients in the standard heparin group reported excessive bleeding.

The level of satisfaction for tinzaparin was extremely good for both patients and nurses. Ten patients and 12 nurses were "much more satisfied with tinzaparin than with standard heparin", 8 patients and 8 nurses were "more satisfied", 12 patients and 1 nurse were "equally satisfied", and 0 patients and 0 nurses were "less satisfied" or "much less satisfied" with tinzaparin than with standard heparin. The reason for satisfaction was less bleeding for the patients, and the simplicity and rapidity of administration for the nurses.

The time spent for anticoagulation during the session was 5 minutes with standard heparin without ACTESTER monitoring, 25 to 30 minutes with standard heparin with ACTESTER monitoring, and 1 minute with tinzaparin.

Clinical conclusions
The effectiveness analysis showed that tinzaparin represented a simple alternative way to offer anticoagulation during maintenance haemodialysis. It was associated with less postdialysis bleeding and was preferred by patients and nurses. The presence of more clots in the venous and arterial bubble traps was not unexpected, due to the precaution in the initial dosage of tinzaparin, which required increases in most of the patients.

Measure of benefits used in the economic analysis
No summary benefit measure was used in the economic analysis. A cost-consequences analysis was therefore carried out.

Direct costs
Discounting was irrelevant due to the short time horizon of the study. The unit costs and the quantities of resources were reported only for the drug costs. The cost analysis included the costs of the drugs (standard heparin and tinzaparin), the nursing time spent with both regimens, ACTESTER monitoring with heparin, and the syringes. The cost of the dialyser was not included in the analysis. The cost/resource boundary adopted appears to have been that of the hospital. The source of the cost data was not explicitly stated, but the unit costs were presumably derived from the study hospital. The quantities of resources used were estimated using actual data derived from the trial. No price year was reported.

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

Indirect Costs
The indirect costs were not included in the analysis.

Currency
Canadian dollars (Can$).

Sensitivity analysis
No sensitivity analysis was carried out.
Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The cost of the drug for one session was Can$6.91 for tinzaparin and Can$1.17 for standard heparin. When nursing time was included, the cost of using tinzaparin for one session increased to Can$7.33. The corresponding cost for standard heparin increased to Can$7.62, assuming that 22% of the sessions required ACTESTER monitoring, and that one ACTESTER device was necessary for 8 to 10 dialysis stations.

Synthesis of costs and benefits
Not relevant.

Authors' conclusions
The experience with tinzaparin was positive. It represented an easy and simple way to offer anticoagulation during maintenance haemodialysis. In addition, the patients and the nurses preferred tinzaparin to standard heparin. The use of tinzaparin saved nursing time, thus resulting in costs similar to those associated with standard heparin, despite the higher initial acquisition cost.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear. The drugs studied represented two forms of heparin currently available for haemodialysis. Standard heparin represented the usual intervention, while tinzaparin was considered as a recently available alternative treatment. You should assess whether these heparins are used in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used a prospective, randomised crossover trial, thus enhancing the internal validity of the study. In addition, the study groups were completely comparable at baseline and statistical analyses were carried out to account for the potential "order" effect in the crossover design. However, the sample size was somewhat small and power calculations were not performed. The method of randomisation was not reported. The authors stated that no washout period was planned between both anticoagulation regimens, since standard heparin represented current practice at their unit.

Validity of estimate of measure of benefit
No summary benefit measure was used and the health outcomes were left disaggregated. A cost-consequences analysis was therefore carried out.

Validity of estimate of costs
The perspective adopted in the analysis appears to have been that of the hospital, although this was not explicitly stated. Only those cost items strictly related to heparin usage were included in the analysis. The cost of the dialyser was excluded, but the authors did not comment on the impact of this omission. The unit costs and the quantities of resources were not reported separately for all of the cost items included in the analysis. No price year was reported, thus making any reflation exercise to other settings difficult. The costs were treated deterministically and statistical analyses were not carried out on the quantities.

Other issues
The authors made some comparisons of their findings with those from other studies. The issue of the external validity of the study results to other settings was not addressed and sensitivity analyses were not carried out. Thus, the external
validity of the study was limited. A population of chronic adult haemodialysis patients was enrolled in the study and this was reflected in the study conclusions.

**Implications of the study**
The authors recommend the use of tinzaparin as an alternative to standard heparin. It offers more advantages, such as suitability for once-daily dosing, longer half-life and a higher bioavailability when injected subcutaneously.

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