Comparison of low-molecular-weight heparin (enoxaparin sodium) and standard unfractionated heparin for haemodialysis anticoagulation

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Abstract

Background. Low-molecular-weight heparin (LMWH) has been suggested as providing safe, efficient, convenient and possibly more cost-effective anticoagulation for haemodialysis (HD) than unfractionated heparin, with fewer side-effects and possible benefits on uraemic dyslipidaemia.

Methods. In this prospective, randomized, cross-over study we compared the safety, clinical efficacy and cost effectiveness of Clexane (enoxaparin sodium; Rhône-Poulenc Rorer) with unfractionated heparin in 36 chronic HD patients. They were randomly assigned to either Clexane (1 mg/kg body weight, equivalent to 100 IU) or standard heparin, and followed prospectively for 12 weeks (36 dialyses) before crossing over to the alternate therapy for a further 12 weeks. Heparin anticoagulation was monitored using activated coagulation times.

Results. Dialysis with Clexane resulted in less frequent minor fibrin/clot formation in the dialyser and lines than with heparin (P<0.001), but was accompanied by increased frequency of minor haemorrhage between dialyses (P<0.001). Clexane dose reduction (to a mean of 0.69 mg/kg) eliminated excess minor haemorrhage without increasing clotting frequencies. Mean vascular compression times were similar in both groups. Over 24 weeks, no changes in standard serum lipid profiles were observed.

Conclusions. This study suggests that a single-dose protocol of Clexane is an effective and very convenient alternative to sodium heparin, but currently direct costs are about 16% more. We recommend an initial dose of 0.70 mg/kg.

Key words: anticoagulation; haemodialysis; heparin; lipids; low-molecular-weight heparins

Introduction

Heparin has been in widespread use for decades for anticoagulation during haemodialysis (HD) therapy.

It’s principal constituent is a mucopolysaccharide comprising \(\beta\)-glucuronic acid and \(\beta\)-glucosamine, both sulphated, in 1,4-linkage, with a spread of molecular weights of between 6000 and 30000 daltons (mean 15000). Although standard systemic heparinization for haemodialysis is relatively safe and effective, long-term heparin use is associated with complications including platelet dysfunction [1], thrombocytopenia [2], lipid abnormalities [3], allergic reactions, osteoporosis [4], and an increased risk of haemorrhage [5,6]. About a decade ago, low-molecular-weight (LMW) fractions of heparin were first introduced with claims of potential therapeutic advantages over unfractionated heparin [7-8]. These products have molecular weights in the range 1000-10000 (means 4000-6000 daltons), depending on the preparation. Their size profile results in LMW heparins having different activities with respect to plasma antithrombin III, Factor Xa and Factor IXa. The various preparations on the market are thus not exactly interchangeable. LMW heparins bind less to plasma proteins, platelets, and the endothelium than heparin, which improves their bioavailability and purportedly reduces complications [9]. LMW heparins apparently do not stimulate plasma lipase activity to the same extent as unfractionated heparin [10]; however, their effect on uraemic dyslipidaemia is controversial [11], with some [12-15] but not all studies [16-18] noting a beneficial effect.

Although there are several reported studies comparing a variety of LMW heparins with unfractionated heparin in haemodialysis patients, experience with enoxaparin sodium (Clexane; Rhône-Poulenc Rorer) in this context is limited. In this prospective, randomized, cross-over study we compare the safety, clinical efficacy and cost effectiveness of enoxaparin with unfractionated heparin in 36 chronic renal failure patients stabilized on haemodialysis.

Subjects and methods

Patients and study design

Thirty-six adult patients (17 male, 19 female) in end-stage renal failure requiring maintenance dialysis were recruited...
Enoxaparin vs standard heparin for haemodialysis

Clinical monitoring

In order to assess the efficacy of anticoagulation, the frequency and degree of fibrin/clot formation in both the dialyzer and lines were graded on a 10-point scale, with 1 indicating no clot formation and 10 very heavy clotting or total occlusion (100%). This assessment was carried out after the blood had been returned to the patient by flushing the dialyzer and lines with normal saline. Episodes of adverse events such as haemorrhage or thrombosis either during or between dialyses were also noted. Haemorrhages were categorized as slight/moderate, or severe. The Clexane dose was reduced by 0.2 mg/kg if indicated by excess bleeding from needle puncture sites during or between dialyses.

Post-HD haemostasis was assessed by recording vascular access compression times with a stopwatch, observing the time from needle removal to cessation of spontaneous bleeding/oozing from the puncture site.

Laboratory estimations

Fasting standard lipid profiles were determined pre-dialysis at baseline (week 0) and at the end of each arm of the study. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL), and triglyceride concentrations (Trigs) were measured on a high-throughput autoanalyser (Hitachi 747) using reagents supplied by Boehringer Mannheim (Germany). Low-density lipoprotein cholesterol (LDL) and very-low-density lipoprotein cholesterol (VLDL) were calculated using Friedwald’s equation (LDL = TC – Trigs/2.2; VLDL = TC – [LDL + HDL]).

Statistical methods

The significance of differences between groups was determined using analysis of variance (ANOVA) for parametric data or Kruskal–Wallis ANOVA on ranks for non-parametric data as appropriate. Paired data was compared using the paired t-test. Non-parametric data was compared using Mann–Whitney rank sum test. The significance of proportions was assessed by the z-test. A probability P < 0.05 was considered significant. Data are expressed as means ± SD except where otherwise indicated.

Results

The study was designed as a prospective, randomized, cross-over study, with patients randomly assigned to receive either unfractionated heparin or Clexane as the first mode of treatment. However, as no difference was noted between the two sections of the study for any of the parameters measured, data for each phase was pooled. Five subjects did not finish the study: three received renal transplants, one changed to CAPD, and one required hospitalization for amputation of a leg because of arterial occlusive disease.

Overall, 94% of all dialysis sessions with Clexane and 89% of sessions using unfractionated heparin were performed without or with the appearance of only minor clots in the dialyzer and/or blood lines (Figures 1, 2). Lines and dialysers were more frequently clear when Clexane was used (P < 0.001). Minor clot formation (grades 2–3) was less common with Clexane.

Table 1. Clinical characteristics of subjects (means ± SD)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>68.5 (22–85)*</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>17/19</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>66.1 ± 16.4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.1 ± 5.0</td>
</tr>
<tr>
<td>Time on dialysis, months</td>
<td>30.0 (1–136)*</td>
</tr>
</tbody>
</table>

*Median (range).
Table 2. Frequency of adverse events, during and between dialysis sessions

<table>
<thead>
<tr>
<th></th>
<th>Clexanea</th>
<th>Titrated Clexaneb</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemorrhage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>slight</td>
<td>3.5</td>
<td>3.5</td>
<td>2.2</td>
</tr>
<tr>
<td>moderate</td>
<td>1.5</td>
<td>0.9</td>
<td>1.2</td>
</tr>
<tr>
<td>severe</td>
<td>0.1</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Between</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>slight</td>
<td>7.7c</td>
<td>4.3</td>
<td>2.8</td>
</tr>
<tr>
<td>moderate</td>
<td>1.8</td>
<td>0.9</td>
<td>1.1</td>
</tr>
<tr>
<td>severe</td>
<td>0.1</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Thrombosis</strong></td>
<td>0</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Cannulation</strong></td>
<td>0.4</td>
<td>0.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*a*Includes all dialyses.
*b*Results after excluding dialyses prior to and during dose adjustment.
*c*Clexane vs heparin, *P*<0.001.

anticoagulation (*P*<0.001). The appearance of significant clots (grades 4–10) in both lines and dialysers was infrequent, with no difference using either type of heparin.

Clexane use was accompanied by a significantly higher frequency of minor haemorrhage between dialyses (7.7 vs 2.8%; *P*<0.001) (Table 2). During the course of the Clexane arm of the study, prolonged or recurrent blood oozing from needle puncture sites between dialyses in a few patients suggested that the dose recommended by the manufacturer might have been excessive for some patients. Consequently the Clexane dose was reviewed during the trial, and the dose reduced in those affected patients. The mean dose in our patients at the end of the study was 0.69 ± 0.25 mg/kg body weight (range 0.29–1.25 mg/kg; Figure 3). One patient experienced significant extracorporeal clotting, and eventually required a dose of 1.25 mg/kg. Ninety per cent of patients were anticoagulated with 0.34–1.08 mg/kg. After Clexane dose reduction, the frequency of minor haemorrhagic events decreased by 44% (from 7.7 to 4.3%; Table 2) eliminating the difference between the two groups (*P*=0.087). The frequency of minor clotting (grades 2–4) was unchanged, but the frequency of clear dia-
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Interestingly, the frequency of moderate occlusion (grade 4) and severe occlusion (grades 8–10) of the dialysers actually fell after dose titration ($P < 0.05$).

A measure of haemostasis at the puncture sites was obtained by recording vascular access clotting times at the end of haemodialysis with a stop-watch. There was no significant difference in clotting times for either anticoagulation modality (Table 3). Three patients received packed-cell transfusions while on Clexane compared to two during the heparin arm. Intravenous iron (iron polymaltose complex (Ferrum H, Sigma Pharmaceuticals Pty Ltd, Victoria, Australia) equivalent to 600 mg elemental iron) was given according to our unit’s protocol (serum ferritin $< 200 \mu g/l \pm$ transferrin saturation $< 20\%$ on routine monthly tests), 10 times in the Clexane and eight times in the heparin phase of the study.

To determine whether the type of anticoagulation had any effect on dialyser uremic solute clearance, Kt/Vurea values were obtained using the Theraps management system (Cobe, Colorado, USA). Data was available for 20 patients. There was no difference between the groups (1.45 ± 0.16 for Clexane vs 1.46 ± 0.13 for heparin; $P = 0.790$).

No changes in serum lipids were observed with either anticoagulant (Table 4).

The cost per treatment was slightly higher with Clexane: $37.26$ Australian dollars ($US 24.22$) vs $31.55$ ($US 20.51$) with sodium heparin. The median cost of adverse events arising from Clexane anticoagulation was slightly higher than with heparin (1.39 cents vs 0.44 cents Aus per patient per dialysis). This difference, which was not statistically significant ($P = 0.081$), was reduced if the period after dose titration only was considered (0.64 cents vs 0.44 cents; $P = 0.598$).

### Table 3. Vascular access clotting times in ESRF patients dialysed high in many patients, and a starting dose of

<table>
<thead>
<tr>
<th>Vascular access clotting times (s)</th>
<th>Clexane</th>
<th>Clexane after dose titration</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial</td>
<td>388 ± 164</td>
<td>390 ± 166</td>
<td>331 ± 135</td>
</tr>
<tr>
<td>Venous</td>
<td>378 ± 147</td>
<td>380 ± 161</td>
<td>327 ± 142</td>
</tr>
</tbody>
</table>

### Table 4. Concentrations of lipids before and after 12 weeks of haemodialysis using either Clexane or unfractionated sodium heparin (means ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Clexane</th>
<th>Heparin</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4.87 ± 0.93</td>
<td>4.84 ± 0.87</td>
</tr>
<tr>
<td>LDL</td>
<td>3.05 ± 0.76</td>
<td>3.06 ± 0.74</td>
</tr>
<tr>
<td>HDL</td>
<td>1.11 ± 0.40</td>
<td>1.08 ± 0.23</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.68 ± 0.21</td>
<td>0.71 ± 0.32</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>1.51 ± 0.44</td>
<td>1.57 ± 0.69</td>
</tr>
</tbody>
</table>

Discussion

While the benefits of LMW heparin over standard, unfractionated heparin in the treatment and prophylaxis of venous thromboembolism are well established, the relative merits of LMW heparin for haemodialysis coagulation are less clear. The ease of administration of LMW heparin (single bolus pre-dialysis) and lack of laboratory monitoring would seem clear advantages. However, early in the course of the Clexane arm of the study, we observed an increased frequency of minor interdialytic haemorrhage (none requiring clinical intervention). This problem may not become apparent until after several (4–8) dialyses. Moderate and severe haemorrhagic events, however, were rare in both heparin groups; moreover, there was no difference in the frequency of haemorrhage or thrombosis between the groups. If the initial phase of minor bleeding between dialyses is discounted, our observations are in line with earlier studies comparing Fragmin [19], Braun 21-23Kt/Vurea values were obtained using the Theraps [20], and Fraxiparin [21] with unfractionated heparin.

While the study was not specifically a dose-finding study, we began with the manufacturer’s recommended dose for Clexane. The bleeding tendency between dialyses led to a re-examination of patients’ doses, and no changes in serum lipids were observed with either anticoagulant. Dose reduction decreased the frequency of minor bleeding in our patients by 44% without affecting the frequency of clotting in both the dialyser and blood lines. However, the frequency of minor bleeding was still significantly higher with enoxaparin than with unfractionated heparin (4.3 vs 2.8%, $P < 0.001$).

The primary purpose of anticoagulation during haemodialysis is of course the prevention of thrombosis in the extracorporeal circuit, and in this respect Clexane was more effective than unfractionated heparin. This accords with previous studies of enoxaparin. Vukusich et al. (1995) for example, found clot formation and arteriovenous fistula compression times to be similar for enoxaparin (0.5 mg/kg, the remainder requiring 0.6–0.9 mg/kg (mean 0.62 ± 0.16 mg/kg) [22]. In an extended trial involving 115 consecutive haemodialyses in 35 HD patients, other researchers used enoxaparin 0.88 mg/kg body weight (range 0.33–1.0 mg/kg) [23]. In our view, the recommended dose of 1 mg Clexane/kg BW for haemodialysis is too high in many patients, and a starting dose of 0.75 mg/kg would seem more appropriate. Dose reduction decreased the frequency of minor bleeding in our patients by 44% without affecting the frequency of clotting in both the dialyser and blood lines. However, the frequency of minor bleeding was still significantly higher with enoxaparin than with unfractionated heparin (4.3 vs 2.8%, $P < 0.001$).

### A previously unreported but relevant observation is that in the 20 patients in whom Kt/Vurea values were measured, these values were similar for both Clexane and heparin. This suggested that blood flow through
the dialysers, and hence solute clearances, were not significantly affected by the choice of anticoagulant.

In addition to its anticoagulation properties, unfractionated heparin is known to release lipoprotein lipase from its active site at the capillary endothelial surface. Preliminary studies with LMWH suggested beneficial effects on the lipid metabolism of haemodialysis patients, but this has not been supported by later, larger studies, at least in the short term [11,18]. The cross-sectional, multicentre study of Kronenberg et al. [18] failed to observe any benefit on lipids in 153 HD patients treated with three different LMWH preparations (dalteparin (Kabi Vitrum, Sweden), Sandoparin (Sandoz, Germany) and enoxaparin) and a similar preparation from its active site at the capillary endothelial surface.

failed to observe any benefit on lipids in 153 HD patients. Currently the direct cost in Australia is a little more than standard heparin by about 16%. However, with more widespread usage the price of Clexane is likely to reduce and the small extra cost is counterbalanced by the convenience of administration.

Addendum

A reduction in the cost of enoxaparin as well as the availability of pre-loaded syringes in multiple strengths (20, 40, 60, 80 and 100 mg/ml) has lowered the cost of using enoxaparin. As the price of the 60 mg/ml syringe is now 26% less than the 100 mg/ml ampoule as used in the study ($6.12 vs $8.13 Australian), the average cost per treatment has effectively decreased from $37.26 Australian (US$ 24.22) to $35.25 Australian (US$ 22.91). This is approximately 10.5% higher than the cost of heparin anticoagulation.

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