Heparin versus danaproid for prevention of venous thromboembolism after hip surgery

J Nakase,1 Y Toribatake,1 Y Mouri,1 H Seki,2 K Kitaoka,2 K Tomita3
1 Department of Orthopedics, Kouseiren-Takaoka Hospital, Takaoka, Toyama, Japan
2 Department of Radiology, Kouseiren-Takaoka Hospital, Takaoka, Toyama, Japan
3 Department of Orthopedics, Kanazawa University Hospital, Kanazawa, Ishikawa, Japan

ABSTRACT

Purpose. To compare the prevalence of deep vein thrombosis (DVT), pulmonary thromboembolism (PTE), and bleeding complications in patients receiving heparin or danaproid after hemiarthroplasty or osteosynthesis for hip fractures.

Methods. 37 men and 138 women aged 47 to 100 (mean, 80) years underwent either hemiarthroplasty or osteosynthesis for hip fractures; 5 patients with dementia were excluded. All patients received preoperative elastic stocking and postoperative intermittent pneumatic compression. They were divided into 3 groups based on their admission period: controls (n=71), unfractionated heparin (n=44), and danaproid sodium (n=55). Drugs were administered from postoperative day 1 to 7. At day 7, all patients undertook radioisotope venography of the legs and lung perfusion scintigraphy.

Results. In the control, heparin, and danaproid groups respectively, the DVT rates were 31%, 9.1%, and 5.5%, and the PTE rates were 5.6%, 4.5%, and 1.8%. Only the DVT rate in the control group was significantly higher than that in the heparin and danaproid groups. In the heparin group, one patient had gastrointestinal bleeding, 5 developed wound haematomas, and one had leakage from the drain site for 2 weeks.

Conclusion. Danaproid sodium appeared more effective and safer than heparin, with no bleeding complications occurred.

Key words: danaproid; hemorrhage; heparin; hip fractures; pulmonary embolism; thromboembolism; venous thrombosis

INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) are interrelated and collectively known as venous thromboembolism (VTE), which is a serious postoperative complication. The incidence of VTE is lower in Japanese than European or American populations. Hip fracture is a
risk factor for VTE, according to the Japanese Guideline for Prevention of Venous Thromboembolism. Prophylactic anticoagulants are underutilised owing to the perceived risk of postoperative bleeding. The DVT rate can be as high as 31%, even with physical prophylaxes such as elastic stockings and intermittent pneumatic compression. We compared the prevalence of DVT, PTE, and bleeding complications in patients receiving heparin or danaproid after hemiarthroplasty or osteosynthesis for hip fractures.

MATERIALS AND METHODS

The ethics committee of our hospital approved this study, and informed consent was given by each patient. Between August 2003 and December 2005, 37 men and 138 women aged 47 to 100 (mean, 80) years underwent either hemiarthroplasty or osteosynthesis for hip fractures. Five patients with dementia were excluded because of inability to remain still during venography.

All patients wore elastic stockings preoperatively and had intermittent pneumatic compression of the legs postoperatively. They were divided into 3 groups based on their period of admission. Patients treated in the first year were controls (n=71), those treated in the next 8 months received unfractionated heparin subcutaneously at a dose of 5000 U every 12 hours (n=44), and those treated in the last 8 months received danaproid sodium (low-molecular-weight heparinoid) intravenously at a dose of 1250 anti-Xa units of activity once a day (n=55). These drugs were administered from postoperative day 1 to 7 (the day of nuclear medicine diagnostic testing).

On day 7, all patients underwent radioisotope venography of the legs and lung perfusion scintigraphy using $^{99m}$Tc-MAA. DVT was defined as obturation or contraction/bypass or abnormal deposition in the veins of the legs (Fig. 1). PTE was defined as a lung perfusion defect (Fig. 2). Bleeding complications were defined as a decrease in haemoglobin level; 25 patients (7 controls, 8 on heparin, and 10 on danaproid) who received blood transfusions were excluded from the analysis of bleeding complications.

Because a drain was not used in osteosynthesis, postoperative blood loss was compared only among patients who underwent hemiarthroplasty. The Kruskal-Wallis test and Fisher’s exact test were used for comparison. A p value of <0.01 was considered significant.

RESULTS

Respectively in the control, heparin, and danaproid
groups, the DVT rates were 31%, 9%, and 6%; the PTE rates were 6%, 5%, and 2%; the median postoperative blood losses were 187 g, 151 g, and 201 g; and the median decreases in haemoglobin level were 18%, 14%, and 16%. Only the DVT rate in the control group was significantly higher than that in the heparin and danaproid groups (p=0.0002, Table).

No serious bleeding complications occurred in the heparin and danaproid groups. In the former group, one patient had gastrointestinal bleeding of unknown aetiology, 5 developed wound haematomas, and one had leakage from the drain site for 2 weeks.

**DISCUSSION**

In patients undergoing surgery for hip fracture, 36 to 60% develop DVT and 4.3 to 24% develop lethal PTE when no prophylaxis was used; the DVT rate decreases to 25% when elastic stockings and intermittent pneumatic compression are used, which was similar to that in our controls (31%).

Unfractionated heparin is stable and does not require monitoring of coagulation times when administered at a low dose. It decreases the rates of DVT and PTE by 60 to 70%, and is espoused as more effective than low-molecular-weight heparin (DVT rate: 14.3% vs 31.8%) or no prophylaxis (DVT rate: 22.9% vs 59.4%). None of 49 hip fracture patients receiving unfractionated heparin developed DVT. Nonetheless, as heparin induces bleeding complications and even thrombocytopenia, careful monitoring is needed.

The anticoagulation effect of danaproid is characterised by higher selectivity for anti-Xa activity than heparin and low-molecular-weight heparin. The anti-Xa to anti-thrombin activity ratio of heparin is about one; that of low-molecular-weight heparin is about 2 to 4 and that of danaproid is ≥22. Direct inhibition of thrombin is effective for inhibiting thrombus formation. Heparin also inhibits haemostatic plug formation and increases the risk of bleeding. Danaproid selectively inhibits the factor Xa and hence thrombus formation without inducing bleeding. Danaproid resulted in the lowest DVT rate when compared to enoxaparin and dalteparin; the respective rates were 5.7%, 15.4%, and 8.8%. When compared to dose-adjusted warfarin, the respective rates were 7% and 21%.

DVT and PTE cause delay in rehabilitation, decline in activities of daily living, and even death. To minimise the risk of bleeding complications, we replaced unfractionated heparin with danaproid sodium. Low-molecular-weight heparin is superior to unfractionated heparin. Danaproid appeared more effective and safer than heparin, with no bleeding complications occurred.

**REFERENCES**


---

**Table**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (n=71)</th>
<th>Heparin (n=44)</th>
<th>Danaproid (n=55)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (range) age (years)</td>
<td>80 (56–100)</td>
<td>82 (57–94)</td>
<td>78 (47–94)</td>
<td>0.08</td>
</tr>
<tr>
<td>No. of men/women</td>
<td>18/53</td>
<td>6/38</td>
<td>12/43</td>
<td>0.32</td>
</tr>
<tr>
<td>Mean (range) time to surgery (days)</td>
<td>6.7 (2–15)</td>
<td>6.8 (2–15)</td>
<td>6.5 (2–12)</td>
<td>0.44</td>
</tr>
<tr>
<td>No. of hemiarthroplasty</td>
<td>33</td>
<td>16</td>
<td>17</td>
<td>0.19</td>
</tr>
<tr>
<td>No. of osteosynthesis</td>
<td>38</td>
<td>28</td>
<td>38</td>
<td>0.19</td>
</tr>
<tr>
<td>No. (%) of deep vein thrombosis</td>
<td>22 (31)</td>
<td>4 (9)</td>
<td>3 (6)</td>
<td>0.0002</td>
</tr>
<tr>
<td>No. (%) of pulmonary thromboembolism</td>
<td>4 (6)</td>
<td>2 (5)</td>
<td>1 (2)</td>
<td>0.08</td>
</tr>
<tr>
<td>Median decrease in haemoglobin level (%)</td>
<td>18.2</td>
<td>13.8</td>
<td>15.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Median postoperative blood loss (g)</td>
<td>187</td>
<td>151</td>
<td>201</td>
<td>0.66</td>
</tr>
<tr>
<td>No. (%) of wound haematoma</td>
<td>0</td>
<td>5 (11)</td>
<td>0</td>
<td>0.0001</td>
</tr>
</tbody>
</table>


