Diagnostic and therapeutic management of venous and arterial disease

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CHAPTER 6

USE OF AN ALGORITHM FOR THE ADMINISTRATION OF SUBCUTANEOUS HEPARIN IN THE TREATMENT OF DEEP VEIN THROMBOSIS


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Abstract

Background - Despite the widespread use of subcutaneous heparin in the initial treatment of deep-vein thrombosis, there are no guidelines for achieving adequate anticoagulation with this drug.

Objective - To implement a weight-based algorithm for the administration of subcutaneous unfractionated heparin following an intravenous loading dose.

Design - Prospective cohort study.

Setting - University Hospital.

Participants - 70 outpatients with proximal venous thrombosis.

Intervention - An intravenous bolus of heparin followed by a subcutaneous injection of heparin in doses adjusted for body weight. Subsequent adjustments of the subcutaneous heparin dose were scheduled twice daily according to the algorithm; the activated partial thromboplastin time (aPTT) was measured in the mid-interval (target range, 50 to 90 seconds).

Results - The therapeutic threshold aPTT (≥50 seconds) was achieved in 61 patients (87%) within 24 hours and in 69 patients (99%) within 48 hours. In 7 patients (10%), a supratherapeutic aPTT lasted more than 12 hours. No major bleeding episodes or cases of heparin-induced thrombocytopenia were seen. Three patients (4.3% [95% CI, 0.9% to 12.0%]) has recurrent thromboembolism during 3 months of follow-up.
Conclusions - The administration of subcutaneous heparin according to a weight-based algorithm allows the rapid achievement of effective and safe anticoagulation in patients with deep venous thrombosis.

Introduction

Patients with deep venous thrombosis of the lower extremities are usually treated with an initial course of unfractionated or low-molecular-weight heparin, followed by long-term treatment with oral anticoagulation. The use of nomograms for the intravenous administration of unfractionated heparin assures that almost all patients will promptly achieve sustained anticoagulation. Subcutaneous heparin has been shown to be as effective and safe as intravenous heparin; in addition, low-molecular-weight heparins may facilitate the early discharge of suitable patients from the hospital, with the accompanying advantage of a relatively low cost. However, no accepted guidelines exist with which to achieve adequate anticoagulation with subcutaneous administration of heparin. We implemented a weight-based algorithm for the subcutaneous administration of unfractionated heparin and evaluated the efficacy and safety of this therapy in 70 outpatients with proximal venous thrombosis.

Methods

Patients

Eligible patients were consenting symptomatic outpatients who had a first episode of proximal venous thrombosis, as assessed by compression ultrasoundography. Exclusion criteria were contraindications to anticoagulation, ongoing full-dose anticoagulant therapy, pregnancy, and poor life expectancy. The institutional ethical board approved the investigation.

Intervention

Patients were given an intravenous bolus of sodium heparin (Liquemin, Roche, Basel, Switzerland) and a subcutaneous injection of calcium heparin (Calciparina, Italfarmaco, Milan, Italy) in doses adjusted according to body weight (Table). The first activated partial thromboplastin time (aPTT) was done after 6 hours, and subsequent dose adjustments during the first 48 hours were scheduled twice daily according to the algorithm shown in the Table. The aPTT was performed in the mid-interval. Adjustments were arranged in "steps" to be run up or down according to aPTTs, regardless of body weight. The target aPTT range
**Table** - Algorithm for the adjustment of subcutaneous heparin dosages

Administer an intravenous (IV) bolus and a subcutaneous (SC) injection of heparin in doses adjusted to body weight.* Perform the first aPTT after 6 hours, and then proceed as follows:

<table>
<thead>
<tr>
<th>aPTT</th>
<th>Dosage adjustment and time to retest</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heparin regimen</td>
</tr>
<tr>
<td>≤ 120 seconds</td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>One step up †</td>
</tr>
<tr>
<td>50-90</td>
<td>Same step</td>
</tr>
<tr>
<td>91-120</td>
<td>One step down</td>
</tr>
<tr>
<td>&gt; 120</td>
<td>Withhold heparin treatment</td>
</tr>
</tbody>
</table>

Withhold heparin treatment, perform aPTT after 6 hours, and proceed as follows:

<table>
<thead>
<tr>
<th></th>
<th>Dosage adjustment and time to retest</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>Same step</td>
</tr>
<tr>
<td>50-90</td>
<td>One step down</td>
</tr>
<tr>
<td>91-120</td>
<td>Two steps down</td>
</tr>
<tr>
<td>&gt; 120</td>
<td>Withhold heparin treatment</td>
</tr>
</tbody>
</table>

* Weight (Kg) | IV bolus (U) | SC injection (U) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>4000</td>
<td>12 500</td>
</tr>
<tr>
<td>50-70</td>
<td>5000</td>
<td>15 000</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>6000</td>
<td>17 500</td>
</tr>
</tbody>
</table>

† Steps (U): 10 000 12 500 15 000 17 500 21 250 25 000 30 000

‡ repeat aPTT until a value < 120 sec is obtained, then adjust heparin dosage according to the schedule given for aPTT > 120 seconds

(50 to 90 seconds) was calibrated to correspond to a heparin plasma level (as expressed by antifactor Xa [aXa] activity) of 0.35 to 0.70 U/ml.

To avoid unnecessary overanticoagulation, an aXa assay was scheduled if the aPTT was subtherapeutic 6 hours after the administration of 25 000 U of heparin. If the aXa level exceeded 0.35 U/ml, the heparin dose was not modified. After the first 48 hours, heparin administration was managed on the basis of daily aPTT determinations.

Sodium warfarin was begun on the first or second day and was continued for 12 weeks, with the dose adjusted to achieve an international normalised ratio of 2.0 to 3.0. Heparin therapy was discontinued if the international normalised ratio in patients who had received the study drug for at least 5 days was greater than 2.0 for 2 consecutive days.
Clinical evaluation

Patients were examined daily for signs and symptoms of recurrent thromboembolism, bleeding, or the occurrence of heparin-induced thrombocytopenia (decrease in platelet count to <10^9 cells/L or to >50% below the baseline count).

Follow-up visits were scheduled after 1 and 3 months. Patients were asked to return to the study center if clinical manifestations of recurrent thromboembolism occurred. Recurrent venous thromboembolism was diagnosed according to standard methods.\(^9\)\(^{10}\) Bleeding was defined as major if it was intracranial or retroperitoneal or was associated with a decrease in the haemoglobin level of at least 2.0 g/dL. Autopsy was intended for all decedents in whom pulmonary embolism could not be excluded.

Study outcomes and analysis

We determined the proportion of patients who achieved the therapeutic threshold (aPTT ≥50 seconds) within 24 and 48 hours and the time elapsed from initiation of heparin therapy until achievement of the threshold aPTT. We calculated the percentage of patients with supratherapeutic aPTTs that persisted for more than 12 hours. We also evaluated the rate of recurrent thromboembolism during heparin treatment and follow-up and the rate of major bleeding occurring during heparin treatment and during the following 48 hours.

Descriptive statistics were calculated according to standard methods; 95% CIs were estimated by using the exact method. The time from initiation of heparin therapy until achievement of the aPTT threshold was calculated according to Kaplan-Meier method.

Results

Patients

Twenty-seven of 97 eligible patients were excluded because of ongoing full-dose anticoagulant therapy (15 patients), contraindications to heparin (4 patients), poor life expectancy (3 patients), and pregnancy (1 patient). Thus, 70 patients were enrolled (25 men; median age, 65 years). Three patients weighed less than 50 kg, 21 weighed 50 to 70 Kg, and 46 weighed more than 70 kg. Risk factors for thrombosis were identifiable in 51 patients: cancer (20 patients), prolonged immobilisation (14 patients), recent trauma (9 patients), thrombophilia (5 patients), and oestrogen therapy (3 patients).
**Biological outcomes**

Eighty-seven percent of patients (61 of 70) achieved the aPTT threshold within 24 hours, and 99% (69 of 70) achieved the threshold in 48 hours. The Figure shows the Kaplan-Meier curve for the heparin therapeutic threshold. Seven patients (10.0% [95% CI, 4.1% to 19.5%]) had supratherapeutic aPTTs that persisted for more than 12 hours. In 2 out of the 4 patients who had a subtherapeutic aPTT despite the administration of 25 000 U of heparin, the aXa assay showed a plasma heparin level greater than 0.35 U/mL. The mean (±SD) heparin doses administered were 39700 ± 5300 U during the first day and 30500 ± 10800 U during the second day. No patient required less than 10000 U or more than 30000 U twice daily to prolong the aPTT(or aXa) level. The median duration of heparin treatment was 6.5 days (range, 5 to 12 days).

**Clinical outcomes**

During initial period of heparin treatment and follow-up, thromboembolism...
recurred in three patients (4.3% [95% CI, 0.9% to 12%]). One of the three (age, 93 years) died of autopsy-proven pulmonary embolism within 5 days after heparin treatment began. Both the aPTT and the international normalised ratio were in the therapeutic range. The two other patients had a contralateral thrombosis (one after 8 weeks and one after 10 weeks), as assessed by compression ultrasonography. In all three patients, the aPTT threshold had been achieved within 24 hours of initiation of heparin therapy. No major bleeding episodes or heparin-induced thrombocytopenia occurred during heparin treatment (0% [95% CI, 0.0% to 5.0%]), and no patient was lost to follow-up. Five patients died during the follow-up period: 4 died of cancer (one after 65 days, one after 72 days, one after 80 days, and one after 85 days), and one died of pleural haemorrhage that occurred 1 month after heparin therapy began.

Discussion

Our results suggest that the use of a weight-based algorithm for the subcutaneous injection of unfractionated heparin allows the rapid achievement of correct anticoagulation in almost all patients with deep venous thrombosis while avoiding prolonged periods of excessive anticoagulation. The therapeutic threshold was achieved within 24 hours in 87% of patients, and within 48 hours in 99%. In only 10% of patients did supratherapeutic aPTTs persist for more than 12 hours. No patient had major bleeding or heparin-induced thrombocytopenia, and thromboembolism recurred in only in 3 patients (4.3%). These results are consistent with those reported in recent studies done with either intravenous unfractionated heparin according to standardized guidelines or fixed-dose low-molecular-weight heparins.\(^3,5,11-13\) An intravenous loading dose was chosen because of the poor bioavailability of subcutaneous heparin,\(^8\) and weight-adjusted heparin doses were chosen because body weight is the single best predictor of individual heparin requirements.\(^5,14,15\) The combination of an initial intravenous bolus and weight-adjusted heparin doses probably explains the high biological success rates achieved with our protocol, rates that are similar to those recently reported with the use of a weight-based intravenous heparin nomogram.\(^5,16\) Of interest, the mean daily amount of heparin required to prolong the aPTT during the first 24 hours (almost 40000 U), was greater than the dose (30000 to 35000 U) usually required to attain a proper anticoagulation with intravenous administration.\(^1,3-5,8\) The implication of this finding is that the common
practice of injecting as much subcutaneous heparin as is commonly adminis-
tered intravenously for the initial treatment of patients with thrombotic disor-
ders is likely to produce insufficient anticoagulation, thereby increasing the like-
lihood of recurrent thromboembolism.\textsuperscript{17-19}

A few considerations deserve a careful analysis. Because of a relatively small sample size and the lack of a control group, our results should be validated in other cohorts of patients to ensure external validity. In addition, since we con-
fined our investigation to symptomatic outpatients with a first episode of venous thrombosis, widespread generalization of this therapeutic regimen requires proper evaluation in patients who develop thrombosis during hospi-
talisation and in those presenting with pulmonary embolism or recurrent thromboembolism.

In conclusion, the use of a weight-based algorithm for the subcutaneous administration of unfractionated heparin may greatly simplify the initial treat-
ment of venous thromboembolic disorders. It enables the early mobilization of patients with venous thrombosis and allows the early discharge of suitable patients. The relatively low cost of unfractionated heparin makes this approach attractive in comparison with the use of low-molecular-weight heparins. This strategy has major implications for the acute treatment of a broad spectrum of conditions in which heparin is indicated, such as unstable angina and myocar-
dial infarction.

References

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