Validation of a Weight-Based Nomogram for the Use of Intravenous Heparin in Transient Ischemic Attack or Stroke

Cory Toth, MD; Chris Voll, MD, PhD

Background and Purpose—Intravenous heparin therapy is often used in patients presenting with transient ischemic attack (TIA) or stroke as either bridging therapy for anticoagulation with warfarin or primary therapy in suspected intracranial arterial dissection, crescendo TIAs, or suspected hypercoagulable states. We attempted to validate the use of a weight-based nomogram for heparin-adjusted therapy during hospital admission of patients with TIA or stroke.

Methods—A prospective, single-blinded, randomized, clinical trial was undertaken to compare the use of a specially designed, weight-based heparin nomogram against the traditional method of physician-ordered heparin therapy for patients admitted with TIA or stroke. The trial was not designed to examine the efficacy of heparin therapy but to examine the use of the nomogram for labor requirements, costs of monitoring, safety, length of heparin therapy, and user-friendliness.

Results—Pretreatment clinical factors were comparable between those randomized to use of the nomogram (n=101) and to usual care (n=105). Nomogram patients had a significantly lower first activated partial thromboplastin time than nonnomogram patients (60.6±16.8 versus 69.8±28.7 seconds). Patients treated by nomogram achieved a therapeutic range of anticoagulation sooner than nonnomogram patients (13.4±17.0 versus 17.9±14.1 hours). The fraction of time during which anticoagulation was therapeutic was significantly greater in patients on nomogram therapy (74±25% versus 67±26%). Nomogram patients also had significantly fewer supratherapeutic coagulation results, significantly fewer dose adjustment mistakes, significantly fewer calls to house staff regarding anticoagulation, and significantly fewer total complications than nonnomogram patients. The times required for discontinuation of heparin and discharge from hospital were not significantly different. A survey of house staff and nursing staff showed a preference for nomogram use.

Conclusions—The heparin nomogram is a user-friendly method of maintaining heparin infusions and is associated with improved anticoagulation measures, fewer total complications related to heparin therapy, fewer mistakes in heparin dosage adjustment, and decreased labor on the part of house staff and nursing staff. (Stroke. 2002;33:670-674.)

Key Words: heparin ■ ischemic attack, transient ■ nomogram ■ stroke

Fixed intravenous heparin dosing provides a variable degree of anticoagulation between different patients. This may be due to a heparin resistance phenomenon, heparin-neutralizing proteins, and nonlinear pharmacodynamics.1–3 All of these factors lead to variability in the half-life of intravenous heparin, resulting in interpatient dosing variability. Clinically, these factors lead to difficulty in achieving a therapeutic range for heparin dosing and can frequently lead to subtherapeutic and supratherapeutic anticoagulation levels. The risk of major bleeding with supratherapeutic anticoagulation is suspected to be greater, but this has not been proved in studies of venous thrombosis.4 Conversely, the risk of a recurrent thromboembolic event is increased with subtherapeutic levels of anticoagulation in several trials.5,6 Therefore, a method of controlling the degree of anticoagulation to avoid subtherapeutic and supratherapeutic anticoagulation would be expected to provide benefit to the patient requiring intravenous anticoagulation.

Over the past decade, the use of heparin weight-based nomograms has been studied in internal medicine. No such nomograms have been designed or validated for transient ischemic attack (TIA) or stroke by either neurologists or internists. Benefits such as a more rapid time to therapeutic anticoagulation, more rapid correction of activated partial thromboplastin time (aPTT) values outside the therapeutic range, and fewer aPTT values outside the therapeutic range were found with the use of nomograms in patients with deep-vein thrombosis.7–10

The objective of this study was to evaluate a weight-based nomogram for heparin dosing in TIA and/or stroke. This nomogram would possess qualities such as rapid time to attain therapeutic anticoagulation range, rapid reattainment of
HEPARIN-ADJUSTED NOMOGRAM FOR STROKE/TRANSIENT ISCHEMIC ATTCK

PHYSICIAN’S ORDERS

DATE TIME PROCESSED AT BY:

1. Medication is provided intravenously. No intramuscular injections.
2. aPTT, INR, and CBC must be drawn prior to start of therapy.
3. CBC must be drawn at least every three days during therapy.
4. If patient has a transient ischemic attack, a bolus of intravenous heparin may be given at the discretion of the admitting physician. Suggested IV heparin bolus is 50U/kg to a maximum of 5000U. If a bolus is desired, this must be indicated:
   - Give __ __ U IV heparin as a bolus.
5. Initial dosing for continuous infusion of intravenous heparin:
   - <50 500U/hr = 10mL/hr
   - 50-59 600U/hr = 12mL/hr
   - 60-69 700U/hr = 14mL/hr
   - 70-79 800U/hr = 16mL/hr
   - 80-89 900U/hr = 18mL/hr
   - 90-99 1000U/hr = 20mL/hr
   - 100-109 1100U/hr = 22mL/hr
   - 110-119 1200U/hr = 24mL/hr
   - >119 1400U/hr = 28mL/hr

6. aPTT is to be drawn six hours after heparin therapy initiation.

7. Adjusted heparin therapy as according to aPTT based on sliding scale:

<table>
<thead>
<tr>
<th>aPTT Length</th>
<th>STOP HEPARIN</th>
<th>Dose Change</th>
<th>aPTT APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>——</td>
<td>Increase by 250 U/hr</td>
<td>6 hours</td>
</tr>
<tr>
<td>40-49</td>
<td>——</td>
<td>Increase by 150 U/hr</td>
<td>6 hours</td>
</tr>
<tr>
<td>50-59</td>
<td>——</td>
<td>Increase by 100 U/hr</td>
<td>6 hours</td>
</tr>
<tr>
<td>60-90</td>
<td>——</td>
<td>Next s/m.</td>
<td>6 hours</td>
</tr>
<tr>
<td>91-100</td>
<td>——</td>
<td>Decrease by 100 U/hr</td>
<td>6 hours</td>
</tr>
<tr>
<td>101-120</td>
<td>——</td>
<td>Decrease by 150 U/hr</td>
<td>6 hours</td>
</tr>
<tr>
<td>&gt; 120</td>
<td>60 minutes</td>
<td>Decrease by 250 U/hr</td>
<td>6 hours</td>
</tr>
</tbody>
</table>

8. If significant bleeding occurs, stop heparin and call physician to reassess.

Physician’s signature: __________ Date: __________

Figure 1. Weight-based nomogram used for heparin therapy in nomogram patients.

therapeutic range when the aPTT falls out of therapeutic range, no increased risk of complications from heparin therapy, and a user-friendly format for house staff and nursing staff to use. This study was not designed to examine efficacy of intravenous heparin in stroke, which is controversial, but instead to examine the parameters of anticoagulation and clinical relationships with intravenous heparin use.

Materials and Methods

A nomogram to be used in management of patients with TIA or stroke, regardless of pathogenesis, was designed with 4 specific concepts in mind. The first was an option to provide an initial bolus of intravenous heparin at the discretion of the ordering physician in the case of a patient with TIA but not in a clinical situation of stroke. The bolus, if provided, would be 50 IU/kg to a maximum of 5000 IU, 50% to 60% of the size of the bolus provided by internal medicine nomograms. Second, initial infusion rates were to be 25% to 30% lower than with internal medicine nomograms, within the range of 10 to 12 IU/kg. Third, an adjusted therapeutic range was to be defined as 60 to 90 seconds compared with the therapeutic range of internal medicine nomograms, which is typically 60 to 109 seconds. Fourth, a downward adjustment was to be made in maintenance doses (25% less than with the internal medicine nomogram) of intravenous heparin to obtain therapeutic aPTT values after heparin therapy was begun.

Figure 1 displays the nomogram designed for validation in this study. All nursing staff and house staff attended an educational session regarding the nomogram before the start of the study.

After completion of a successful trial period for safety assessment of nomogram use and with continuing ethics committee approval, a prospective, single-blind, randomized, human clinical trial to examine the use of the nomogram was initiated. All patients enrolled in the study were admitted with a diagnosis of TIA and/or stroke to a neurology ward at Royal University Hospital, Saskatoon, Saskatchewan, Canada, from June 1999 through July 2001, as selected by the local ethics committee.

Inclusion criteria for enrollment consisted of the following: (1) age ≥18 years of age and (2) anticoagulation required for TIA(s) and/or stroke(s) because of suspected or known cardiac source, suspected hypercoagulable state, multiple vascular territory TIsAs and/or stroke(s) of unknown etiology, failure of antiplatelet therapy for prophylaxis of stroke, or other miscellaneous proposed pathogeneses of TIA and/or stroke in which intravenous heparin therapy was deemed necessary by the attending neurologist.

Exclusion criteria for enrollment consisted of the following: (1) thrombolytic therapy in the last 24 hours; (2) current active hemorrhage, either cerebral or otherwise; (3) previous history of intracranial hemorrhage; (4) stroke with suspected propensity to transform into hemorrhage; (5) history of heparin-related complication(s) and/or allergy; (6) lack of informed consent; and (7) pregnancy or breast-feeding.

All patients enrolled were required to give informed, witnessed consent. If for some reason the patient was unable to give consent, a first-degree relative was required to give consent. Randomization was performed with random allocation through a predesigned envelope system (C.T.), with envelopes opened by the enrolling physician. Allocation concealment was maintained until the clinical decision to use heparin therapy was made, after inclusion criteria were met and complete consent was obtained. Physicians were not blinded to the method of heparin dosing, but patients were blinded to method of heparin dosing system.

For patients randomized to nomogram therapy, the admitting physician completed the nomogram. An intravenous bolus was provided if indicated by the completed nomogram. The initial infusion rate of intravenous heparin was determined by the nomogram, and an aPTT was obtained 6 hours after initiation of intravenous heparin therapy. After the return of the aPTT results, nurses made changes in heparin therapy by following instructions provided by the nomogram. House staff or attending physicians were contacted regarding heparin therapy only if the nomogram indicated for this to occur.

For patients randomized to physician-mediated therapy, the physician ordered initial heparin dosing, including possible intravenous heparin bolus and the rate of initial continuous infusion, with an aPTT ordered 6 hours after initiation of therapy. The results of aPTTs were called to the physician on call, who determined whether any changes in heparin therapy were needed and reordered an aPTT as necessary. The particular physician responsible for the patient monitoring was met and complete consent was obtained. Physicians were not blinded to the method of heparin dosing, but patients were blinded to method of heparin dosing system.

| TABLE 1. Characteristics of Patients Before Intravenous Heparin Therapy |
|-----------------|-----------------|-----------------|-----------------|
| Characteristics | Nomogram          | No Nomogram      | P               |
| Patients, n (%) | 101 (49)         | 105 (51)        | 0.11            |
| Age, y           | 64.1 ± 16.2      | 67.7 ± 15.7     | 0.06            |
| Male sex, n      | 65               | 53              |                 |
| Indication, n (%)| 0 (0)            | 3 (3)           |                 |
| Antithrombotic failure | 59 (58) | 53 (51) | 0.83 |
| Cardioembolic stroke | 17 (17) | 9 (9) | 0.83 |
| Crescendo TIA    | 3 (3)            | 13 (12)         |                 |
| Arterial dissection | 15 (15) | 14 (13) | 0.95 |
| Other            | 7 (7)            | 13 (12)         |                 |
| Preheparin CBC and aPTT drawn, n (%) | 98 (97) | 97 (92) | 0.11 |
| Bolus given, n (%) | 16 (16) | 17 (16) | 0.95 |

CBC indicates complete blood count. Mann-Whitney U test was used to determine statistical significance.
determined dosing in this manner, and each change was intuitive and individual to that physician.

All measurements of aPTT were performed on blood collected in Vacutainer tubes containing buffered citrate and were processed with the use of thromboplastin Actin FS (Dade). Heparin solutions were provided by the Department of Pharmaceutical Services at Royal University Hospital, Saskatoon, Saskatchewan. Heparin product used was identical for both groups of patients. End-point measurements consisted of the following: (1) the time required for the first aPTT > 60 seconds; (2) the time required to achieve therapeutic aPTT range (60 to 90 seconds); (3) the number of aPTT measurements recorded and number of changes in heparin infusion rate recorded; (4) the number of supratherapeutic aPTTs results recorded (aPTT > 90 seconds); (5) the number of mistakes recorded during maintenance of heparin therapy (defined as a failure to increase heparin therapy when aPTT was subtherapeutic, a failure to decrease heparin therapy when aPTT was supratherapeutic, or an incorrect adjustment of heparin therapy while aPTT was within therapeutic range); (6) the number of calls to house staff recorded for each patient regarding heparin therapy; and (7) the incidence of anticoagulation-related complications recorded for each patient. Major complications were defined as a hemorrhage with reduction in hemoglobin of ≥20 g/L that required a transfusion of packed red blood cells or retropitoneal, intracranial, or intraarticular bleeding. Minor complications were defined as any bleeding that did not meet the above criteria. Total complications were the sum of major and minor complications. Any instances of thrombocytopenia, skin necrosis, allergy, alopecia, or hypoaaldosteronism were recorded. Other end-point measurements included the incidence of cerebrovascular or cardiovascular events, including TIA, stroke, myocardial infarction, and unstable angina; length of hospital stay; and length of heparin therapy while in hospital.

An additional measure of the fraction of time within therapeutic range expressed as a percentage of total heparin therapy duration was calculated by use of all aPTT measurements. For best approximation, we selected all periods of time starting with a therapeutic-range aPTT until heparin was discontinued or until aPTT was measured outside the therapeutic range. These time periods were then expressed as a fraction of the total duration of heparin therapy to calculate the percentage of time during which anticoagulation was within therapeutic range.

For those patients on nomogram, a complete blood count was drawn every 3 days to detect thrombocytopenia and blood loss. For patients not on nomogram, a complete blood count was ordered as clinically indicated by physicians. Liver enzymes were drawn as clinically indicated in both groups.

All data were analyzed by Kaplan-Meier (Wilcoxon rank sum) statistics or Mann-Whitney U test. All tests of statistical significance were 2 tailed; α was set at 0.05. Analyses of all data were performed with intention-to-treat analysis, with no patient data excluded once randomization allocation occurred. After study completion, a survey to gauge satisfaction with both methods of heparin delivery was provided to all nursing staff and house staff who were recorded as being responsible for heparin therapy for ≥1 patient enrolled in the study.

**Results**

Two hundred six patients were enrolled and randomized between August 1999 and March 2001 at Royal University Hospital, Saskatoon, Saskatchewan, Canada. Data for each group of patients before therapy are provided in Table 1. A total of 12 patients were excluded from the study: 9 patients failed to meet inclusion criteria, and 3 patients declined...
participation. One hundred one patients were randomized to nomogram therapy, and 105 patients had heparin maintained by physician modulation (no nomogram). Figure 2 demonstrates the flow of patients through this study. The treatment groups were similar with respect to pretreatment clinical parameters (Table 1). The average size of the heparin bolus, for patients selected to receive this, was 4556±1625 IU and was not significantly different between study groups.

End points of anticoagulation are presented in Table 2. The first aPTT was significantly different between the 2 groups, with a statistically significant lower value for patients on nomogram. A histogram demonstrating the range of first aPTTs with or without nomogram is displayed in Figure 3. The time required to achieve a therapeutic-range aPTT (60 to 90 seconds) was significantly less for nomogram therapy (Figure 4). Patients on nomogram therapy were within therapeutic range for a significantly greater time than nonnomogram patients (74±25% versus 67±26%; Mann-Whitney U test, P<0.05). Other end-point measures that demonstrated significant differences included the number of supratherapeutic aPTTs, number of calls to house staff, number of mistakes made with regard to anticoagulation, and number of total complications (Table 3). There were no patients with documented complications of heparin-induced thrombocytopenia, skin necrosis, alopecia, hypoaldosteronism, and liver enzyme elevation. One patient in the nomogram group developed an erythematous rash over the torso 10 hours after starting heparin and was deemed to have a possible heparin allergy, resulting in discontinuation of heparin therapy. Clinical reasons for discontinuation of intravenous heparin were similar between the 2 groups.

After completion of patient enrollment but before data analysis, a survey of nursing staff and house staff involved with care of patients in the trial was undertaken. The question

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nomogram</th>
<th>No Nomogram</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason for discontinuation of heparin, n</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Complication</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>15</td>
<td>0.78</td>
</tr>
<tr>
<td>Transfer from hospital</td>
<td>20</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Changed to antplatelet agents</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Taken for surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic INR achieved</td>
<td>53</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Major complications, n (%)</td>
<td>2 (2.0)</td>
<td>6 (5.7)</td>
<td>0.17</td>
</tr>
<tr>
<td>Minor complications, n (%)</td>
<td>0 (0)</td>
<td>3 (2.8)</td>
<td>0.09</td>
</tr>
<tr>
<td>Total complications, n (%)</td>
<td>2 (2.0)</td>
<td>9 (8.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cerebrovascular/cardiovascular events while on heparin, n (%)</td>
<td>6 (5.9)</td>
<td>5 (4.8)</td>
<td>0.71</td>
</tr>
<tr>
<td>Time to discontinue heparin, d</td>
<td>4.0±2.8</td>
<td>4.6±3.8</td>
<td>0.33</td>
</tr>
<tr>
<td>Time to discharge from hospital, d</td>
<td>7.1±5.9</td>
<td>7.9±8.6</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Mann-Whitney U test was used to determine statistical significance.
“Do you prefer to use a heparin nomogram or do you prefer physician-ordered heparin?” was proposed to 52 nurses and 14 residents. Responses were received from 26 nurses (50% return rate) and 8 residents (57% return rate). A total of 94% of responders favored the use of the nomogram, and 6% of responders had no preference.

Discussion

The use of heparin as bridging therapy until oral warfarin achieves therapeutic levels remains common practice, even though clear proof of efficacy is lacking in patients with TIA and stroke. Anticoagulation is also used for patients with intracranial arterial dissection and crescendo TIAs, although proof of efficacy is again lacking.11 Therapeutic trials of subcutaneous heparin12 and low-molecular-weight heparin13–15 have failed to demonstrate efficacy in the treatment of acute stroke. Therefore, the overall use of heparin in therapy of acute stroke appears to have no therapeutic benefit, with a theoretical prophylactic benefit in patients who may later benefit from oral anticoagulation.

Even though studies have failed to demonstrate clear efficacy of heparin or low-molecular-weight heparin in acute stroke syndromes,12–15 many neurologists continue to believe in the efficacy in specific stroke syndromes such as arterial dissection, cardioembolic stroke, hypercoagulability, and crescendo TIA. The uncommon complication of transient hypercoagulability in patients with protein C deficiency who are started on warfarin therapy alone16,17 is another reason that intravenous heparin will probably continue to have a therapeutic role in TIA and stroke in the near future. Therefore, a method of intravenous heparin delivery that is least laborious, least likely to produce complications, and most likely to prevent recurrent episodes is optimal.

In this study, use of a heparin nomogram was associated with significant differences in laboratory values of anticoagulation, providing a theoretical advantage for the patient requiring heparin. Patients receiving nomogram therapy had fewer time periods of subtherapeutic and extratherapeutic anticoagulation levels, which may decrease the risk of recurrent stroke and intracranial hemorrhage. Mistakes in manipulation of maintenance anticoagulation and the number of total complications were also significantly reduced for nomogram patients. Therefore, examination of laboratory end points and some clinical end points suggests that the heparin nomogram for TIA and/or stroke allows theoretically safer anticoagulation.

The number of calls to house staff, a measure of labor for both nursing staff and house staff, was significantly reduced for patients receiving nomogram therapy. In addition, medical personnel involved with the use of the nomogram indicated preference for the use of the nomogram after their experience with both therapies. Therefore, the nomogram did provide a measure of improvement in labor and appears to be a user-friendly system.

In conclusion, we believe that the heparin nomogram developed for this study has been validated and provided a degree of improvement over physician-modulated heparin dosing without a change in clinical events and with fewer anticoagulation-related complications. The heparin nomogram for TIA and/or stroke imparts theoretical improvements in the quality of anticoagulation for those patients requiring intravenous heparin for TIA and/or stroke.

References

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