Evaluation of a Heparin Nomogram in the Treatment of Deep Vein Thrombosis and Pulmonary Embolism

S. Gavura, C.D. Bayliff and M.J. Kovacs

ABSTRACT

Dosing nomograms have been shown to improve heparin therapy administration for patients with venous thromboembolism (VTE). A pre-printed heparin order, with a standardized dosing nomogram, was recently introduced at our institution and we wished to compare patients who had VTE and who were treated with the nomogram with historical controls.

Thirty-four control patients, treated prior to initiation of the heparin nomogram, were compared with 21 patients who were treated according to the nomogram. Baseline characteristics were similar except for age. Twenty-five of 34 control patients (74%) versus 20 of 21 nomogram patients (95%) achieved a therapeutic Activated Partial Thromboplastin Time (aPTT) within the first 24 hours (p=0.04). The mean time to therapeutic aPTT in the control and nomogram groups was 19.3 ± 21.8 hours versus 12.5 ± 12.7 hours, respectively (NS). The mean duration of heparin therapy in the control versus nomogram group was 6.2 ± 1.8 days and 5.1 ± 1.6 days, respectively (p=0.03). The number of days until the initiation of warfarin was 2.6 ± 1.5 days versus 1.8 ± 1.5 days in the control and nomogram group, respectively (p=0.03). The nomogram resulted in a significant improvement in heparin therapy and may result in decreased costs.

Key Words: heparin, nomogram, deep vein thrombosis

RÉSUMÉ

Les nomogrammes posologiques se sont révélés utiles pour améliorer l'héparinothérapie chez les patients souffrant de thrombose veineuse profonde (TVP). Une ordonnance préimprimée d'héparine, avec un nomogramme posologique standardisé, a récemment été utilisée à notre établissement et nous avons voulu comparer les patients souffrant de TVP traités selon la nouvelle méthode des nomogrammes à ceux traités selon l'ancienne méthode.

Trente-quatre patients traités selon l'ancienne méthode (groupe témoin) ont été comparés à 21 patients traités selon la méthode des nomogrammes d'héparine (groupe nomogramme). Les caractéristiques initiales étaient semblables chez tous les patients, sauf en ce qui concerne l'âge. Vingt-cinq des 34 patients du groupe témoin (74 %) contre 20 des 21 patients du groupe nomogramme (95 %) ont atteint un TCA thérapeutique dans les 24 premières heures du traitement (p = 0,04). Le temps moyen pour atteindre un TCA thérapeutique dans le groupe témoin vs le groupe nomogramme était de 19,3 ± 21,8 heures et de 12,5 ± 12,7 heures, respectivement (N.S.). La durée moyenne de l'héparinothérapie dans le groupe témoin comparativement au groupe nomogramme était de 6,2 ± 1,8 jours et de 5,1 ± 1,6 jours, respectivement (p=0,03). Le nombre moyen de jours avant l'instauration du traitement à la warfarine était de 2,6 ± 1,5 jours pour le groupe témoin comparativement à 1,8 ± 1,5 jours pour le groupe nomogramme (p=0,03). L'utilisation du nomogramme a donc considérablement amélioré l'héparinothérapie et pourrait notablement diminuer les coûts.

Mots clés : héparine, nomogramme, thrombose veineuse profonde.

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INTRODUCTION

Heparin is a naturally derived anticoagulant that has been used in the treatment of venous thromboembolism (VTE) for several decades.[1-3] As therapy for VTE, heparin acts by preventing extension of the thrombus, allowing the body's natural thrombolytic activity to lyse the clot.[4] The unstable structure of heparin permits only parenteral administration by either the intravenous or subcutaneous route.[2] It is well established that continuous intravenous heparin is superior to intermittent subcutaneous heparin for the therapy of an acute thromboembolic event.[6] There appears to be a high degree of variability of response to heparin therapy. Differences are related in part to disposition and elimination.[7] Inter-individual variability between a given heparin concentration and a level of anticoagulation is large.[8] The level of anticoagulation is determined by the Activated Partial Thromboplastin Time (aPTT), which reflects the degree of inhibition of

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certain endogenous clotting factors.[2] Since instrument standards and sources of laboratory reagents vary, aPTT values that represent therapeutic heparin levels may vary from institution to institution.[9] As a result, published guidelines that dose heparin based on reported aPTT values tend to be institution-specific.

Accumulated clinical evidence associates a failure to reach adequate anticoagulation with recurrence of VTE.[10-12] A minimum effective degree of anticoagulation has become established as an endpoint for heparin administration.[6] An upper therapeutic level has historically been chosen in an attempt to minimize the potential for undesirable hemorrhage. However, the association between supratherapeutic levels and bleeding is not as well established.[10]

A study by Hull et al suggested that the failure to attain therapeutic anticoagulation within the first 24 hours after diagnosis of VTE is associated with a 15 times greater risk of recurrent VTE.[6] Unfortunately, retrospective audits in other centres have revealed a tendency to under-treat patients, and a failure to achieve prompt anticoagulation.[11-14] Nomograms and other dosing guidelines for physicians have been shown to be effective at decreasing the time to adequate anticoagulation, and maintaining the heparin level within the therapeutic window.[11-13]

To determine the previous practice of anticoagulation of VTE, a retrospective audit of heparin administration was performed. The introduction of a pre-printed heparin nomogram by the Department of Haematology, Victoria Hospital allowed for an audit of anticoagulation with the nomogram. The primary objective was to determine if the nomogram resulted in a greater percentage of patients achieving a therapeutic aPTT within the first 24 hours of therapy, as compared with control group data. Together, these two audits were used to determine the impact of the heparin nomogram and its effect on patient outcomes.

METHODS

All patients who received heparin, followed by warfarin, for the treatment of objectively confirmed VTE were eligible.

Patients were excluded if they were considered to be at high risk of bleeding complications, prior to the initiation of heparin therapy, as defined by one or more of the following:

- major surgery in preceding seven days;
- any coagulation defects (initial INR > 1.2);
- gastrointestinal bleed in previous three months;
- cerebral hemorrhage in previous three months;
- uncontrolled hypertension (SBP> 180 and/or DBP> 120);
- any thrombolytic therapy in preceding seven days; and
- patients on oral antiplatelet agents, including all NSAIDS.

Patients less than the age of 18 and those treated with another nomogram or in the intensive care unit were excluded. Nomogram group patients were identified by the pharmacy department. Any pre-printed heparin order with an indicated diagnosis of VTE was flagged for chart review. All patients treated with the nomogram received a 5,000 unit bolus of heparin followed by a continuous infusion of 40,000 units of heparin per litre of 5% dextrose in water (D5W), starting at 32 mL/hr. The aPTT was ordered to be checked six hours after the initiation of heparin therapy. Further therapy decisions were determined as listed in Table I. Dose changes were transcribed "as per nomogram" on the medication order sheets. The pre-printed order also listed the following comment: "For DVT or PE consider starting warfarin on day two and continue heparin at least five full days."

The therapeutic range for heparin therapy at Victoria Hospital at the time of study was determined to be an aPTT time of 60-85 seconds, based on anti-Xa levels of 0.3-0.7 U/mL.

A control group consisted of patients diagnosed and treated for VTE between February and December 1993, prior to the introduction of the pre-printed heparin nomogram. Control group patients were identified by the Department of Clinical Information and Records Services. The same inclusion and exclusion criteria applied. Control patients received heparin as ordered by the physician. The physician also specified when aPTT tests were to be performed, and when warfarin was to be initiated. Subsequent heparin dose modifications were made by the physician upon notification of the aPTT result.

Table I. Heparin Nomogram

aPTT	BOLUS	HOLD	RATE CHANGE	RECHECK aPTT
< 50 seconds	5000 units	0	+4 cc/h (+160 u/h)	6 hours
50-59 seconds	0	0	+2 cc/h (+80 u/h)	6 hours
60-85 seconds	0	0	no change	next am
86-110 seconds	0	0	-2 cc/h (-80 cc/h)	next am
> 110 seconds	0	60 minutes	-4 cc/h (-160 u/hr)	6 hours

A data collection form was utilized to extract information from the health record. The following information regarding anticoagulation therapy was recorded:

- diagnosis;
- age, weight, and height;
- bolus dose (if given);
- initial rate;
- time first aPTT obtained;
- time to aPTT > 60 seconds;
- number and duration of subtherapeutic aPTTs (< 60 sec.);
- number and duration of supratherapeutic aPTTs (> 85 sec.);
- number and duration of "hold heparin" orders;
- total number of aPTT tests performed;
- "no IM or antiplatelet drugs" orders;
- time to initiation of warfarin therapy;
- duration of heparin therapy;
- average number of dose changes/day;
- incidence of hemorrhage as documented in progress notes; and
- thrombosis extension or pulmonary embolism recurrence as documented in progress notes.

STATISTICAL ANALYSIS

Baseline characteristics were examined using comparative statistics. Results are expressed as mean ±, standard deviation unless otherwise stated. The primary endpoint was the proportion of patients in each group that had achieved a therapeutic degree of anticoagulation within 24 hours of initiation of heparin therapy. Secondary endpoints included: the doses of heparin used; time to achieve therapeutic aPTT; the proportion of sub- and supratherapeutic aPTT results between the two groups; the time to initiation of warfarin; the number of interventions in therapy. For the purposes of this study, interventions were defined as hold heparin orders, bolus doses and rate changes; the duration of heparin therapy; and the duration of hospitalization.

Differences in proportion were analyzed by Fisher's Exact Test and Chi Square as appropriate. Differences in means were compared by Student's t-test.

RESULTS

Of 55 patients eligible for inclusion in the control group, 19 met exclusion criteria, for reasons listed in Table II.

Of 40 patients meeting inclusion criteria in the nomogram group, 19 met exclusion criteria, as shown in Table III.

Baseline characteristics are shown in Table IV. There was a significant difference in the mean age of patients between the groups.

Patients in the nomogram group received a standard loading dose and rate as described in Table V. Variations were noted in loading bolus dose, admixture concentration, and initial rate in the control group. Two of 34 control group patients did not receive a loading dose of heparin.

The proportion of patients reaching a therapeutic level of aPTT within the first 24 hours of therapy was the primary endpoint. Subtherapeutic aPTT values occurred in 9 of 34 patients in the control group (26.4%) versus one of 21 nomogram patients, (4.8%) (p=0.04).

Table II. Patients Excluded from the Control Group

Exclusion Criteria	Number of Patients
INR>1.2 Initially	4
Existing Nomogram	2
Treated In Critical Care Unit	4
Heparin held, unrelated to aPTT	1
Patient transferred out of hospital	1
Pregnant patient	1
Incomplete or missing data	2
Hematoma/Hemorrhage	4

Table III. Patients Excluded from the Nomogram Group

Exclusion Criteria	Number of Patients
INR>1.2 Initially	10
Nomogram Changed or Modified	1
Nomogram Orders not followed	2
Patient switched to or from nomogram	1
Incomplete or missing data	4
No thrombosis documented	2

Table IV. Baseline Characteristics of Groups

	Control (n=34)	Nomogram (n=21)	P
Age (yrs) (mean ±SD)	67.7±14.9	52.1± 15.4	0.00006
Diagnosis of DVT/PE	28/6	15/6	0.27
Weight (kg)(mean ±SD)	77.1 ± 14.5 (n=26)	83.0 ± 25.3 (n=19)	0.36

Table V. Loading Dose and Initial Rate

	Control (Range) (n=34)	Nomogram (n=21)	P
Initial Bolus (U)	5367 (0-10000)	5000	NS
Initial Rate (U/Hr)	1109 (900-1280)	1280	NS

The average time to first aPTT in the control group was 6.8 ± 2.1 hours, and in the nomogram group was 7.0 ± 3 hours (p=0.77).

The average time to therapeutic aPTT in the control group was 19.3 ± 21.8 hours (range 5-85) versus 12.5 ± 12.7 hours (range 6-61.5) in the nomogram group (p=0.69).

In the control group, 13 of 34 patients did not achieve a therapeutic aPTT with the first test. Of this group, only four patients proceeded to achieve a therapeutic aPTT within the first 24 hours. Subtherapeutic aPTT values at 24 hours were observed in nine patients, more than 36 hours in five of these patients, and more than 48 hours in three of these patients .

Fifteen of the 21 nomogram patients achieved a therapeutic aPTT level with the first test. One patient in the nomogram group did not have a aPTT test performed until 18.5 hours after initiation of therapy due to incomplete transcription of the pre-printed order.

The average duration of therapy in the control group was 6.2 ± 1.8 days (range 3.5 - 12.5), versus 5.1 ± 1.6 days (range 2.5-10) in the nomogram group (p=0.03).

Warfarin therapy was initiated in an average of 2.6 ± 1.5 days in the control group (range 1-7 days), and 1.8 ± 1.4 days in the nomogram group (range 1-6 days)(p=0.03).

The incidence of sub- and supratherapeutic aPTT test results were determined on a per course of therapy basis and are shown in Table VI.

Fewer aPTT tests were performed in the nomogram group compared with the control groups. There was no substantial difference in the number of sub- and supratherapeutic aPTTs between the groups.

The number of interventions between the two groups are shown in Table VII.

There were no significant differences between the groups.

Four patients in the control group had recurrent VTE. In all cases this occurred after three months. There were no bleeding events in the control group. One patient in the nomogram group had a bleeding ulcer during therapy. In the control group, two of 34 patients had orders for "No IM injections" (5.8%), and 4 of 34 patients had orders for "No ASA or NSAIDS" (11.7%). Nomogram patients had a pre-printed order for "No IM injections or ASA or NSAIDs or ticlopidine."

DISCUSSION

The heparin nomogram was effective in achieving rapid therapeutic anticoagulation in patients, as defined by the aPTT test. Ninety-five percent of patients treated with the heparin nomogram attained therapeutic anticoagulation within 24 hours, versus 74% in the control group. In addition, the nomogram reduced the duration of heparin therapy and the time to initiation of warfarin therapy. The nomogram also significantly reduced the number of aPTTs performed per course of therapy.

Fewer aPTTs were performed per patient course so there were no additional laboratory costs associated with the new nomogram, and, in fact, some cost avoidance could be achieved. As well, the duration of therapy was reduced suggesting that the total admission time may be reduced.

Control data analysis revealed generally good anticoagulation practice at Victoria Hospital. In contrast, audits at other centres reveal poor performance.[11-14] However, the only other published audit of heparin therapy in London at another teaching hospital revealed findings similar to the nomogram group.[15] Reasons for subtherapeutic concentrations in previous audits included low or absent loading doses, slow and inappropriate response to subtherapeutic levels, and delays in initiation of therapy.[11-14]

Brien et al performed an audit of heparin therapy at St. Joseph's Hospital in London, Ontario in 1986.[15] In a retrospective audit of 79 patients with VTE, they found the majority of patients achieved a therapeutic aPTT within the first 24 hours. Baseline characteristics were comparable to the patient population in this study and the average time to a therapeutic aPTT was 12.8 hours, while duration of heparin therapy averaged 5.4 days. These results are very similar to our nomogram patients and again emphasize how much difference may exist between centres.

Cruickshank et al performed an audit of heparin therapy at McMaster Hospital in Hamilton, Ontario prior

Table VI. Variations in Anticoagulation

	Control (n=34)	Nomogram (n=21)	P
Number of aPTTs performed per patient course (± SD)	10.3 ± 3.4	8.1 ± 3.0	0.018
Number of aPTTs<60s per patient course (± SD)	2.7 ± 2.8	1.5 ± 2.1	0.090
Number of aPTTs>85s per patient course (± SD)	3.6 ± 2.1	3.9 ± 1.5	0.579

Table VII. Interventions in Therapy

Mean Interventions Per Course	Control (n=34)	Nomogram (n=21)	P
Bolus doses (± SD)	0.7 ± 1.2	0.4 ± 0.8	0.291
"Hold Heparin" (± SD)	1.6 ± 1.6	1.3 ± 1.0	0.460
Dose Changes (± SD)	5.1 ± 3.2	4.6 ± 2.8	0.582

to the introduction of their heparin nomogram in 1990.[11] They found the average time to the first therapeutic aPTT was 56.9 hours, with 37% of patients achieving a therapeutic aPTT within 24 hours. This result reflects other audits.[10,14] The nomogram used, almost identical to the one studied in this audit, produced a therapeutic level of anticoagulation in 66% of patients within 24 hours, with the average time to a therapeutic aPTT of 24.3 hours.

Our results were much better than Cruickshank's and likely are due to exclusion bias as patients at high risk of hemorrhage were excluded from this study. In the absence of risk factors clinicians may have treated these patients in our audit more aggressively, decreasing the time until a therapeutic aPTT. The low incidence of hemorrhage observed in our study may also be explained by excluding patients at risk of hemorrhage. Another limitation encountered during medical record audit was the relatively high exclusion rate. This was done in an attempt to ensure consistency between the groups. Unfortunately, the patients in the nomogram group were considerably younger that those in the control group and may have affected our results. This remains a limitation of the study.

Evaluation of practice is a necessary component of quality assurance. Audits of physician practice, when compared with the perceived "standard of practice," illustrate whether one institution is representative of others. Other authors have identified the need for quality assurance of heparin therapy practice due to the inherent difficulties associated with its use.[16,17]

From a practical perspective, a heparin nomogram would be anticipated to facilitate care and workflow. Not only is there less risk in calculating doses and errors in concentration, but the inherent delays encountered by nurses in attempting to contact physicians for dosage changes is averted. Use of low molecular weight heparins in this setting will eventually obviate the need for unfractionated heparin and their nomograms.[18]

In conclusion, this study demonstrates that the heparin nomogram used at our hospital is more effective in achieving rapid anticoagulation within 24 hours than standard practice. Ninety-five percent of patients treated with the heparin nomogram achieved therapeutic anticoagulation within the critical 24 hours. Based on the current standard of practice at Victoria Hospital, the nomogram significantly improved therapy.

The pre-printed heparin nomogram was intended to help physicians with what was felt to be inadequate heparin therapy. The results of this audit illustrated that heparin prescribing at Victoria Hospital may not be as poor as audits at other major centres have suggested. This may be due to be greater emphasis during teaching by area hematologists, or may reflect better education and understanding among physicians.

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