Annals of Internal Medicine | ARTICLE

Brief Communication: Preoperative Anticoagulant Activity after Bridging Low-Molecular-Weight Heparin for Temporary Interruption of Warfarin

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Background: Preoperative low-molecular-weight heparin (LMWH) is often used when warfarin therapy is interrupted for surgery.

Objective: To determine the preoperative anticoagulant activity of LMWH following a standardized "bridging" regimen.

Design: Prospective cohort study.

Setting: Single university hospital.

Patients: Consecutive patients who had warfarin therapy interrupted before an invasive procedure.

Intervention: Enoxaparin, 1 mg/kg of body weight, twice daily. The last dose was administered the evening before surgery.

Measurements: Blood anti–factor Xa heparin levels measured shortly before surgery.

Results: Preoperative anti-Xa heparin levels were obtained in 80 patients at an average of 14 hours after the last dose of enoxaparin was administered. The average anti-Xa heparin level was 0.6 U/mL. The anti-Xa heparin level, measured shortly before surgery, was 0.5 U/mL or greater in 54 (68%) patients and 1.0 U/mL or greater in 13 (16%) patients. A shorter interval since the last dose ($P < 0.001$) and a higher body mass index ($P = 0.001$) were associated with higher preoperative anti-Xa heparin levels.

Limitations: The small sample size limits accurate estimates of the frequency of the clinical outcomes. A single regimen of LMWH was evaluated.

Conclusions: Anti-Xa heparin levels often remain high at the time of surgery if a last dose of a twice-daily regimen of LMWH is given the evening before surgery.

Ann Intern Med. 2007;146:184-187. www.annals.org
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Warfarin is used to prevent arterial and venous thromboembolism (1). When patients require surgery, warfarin therapy must be stopped to avoid increased bleeding (2). However, the antithrombotic effect of warfarin takes 4 to 5 days to recede after it is withdrawn, and patients are at increased risk for thromboembolism during this period (1, 2). Low-molecular-weight heparins (LMWHs) are frequently used as bridging therapy to reduce the risk for arterial and venous thromboembolism when patients no longer receive oral anticoagulation (3, 4). Current recommendations are to give the last dose of twice-daily LMWH 12 to 24 hours before surgery (1). Although cohort studies have reported that bridging therapy with LMWHs is feasible (5–8), concerns remain about its safety (5). In particular, if the last dose of a twice-daily regimen is given the evening before surgery, there may not be sufficient time for elimination of the anticoagulant effect of LMWH (9, 10) Accordingly, we sought to quantify preoperative anticoagulant activity after a standardized twice-daily regimen of bridging LMWH.

METHODS

Study Sample

Consecutive patients attending the thrombosis clinic of the Hamilton General Hospital, Hamilton, Ontario, Canada, who were scheduled to have warfarin therapy interrupted for surgery or for an invasive procedure in the same hospital were potentially eligible. We excluded patients with renal impairment (creatinine levels >200 μmol/L [>2.26 mg/dL] until the first 20 patients were enrolled and those with creatinine levels greater than 150 μmol/L (>1.7 mg/dL) subsequently; those with heparin allergy, including a history of heparin-induced thrombocytopenia; those who were pregnant; and those who were geographically inaccessible. The local research and ethics board approved the study protocol, and all patients provided written informed consent.

Treatment Protocol and Baseline Data

Patients were seen at least 6 days before surgery and baseline data, including sex, age, weight, height, body mass index (BMI), urea, creatinine level, comorbid conditions, and concomitant medications, were recorded. Creatinine clearance was calculated by using the Cockcroft–Gault equation (11). Warfarin was withheld for 4 or 5 days before the planned procedure. Patients or caregivers administered enoxaparin at 1 mg/kg of body weight twice daily

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Context

Twice-daily low-molecular-weight heparin (LMWH) is commonly used as bridging therapy when warfarin anticoagulation is interrupted before surgery. Usual practice is to give the last dose of LMWH 12 to 24 hours before surgery.

Contribution

These investigators found that two thirds of 80 patients who received their last dose of enoxaparin at a mean 14 hours before surgery had markedly elevated anti-Xa heparin levels shortly before surgery was scheduled to begin.

Caution

Administering the final dose of a twice-daily regimen of enoxaparin on the evening before surgery does not allow adequate time for elimination of the anticoagulant activity.

Implications

Potential risks for hemorrhage or thromboembolism could not be evaluated in this small group. Results may differ for other LMWH preparations.

—The Editors

(no upper dose limit), starting 3 days before surgery. The final dose of LMWH was given on the evening (at least 12 hours) before the surgery (7, 8).

If surgical hemostasis was achieved, warfarin therapy was restarted on the evening of surgery and enoxaparin therapy (1 mg/kg twice daily) was restarted on the morning after surgery.

Outcome Measures

The primary outcome measure was blood heparin level measured as anti–factor Xa activity shortly before surgery. Secondary outcome measures included measurement of the middosing heparin level the day before surgery, perioperative bleeding (major and minor), and thromboembolism (arterial and venous) from the time warfarin therapy was stopped preoperatively until 4 to 6 weeks after surgery (when telephone follow-up was done). Data collection was monitored centrally to ensure completeness of records. Anti-Xa heparin level assays were performed after patients had completed follow-up to ensure that the results would not influence clinical management or assessments of outcomes. Clinical outcomes were adjudicated centrally, using standardized criteria, by a thrombosis clinician who was not aware of the patients' baseline data or anti-Xa levels.

Blood Sampling and Laboratory Tests

Heparin levels were measured at the Hemostasis Reference Laboratory, Henderson Research Centre, Hamilton, Ontario, Canada, by using a Stachrome Heparin kit (Diagnostica Stago, Asnieres-Sur-Seine, France) on an AMAX 190 (Trinity Biotech, Bray, Ireland) and an enoxaparin-specific reference curve.

For patients who are being treated with a twice-daily enoxaparin regimen for acute coronary syndromes, a peak anti–factor Xa heparin level of 0.5 U/mL is considered therapeutic (12).

Statistical Analysis

Linear regression analysis was used to determine the influence of clinical variables on middosing interval and residual (preoperative) anti-Xa heparin activity. All analyses were performed by using SPSS, version 10.1 (SPSS Inc., Chicago, Illinois).

Role of the Funding Source

The study was supported by a grant from Hamilton Health Sciences Foundation. The funding source had no role in the study design or execution, collection of data, writing of the manuscript, or decision to submit the manuscript for publication.

RESULTS

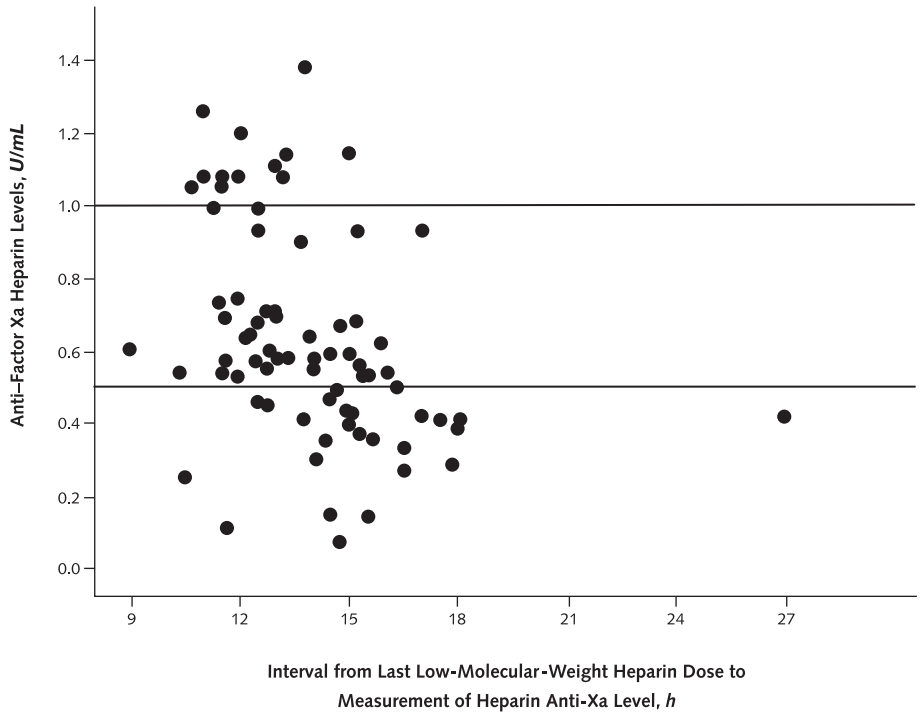
One hundred two patients were enrolled from March 2003 to February 2005. Eight were subsequently excluded because their procedure was canceled. The **Table** shows the baseline characteristics of the 94 patients who received preoperative bridging LMWH. Mean age was 68 years, and 76% of patients were men. The most common indication

Table. **Baseline Characteristics in Participants Receiving Bridging Low-Molecular-Weight Heparin***

Variable	Participants (n = 94)
Mean age (SD), *y*	68 (10)
Women, *n (%)*	20 (24)
Mean weight (SD), *kg*	88 (20.6)
Mean height (SD), *cm*	173 (9.6)
Mean BMI (SD), kg/m^2	29 (5.8)
Creatinine clearance level (SD), *mL/min*†	79 (33.2)
Target INR, %	
2–3	87
2.5–3.5	13
Indication for VKAs, *n (%)*	
Atrial fibrillation	62 (66)
Mechanical heart valve	11 (12)
Venous thromboembolism	9 (10)
Valvular heart disease	5 (5)
Coronary heart disease	5 (5)
Other	2 (2)
Surgery or procedure, *n (%)*	
Percutaneous coronary intervention	52 (55)
Pacemaker or ICD insertion	21 (22)
Endoscopy	4 (4)
Major surgery, *n (%)*	
Carotid endarterectomy	1 (1)
Femoral–popliteal bypass	1 (1)
Knee arthroplasty	1 (1)
Minor surgery, *n (%)*	
Removal or biopsy of skin lesion	4 (4)
Dental extraction	1 (1)
Carpal tunnel release	4 (4)
Other	5 (5)

* BMI = body mass index; ICD = implantable cardiac defibrillator; INR = international normalized ratio; VKAs = vitamin K antagonists.
†Calculated by using the Cockcroft–Gault equation (11).

Figure. **Association between residual anti-Xa level and interval from last dose of low-molecular-weight heparin.**



$R^2 = 0.14$.

for warfarin therapy was atrial fibrillation ($n = 62$), and the most common reasons for temporary interruption of warfarin therapy were endovascular procedures ($n = 73$). Ninety-three (99%) patients completed clinical follow-up at 4 to 6 weeks; 1 patient was lost to follow-up.

Preoperative Heparin Levels

Preoperative anti-Xa heparin levels were measured in 80 patients shortly before surgery, and middosing interval anti-Xa heparin levels were measured in 89 patients the day before surgery. The mean time from the last enoxaparin dose to preoperative anti-Xa heparin measurement was 14 hours, and the mean interval between preoperative anti-Xa heparin measurement and surgery was 97 minutes. The mean anti-Xa heparin level before surgery was 0.6 U/mL (SD, 0.3) (**Figure**). Preoperative anti-Xa heparin levels were 0.1 U/mL (lower limit of detection) or greater in 79 (99%) patients, 0.5 U/mL or greater in 54 (68%), and 1.0 U/mL or greater in 13 (16%). On multivariable linear regression analysis, higher residual anti-Xa heparin levels were associated with shorter intervals since the last injection ($P < 0.001$) and a higher BMI ($P = 0.001$).

Secondary Outcome Measures

The mean anti-Xa level at the middosing interval was 1.3 U/mL. On multivariable linear regression analysis, higher residual anti-Xa levels at the middosing interval were associated with higher BMI ($P < 0.001$) and lower estimated creatinine clearance ($P = 0.045$).

Major bleeding occurred in 1 patient who was admitted to the hospital with lower gastrointestinal hemorrhage 3 days after colonoscopy with polypectomy. This patient required transfusion of 6 units of packed red blood cells and hemicolectomy. He had restarted warfarin and LMWH therapy on the morning after the colonoscopy (international normalized ratio on day of readmission with bleeding, 1.3). Minor bleeding occurred in 3 patients; all episodes were catheter-site hematomas after endovascular procedures (anti-Xa heparin levels were 0.4, 0.6, and 0.7 U/mL and international normalized ratios were 1.0, 1.0, and 1.2, respectively, shortly before the procedure). Thromboembolism occurred in 1 patient. This patient, who had a mechanical mitral valve and chronic atrial fibrillation, had an ischemic stroke 8 days after surgery for removal of a basal-cell carcinoma. He restarted warfarin therapy on the evening of surgery and restarted LMWH the following morning. His international normalized ratio was 2.4 at the time of presentation with ischemic stroke. Residual anti-Xa heparin levels had been 0.4 U/mL. No patient died during follow-up.

DISCUSSION

Our study found that two thirds of patients who received a standardized bridging regimen of preoperative enoxaparin (7, 8) had anti-Xa heparin levels of 0.5 U/mL or greater shortly before their invasive procedure. Higher

preoperative heparin levels were associated with shorter intervals since the last injection of LMWH and with a higher BMI. An increase in operative or procedural bleeding was not noted in our study; however, such bleeding was not routinely assessed and few (3.2%) patients had major surgery. To our knowledge, this is the first study to prospectively measure residual preoperative anti-Xa heparin levels after a standardized preoperative regimen of LMWH.

Without clinical trials that have evaluated bridging therapy with LMWH for temporary interruption of warfarin therapy, the associated risks and benefits are uncertain (1, 13, 14). However, because warfarin therapy is stopped before surgery to avoid operating on patients receiving anticoagulation therapy, it is desirable that bridging regimens should not be associated with substantial residual anticoagulant activity. On the basis of our findings, if a twice-daily regimen of enoxaparin is used and the last dose is given the evening before surgery, a substantial residual anticoagulant effect at the time of surgery can be anticipated in many patients.

Consistent with previous studies, we found that increases in BMI were associated with increases in anti-Xa heparin levels, and a decrease in creatinine clearance was associated with increases in anti-Xa heparin levels (9, 15). However, because both associations were weak, our results do not support routine monitoring of anti-Xa heparin levels in patients with mild renal impairment or obesity. Furthermore, patients with severe renal impairment were excluded from this study, and very few patients who were severely obese were recruited.

Our study has some limitations. First, because all participants received enoxaparin, our findings may not be generalizable to other preparations of LMWH (16). Second, the number of patients that we studied is too small to provide accurate estimates of the frequency of the clinical outcomes of systemic embolism and major bleeding. The strengths of our study include its prospective design, clearly defined sample, completeness of clinical follow-up, and central measurement of anti-Xa heparin levels.

We conclude that preoperative bridging with twice-daily enoxaparin results in high residual anti-Xa heparin levels if the last dose is given the evening before surgery. Although the optimal approach to bridging therapy remains unclear, we would recommend that if a twice-daily regimen of LMWH is used before surgery, the final dose should be given on the morning of the day before surgery. However, we cannot exclude the fact that extending the interval between the last dose of LMWH and surgery may increase the risk for thromboembolism.

From McMaster University and Hamilton Health Sciences Foundation, Hamilton, Ontario, Canada.

Grant Support: This project was funded by an unrestricted grant from the Hamilton Health Sciences Foundation, Hamilton, Ontario, Canada. Drs. Kearon and O'Donnell are supported by the Canadian Institutes of Health Research.

Potential Financial Conflicts of Interest: None disclosed.

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