The Perioperative Management of Antithrombotic Therapies Using Enoxaparin

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INTRODUCTION

Long-term oral anticoagulant therapy is frequently and increasingly prescribed for patients at risk of arterial or venous thromboembolism (VTE). Although elective surgical or invasive procedures have necessitated temporary interruption of anticoagulants, managing these patients has been performed empirically and been poorly investigated. This study was designed to evaluate the adequacy of perioperative anticoagulation using enoxaparin. This was a retrospective, single-center study that evaluated the efficacy and safety of therapeutic-dose enoxaparin for bridging therapy in patients on long-term warfarin at Soonchunhyang University Hospital in Korea between August 2009 and July 2011. Warfarin was discontinued 5 days before surgery, and enoxaparin was administered twice daily by subcutaneous injection at a dose of 1 mg per kg from 3 days before the procedure to the last dose 24 hours before the procedure. Anticoagulation was restarted if proper hemostasis had been confirmed. There were 49 patients, of whom 25 (51%) were men, and the mean age was 63 years. Thirty-four (69%) received warfarin therapy for VTE, and 9 (18%) for atrial fibrillation. Twenty-nine patients (59%) underwent major surgery and 20 (41%) minor surgery. The mean postoperative duration of enoxaparin was 4 days. No patients had thromboembolic complications through 30 days after the procedure. The overall 30-day mortality rate was 0%. In conclusion, our findings demonstrate that bridging therapy with therapeutic-dose enoxaparin is feasible and associated with a low incidence of major bleeding and no thromboembolic complications. However, the optimal approach to managing patients perioperatively is uncertain and requires further evaluation.

Keywords: Thromboembolism; Anticoagulation; Vitamin K Antagonist; Bridging; Low-Molecular-Weight Heparin

STUDY DESIGN

This was a retrospective, single-center study that evaluated the efficacy and safety of therapeutic-dose enoxaparin combined with which bridging therapy was planned for invasive proce-
dures or surgeries in patients on long-term warfarin. The study population had been admitted to Soonchunhyang University Hospital in Korea between August 2009 and July 2011. The primary purpose of this study was to investigate the incidence of thromboembolic or bleeding events during the perioperative period in patients who had received bridging anticoagulation with enoxaparin.

**Study sample**

The patients were aged 18 years and over and were receiving warfarin therapy for atrial fibrillation, VTE, or mechanical heart valves; they had been referred to the Anticoagulation Clinic to use proper therapeutic-dose LMWH as a perioperative bridging therapy before undergoing major or minor surgery or invasive procedures that necessitated temporary interruption of warfarin. Patients were excluded if they had had ischemic stroke 3 months before enrollment, any previous hemorrhagic stroke, active bleeding, recent gastrointestinal bleeding, a bleeding disorder, thrombocytopenia, or pregnancy.

Major surgeries or procedures included intraabdominal surgery, intrathoracic surgery, major orthopedic surgery, peripheral arterial revascularization (e.g., abdominal aortic aneurysm repair, vascular bypass), urologic surgery (e.g., prostatectomy, bladder tumor resection), permanent pacemaker or internal defibrillator insertion, a major procedure (e.g., colonic polypectomy, biopsy of kidney or prostate), and any other surgery or procedure lasting ≥ 1 hour (10).

Minor surgeries or procedures included gastrointestinal endoscopy, cardiac catheterization, dental surgery or other dental procedure, dermatologic surgery or other dermatologic procedure, cataract removal or other ophthalmologic procedure, and any other surgery or procedure lasting < 1 hour (Table 1).

**Perioperative management of anticoagulation**

Warfarin was discontinued 5 days before surgery. Three days before the procedure, enoxaparin was administered twice daily

| Table 1. Baseline characteristics of patients receiving bridging anticoagulation |
|---------------------------------|------------------|
| Characteristics                        | Value             |
| No. of patients                     | 49 (100.0)        |
| Male                               | 25 (51.0)         |
| Age, mean (range), yr              | 63 (19–84)        |
| VTE                                | 34 (69.4)         |
| Atrial fibrillation, CHA2DS2-VASc score* | 9 (18.4)         |
| 0 or 1                             | 1                |
| 2–5                                | 7                |
| 6–9                                | 1                |
| Replacement of cardiac valve (mechanical) | 3 (6.1)         |
| Others                             | 3 (6.1)          |
| Reasons of bridging anticoagulation |                   |
| Major surgery/procedure            | 29 (59.2)        |
| Closed thoracostomy and pleurodesis | 1               |
| Colonoscopic Miles's operation and colostomy | 1         |
| Colon Hartman operation and colostomy | 1            |
| Segmental resection of small bowel | 1                |
| Distal gastrectomy                 | 1                |
| Goretx graft                       | 1                |
| Cranioplasty                       | 1                |
| Trabeculectomy                     | 1                |
| Iliac bone graft, curettage, and debridement | 1           |
| Total knee replacement therapy     | 3                |
| Knee arthroscopic reconstruction   | 2                |
| Vertebroplasty                     | 3                |
| Hip operation                      | 1                |
| Open reduction and internal fixator | 1              |
| Removal of external fixator        | 2                |
| Incision and drainage of abscess in left | 1             |
| Gastroilectomy                     | 1                |
| Percutaneous nephrolithotomy       | 1                |
| Urethral balloon dilatation        | 1                |
| Bilateral oophorectomy             | 1                |
| Flap coverage & split thickness skin graft | 3       |
| Minor surgery/procedure            | 20 (40.8)        |
| Percutaneous endoscopic gastroscopy | 2               |
| Pyloric stent insertion            | 1                |
| Colonoscopic biopsy                | 2                |
| Bronchoscopic biopsy               | 1                |
| Prostatic biopsy                   | 1                |
| Cystolitholapaxy                   | 3                |

**Characteristics of patients with VTE**

| Characteristic                      | Value      |
|------------------------------------|------------|
| Warfarin naïve (< 90 day)          | 20 (40.8)  |
| Warfarin experienced (> 90 day)    | 29 (59.2)  |
| Experience on warfarin in patient with VTE (n = 34) |                   |
| Warfarin naïve (< 90 day)          | 15 (44.1)  |
| Warfarin experienced (> 90 day)    | 19 (55.9)  |

**Duration of experience on warfarin, median (IQR), days**

| Comorbid condition | Value            |
|--------------------|------------------|
| Active malignancy (within 6 mon) | 16 (32.7) |
| CHF                | 3 (6.1)          |
| CVA or TIA         | 3 (6.1)          |
| Ischemic heart disease | 4 (8.2)        |
| Renal insufficiency (GFR < 30 mL/min) | 10 (20.4) |

Values are presented as number (%).

VTE = venous thromboembolism, IQR = interquartile range, CHF = congestive heart failure, CVA = cerebrovascular accident, TIA = transient ischemic attack, GFR = glomerular filtration rate.

*The CHA2DS2-VASc score is a measure of the risk of stroke in which congestive heart failure, hypertension, an age of 65 to 74, diabetes mellitus, vascular disease (e.g., prior myocardial infarction, aortic plaque, or peripheral arterial disease), female gender are each assigned 1 point and previous stroke, transient ischemic attack, thromboembolism or age older than 75 is assigned 2 points; the score is calculated by summing all the points for a given patient.

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by subcutaneous injection at a dose of 1 mg per kg; the last preoperative dose was administered on the morning before the procedure. On the day before or on the morning of the procedure, the international normalized ratio (INR) was measured to ensure that it was normalized ($\leq 1.3$).

Subcutaneous enoxaparin was reinitiated at a dose of 1 mg per kg twice daily 48–72 hours after a major surgery or procedure and 12–24 hours after a minor surgery or procedure provided that adequate hemostasis had been achieved; the first postoperative dose of enoxaparin could have been delayed if the surgeon assessed that the hemostasis was inadequate.

Warfarin was restarted on the day enoxaparin was started or on the following day. The warfarin dose was double the patient’s usual daily dose for the first 2 days and then the same as the usual daily dose. Treatment with enoxaparin was continued until the INR was within the target range for 2 consecutive days. The same perioperative protocol was applied to patients with mechanical valve.

Outcomes
The primary efficacy outcome was the incidence of acute thromboembolic events within 30 days after the procedure (e.g., ischemic stroke, transient ischemic attack, systemic embolism, or symptomatic VTE). The secondary efficacy outcome was the rate of all-cause mortality.

The primary safety outcome was the incidence of major bleeding within 30 days after the procedure, and major bleeding was defined as overt bleeding leading to a $\geq 2$ g/dL drop in hemoglobin, transfusion of $\geq 2$ units of packed red blood cells (RBCs), need for re-operation or invasive intervention, any bleeding at a critical anatomic site (e.g., intracranial, retroperitoneal, intraocular, or pericardial), or fatal bleeding.

Ethics statement
The study protocol was reviewed and approved by Institutional Review Board of the Soonchunhyang University College of Medicine (IRB No. SCHUH 2016-11-017). Informed consent was waived by the IRB.

RESULTS

Patient and procedure characteristics
In total, 49 patients (25 men, 24 women; mean age, 63 years; range, 19–84 years) were included in the study between August 2009 and July 2011 (Table 1). Approximately two-thirds of the patients had received warfarin therapy for prior VTE and one-fifth for atrial fibrillation. Twenty-nine patients (59.2%) underwent major surgery and 20 patients (40.8%) minor surgery. Twenty patients (40.8%) received warfarin therapy less than or equal to 90 days before the procedure, and 29 patients (59.2%) received it for more than 90 days. The mean duration on warfarin was 122 days. Among 34 patients with VTE, 19 patients (55.9%) had experienced warfarin for more than 90 days before procedure, including 8 patients (23.5%) with active cancer. There were various comorbidities, including active malignancy in 16 patients (32.7%), congestive heart failure in 3 patients (6.1%), cerebrovascular accident or transient ischemic attack in 3 patients (6.1%), ischemic heart disease in 4 patients (8.2%), and renal insufficiency in 10 patients (20.4%).

Adherence to bridging anticoagulation protocol
The mean INR before warfarin was withheld was 2.31 (range, 0.89–5.24; Table 2). The mean preoperative durations of warfarin interruption and enoxaparin administration were 6.7 days (range, 2–42), and 4 days (range, 0–15), respectively. Three patients (6.1%) received preoperative vitamin K to normalize the INR.

The enoxaparin was restarted a mean 39 hours (range, 11–150) after a surgery or procedure, and the mean postoperative enoxaparin duration was 4 days (range, 1–14). In only 28 patients (57.1%) was enoxaparin administered until the INR was within the therapeutic range for 2 consecutive days; in other words, enoxaparin was reinitiated at a dose of 1 mg per kg twice daily 48–72 hours after a major surgery or procedure and 12–24 hours after a minor surgery or procedure provided that adequate hemostasis had been achieved; the first postoperative dose of enoxaparin could have been delayed if the surgeon assessed that the hemostasis was inadequate.

Warfarin was restarted on the day enoxaparin was started or on the following day. The warfarin dose was double the patient’s usual daily dose for the first 2 days and then the same as the usual daily dose. Treatment with enoxaparin was continued until the INR was within the target range for 2 consecutive days. The same perioperative protocol was applied to patients with mechanical valve.

Table 2. Perioperative status and adherence to bridging protocol ($n = 49$)

| Perioperative status | Value |
|----------------------|-------|
| Pre-operative management |       |
| Pre-bridging INR, mean (range) | 2.31 (0.89–5.24) |
| Pre-op INR, mean (range) | 1.18 (0.87–2.10) |
| Pre-op duration of warfarin interruption, days, mean (range) | 6.7 (2–42) |
| Pre-op duration of LMWH, mean (range) | 4 (0–15) |
| Vitamin K required | 3 (6.1) |
| Post-operative management |       |
| Time to first dose in post-operative, median (IQR), hr | 28.5 (19–56) |
| Post-operative duration of LMWH, mean (range) | 4 (1–14) |
| Adherence to LMWH use until reaching therapeutic range of INR on 2 consecutive days | 28 (57.1) |
| Post-operative day of initiating warfarin, mean (range) | 3 (0–39) |
| Post-operative day reaching therapeutic range of INR on 2 consecutive days, mean (range) | 15 (4–47) |

Values are presented as number (%).
INR = international normalized ratio, LMWH = low-molecular-weight heparin, IQR = interquartile range.
Two major bleeding events in this study occurred following a major orthopedic surgery and a urologic procedure, both of which are associated with high risk of bleeding (6). Of the 49 patients in this study, 29 (59%) underwent major surgeries or procedures that had high risk of bleeding. The rates of major bleeding for minor and major surgeries or procedures, 0% and 4.1%, respectively, corresponded well with those (0.9%–6.7%) reported in recent, large, prospective studies of bridging therapy in which major bleeding occurred in patients who underwent major surgery (5,7,10,18).

LMWH is the preferred bridging regimen. It has greater bioavailability and a more predictable dose response than unfractionated heparin (UFH) (5,7,18,19). Jaffer et al. (20) reported that the risk of major bleeding is strongly associated with the use of postoperative therapeutic doses of heparin/LMWH based on the analysis of practice patterns at 9 hospitals. Low-dose LMWH/UFH may be considered an alternative option during resumption of anticoagulant bridging, particularly after major surgery (12).

Recently there are controversial views on perioperative anticoagulation in regard to bleeding complication. Douketis et al. (21) showed forgoing bridging anticoagulation was noninferior to perioperative bridging with LMWH for patients with atrial fibrillation who need to interrupt the warfarin for an elective operation. Mathew et al. (22) reported that therapeutic dose bridging was associated with 2.5 to 3-fold increased risk of major bleeding compared with prophylactic dose bridging.

Because there is no consensus on a bridging protocol, clinicians must estimate and balance the risk of postoperative major bleeding and thromboembolic events in patients who receive full-dose parenteral anticoagulation perioperatively while oral anticoagulant therapy is interrupted (23-25). The first step in bridging management is to assess the risk of thromboembolic events during cessation of anticoagulation. This study suggests that bridging therapy with a therapeutic twice-daily dose of enoxaparin can be used safely for patients who are undergoing major or minor surgeries or procedures.

Recently, direct oral anticoagulants (DOACs) (i.e., dabigatran, rivaroxaban, apixaban, or edoxaban) are being increasingly prescribed to treat VTE and prevent stroke in atrial fibrillation. Annually, approximately 10% of those patients will need to interrupt DOACs for an elective procedure (26,27). The study on the safety of perioperative management of DOACs using a specified protocol based on the creatinine clearance and procedure-related bleeding risk is underway, and the results are expected.

To our knowledge, this is the first study in Korea that assessed efficacy and safety in bridging therapy with LMWH during temporary interruption for an elective procedure or surgery in patients who were on chronic oral anticoagulant therapy. However, there are limitations to this study that should be addressed. Firstly, this was retrospective study at a single center. Secondly, the population size of this study was too small (n = 49) to gen-

Table 3. Outcomes in patients receiving bridging anticoagulation (n = 49)

| Parameters                  | Value       |
|-----------------------------|-------------|
| Efficacy outcome measure (30-day) |             |
| Recurrent VTE               | 0 (0.0)     |
| All-cause mortality         | 0 (0.0)     |
| Safety outcome measure (30-day) |             |
| Major bleeding              | 2 (4.1)     |

Values are presented as number (%).

VTE = venous thromboembolism.
eralize the result of this study to clinical practice. Thirdly, there was no comparable group regarding perioperative bridging therapy. Fourthly, the post-procedural patient follow-up was limited to 30 days. Consequently, our findings may underestimate the risk of thromboembolic events because clinical manifestations of periprocedural thrombus formation, such as embolic stroke or valve thrombosis, may be delayed over a month after warfarin interruption (28-30). Consequently, our findings may not be generalizable to all patients planning to undergo bridging.

In conclusion, our findings demonstrate that bridging therapy with therapeutic-dose enoxaparin is feasible and associated with a low incidence of major bleeding and thromboembolic complications. However, the optimal approach to managing patients who require temporary interruption of warfarin or DOACs for invasive procedures is still uncertain and requires evaluation in randomized controlled trials.

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DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conceptualization: Hwang HG, Uh ST, Kim YK. Data curation: Koo SM, Kim YK. Formal analysis: Hwang HG, Uh ST, Kim YK. Investigation: Hwang HG, Kim YK. Writing - original draft: Hwang HG, Kim YK. Writing - review & editing: Hwang HG, Kim YK.

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