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Low–Molecular-Weight-Heparins as Periprocedural Anticoagulation for Patients on Long-Term Warfarin Therapy: A Standardized Bridging Therapy Protocol

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***Abstract. Background*: Over 2 million patients in North America are on warfarin anticoagulation therapy for prevention of thromboembolism. Suspension of warfarin therapy is often required to prepare patients for invasive procedures or surgeries. To protect these patients against thromboembolism while they are off warfarin, shorter-acting parenteral agents such as low-molecular-weight heparins (LMWHs) are often used. We conducted a retrospective observational study of our anticoagulation clinic patients to assess the safety and efficacy of LMWHs using a standardized protocol for periprocedural anticoagulation therapy.**

***Methods*: We included 69 consecutive patients who required interruption of their long-term warfarin therapy between August 2001 and August 2002, and were deemed by the treating physician to be at high enough risk for perioperative thromboembolism to justify bridging anticoagulation. We used a standard bridging therapy protocol in our anticoagulation clinic. Sixty-six patients received enoxaparin and three patients received tinzaparin for a mean duration of 7.7 days postoperatively. Outcomes were assessed for 30 days post-procedure. Safety outcomes included major bleeding and minor bleeding. Efficacy outcomes included thromboembolic event or death.**

***Results*: There were two major bleeding events, one minor bleeding event, and no cases of thromboembolism. Twelve patients experienced some bruising around the injection site.**

***Conclusions*: LMWH administration using our standard outpatient bridging protocol for perioperative anticoagulation appears to be relatively safe and efficacious, offering an alternative to inpatient administration of intravenous unfractionated heparin (UFH). Our study provides additional evidence to the limited published observational data regarding the safety and efficacy of LMWH as bridging therapy in the perioperative and periprocedural setting. Large, multicenter, randomized controlled trials are necessary to fully assess the safety and efficacy of LMWH for perioperative anticoagulation.**

***Abbreviated Abstract.* We conducted a retrospective observational study of 69 consecutive anticoagulation clinic patients on warfarin between August 2001 and August 2002, who were undergoing a procedure or surgery. The study was done to assess the safety and efficacy of an outpatient LMWH bridging protocol. Sixty-six patients received enoxaparin and three patients received tinzaparin for a mean duration of 3 days preoperatively and 7.7 days postoperatively. Outcomes were assessed for 30 days post-procedure. Safety outcomes included major bleeding and minor bleeding. Efficacy outcomes included thromboembolic event or death. There were two major bleeding events, one minor bleeding event, and no cases of thromboembolism. Twelve patients experienced some bruising around the injection site.**

***Key Words.* low-molecular-weight-heparins, periprocedural, bridging therapy, surgery**

Introduction

Over 2 million patients in North America are on warfarin therapy for prevention of thromboembolism [1]. Although effective, warfarin therapy poses a major problem for patients needing surgery or invasive procedures because most patients require discontinuation of warfarin during the periprocedural and perioperative period. During the approximate 5-day period necessary for the antithrombotic

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effect of warfarin to subside, patients may be at increased risk for developing a thromboembolism. Typically, surgery can be safely performed when the patient's international normalized ratio (INR) is lower than 1.5. This target INR is usually achieved within 5 days if the INR is between 2 and 3 while the patient is receiving warfarin [2]. Discontinuation of oral anticoagulation may also be associated with a rebound hypercoagulable state which has been described but has not been validated in clinical practice [3–5]. Surgery also poses an increased risk for the development of venous thromboembolism (VTE) due to associated immobilization.

To minimize the risk of thromboembolism, some patients may be treated with intravenous (IV) unfractionated heparin (UFH) in the hospital. Alternatively, as outpatients, patients may be treated with subcutaneous (SQ) low–molecular-weight heparin (LMWH) prior to surgery. Currently, IV UFH is widely substituted in the periprocedural period for chronic oral anticoagulation [6]. Periprocedural anticoagulation, however, may be accompanied by an increased risk of both intraoperative and postoperative bleeding regardless of the treatment modality. Hemorrhagic and thrombotic risks must therefore be balanced by assessing the risk profile for individual patients. LMWH offers several advantages over UFH during warfarin interruption for periprocedural anticoagulation. In contrast to UFH, routine laboratory monitoring of LMWH is not required to achieve therapeutic dosing. The use of outpatient periprocedural therapy with LMWH has increased because LMWH offers a simpler alternative to UFH with the added advantages of subcutaneous dosing, a predictable anticoagulant response, and less heparin-induced thrombocytopenia (HIT) compared with UFH. To date, however, the safety and efficacy of this strategy have been shown only in observational studies [7–13]. Randomized clinical trials are therefore necessary to evaluate the full scope of this strategy.

To further examine the efficacy and safety of LMWH therapy during warfarin interruption for periprocedural anticoagulation, we conducted a retrospective observational study of anticoagulation clinic patients at our institution who were administered periprocedural LMWH in a standard bridging protocol.

Methods

Inclusion criteria

This study included 69 consecutive patients (19 with mechanical valves) who required interruption of their long-term warfarin therapy for a planned surgical procedure (inpatient or outpatient) between August 2001 and August 2002 and were deemed by the referring physician to be at sufficiently high risk for perioperative thromboembolism to justify bridging therapy.

Exclusion criteria

We excluded patients with calculated creatinine clearance <30 ml/min, morbid obesity (weight >150 kg), history of non-adherance to medical therapy, history of liver disease, known pregnancy, history of bleeding disorder, recent intracranial hemorrhage, history of heparin-induced thrombocytopenia and those unlikely to be able to comply with outpatient treatment. The institutional review board at the Cleveland Clinic Foundation, Cleveland, Ohio, approved this study.

Data collection

Baseline patient demographics assessed included age, sex, and weight. Serum creatinine levels were determined. The presence of comorbidities, including hypertension, diabetes, and coronary artery disease, was evaluated. Indications for anticoagulation were noted, as well as the procedures for which patients received periprocedural anticoagulation.

Periprocedural protocol

We used a standard bridging therapy protocol in our anticoagulation clinic that incorporated the LMWH enoxaparin or the LMWH tinzaparin (Table 1). The pre-operative protocol employed 1 mg/kg of the LMWH enoxaparin, administered subcutaneously every 12 hours, or 175 IU/kg of the LMWH tinzaparin administered subcutaneously every 24 hours beginning 36 hours after stopping warfarin and stopped about 24 hours before surgery. Postoperatively, patients at low risk of bleeding (based on the Johns Hopkins classification and upon the impression of the Surgeon and other treating physicians) had anticoagulation re-started at the same dose, on the day of or day following surgery. Patients at high risk of bleeding had their dose of enoxaparin reduced to 30 mg SQ q12h or tinzaparin 75 IU/kg daily. Sixty-six patients received enoxaparin and three patients received tinzaparin. LMWH was used for a mean duration of 3 days preoperatively and 7.7 days postoperatively (generally used until the INR was therapeutic on warfarin).

Outcome measures

Outcomes were assessed for a 30-day period after the procedure. The safety outcomes included major bleeding and minor bleeding. Major bleeding was defined as intracranial bleeding, retroperitoneal bleeding, bleeding into a major organ, or any bleeding requiring hospitalization, requiring the transfusion

Table 1. *Bridge Therapy Protocol*

Preoperative protocol
- If preoperative INR 2-3, stop warfarin 5 days before surgery (4 doses).
- If preoperative INR 3-4.5, stop warfarin 6 days before surgery (5 doses).
- Start: enoxaparin 1 mg/kg SQ *q* 12 hours or tinzaparin 175 IU/kg SQ *q* 24 hours, 36 hours after last warfarin dose.
- Last dose of LMWH approximately 24 hours prior to procedure.
- Discuss plan with surgeon, anesthesiologist, and patient.
- Discussion of risks and benefits of LMWH with patient
- Instruction on self-administration of LMWH
- Discussion of signs and symptoms of bleeding and thromboembolism.
- What to do in the event of an emergency.
- Written instructions for patient.

Postoperative protocol
- Restart LMWH approximately 24 hours post-procedure at 1 mg/kg SQ *q* 12 hours; consider 30 mg SQ *q* 12 hours or 75 IU/lkg of Tinzaparin on postoperative day 1 only if patient is high risk for bleeding.
- Discuss plan with surgeon.
- Start warfarin 5 mg daily or patient's preoperative dose on postoperative day 1.
- Check daily PT/INR until patient is discharged and periodically thereafter until INR is in therapeutic range.
- CBC with platelets at day 3 and day 7 (HIT screening).
- Discontinue LMWH when INR is 2–3 for 2 consecutive days.

INR = international normalized ratio, SQ = subcutaneous, LMWH = low–molecular-weight heparin; PT = prothrombin time; CBC = complete blood count, HIT = heparin-induced thrombocytopenia.

of at least two units of red cells, or requiring discontinuation of LMWH. Minor bleeding was defined as any non-major bleeding requiring medical attention. Bruising around the injection site was also assessed. We did not include a drop in hemoglobin as a criterion for bleeding since it is not unusual for patients to have a drop in hemoglobin in the perioperative setting due to expected procedure-related blood loss and hemodilution from intravenous crystalloids. The efficacy outcomes included prevention of thromboembolic event (TE) or death. A TE was defined as a transient ischemic attack confirmed by a consulting neurologist; a stroke determined by magnetic resonance imaging or computed tomography (CT) scan and confirmed by neurologist; a peripheral embolus confirmed angiographically or surgically; a pulmonary embolism (PE) defined by a high probability nuclear lung scan, helical CT, or pulmonary arteriogram, or confirmed at autopsy; deep vein thrombosis confirmed by ultrasonography or venogram; or sudden death from TE (autopsy-assessed) or in the absence of an autopsy, deemed to be a "vascular" death.

Table 2. *Patient Characteristics*

Characteristic	No. of patients ($N = 69$)	(%)
Age (y)		
Mean	60.7	
Range	31–86	
Sex		
Male	39	57
Female	30	43
Weight (kg)		
Mean	83.4	
Range	40–140	
Serum creatinine (mg/dL)		
Range	0.3–1.8	
Hypertension	25	36.2
Diabetes	3	4.3
Coronary artery disease	10	14.5

Statistics

Descriptive statistics are reported as appropriate. 95% confidence intervals for proportions were computed using the score confidence interval method (JMP 5.0.1, SAS Institute, Cary, NC).

Results

Baseline patient demographics

Of the 69 patients enrolled, 39 (57%) were men and 30 (43%) were women. The mean age was 60.7 years and the mean weight was 83.4 kg. Hypertension was the most frequently reported comorbidity (36.2% of patients) (Table 2).

Indications for long-term anticoagulation

The indications for long-term warfarin therapy in these patients are listed in Table 3. The most common indication for bridging therapy was atrial fibrillation (21 of 69 patients [30.4%]) followed by prosthetic heart valves (16 of 69 patients [23.2%]).

Procedures

Patients underwent a variety of inpatient and outpatient procedures. Cardiac procedures were performed most commonly. Of these patients, 5 patients underwent an angiogram, 8 patients underwent cardiac catheterization, and 9 had implantable cardiac defibrillator and/or permanent pacemaker (ICD/PPM) placement. A detailed list of procedures is shown in Table 4. These procedures fell into the broad categories of gastrointestinal procedures, general surgery, gynecologic surgery, ophthalmologic surgery, orthopaedic surgery, pulmonary surgery, and urologic surgery. Bleeding risk was stratified using the Johns Hopkins Surgical Classification [14].

Table 3. *Indications for Long-Term Anticoagulation*

	No. of Patients ($N = 69$)	(%)
Atrial fibrillation alone	21	30.4
Atrial fibrillation + stroke	6	8.7
Atrial fibrillation + prosthetic valve	4	5.8
Prosthetic heart valves alone	16	23.2
−Aortic valve replacement	8	11.6
St. Jude	5	7.2
Carbomedic	3	4.3
−Mitral valve replacement	6	8.7
St. Jude	4	5.8
Medtronic	2	2.9
−Mitral + tricuspid replacement	1	1.4
St. Jude		
Carpentier-Edwards		
−Mitral + aortic + tricuspid replacement	1	1.4
All Carpentier-Edwards		
VTE	10	14.5
Hypercoagulable state causing VTE	8	11.6
Multiple strokes	3	4.3
Arterial thrombosis	1	1.4

VTE = venous thromboembolism.

Efficacy and safety outcomes

There were two major bleeding events (2.9% of patients, 95% CI 0.8%–10.0%). One of these events occurred in an 85 year-old man on chronic warfarin for a recent DVT who required hardware removal following a left arm surgery. He had been re-started on full-dose LMWH (1 mg/kg twice daily of enoxaparin) the evening of surgery and developed bleeding on post-operative day 2 from the surgical incision site. The episode was associated with hypotension and he required transfusion of fresh frozen plasma and packed red blood cells. The second patient was a 73 year-old man on warfarin for atrial fibrillation who underwent automated internal cardiac defibrillator placement. He received full-dose LMWH (1 mg/kg twice daily of enoxaparin) and was re-started on warfarin post-operatively. He suffered from bleeding in the device pocket and required surgical evacuation of 1300 cc of blood on post-operative day 3. Minor bleeding occurred in one patient (1.4% of patients, 95% CI 0.3–7.8%) who had a scrotal hematoma following hernia repair, but this resolved spontaneously and reversal of anticoagulation was not required. Twelve patients experienced some bruising around the injection site. There were no cases of thromboembolism in our study (Table 5).

Discussion

We found that periprocedural LMWH therapy using a standard protocol provides relatively safe anticoagulation therapy for patients who require

Table 4. *Procedures for which Periprocedural Anticoagulation was Given*

Procedures/surgery (Johns Hopkins Surgical Classification [14] is listed in parentheses)	Number of patients	Procedure/ surgery	Number of patients
Cardiac procedures		Miscellaneous	
Angiogram (1)	5	Bone marrow biopsy (1)	3
Cardiac catheterization (1)	8	Dental procedure (1)	1
ICD/PPM placement (1)	9	Fasciotomy closure (1)	1
Gastrointestinal procedures		Loop ileostomy closure (1)	1
Colonoscopy with biopsy (1)	5	Skin flap (3)	1
EGD with biopsy (1)	1	Vocal cord nodule removal (2)	1
Liver biopsy (1)	1	Ophthalmologic surgery (1)	2
PEG tube (1)	1	Orthopedic surgery	
General surgery		Hardware removal (4)	1
Breast mass excision (1)	1	Hip replacement (3)	1
Cholecystectomy (3)	3	Knee arthroscopy (2)	2
Hernia repair (2)	2	Knee replacement (3)	1
Muscle biopsy (1)	1	Spine surgery (4)	3
Gynecologic surgery		Pulmonary surgery	
Hysterectomy (3)	2	Bronchoscopy (1)	1
Hysteroscopy, D&C (2)	1	Thoracentesis (1)	1
Sebaceous cyst excision (1)	1	Urologic surgery	
Vaginal sling construction (3)	1	Bladder biopsy (2)	2
		Lymphocele repair (3)	1
		Nephrectomy (4)	1
		Stone removal (3)	2
		TURP (3)	1

ICD/PPM = implantable cardiac defibrillator/permanent pacemaker; EGD = esophagogastroduodenoscopy; PEG = percutaneous endoscopic gastrostomy; D&C = dilation and curettage; TURP = transurethral resection of the prostate.

Table 5. *Results of LMWH Bridging Therapy* at 30 days*

Outcome	No. of events	Percentage (95% confidence interval)
Major Bleeding†	2	2.9 (0.8%–10.0%)
• Hemorrhage from incision and drain sites in left upper extremity after hardware removal. Bleeding started on post-operative day 2		
• Hematoma developed at the site of the ICD/PPM and this was drained 3 days after implantation		
Minor bleeding (scrotal hematoma following hernia repair)‡	1	1.4 (0.3%–7.8%)
Bruising around injection site	12	17.4 (10.2%–27.9%)
Thromboembolism	0	0 (0.0%–5.3%)

LMWH = low–molecular-weight heparin.

*LMWH therapy: range = 4–18 days; mean = 7.7 days.

†Intracranial bleed, retroperitoneal bleed, a bleed requiring transfusion or any other bleed necessitating stopping LMWH.

‡Any non-major bleed requiring medical attention.

warfarin therapy interruption. LMWH therapy during warfarin interruption is an off-label use, although it is a widely implemented practice despite the lack of randomized clinical trials. Our findings contribute valuable data on the use of LMWH in periprocedural anticoagulation therapy for patients who require warfarin therapy interruption. In our anticoagulation clinic patients are followed very closely and therefore we know no events were missed during the 30-day follow-up of this study. Moreover, since a standard protocol was used we know there was minimal variability except in patients who were at high risk of bleeding and received prophylactic doses of LMWH on post-operative day 1.

While our findings point to the efficacy and safety of LMWH use in periprocedural anticoagulation therapy, they must be tempered by certain intrinsic limitations of the study including the retrospective design, small size and absence of randomization and blinding. Furthermore, we did not collect data on patients who underwent different periprocedural management strategies, such as intravenous heparin bridging or no bridging therapy at all. Finally, we did not undertake a full assessment of all patient-associated risk factors for bleeding or thrombosis. As such, we are unable to determine whether the presence or absence of various comorbidities may have influenced the lack of thromboembolic events and the relatively few bleeding events evident in our study. Although the lack of a UFH comparison arm in this study limits clinical interpretation of the low rate of thromboembolic and bleeding events we suspect that large, multicenter, randomized controlled trials comparing LMWH to UFH and LMWH to placebo are unlikely to be conducted in the near future. As such, clinicians need to make management decisions for this common clinical problem based on available literature.

Recently, other authors have reported similar findings with LMWH bridging [7, 15]. In particular, Douketis et al recently reported on a similar protocol using the LMWH dalteparin, 100 IU/kg SQ twice daily [7]. Among 650 patients, there were 2 thromboembolic events (0.3%), 2 deaths (0.3%), and 6 major bleeding episodes (0.9%). This study was similar to ours in that anticoagulation intensity postoperatively was determined based upon risk of bleeding. It differed from ours in that all patients were on chronic warfarin for cardioembolism prevention and all patients received briding anticoagulation regardless of their estimated embolic risk. In contrast, some of our patients were on anticoagulation for prevention of VTE, and we included only those patients deemed to be at sufficiently high risk for thrombosis to justify bridging therapy. Kovacs et al. [15] recently published an observational study of 224 patients at risk for cardioembolism. They found that 2 patients (0.9%) suffered cardioembolic events and 15 major bleeding events (6.7%). Collectively, our study and these other studies suggest that LMWH is a viable option for peri-operative bridging anticoagulation, but none of these studies compared LMWH to UFH or to no bridging anticoagulation, so the optimal management of patients on warfarin in the perioperative setting remains to be determined.

Although IV UFH has been the traditional perioperative anticoagulant, it is important to note the limitations of this strategy, including complexity of dosing, frequent assessment of the activated partial thromboplastin time (aPTT), and, importantly, the cost associated with hospitalization. Furthermore, only limited observational data exist to support the notion that heparin bridging is safe or efficacious. In fact, there are more published case series of LMWH bridging than UFH bridging. We therefore discourage the use of IV UFH as bridging anticoagulation except when there are contraindications to LMWH.

In summary, our study suggests that LMWH administration using a standardized bridging protocol for perioperative anticoagulation has an acceptably low rate of bleeding complications and thromboembolic complications, offering a reasonable alternative to inpatient administration of IV UFH. Our study provides additional evidence to the limited published observational data regarding the safety and efficacy of using LMWH as bridging therapy in the perioperative setting. To fully assess the safety and efficacy of LMWH for perioperative anticoagulation, large, multicenter, randomized controlled trials will be necessary.

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