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Intermediate-Dose Enoxaparin after Cardiac Ablation Procedures

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ABSTRACT

Objective: Ablation of foci within the atria has been shown to resolve symptoms of atrial fibrillation and atrial flutter. However, no standard has been established for anticoagulation after the procedure. Enoxaparin has been well described in the literature as a means to provide anticoagulation after ablation procedures. The only enoxaparin doses previously studied were 0.5 mg/kg and 1 mg/kg, both given every 12 hours. The purpose of the study was to compare the incidence of a major bleed or vascular complication in patients who received enoxaparin doses between 0.5 mg/kg and 1 mg/kg every 12 hours with patients who received either 0.5 mg/kg or 1 mg/kg every 12 hours.
Methods: This IRB-approved, single-center, retrospective, cohort study included subjects greater than 18 years of age who received an atrial fibrillation or atrial flutter ablation procedure and at least one dose of enoxaparin post-ablation.
Results: There were 119 subjects who satisfied the inclusion criteria. The primary outcome, incidence of major bleeding or vascular complication, did not demonstrate a statistically significant difference between groups (p = 0.92). The incidences were 4.8% with enoxaparin ≥ 1 mg/kg, 3% with enoxaparin between 0.5 mg/kg and 1 mg/kg, and 3.2% with enoxaparin ≤ 0.5 mg/kg. No subject experienced an ischemic stroke or transient ischemic attack within 28 days of a cardiac ablation procedure.
Conclusion: Significant increases in major bleeding or vascular complications may not exist with an intermediate dose of enoxaparin provided after a cardiac ablation procedure.

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Introduction

Ablation of foci within the atria has been shown to lead to a resolution of atrial fibrillation (AF) in 71% to 84% of patients without the use of anti-arrhythmic therapy. (1) Catheter ablation procedures are safe and effective. However, peri- and post-procedural complications, including transient ischemic attack, stroke, procedure-related death and cardiac tamponade, have been reported in the literature. (1) The causes for these complications are multifactorial, with anticoagulation administered surrounding the procedure acting as a contributing factor. (2) Current practice standards indicate that patients should receive anticoagulation before, during and after a cardiac ablation procedure; however, the most effective and safest method of anticoagulation is debated. (2) At the research site, the interventional electrophysiologist performed cardiac ablation procedures with enoxaparin therapy provided peri-procedurally. Pharmacists verified and dispensed enoxaparin doses for patient use.

Initial studies established enoxaparin 1 mg/kg every 12 hours as a potential option for anticoagulation following cardiac ablation procedures until the subject's PT/INR was within therapeutic range. However, further studies demonstrated a potentially higher than acceptable rate of major bleeding with this dosing regimen. (3-6). The reported incidence of subjects experiencing an ischemic stroke ranged from 0 to 2%, and the incidence of major bleed was between 1% and 7%. (3-6) In an effort to reduce major bleeds, enoxaparin 0.5 mg/kg every 12 hours was studied. Major bleeds occur between 0 and 2% with the lower enoxaparin dosing, but the incidence of ischemic stroke is greater, 1% to 3%, compared to the higher daily dosing. (3-8) Intermediate doses of enoxaparin between 0.5 mg/kg and 1 mg/kg every 12 hours have been studied in very few instances; however, none of the studies included subjects who received a cardiac ablation procedure. (9-11). The present study was undertaken to describe the incidence of major bleeding and vascular complications after cardiac catheter ablation procedures with intermediate doses of enoxaparin compared to 0.5 mg/kg and 1 mg/kg enoxaparin doses.

Methods

The study was a single-center, retrospective, cohort study of all patients who underwent an atrial fibrillation or atrial flutter catheter ablation procedure between July 2006 and September 2012 and had at least one documented dose of enoxaparin provided after the ablation procedure. Patients were identified from an ongoing registry of cardiac catheter ablation procedures performed at our institution. All patients were at least 18 years of age. A patient was excluded if the platelet count was < 50 $x10^3$/dL or the creatinine clearance was < 30 mL/min before the procedure. All patients with a documented heparin allergy were excluded.

We compared procedural, clinical and follow-up information for all patients who received intermediate doses of enoxaparin to the information for those receiving more established (0.5 mg/kg and 1 mg/kg) enoxaparin doses. Demographic data, laboratory values, dosages and dosing variables, perioperative anticoagulation and outcome variables were obtained from chart review. These data were stored electronically in a password protected database. All but 2 patients had a documented follow-up with the operating physician within 6 weeks of the cardiac ablation procedure. All patients were provided written informed consent for the cardiac ablation procedure, and the institutional review board at Georgia Regents Medical Center approved the study.

Cardiac ablation procedures were performed according to standard clinical practice. One hundred ten of 119 patients who received a cardiac ablation procedure were on warfarin therapy until the warfarin was discontinued three to five days prior to the

procedure. The remaining patients were on rivaroxaban (n = 1), dabigatran (n = 1) and aspirin (n = 7). Patients previously on warfarin received pre-operative bridging with enoxaparin using a 1 mg/kg every 12 hours dosing regimen, which is standard practice at our institution. No patients continued warfarin through the procedure. All patients undergoing a cardiac ablation procedure in whom an INR value was obtained prior to the procedure had a value < 1.7. Patients undergoing ablation procedures were administered anesthesia by an anesthesiologist. Multiple sheaths were inserted into the femoral veins to permit intra-cardiac catheter transit. Hemodynamic monitoring was accomplished via a femoral arterial sheath in all patients undergoing left atrial access. For left atrial procedures, patients underwent transseptal access. At the time of transseptal puncture, patients were anti-coagulated with a heparin bolus, typically 100 units/kg, and an infusion was initiated to maintain activated clotted times (ACT) > 300 seconds. Catheter ablation was performed by conventional electrophysiologic methods. At the conclusion of left atrial ablation, the catheters were removed from the left atrium and heparin was discontinued. Heparin was reversed with a protamine infusion, typically 80 to 100 mg IV. Hemostasis following sheath removal was accomplished with manual compression.

The analyzed safety and primary end point was major bleeding or vascular complication. This was defined as a drop in admission hemoglobin > 5 g/dL any time before discharge that necessitated transfusion of blood products, hematoma that increased the patient's in-hospital length of stay as determined by the investigators, cardiac tamponade or vascular complication that required surgical repair within 28 days of the procedure. This novel endpoint was used to assess major events that negatively effect patients' safety or quality of life. The secondary end point was ischemic stroke or transient ischemic attack (TIA) within 28 days of the procedure. All data were extracted from electronic medical records by the investigators.

In order to achieve 80% power with an alpha = 0.05 to detect a clinically significant 1% reduction in the incidence of major bleeding or vascular complications, a total of 800 patients needed to be included in the analysis. All statistics were performed using GraphPad Software (La Jolla, CA). Nominal, categorical and continuous variables were compared using the ANOVA test, Kruskal-Wallis test, chi-square test or the Fisher exact test, as appropriate. Statistical significance was set at $p < 0.05$.

Results

Initially, 448 patients were identified from the registry for potential inclusion in the study. After inclusion and exclusion criteria were applied, 229 patients were excluded from the analysis because they received cardiac ablation procedures for indications other than atrial fibrillation or atrial flutter. This left 119 patients for evaluation. The baseline and clinical characteristics were similar between the three groups (Table 1), with the exception of heart failure ($p = 0.03$).

A range of enoxaparin doses ≤ 0.5 mg/kg and ≥ 1 mg/kg resulted from rounding dose to conform to available enoxaparin syringe sizes. Patients in the ≤ 0.5 mg/kg group received enoxaparin doses between 0.35 mg/kg and 0.5 mg/kg, and patients in the ≥ 1 mg/kg group received enoxaparin doses between 1 mg/kg and 1.12 mg/kg. All 31 patients in the ≤ 0.5 mg/kg group were on warfarin before the procedure and at discharge, compared to 61 of 67 (91%) before and 66 of 67 (99%) at discharge for the 0.5 mg/kg to 1 mg/kg group and 18 of 21 (86%) before and 21 of 21 (100%) at discharge for the ≥ 1 mg/kg group. These differences were not statistically significant ($p > 0.05$). All patients who were discharged on warfarin were started on the therapy the night of the cardiac ablation procedure. All patients were discharged on enoxaparin. The incidences of 28-day

Table 1. Baseline and clinical characteristics

Characteristic	Dose ≤ 0.5 (n=31)	0.5 < Dose < 1 (n=67)	Dose ≥ 1 (n=21)	p-value
Age (years) (SD)	61 (10)	58.7 (12)	62.9 (15)	0.33
Gender (male)	22 (71%)	41 (61%)	17 (81%)	0.21
Actual body weight (kg)	90	93	93	0.32
Ethnicity				
Caucasian	27 (87%)	59 (88%)	17 (81%)	0.7
African American	3 (10%)	6 (9%)	4 (19%)	0.42
Other	1 (3%)	2 (3%)	0	0.72
Type of arrhythmia				
Paroxysmal atrial fibrillation	13 (42%)	24 (36%)	6 (29%)	0.61
Persistent/permanent atrial fibrillation	11 (35%)	23 (33%)	4 (19%)	0.38
Atrial flutter	7 (23%)	20 (30%)	11 (52%)	0.053
Creatinine clearance				
>80 mL/min	16 (52%)	25 (37%)	8 (38%)	0.39
50-80 mL/min	12 (39%)	34 (51%)	9 (43%)	0.51
30-50 mL/min	1 (3%)	2 (3%)	2 (9%)	0.41
Unknown	2 (6%)	6 (9%)	2 (9%)	0.9
Hypertension	26 (84%)	52 (78%)	17 (80%)	0.77
Heart failure	7 (23%)	13 (19%)	10 (48%)	0.03
Diabetes	6 (19%)	12 (18%)	6 (29%)	0.56
Previous stroke / transient ischemic attack	2 (7%)	4 (6%)	1 (5%)	0.97
Preoperative				
Platelet count ($x10^3$/dL)	193 (41)	204 (61)	208 (76)	0.74
Hemoglobin (g/dL)	13 (1.8)	13.5 (1.6)	14.2 (2.2)	0.055
Postoperative				
Platelet count ($x10^3$/dL)	189 (44)	186 (54)	170 (84)	0.24
Hemoglobin (g/dL)	11.8 (1.7)	12.3 (1.3)	12.4 (1.7)	0.57

major bleeding or vascular complication and 28-day ischemic stroke were not statistically different between the 3 groups (Table 2). Each patient who developed a major bleeding or vascular complication is described further (Table 3).

Discussion

The present study evaluated the safety of an intermediate dose of enoxaparin compared to two established doses in the post-ablation patient population. There was no statistically significant difference in the incidence of major bleeding or vascular complication between the three groups within 28 days of the cardiac ablation procedure (p = 0.92). Additionally, no patients experienced an ischemic stroke during this time frame. These results are especially encouraging when consideration is given to the pre-filled syringe sizes available for enoxaparin. Often enoxaparin doses are prescribed between 0.5 mg/kg and 1 mg/kg in order to conform to the available syringes. This study has demonstrated that there appears to be no additional risk

Table 2. Primary and secondary outcomes

Outcome	Dose ≤ 0.5 (n=31)	0.5 < Dose < 1 (n=67)	Dose ≥ 1 (n=21)	p-value
Major bleed or vascular complication	1 (3.2%)	2 (3%)	1 (4.8%)	0.92
Ischemic stroke or transient ischemic attack	0	0	0	1

Table 3. Individual patients who experienced a major bleeding or vascular complication

Patient	1	2	3	4
Gender	Male	Male	Female	Male
Age (years)	53	75	57	66
Anticoagulant pre-ablation	Warfarin	Warfarin	Warfarin	Warfarin
Anticoagulant post-ablation	Warfarin	Warfarin	Warfarin	Warfarin
Enoxaparin dose (mg/kg)	1.01	0.9	0.6	0.46
CrCl (mL/min)	75	69	69	79
Hypertension	Yes	Yes	No	Yes
Heart failure	Yes	No	No	Yes
Diabetes	No	No	No	No
Previous stroke, TIA or thromboembolism	No	No	No	No
Major bleeding or vascular complication	Groin hematoma	Groin hematoma	Groin hematoma	Groin hematoma
Ischemic stroke	No	No	No	No

of major bleeding or vascular complications with these intermediate doses, and individualized patient doses that occur within this range may be appropriate.

The 3 previously described studies that evaluated enoxaparin doses between 0.5 mg/kg and 1 mg/kg twice daily predominately focused on the population of patients with renal impairment and an acute coronary syndrome. (9-11) Hulot et al used simulations to describe patients with varying degrees of renal insufficiency receiving enoxaparin in the initial treatment of non-ST-segment elevation myocardial infarctions. The authors concluded that enoxaparin accumulates in these patients and lower doses may be appropriate. (9) Green et al measured anti-Xa concentrations for 38 patients with acute coronary syndromes and developed a dosing algorithm based on estimated glomerular filtration rate that increased from 0.3 mg/kg to 1 mg/kg every 12 hours as renal function increased. (10) Kruse and Lee used empiric dose reductions in patients with moderate and severe renal dysfunction, including 0.75 mg/kg every 12 hours for creatinine clearances between 30 mL/min and 60 mL/ min. Their dosing strategy found 60% to 80% of the patients had a therapeutic anti-Xa level at 28 hours. (11) The creatinine clearances for the 4 patients in this study who experienced a major bleeding or vascular complication were between 70 mL/min and 90 mL/min.

In recent years, other novel concepts for anticoagulation surrounding cardiac ablation procedures have been described. (6-7, 12-15) Not all physicians are comfortable performing an ablation procedure while the patient is on continuous, therapeutic anticoagulation with warfarin. However, recent studies do suggest that therapeutic anticoagulation with warfarin may be used surrounding cardiac ablation procedures without an increase in major bleeding complications or strokes or transient ischemic attacks. (6-7) Also, many patients are not suitable candidates for the oral direct thrombin inhibitor or factor Xa inhibitors due to precautions and contraindications associated with the medications. (16-19) Dabigatran may possess similar or greater bleeding complications compared to therapeutic warfarin, depending on when the last dose is provided before the cardiac ablation procedure. (12-15) Based on the results of a sub-group analysis of the ROCKET-AF trial, there may not be a difference in the incidence of stroke, systemic embolism or death between rivaroxaban and warfarin when continued through a cardiac ablation procedure. (20) Results from the use of apixaban in this manner are not currently described.

The study does possess certain limitations. The retrospective and single-center study design necessitate reliance on accurate patient records and increase the potential for selection bias. The study was unable to reach 80% power given the smaller than desired sample size. While it is possible that patients developed either a major bleeding or vascular complication or a stroke or transient ischemic attack, every patient had a follow-up appointment with the operating electrophysiologist within 3 months of the procedure, including all but 2 patients within six weeks. Although more electrophysiologists are performing cardiac ablation procedures with continuous oral anticoagulation rather than peri-procedural enoxaparin, many patients are not adequate candidates for a novel oral anticoagulant or the physician may be hesitant to operate on a patient with a therapeutic INR.

The present study provides evidence for a novel dosing strategy for enoxaparin that electrophysiologists who are reluctant to move away from enoxaparin or patients who are unable to take other oral anticoagulants may see as beneficial. Additionally, many pharmacists will find this study helpful when evaluating intermediate-dose enoxaparin orders. The strength of the study is the intermediate enoxaparin dose described has never been evaluated in patients undergoing cardiac ablation procedures. There

was no statistically significant difference in major bleeding or vascular complications, and no patients in any group experienced an ischemic stroke.

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