

Ghannam

Official Title: Use of protamine for heparin reversal after catheter ablation of atrial fibrillation

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Introduction:

Catheter based ablation is a well-established and highly effective treatment for atrial fibrillation and the use of such therapies are increasing [1, 2]. To mitigate the risk of intraprocedural thromboembolism, intravenous heparin is administered to maintain an activated clotting time(ACT) of >300s [3]. At the completion of a procedure it can take several hours for a patient's ACT to normalize and for sheaths to be removed. However prolonged sheath presence may increase the risk of vascular complications which may not be infrequent (up to 6-9%) and can be associated with morbidity and increase in costs. A common strategy is to administer protamine sulfate to rapidly (within 5min) neutralize the effect of heparin to expedite sheath removal and patient ambulation and length of stay. Both of these approaches are standard of care practices, have been widely used and reported as case series. However, despite wide-spread clinical use, these two approaches have not been evaluated in a prospective, randomized manner. The objective of this study is to evaluate the safety, efficacy and efficiency of rapid anticoagulation reversal with protamine sulfate versus routine ACT monitoring in patients undergoing catheter based ablation of atrial fibrillation.

Background:

Protamine Sulfate:

Protamine has been used to facilitate in-laboratory sheath removal after percutaneous coronary interventions for over twenty years [4] and has been shown to decrease time to ambulation without increased rates of thrombosis or access site complications[5]. Protamine reversal of heparin anticoagulation also has an established track record in patients undergoing peripheral endovascular intervention[6] and is used commonly after cardiopulmonary bypass as well[7]. Protamine sulfate is a highly basic protein that forms stable compounds with acidic heparin to neutralize the anticoagulation effects and is itself not a procoagulant agent[8]. While randomized trials and larger studies are needed, it has not been shown to significantly increase rates of post-procedure thrombosis [4-7, 9, 10]. Further catheter ablation for atrial fibrillation is performed via venous approach and under **uninterrupted anticoagulation**.

Protamine can cause hypersensitivity reactions leading to rash, hypotension, pulmonary edema, and cardiovascular collapse[8]. Chilukuri et al reported on 242 patients undergoing atrial fibrillation ablation who received protamine for sheath removal and reported adverse reactions to protamine in 1.2% of cases which was similar to prior reports of protamine exposure[11].

Vascular Complications after ablation procedures:

Vascular access for ablation procedures can be complicated often requiring multiple venous access sites and long procedure and patient flat-time. These factors are known to be associated with increased rates of vascular complications [12, 13]. Patient specific factors, such as the use of antiplatelet agents and female gender, can increase the risk as well[14]. Newer technologies such as cryotherapy techniques require placement of large diameter sheaths which may raise the risk of vascular access complications [12]. Bleeding and thromboembolic complications after atrial fibrillation ablations are common and have been on the rise, predominantly due to increased vascular access complications [15]. Current guidelines recommend intraprocedural heparin be administered prior to or immediately following transeptal puncture [3] and this periprocedural anticoagulation may contribute to the rate of vascular access site complications [9]. A large study of Medicare beneficiaries reported the incidence of any vascular complication from AF ablation to be 6.9%[15] in 2006 up from 5.4% in 2001[15].

The rate of occult femoral DVT after placement of multiple venous sheaths has been reported in several series and ranges from approximately 5-18%[12, 13, 16]. Davutoglu et al performed serial vascular ultrasounds in 27 patients undergoing electrophysiology studies and found that post-procedural occult femoral DVTs were present in 62.5% of patients [13]. This rate was decreased to 18% with the use of prophylactic low-molecular weight heparin (p=0.02). Nearly all cases resolved after treatment with warfarin. Chen et al[16] examined 54 patients undergoing electrophysiology study (EPS) and/or RFA ablation, with routine heparinization only administered for left-sided ablation procedures, pre- and post-procedural vascular ultrasounds were performed. There was a 17.6% incidence of non-occlusive DVT in patients who underwent placement of multiple sheaths, this incidence was not significantly affected by the use of intraprocedural heparin. In these series, the DVTs were asymptomatic and demonstrated regression or resolution on follow-up imaging. In our series DVT has not been a concern. Further catheter ablation for atrial fibrillation is performed via venous approach and under **uninterrupted anticoagulation.**

Clinical diagnosis of hematoma formation immediately after EPS or ablation was reported by Dalsgaard et al[17]. The rate of hematoma formation immediately after EP procedures was 10%, with 27% of patients reporting a significant hematoma after 14 days. The rate of hematoma formation was higher in patients undergoing atrial fibrillation/flutter procedures than in those undergoing VT/VES procedures both immediately after the procedure (19% vs 5%) and at 14 days (31%vs 11%). Due to insidious nature of venous bleeding, the prevalence of hematomas can be higher after venous access. A critical factor on the true prevalence of hematomas reported in the literature is the rigor with which hematomas were assessed and reported explain the wide variation in prior reports.

Protamine administration after ablation procedures:

Several non-randomized, single center studies have reported on the safety and efficacy of protamine use in patients undergoing electrophysiology studies and ablations (Table 1). Patel et al performed a retrospective cohort evaluation comparing 116 patients who received protamine sulfate against 42 who did not [2]. The majority of patients (138/158) had undergone an atrial ablation while only a minority (11/158) underwent ventricular ablation procedures. They reported no significant differences in bleeding or thromboembolic events between the two groups. Routine imaging including vascular ultrasound was not utilized and bleeding events were defined as blood loss requiring transfusion, hematoma requiring intervention, or intracranial hemorrhage. Using these clinical definitions, the authors concluded that a randomized clinical trial of 1606 patients would be necessary to fully evaluate the use of protamine.

Conte et al reported on 54 consecutive patients receiving protamine after cryoballoon ablation of atrial fibrillation compared to 53 historic controls who did not[9]. The use of protamine was associated with less intensive care monitoring time as well as fewer vascular complications (11% vs 0%, p<0.01), primarily fewer minor groin hematomas treated conservatively). Gurses et al performed a retrospective study examining protamine use after the use of cryoballoon therapy for AF[10]. In this larger study of 380 patients the authors concluded that routine use of protamine was associated with a shorter time to sheath removal, faster mobilization, shorter hospital stay as well as fewer vascular access complications (hematoma/pseudoaneurysm or arteriovenous fistula, 6.3% vs 1.0%, p=0.011) without an increase in thrombotic events (TIA, CVA, DVT).

Frankel Cardiovascular Center Experience:

The University of Michigan is a high-volume ablation center with particular expertise in treating atrial fibrillation using both radiofrequency and cryoballoon ablation techniques. The Cardiac Arrhythmia Service performs approximately 1,100 ablation procedures per year including nearly 700 procedures for atrial arrhythmias primarily for atrial fibrillation. Protamine has not been incorporated into routine lab protocols for post-procedure care and is administered based on operator preference. Owing to the very low risk of significant complications specifically embolic events (<0.5%) over the years with the current approach, protamine has not been routinely used unless there is a clinical need. However, published case series suggest that protamine can safely be utilized to expedite vascular hemostasis. Therefore there is both a scientific and clinical need to determine whether each approach is comparable and whether one is superior to the other. There already is sufficient body of literature from this and other institutions demonstrating the utility of either approach.

A brief audit of recent procedures shows that in cases where rapid reversal with protamine is not used, the average time from patient arrival to the post-procedure unit to sheath removal is 204 ± 47 minutes; this delay is nearly entirely attributed to the time required for the critical

decrease in ACT to allow safe sheath removal. This prolongs patient time to ambulation and may contribute to outcomes.

Summary:

The use of protamine sulfate for rapid heparin neutralization and early sheath removal after catheter based therapies has been used with good results in a variety of clinical settings. However, much of the safety and efficacy data are derived from small, non-randomized, and retrospective series and have been performed in patients undergoing coronary and vascular interventions involving single vessel access. Ablation procedures involve the use of more vascular access, larger diameter sheaths, prolonged procedure times, more intensive anticoagulation protocols, and carries the risk of ablation lesion related thrombosis[3] which limits the applicability of the existing data. The few studies examining the use of protamine for atrial ablation have all been small, non-randomized cohorts but have suggested improved vascular access outcomes as well as decreased time to patient ambulation. Randomized prospective data are needed to corroborate these findings.

Objective and Hypothesis:

The objective of this study is to evaluate the safety, efficacy and efficiency of rapid anticoagulation reversal with protamine sulfate vs routine ACT monitoring in patients undergoing catheter based ablation of atrial fibrillation. We hypothesize that the routine use of protamine sulfate will facilitate early sheath removal, early ambulation, and improve patient comfort with a significant decrease in the rate of vascular access site complications and time to ambulation. The primary study endpoint will be the 30-day occurrence of vascular access site complications (major or minor groin bleeding including hematoma formation, aneurysm, pseudoaneurysm, AV fistula, deep venous thrombosis).

Methods and Study Protocol:

Study design:

Single center, controlled, prospective, superiority, parallel-group, open-label, randomized clinical trial.

Study Site:

Electrophysiology laboratories and outpatient clinics at the University of Michigan Health System Frankel Cardiovascular Center.

Study Population and Enrollment:

Adult patients undergoing clinically indicated RFA or cryoballoon ablation for atrial fibrillation or atrial flutter (left atrial) will be prospectively enrolled. Consideration for enrollment and obtainment of patient consent will be performed in the pre-operative setting in the cardiac procedures unit prior to the ablation procedure. Consent will be obtained by the study coordinator using both verbal and written study information.

Inclusion Criteria:

- Patient's referred for RFA or cryoablation for atrial fibrillation or atrial flutter (left atrial).
- Age ≥ 18 year
- Patients who are mentally and linguistically able to understand the aim of the trial, comply with the trial protocol, verbally acknowledge the risks, benefits, and alternatives in this trial.

Exclusion Criteria:

- Previous intolerance or allergy to heparin products.
- Current or prior administration of protamine products
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- History of femoral access site complications including hematoma, AV fistula, pseudoaneurysm, aneurysm.
- Known lower extremity venous thrombosis.
- Coagulopathy or blood dyscrasias.
- Active malignancy.
- Thrombocytosis (platelet count $>600k/\mu l$) or thrombocytopenia (platelet count $<100k/\mu l$)
- Planned use of vascular closure device

Randomization:

A randomization will be performed in a block manner. Patients will be randomized to one of two parallel treatment strategies, namely protamine sulfate group or standard sheath removal group (control).

Pre-Procedural and Procedural Management:

A pre-procedure groin and lower extremity examination will be documented. Patients on warfarin will continue on uninterrupted therapeutic anticoagulation through the procedure. Patients on direct-acting oral anticoagulants will discontinue the medication one dose prior to their procedure and will resume taking it after hemostasis has been achieved post-procedurally. Prior to heparin administration, ACT will be checked as a target for anticoagulation reversal prior to sheath removal.

Patients will undergo routine pre-procedural assessment and selection of radio frequency ablation (RFA) or cryoablation at the discretion of the treating physician. Procedural endpoints and ablation targets (i.e. pulmonary vein isolation, targeting of complex atrial fractionated electrograms, linear ablation lines, et cetera) are not specified by this protocol and will be performed at the discretion of the treating physician and in accordance with the ablation method selected. An intraprocedural targeted ACT of 300-400s is recommended in accordance with the current guidelines.

Vascular access will be obtained using fluoroscopic and ultrasound guidance using the standard modified-Seldinger technique. Patients undergoing RFA will have right femoral vein access with the use of two 8.5F long-sheaths and one 8F short-sheath. Patients undergoing cryoballoon ablation will have right or both femoral vein access with the use of a 14F long-sheath and 8F short sheath.

Postprocedural management:

Patients randomized to the intervention group will receive a test dose of protamine sulfate 0.5 mg with close monitoring for adverse reactions. If no reactions occur after 5 minutes patients will continue with the intervention group or otherwise undergo routine sheath removal. Protamine sulfate dose will be determined by the amount of heparin received during the last hour of the procedure (1mg of protamine per 100 units of heparin, maximum of 50 mg) and will be administered over 5 minutes, with close hemodynamic monitoring during and after the infusion. ACT levels will then be monitored with a goal ACT of <200s or return to preprocedural baseline.

The non-intervention group will undergo routine ACT measurements beginning 90min after the cessation of the procedure with a goal ACT<200s or return to preprocedural baseline before sheath removal.

Manual compression using the standard technique by professional staff, will be applied until hemostasis is achieved, followed by a 6-hour period of flat time before ambulation. Patients will be monitored overnight for post-procedural observation which is the current standard of care in our laboratory.

Immediately after the sheath removal and the morning after the procedure, detailed examination of both groins will be performed for signs of bleeding, hematoma, aneurysm, or fistula as standard of care and will be carefully documented. Patients with signs or symptoms of vascular complications will undergo duplex venous ultrasound as usual standard of care. In addition Hemoglobin and hematocrit levels will be documented before and the morning after the procedure as per routine clinical care protocol.

Post-procedural anticoagulation will be administered for at least two months per national guideline recommendations; choice of anticoagulation and duration beyond two months will be at the discretion of the treating physician.

Data Collection and Analysis:

Baseline demographic, clinical, procedural and ultrasound data will be collected. Patients will be monitored overnight post procedure (18-24 hours) with routine assessment of clinical access site, neurologic checks, and patient comfort scores. Patients will have one-week phone follow up and three month clinical visits to assess thromboembolic and bleeding events as well as procedural outcomes. Data collection formed is shown (see attached form).

Vascular ultrasound will be obtained if clinically indicated as described above. Results will be interpreted by two independent, qualified readers to ensure standardization and accuracy. Discrepant interpretations will be jointly reviewed for agreement.

Study endpoints:

The primary study outcome will be total time to ambulation; the start time (time zero) will be procedural termination. Secondary endpoints will include the 90-day occurrence of vascular access site complications defined as hematoma formation, aneurysm, pseudoaneurysm, arteriovenous fistula formation, access-site related major bleeding (defined as BARC type 3a or 5[18]), or procedural intervention for access complications (surgical repair, thrombin injection, et cetera). Additional exploratory endpoints will be the time to achieve hemostasis, duration of manual compression, need for repeat manual compressions, the total number of re-bleeding events, patient reported hematoma on 7 day phone call, and patient reported groin pain at discharge, 7 day phone call, and follow up appointment.

Safety endpoints:

Safety endpoints will be thrombotic events defined as stroke or transient ischemic attack, deep vein thrombosis, pulmonary embolism, lower extremity thromboembolic events, acute myocardial infarction, or death. There is no plan for an interim analysis.

Statistical Analysis:

Based on preexisting studies and an audit of quality data from our own laboratory, we anticipate a baseline time-to-ambulation of 360 ± 180 min with a reduction to 270 min with the use of protamine. We estimate that the enrollment of 150 patients would provide 80% power to detect the anticipated difference in the primary outcome at the 5% two-sided level of significance, assuming a 10% loss to follow up. Prespecified sub-groups for secondary analysis include sex, age, clinical comorbidites (BMI, diabetes, CHF), ablation method, use of antiplatelet medications, prior ablation procedure, prior coronary angiography or intervention.

Data will be reported as means and standard deviations or as absolute values and percentages where appropriate. The Chi Square and Fisher's exact test will be used to compare categorical

variables. Unpaired or paired Student's t-test or the Mann-Whitney test will be used as appropriate. A P value less than 0.05 will be considered statistically significant.

Clinical Significance:

This study will be the first to examine in a prospective, randomized manner the use of protamine sulfate to facilitate early sheath removal after atrial fibrillation ablation. Vascular complications after interventions are associated with increased patient discomfort, morbidity, and costs[17] and administration of protamine may be a safe and simple way to lower these rates. Future studies would incorporate cost effectiveness studies or expansion of protamine use into ventricular ablation procedures. The results of this study will impact the clinical practice and current guidelines of care for the growing number of patients who undergo atrial fibrillation ablation.

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Study	Design	Procedure	Protamine n(%)	No Protamine n(%)	Notes
Patel 2007	Retrospective, single center, pilot study	Atrial and ventricular ablation procedures	2/116(1.7%)	0/42(0%)	p=0.839. No routine imaging used. Only 34 patients underwent ventricular tachycardia ablation, outcomes were not reported separately.
Conte 2014	Prospective enrolled cohort compared to retrospectively obtained control group	Cryoballoon for AF	6/54 (0%)	11/53(11%)	p=0.01 for reduction in vascular events. No routine imaging used
Gurses 2015	Retrospective, single center	Cryoballoon for AF	2/188(1.1%)	12/192 (6.3%)	p=0.01 for reduction of vascular events. No thromboembolic events noted. No routine use of imaging. Significant reduction in time to sheath removal, mobilization and hospital stay.

Table 1: Vascular events among studies of protamine administration during electrophysiology procedures and ablations.