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Real-life experience with a new anticoagulation regimen for patients undergoing left-sided ablation procedures

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ABSTRACT

Background: Current guidelines for anticoagulation during left-sided procedures recommend the administration of unfractionated heparin (UFH) with an initial bolus of 50–100 U/kg, followed by continuous infusion to maintain an activated clotting time (ACT) ≥ 300 s. Our objective was to compare the effectiveness of this standard regimen (100 U/kg bolus) to a more aggressive approach (200 U/kg bolus).

Methods: We collected data on a series of consecutive patients undergoing left sided ablation procedures. Patients with an INR ≥2.0 on the day of the procedure were excluded. Procedural anticoagulation was performed using one of two UFH regimens: 1) 100 U/kg bolus, followed by 10 U/kg/hour infusion or 2) 200 U/kg bolus, followed by 20 U/kg/hour infusion. ACT was measured 10 min after the second bolus and then controlled every 20 min. Heparin was titrated throughout the procedure to maintain an ACT 300–400 s.

Results: 145 consecutive patients were included in the study: 34 received an initial bolus of 100 U/kg and 111 received 200 U/kg. The mean time required to reach an ACT ≥300 s was 15.25 min (95% CI 12.97–17.03) in the 200 U/kg group and 51.23 min (95% CI 40.65–61.81) in the 100 U/kg group ($p < 0.001$). There was no difference between groups with regard to thromboembolic or hemorrhagic complications.

Conclusion: Current anticoagulation guidelines for left-sided ablation procedures almost universally fail to achieve an initial ACT ≥300 s. A 200 U/kg heparin bolus is much more effective to promptly reach the target ACT, with a low rate of overshoot.

1. Introduction

Over the past decade, the number of patients undergoing left-sided ablation procedures increased dramatically, mainly because of the advent of pulmonary vein isolation as an effective treatment for atrial fibrillation (AF). In experienced centers, the risk of major complication associated with left sided interventions is relatively low. Thromboembolic complications nevertheless happen in approximately 1% of procedures [1]. The potentially dramatic consequences of ischemic strokes make them one of the most feared adverse events related to ablation procedures involving systemic circulation.

Various precautions can be taken before, during and after left sided ablation procedures in order to minimize the risk of thromboembolic events. As such, procedural anticoagulation with unfractionated heparin (UFH) is universally recommended in order to avoid thrombus formation while catheters are maneuvered in the systemic circulation. For AF ablation, current guidelines state that heparin should be titrated to maintain an activated clotting time of (ACT) 300–400 s. However, the dose of heparin to be administered as a bolus and the rate of infusion are not clearly defined. While the 2007 HRS/EHRA/ECAS guidelines recommended a 100 U/kg bolus, followed by a 10 U/kg/hour infusion, the 2012 update of the same guidelines makes no mention of the optimal initial UFH dosage [2].

Among effective strategies to prevent thromboembolic complications, targeting a higher ACT value [3] and giving UFH prior to left-sided access [4] are know to reduce spontaneous echo contrast as well as thrombus formation on catheters. These findings should

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emphasize the importance of using an UFH regimen that allows efficient and reproducible therapeutic ACTs early into the procedure. In our experience, the 100 U/kg bolus followed by a 10 U/kg/hour infusion is ineffective at reaching an initial ACT >300 s, which exposes patients to a significant delay in anticoagulation, hence potentially increasing thromboembolic complications.

2. Methods

This is a single-center pre/post-test prospective study of consecutive patients undergoing left-sided ablation procedures between February 2012 and January 2014. The study was approved by the Institutional Committee on Human Research. Patients were included if all ACT's were documented throughout the procedure and were excluded if they were on warfarin with an INR ≥2.

The first patients of our series (pre-test) received a 100 U/kg UFH bolus prior to transeptal punctures or immediately following arterial access, followed by a 10 U/kg/hour infusion. The following patients (post-test) received a 200 U/kg bolus, followed by a 20 U/kg/hour infusion. Initial ACT was measured immediately following transeptal or arterial access, and was retested every 20 min using an ACT Plus Automated Coagulation Timer System (Medtronic, Minneapolis MN United States). Infusion was then titrated in a similar fashion in both groups targeting an ACT between 300 and 400 s. ACT's were recorded until the last catheter was pulled from the left-sided cavities. All ACT values were documented, as well as the time at which they were obtained. Additional UFH boluses required to reach the target ACT were also documented but left to the discretion of the operator.

Warfarin was discontinued 48–96 h before the procedure, while NOACs were stopped 24 h prior. Since atrial fibrillation ablation in is performed without stopping warfarin in our center and given the fact that patients with an INR ≥2 were excluded form the study, most patients undergoing atrial fibrillation ablation in this study were anticoagulated with a NOAC. After the procedure, in patients previously treated with a NOAC, oral anticoagulation was restarted with the same agent 6 h after sheath removal. Patients on warfarin with an INR <2 were started on IV heparin or low-molecular weight heparin 6 h after sheath removal and continued until INR was therapeutic.

Major procedural complications were recorded up to 30 days after the procedure. Hemorrhagic complications included bleeding requiring transfusion or prolonging hospitalization, as well as pericardial effusion requiring drainage. Thromboembolic complications included neurologic, systemic and pulmonary embolic events.

Primary endpoint was the time to first ACT ≥300 s, T0 representing the time at which the first UFH bolus was given. Secondary endpoints included the proportion of patients with therapeutic (300–400 s) and supra-therapeutic (≥450 s) ACTs at each time point during the procedure, as well as a pre-specified analysis of patients according to weight quartile.

2.1. Statistical analysis

Continuous variables were compared using non-parametric Mann-Whitney test when data analysis suggested a non-normal distribution, and Student t-test when they were normally distributed. Proportions were compared using Chi-Square or Fisher's exact tests as appropriate. A bilateral p-value < 0.05 was considered statistically significant. All analyses were performed using SAS University Edition (SAS Institute Inc. North Carolina, USA).

3. Results

3.1. Baseline characteristics

A total of 145 patients met inclusion/exclusion criteria. The first 34 patients received a 100 U/kg UFH bolus, while the following 111 patients received the 200 U/kg bolus. Baseline characteristics as well as proportion of patients treated with warfarin, novel oral anticoagulants (NOACs) or no anticoagulant prior to the intervention are similar between groups (Table 1).

The majority of patient underwent either pulmonary vein isolation or left-sided (atypical) atrial flutter ablation. Remaining patients either had ventricular arrhythmia ablation or ablation for supraventricular tachycardia originating from the left atrium (Table 2). Procedural time was significantly longer in the 200 U/kg group (183.8 min - 95% CI 166.2–201.4) compared to the 100 U/kg group (157.2 min–95% CI 147.2–167.2) (p-value 0.0108).

Regarding heparin dosages, while the initial bolus was higher in the 200 U/kg group, additional boluses of UFH were significantly higher in the 100 U/kg group (1122 U vs 5754 U, p < 0.001) (Table 2). Mean ACT's were significantly higher in the 200 U/kg group throughout the procedure, but the difference reached statistical significance only for the first four ACT measurements (Fig. 1).

3.2. Primary outcome: time to first ACT ≥300 s

Subjects in the 200 U/kg group took a mean of 15.25 min (95% C.I 12.97–17.03) to reach an ACT ≥ 300 s, while it took an average of 51.23 min (95% C.I 40.65–61.81) in the 100 U/kg group (Table 3). The difference was statistically significant (p < 0.0001). Moreover, only 5.9% (n = 2) of subjects in the 100 U/kg group had an initial ACT ≥ 300 s, while 89,2% (n = 99) of subjects in the 200 U/kg group did. The difference was statistically significant (p < 0.0001).

3.3. Secondary outcomes

The proportion of patients with a therapeutic ACT (300–400 s) was significantly higher in the 200 U/kg group for the first two ACT measurements (Fig. 2). There was no significant difference in the proportion of patients with supratherapeutic ACT (>450 s) throughout the procedure between the groups (Fig. 3). Among patients with an initial ACT >450 s in the 200 U/kg group (n = 14), the mean INR was significantly higher (1.50, 95% CI 1.37–1.63) compared to patients with an initial ACT < 450 s in this same 200 U/kg group (1.12, 95% CI 1.09–1.16) (p value < 0.0001).

An analysis of variance was also performed on the mean initial ACT according to weight quartile in both groups. We found no significant difference in mean initial ACTs between weight quartiles for both the 100 U/kg group (p = 0.48) and 200 U/kg group (p = 0.17) (Fig. 4).

Finally, there was no significant difference in hemorrhagic (8.8% 100 U/kg vs 3.4% 200 U/kg p = 0.7) or ischemic (0% 100 U/kg vs 0.8% 200 U/kg p = 1) complications at 30 days between groups. When looking specifically at hemorrhagic complications, in the 200 U/kg group, 3 patients had pericardial effusions, 1 associated with tamponade requiring periprocedural percutaneous drainage in the electrophysiology lab and 2 presenting in the following weeks with symptomatic pericardial effusion requiring elective drainage. 4 other patients had groin hematoma, 1 requiring transfusion of 2 units packed red cells and 3 prolonging their hospital stay by 2–3 days due to pain. Finally, one patient died suddenly of pulseless electrical arrest <24 h following VT ablation of unknown cause. Of note, no hemorrhagic etiology was identified in that patient following head and thoracoabdominal CT and transthoracic echocardiogram. In the 100 U/kg group, 1 patient had an access related