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.

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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 known to reduce spontaneous echo contrast as well as thrombus formation on catheters. These findings should
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 restated 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, To 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 200 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).
hematoma and one patient had a pericardial effusion requiring drainage 24 h after the procedure. Finally, among patients who experienced an hemorrhagic complication in the 200 U/kg group the mean initial ACT was 397.33 (Range 319–474 s).

4. Discussion

This study shows that current recommendations to administer 100 U/kg initial UFH bolus followed by a 10 U/kg/hour infusion almost universally fails to reach a therapeutic ACT on the initial measurement. Using a higher initial UFH bolus (200 U/kg) and infusion rate (20 U/kg/hour) allows reaching a therapeutic ACT significantly faster than standard dosages. Quantitatively, patients in the standard treatment arm (100 U/kg bolus) spent 35 more

Table 1
Baseline characteristics.

|                      | 100 U/kg (n = 34) | 200 U/kg (n = 111) | p value |
|----------------------|-------------------|-------------------|---------|
| Age (years)          | 60.4 ± 11.9       | 59.4 ± 12.9       | 0.59    |
| Male Sex (%)         | 64.7 (22)         | 70 (78)           | 0.55    |
| Baseline INR         | 1.2 ± 0.2         | 1.16 ± 0.2        | 0.35    |
| BMI                  | 28.4 ± 7.2        | 28.3 ± 5.8        | 0.41    |
| Weight (kg)          | 81.7 ± 24.3       | 86.1 ± 20.8       | 0.25    |
| Creatinine Clearance (ml/min) | 90.3 ± 44.9     | 85.6 ± 25.9       | 0.81    |
| Warfarin (%)         | 9 (3)             | 12.6 (14)         | 0.76    |
| NOAC (%)             | 41 (14)           | 56.8 (43)         | 0.32    |
| No anticoagulant (%) | 50 (17)           | 20.6 (34)         | 0.07    |

Warfarin was discontinued 48–96 h prior to the procedure. Novel anticoagulants (NOAC) were discontinued 24 h prior to the procedure.

Table 2
Procedural data.

|                      | 100 U/kg (n = 34) | 200 U/kg (n = 111) | p value |
|----------------------|-------------------|-------------------|---------|
| Type of procedure (%) |                   |                   |         |
| - Atrial fibrillation/Atypical flutter | 58.8 (20)        | 76.6 (85)         | 0.051   |
| - Ventricular Tachycardia/PVC | 35.3 (12)         | 18.0 (20)         | 0.056   |
| - SVT (AT/left-sided pathway) | 5.9 (2)          | 5.4 (6)           | 1.000   |
| Procedure duration (mins) | 183.8 (50.4)     | 157.2 (51.2)      | 0.0108  |
| Heparin Bolus – Initial (U) | 8385 ± 2418     | 17370 ± 40722     |         |
| Heparin Bolus – Additional (U) | 5754 ± 1035     | 1122 ± 1302       |         |

SVT: Supraventricular tachycardia.
PVC: Premature ventricular contraction.

Table 3
Time to first ACT ≥300 s.

|                      | 100 U/kg (n = 34) | 200 U/kg (n = 111) | p value |
|----------------------|-------------------|-------------------|---------|
| Time (mins)          | 15.3 (95% CI 13.0–17.0) | 51.2 (95% CI 40.7–61.8) | <0.001  |

T0 – Time of first unfractionated heparin bolus.

Fig. 1. Mean ACT (secs) with standard deviation throughout the procedure.

Fig. 2. Proportion of patients with an ACT 300–400 s.

Fig. 3. Proportion of patients with a supratherapeutic ACT (>450 s).
minutes with a sub-therapeutic ACT compared to patients in the 200 U/kg group. While this study was underpowered to assess clinical outcomes, this period of time is probably clinically significant and could represent a critical period for the formation of thrombus on catheters and sheaths, which could lead to thromboembolic complications. Previous studies showing increase in spontaneous echo contrast and catheter thrombi formation in patients with less intense anticoagulation (250–300 s vs >300 s) [3] and delayed administration of UFH (before vs after transseptal access) support this assumption [4]. The fact that additional boluses of UFH were significantly higher in the 100 U/kg group compared to the 200 U/kg group also suggests that the smaller dosage is ineffective at promptly reaching the target ACT, leading to more adjustments by the operator throughout the procedure. Procedural time was significantly longer in the 200 U/kg group compared to the 100 U/kg group. This finding is most likely related to a higher number of patients undergoing SVT ablation in the 100 U/kg group. Even though numbers are small, these procedures are usually much shorter that AF or VT ablations, which could have influenced the mean procedural time.

Unfractionated heparin has a distribution volume of 40–70 ml/kg that is proportional to blood volume. As obese patients have a higher blood volume, it is accepted that they generally require higher heparin doses in order to reach therapeutic ACT. This is why weight-based nomograms are known to be more efficient at reaching target values of anticoagulation with UFH [6]. This was confirmed in the present study by the finding that initial mean ACT was similar between weight quartile for both the 100 U/kg and 200 U/kg groups. This remained true even with very overweight patients. The heaviest patient in the 200 U/kg group weighted 130 kg and received and initial bolus of 26000 units of UFH. His first ACT following the bolus was only 290 s.

Although our study was not powered to draw conclusions on clinical endpoints, a 200 U/kg bolus followed by a 20 U/kg/hour infusion of UFH for left-sided ablation procedures appears to be safe, with similar 30 days hemorrhagic and ischemic complications. A limitation of this study is that patients with a therapeutic INR were excluded from the analysis. While many patients with higher baseline thromboembolic risk now undergo the ablation procedure with therapeutic INR, a 200 U/kg UFH bolus cannot be recommended in this population because of a known interaction between therapeutic INR and ACT response to UFH [5]. As NOACs are now considered the standard of care to prevent thromboembolic complications in patients with AF, the number of patients treated with warfarin is decreasing steadily. As the current practice is to withhold NOACs 24–48 h prior to ablation procedures, the results of our study apply to this growing population. While studies have evaluated the safety of performing pulmonary vein isolation in patients without interruption of NOACs, their results are somewhat conflicting.

It was found that 11.7% of patients in the 200 U/kg group had an initial ACT >450 s. While there was no statistically significant difference between this proportion and the 2.9% from the 100 U/kg group, this could be the result of a small sample size and reflect a lack of power. While this might represent an argument against using a higher initial heparin bolus to prevent suprathretapeutic ACTs, it is worth noting that the subgroup of patients with an initial ACT >450 s in the 200 U/kg group had a significantly higher baseline INR than their counterparts with an initial ACT <450 s. This finding is consistent with previous studies describing an increased response to UFH in patients with elevated baseline INR. Until further data are available, limiting the higher initial heparin bolus strategy to patients with a normal baseline INR seems reasonable.

Finally, even though there was no formal protocol to adjust heparin infusion throughout the procedure, ablations were performed by only 3 operators from a single center, limiting major management variations between patients.

5. Conclusions

Anticoagulation with UFH represents one of the cornerstone strategies to reduce thromboembolic complications during left-sided ablation procedures. The current standard of care of 100 U/kg UFH bolus followed by a 10 U/kg/hour infusion is ineffective at promptly reaching a target ACT of 300–400 s. A strategy using a higher heparin dosage, with an initial bolus of 200 U/kg followed by a 20 U/kg/hour infusion was significantly more effective at rapidly reaching a therapeutic ACT in patients undergoing left-sided ablation procedure, without significant increase in hemorrhagic complications. Before incorporating this strategy in clinical practice, larger clinical studies assessing the impact of this regimen on specific safety clinical endpoints will be necessary.

Disclosures

No conflict of interest to disclose. No relationship with industry.

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