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Practice Guidelines

Comparison of peri-procedural anticoagulation with rivaroxaban and apixaban during radiofrequency ablation of atrial fibrillation

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ABSTRACT

Introduction: Prospective studies on rivaroxaban and apixaban have shown the safety and efficacy of direct anticoagulation agents (DOAC)s used peri-procedurally during radiofrequency ablation (RFA) of atrial fibrillation (AF). Studies comparing the two agents have not been performed.

Methods: Consecutive patients from a prospective registry who underwent RFA of AF between April 2012 and March 2015 and were on apixaban or rivaroxaban were studied. Clinical variables and outcomes were noted.

Results: There were a total of 358 patients (n = 56 on apixaban and n = 302 on rivaroxaban). There were no differences in baseline characteristics between both groups. The last dose of rivaroxaban was administered the night before the procedure in 96% of patients. In patients on apixaban, 48% of patients whose procedure was in the afternoon took the medication on the morning of the procedure. TIA/CVA occurred in 2 patients (0.6%) in rivaroxaban group with none in apixaban group (p = 0.4). There was no difference in the rate of pericardial effusion between apixaban and rivaroxaban groups [1.7% vs 0.6% (p = 0.4)]. Five percent of patients in both groups had groin complications (p = 0.9). In apixaban group, all groin complications were small hematomas except one patient who had a pseudoaneurysm (1.6%). One pseudo-aneurysm, 1 fistula and 3 large hematomas were noted in patients on rivaroxaban (1.7%) with the rest being small hematomas. DOACs were restarted post procedure typically 4 h post hemostasis.

Conclusions: Peri-procedural uninterrupted use of apixaban and rivaroxaban during AF RFA is safe and there are no major differences between both groups.

1. Introduction

Atrial fibrillation (AF) is associated with significant morbidity and mortality and AF ablation is recommended for symptomatic patients with drug refractory AF [1,2]. AF radiofrequency ablation (RFA) is associated with potential bleeding risks and thromboembolic complications given *trans*-septal entry into the left atrium and long procedure times [3,4]. Peri-procedural anticoagulation is critical to reduce the risk of thromboembolic complications resulting from thrombus formation on catheters, char formation, endothelial denudation, inflammation and de novo clot formation [3–6]. Observational and randomized control trials have established the safety and efficacy of uninterrupted warfarin therapy in the therapeutic range over interrupted warfarin therapy with heparin bridging in the peri-procedural setting [7–9].

The newer direct oral anticoagulants (DOACs - dabigatran, rivaroxaban and apixaban), are being increasingly preferred in the treatment of AF as they have a predictable anticoagulant effect without any of the nuances associated with warfarin use [10–12]. Several studies evaluated the un-interrupted use of NOACs in the peri-procedural setting. Initial studies with dabigatran were associated with mixed results [13,14] but the randomized control study Re-CIRCUIT established the safety of dabigatran in the peri-procedural setting as compared to warfarin [15]. Prospective observational studies on both rivaroxaban and apixaban showed

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comparable efficacy with uninterrupted warfarin in reducing peri-procedural thromboembolic complications without increased bleeding risks but studies directly comparing the two agents are lacking [16,17]. Randomized studies comparing the three NOACs are unlikely to be conducted.

We thus sought to compare the two agents in the peri-procedural setting with regards to bleeding and thromboembolic complications.

2. Methods

Data was obtained from a prospective observational registry maintained at one academic institution where a large volume of atrial fibrillation ablations are performed every year. The study protocol was approved by the institutional review board. Data of all patients on apixaban and rivaroxaban undergoing AF ablation between April 2012 and March 2015 were retrieved. All clinical and demographic variables were obtained from the registry. Outcomes data at follow-up regarding thromboembolic complications within 3 months, major and minor bleeding complications were also obtained from the registry and reconfirmed by thorough chart review.

2.1. Definitions

Cerebrovascular accident (CVA) and/or transient ischemic attacks (TIA) after ruling out intracranial hemorrhage were considered as thromboembolic complications. Major bleeding complications were defined as large groin hematomas requiring surgery or blood transfusions or pericardial tamponade requiring drainage. Minor bleeding complications were defined as groin hematomas, fistulas or pseudo-aneurysms that did not require any intervention or blood transfusion, pericardial effusions that resolved spontaneously without intervention.

2.2. Study endpoints

Our primary safety endpoint was a composite of thromboembolic and bleeding complications. Our secondary endpoints were bleeding (major and minor) and thromboembolic complications.

2.3. Peri-procedural anticoagulation

Patients included in the study were on 20 mg of rivaroxaban taken once a day for at least 30 days prior to the procedure. Similarly, patients on apixaban were on 5 mg bid or 2.5 mg bid based on age, weight and kidney function for at least a month prior to the procedure. These agents were continued without interruption in the peri-procedural setting in the majority of patients. Patients on rivaroxaban were asked to take their dose in the evening so that their last dose was on the evening prior to the procedure day. Following the procedure 4–6 h after sheath removal, rivaroxaban was started if no complications occurred during the procedure. Similarly, the last dose of apixaban was given either the evening of the procedure (if procedure in the morning) or the morning of the procedure (if procedure in the afternoon) according to operator preference. Apixaban was resumed 4 h following sheath removal if no complications occurred during the procedure. Transesophageal echo was performed on all patients prior to the procedure to exclude any clots in the left atrial appendage.

2.4. Ablation procedure

Patients underwent pulmonary vein antral isolation (PVAI) with a double *trans*-septal approach described previously [18]. Briefly, with the help of intra-cardiac echocardiography, two *trans*-septal accesses were obtained using standard needles and sheaths. A bolus of 100–180 U/kg of Unfractionated heparin (UH) was administered just prior to *trans*-septal puncture based on institutional protocol. Activated clotting time (ACT) was measured every 15 min subsequently while administering weight-based boluses of UH to keep ACT between 300 and 400 s. The left atrium was mapped using a circular mapping catheter (Lasso, Biosense Webster Inc., Diamond Bar, California; or Spiral, St. Jude Medical, Minneapolis, Minnesota). Electrical isolation was accomplished by ablating the antrum of pulmonary veins with 3.5-mm open irrigated tip catheter (ThermoCool, Biosense Webster Inc.). Anterior segments were ablated with a maximum of 40 Watts while posterior segments were ablated with 30 Watts of radiofrequency energy. All 4 veins were isolated in patients with paroxysmal AF and additional substrate modification on the posterior wall was performed in patients with persistent AF and re-do procedures. Direct current cardioversion to restore sinus rhythm was performed following ablation if patients did not convert to sinus rhythm with ablation. Intravenous adenosine was used to confirm pulmonary vein (PV) isolation in some patients. Isoproterenol challenge up to 20 μg/min was given following ablation to assess non-PV triggers. All ablation was performed with 3D mapping and intra-cardiac echo guidance. Mean procedure and fluoroscopic times were recorded. Post procedure 40 units of protamine was administered prior to sheath removal. If ACT was still elevated, an additional 20 units was given. Sheaths were removed after ACT was reduced to 240 s or less. Hemostasis was routinely achieved by manual compression after removal of n the sheaths.

Table 1
Baseline characteristics.

Variables	Apixaban	Rivaroxaban	p value
	n = 56	n = 302	
Age (years)	60 ± 10	60 ± 10	0.9
Caucasian (%)	80	90	0.03
Males (%)	74	63	0.2
Body mass Index	30 ± 8	29 ± 9	0.2
Ejection fraction (%)	50 ± 8	56 ± 8	0.6
Cardiomyopathy (%)	7	8	0.9
Stroke (%)	4	8	0.4
Diabetes (%)	14	22	0.2
Hypertension (%)	76	67	0.2
Coronary Artery Disease (%)	7	17	0.04
Paroxysmal AF (%)	56	60	0.12
Persistent AF (%)	32	31	0.8
Duration of AF (years)	6 ± 6	6 ± 6	0.9
Left Atrial size (cm)	4.3 ± 0.8	4.2 ± 0.6	0.7
Aspirin (%)	26	37	0.2
CHADS2 score	1.2 ± 1	1.1 ± 1	0.8
HAS-BLED score	1.27 ± 0.8	1.21 ± 0.7	0.7

2.5. Statistical analysis

All categorical data were expressed in percentages and analyzed by chi square or Fischer exact test as appropriate. All continuous data was expressed in mean and standard deviation and t-tests were used. A p value of <0.05 was considered significant. SAS 9.4 (SAS Inc, North Carolina, USA) was used for statistical analysis.

3. Results

There were a total of 368 patients who underwent RFA of AF within this time period. 10 patients were excluded due to lack of data. Final sample comprised of 358 patients with n = 56 patients on apixaban and n = 302 on rivaroxaban. There were no significant differences in baseline characteristics between both groups except

Table 2
Outcomes.

Outcomes	Apixaban	Rivaroxaban	p value
	n = 56 (%)	N = 302 (%)	
Composite of CVA and bleeding	4 (7.1)	19 (6.2)	0.7
CVA/TIA	0	2 (0.6)	0.9
Major bleeding	0	0	
Minor bleeding	4 (7.1)	17 (5.6)	0.7
a) pericardial effusion	1 (1.7)	2 (0.6)	0.4
b) groin bleeding	3 (5.3)	15 (4.9)	0.9

for race (see Table 1). Mean age of the population was 60 ± 10 years with 89% Caucasians and 65% males. Paroxysmal AF was present in 58% of patients, persistent AF in 31% and long standing persistent in 9% of patients. Mean CHADS2 (congestive heart failure, hypertension, age, diabetes mellitus, and prior stroke, transient ischemic attack, or thromboembolism) score was 1.2 ± 0.9. Aspirin was used in 31% of patients. Mean INR in these patients was 1.4. Mean procedure duration was similar in both groups (2.7 ± 1 h vs 2.1 ± 0.7 h, p = NS).

The last dose of rivaroxaban was administered the night before the procedure in 96% of patients (n = 292) and 2 days prior to the procedure in 4 patients. It was administered on the morning of the procedure in 6 patients. In patients on apixaban (BID dosing), 48% of patients took the medication on the morning of the procedure with the rest on the evening prior to the procedure.

Outcomes – There was no significant different in the rate of composite endpoint of thromboembolism and bleeding in both groups (7% vs 6.2%, p = 0.7). (See Table 2).

There were no thromboembolic complications in the apixaban group. One patient had a TIA and one patient had an ischemic stroke in the rivaroxaban group in 60 days (0.6%) (p = NS). There were no major bleeding episodes in either group. See Table 2.

There was no difference in the rate of pericardial effusion between both groups (one patient in the apixaban group (1.7%) and two in the rivaroxaban group (0.6%)) with p = 0.4. Five percent of patients in both groups had groin complications (4.9% vs 5%, p = 0.9). In apixaban group, all groin complications were small hematomas except one patient who had a pseudo-aneurysm (1.6%). One pseudo-aneurysm, one fistula and three large hematomas were noted in group B (1.7%) with the rest being small hematomas. No intracranial hemorrhage occurred in either group.

NOACs were restarted post hemostasis on the same night post procedure at a mean duration of 5.1 ± 2 h.

4. Discussion

Our study compared the uninterrupted use of rivaroxaban and apixaban in the peri-procedural setting of AF ablation and found no differences in thromboembolic and/or bleeding complications between the two agents. Randomized studies comparing these agents are unlikely to be conducted and ours is one of the first studies comparing the two NOACs in the peri-procedural setting.

Safety and feasibility of dabigatran in AF ablation was initially studied by our group as part of a multicenter study which demonstrated an increased risk of bleeding. Dabigatran was held on the morning of the procedure in this population [13]. Subsequently other studies were conducted where dabigatran was held the night prior to the procedure and demonstrated a comparable bleeding risk as warfarin [14,18]. However, a meta-analysis demonstrated increased risk of thromboembolic complications associated with dabigatran [19]. As such, there was no consensus on use of dabigatran during AF ablation at the time this study was conducted and hence we did not use dabigatran in our patients [20]. Subsequently, the RE-CIRCUIT randomized study comparing warfarin with dabigatran showed lower bleeding rates with uninterrupted dabigatran.

Following initial prospective trials, randomized trial (VENTURE –AF) comparing rivaroxaban with warfarin during AF ablation was published but demonstrated feasibility similar event rates in both groups [21]. A recent meta-analysis compared warfarin with the DOACS and showed that both interrupted and un-interrupted therapies were safe but comparisons among the DOACs were not made [22].

We thus sought to compare rivaroxaban and apixaban in our study. Patients on rivaroxaban received the last dose the night prior to the procedure in all studies as in our current study. Composite of bleeding and thromboembolic complications in these studies varied from 6% to 13% and is similar to rates obtained in our study. Similarly with apixaban, complication rates around 4% are reported and similar to those reported in our study [17,23,and24]. Apixaban was administered on the morning of the procedure in these studies while in our study half of our patients received the morning dose while the other half had their last dose the night prior to the procedure.

No major complications requiring blood transfusion or surgical interventions occurred in our study population but prothrombin complex concentrate was available for all patients to be used if needed. All patients were typed and crossed prior to the procedure. Also, no adverse events were noted with the use of protamine in our population post procedure.

A prothrombotic state is induced during any AF ablation due to inflammation, presence of catheters in the left atrium, char formation, endothelial denudation etc. [6,25]. Maintaining adequate peri-procedural anticoagulation is thus necessary. A weight-based heparin protocol was used in our institution to achieve adequate ACT target of 350–450 s.

Use of DOACs continues to increase especially since reversal agents for these drugs have become available [26]. A randomized controlled trial comparing uninterrupted warfarin with uninterrupted apixaban for AF ablation (AXAFA) trial is underway [27]. Comparisons between these DOACs are necessary to select the ideal agent with the least complication rates but such randomized studies are unlikely to be conducted. Our observational study compares two of these agents and showed that there were no differences in thromboembolic and bleeding rates between apixaban and rivaroxaban in the peri-procedural setting.

Limitations: This was an observational registry and not a randomized trial. Thus unmeasured differences between the groups may exist. However, data was obtained from a prospective registry and represents data from the real world population. Sample size in the apixaban group was small. The last dose of apixaban was variable with some receiving the night prior and some on the morning of the procedure. This study data is from a single center with high volume and experienced operators and thus may not be generalizable.

5. Conclusions

Peri-procedural un-interrupted use of apixaban and rivaroxaban during AF RFA is safe and there are no major differences in bleeding and thromboembolic complications between the two agents.

Disclosures

Lakkireddy receives speaker honoraria from St. Jude Medical, Boehringer Ingelheim, Jansen, and Bristol Meyers Squibb.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Lakkireddy receives speaker honoraria from St. Jude Medical, Boehringer Ingelheim, Jansen, and Bristol Meyers Squibb.

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