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Original article

Comparative study of hemorrhagic and ischemic complications among anticoagulants in patients undergoing cryoballoon ablation for atrial fibrillation

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ABSTRACT

Objective: Few data exist to evaluate the safety and efficacy of direct oral anticoagulants (DOACs) in patients with atrial fibrillation (AF) undergoing cryoballoon ablation (CB-A). This study is aimed to clarify the usefulness of DOACs in patients undergoing CB-A.
Methods: The patients (average age; 65.8 ± 11.9 years old, male 69%) were stratified into one of five subsets based on the type of anticoagulation (warfarin, apixaban, dabigatran, rivaroxaban, or edoxaban), and underwent CB-A. A brain MRI was performed in all patients the day after the CB-A for AF. A total of 257 (19 on warfarin, 30 on apixaban, 66 on dabigatran, 81 on rivaroxaban, and 61 on edoxaban) patients met the inclusion criteria.
Results: The incidence of silent cerebral ischemic lesion was 1 (11.1%) patients on warfarin, 5 (33.3%) on apixaban, 8 (27.6%) on dabigatran, 10 (21.3%) on rivaroxaban, and 10 (29.4%) on edoxaban ($p = 0.17$). Major ischemic events occurred in one patient (1.6%) on edoxaban and one (5.3%) on warfarin. Minor bleeding complications occurred in 1 patient (5.3%) on warfarin, 2 (6.7%) on apixaban, 1 (1.2%) on rivaroxaban, 5 (7.6%) on dabigatran, and 2 (3.3%) on edoxaban ($p = 0.24$). Of note, major bleeding complications occurred in 2 patients (3.3%) on apixaban, 1 (1.2%) on rivaroxaban, 1 (1.5%) on dabigatran, 1 (1.6%) on edoxaban, and 2 (10.5%) on warfarin ($p < 0.05$).
Conclusions: Warfarin use significantly increased the risk of serious bleeding, in contrast, CB-A did not place the patients at an increased risk of complications under a DOAC treatment. There were no significant differences regarding preventing embolic events among the DOAC drugs.

Introduction

Electrical isolation of pulmonary veins using cryoballoon (CB) ablation (CB-A) has become an increasingly popular technique [1–3]. Even after the successful ablation procedure, anticoagulant treatment is indispensable for preventing strokes for a while [4]. Although direct anticoagulants (DOAC) such as dabigatran, apixaban, rivaroxaban, and edoxaban provide a demonstrated non-inferiority to warfarin for stroke prevention in atrial fibrillation (AF) [5–8], little data has been presented regarding the efficacy and safety of DOACs following CB-A. An ideal periprocedural anticoagulant for AF ablation, in addition to being associated with minimal bleeding and thromboembolic events, should be the same anticoagulant the patient had been taking prior to the procedure, without interrupting the patient's dosing schedule. The aim of this study was to investigate the incidence of hemorrhagic and ischemic events associated with warfarin and DOAC drugs in patients undergoing CB-A.

Methods

Population

The ethics approval was obtained from the institutional review committee, and all patients gave their written informed consent

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prior to the ablation procedure. Consecutive patients who underwent CB-A of AF at our institution were included. All patients undergoing CB-A had either paroxysmal (198 patients: 77.1%) or persistent (59 patients: 22.9%), non-valvular AF. All patients received warfarin or DOAC drugs for oral anticoagulant therapy for at least 4 weeks prior to the ablation. The patients were stratified into one of five subsets based on the type of anticoagulant – warfarin, apixaban, rivaroxaban, dabigatran, or edoxaban. Since the vast majority of patients referred for AF ablation were already receiving oral anticoagulants prior to the referral, the choice of anticoagulant drug was left to the referring physicians, and the patients were continued on the agents previously prescribed. The efficacy and safety of the periprocedural use of anticoagulants were retrospectively analyzed. The exclusion criteria were an age >75 years, advanced structural heart diseases including moderate-to-severe heart valvular stenosis or insufficiency, congenital heart diseases, left ventricular ejection fraction of <40%, left atrial diameter of >50 mm, myocardial infarction or coronary artery bypass graft surgery within the last 3 months, creatinine clearance of <50 ml/min, chronic obstructive pulmonary disease treated with β-sympathomimetic drugs, severe respiratory insufficiency, known bleeding diathesis or intolerance to heparin or oral anticoagulants, previous attempted AF ablation, left atrial thrombus, and severe comorbidities.

For the patients in the warfarin group, the warfarin dose was adjusted to maintain a target international normalizing ratio (INR) of 1.5–2.5, and warfarin was continued throughout the procedural period. The patients on dabigatran and apixaban were instructed to hold the dose the morning of the ablation procedure, and the patients on edoxaban and rivaroxaban held the medication dose the morning prior to the ablation procedure. The patients were not bridged with heparin prior to the ablation procedure. A lack of a physical examination or incomplete medication list excluded any patient from the study.

Ablation procedure

Antiarrhythmics were stopped at least 5 half-lives, and amiodarone discontinued at least 3 months, before the ablation. General anesthesia was used in 100% of the ablation procedures. Transesophageal echocardiography (TEE) was performed in all patients with persistent AF prior to the ablation procedure to exclude the presence of any intracardiac thrombi. One 6.5 Fr, two 7.5 Fr, and one 8.5 Fr, hemostatic sheath were placed into the femoral vein or right jugular vein using a modified Seldinger technique. A decapolar catheter was advanced into the coronary sinus (CS). A transseptal catheterization was performed with biplane fluoroscopy under the guidance of intracardiac echocardiography (SOUNDSTAR, Biosense Webster, Johnson & Johnson, Diamond Bar, CA). Intravenous heparin was administered by a bolus injection just after the trans-septal puncture with an initial dose of 100 unit/kg. The activated clotting time (ACT) was measured from venous blood 10 min after the initial heparin bolus and every 20 min thereafter until a value within the target range was achieved. Further heparin was administered to maintain an ACT of greater than 300 s. Over an exchange length 0.035-inch guide-wire introduced into the left superior pulmonary vein (PV), an 8 Fr trans-septal sheath was exchanged for a 15 Fr deflectable sheath (FlexCath, Medtronic, Minneapolis, MN) to allow the introduction of a 28 mm CB (Arctic Front, Medtronic, Minneapolis, MN). This was the only CB used in all cases. Over a guide-wire introduced fluoroscopically into each targeted PV, the CB was inflated in the left atrium before it was advanced into the PV antrum. Three minute CB applications were applied to each PV, aiming for a trough temperature of less than −40 °C. Any point of contact between the endothelium and balloon was ablated. After each PV antrum was treated with a single CB application, the PV ostia were remapped with the circular mapping catheter (Optima, St. Jude Medical Inc., Minneapolis, MN) and any residual LA-PV connections were treated by focal radiofrequency ablation applications (Thermocool, Biosense Webster, Diamond Bar, CA) to achieve PV isolation without performing a bonus freezing with the CB.

Complications

The complications were categorized as major or minor. Major complications were death, pericardial tamponade, strokes or systemic thromboembolisms, atrio-esophageal fistulae, PV stenosis of >50% requiring intervention, groin complications, or other major bleeding events requiring surgery or a transfusion. Major bleeding was defined as any bleeding severe enough to require a blood transfusion, hematomas requiring surgical intervention, or pericardial bleeding necessitating drainage (cardiac tamponade). Small hematomas and pericardial effusions, which did not require any intervention, were considered minor bleeding complications. Major ischemic event was defined as stroke/transient ischemic attack or systemic thromboembolism. Minor complications included transient ischemic attacks (TIA) and bleeding from any source requiring medical attention, but not requiring a transfusion or surgery. TIAs were subcategorized into those occurring during the ablation or in the first 48 h post-ablation and those occurring from 48 h to 30 days post-ablation.

Occurrences of pericardial effusions that occurred more than 48 h post-procedure and that required drainage were considered late pericardial effusions. Other complications related to the procedure, but unrelated to anticoagulation, were also noted.

Brain MRI examination

A brain MRI was performed the day after the CB-A procedure with a 3.0-T scanner (Achieva, Phillips, The Netherlands) to identify any ischemic cerebral lesions related to the CB-A ablation procedure. The imaging protocol for all images consisted of a T2-weighted axial fluid-attenuated inversion recovery (FLAIR) sequence and a diffusion-weighted imaging (DWI) sequence. According to the latest neuroimaging experts' recommendation, an acute embolic lesion was defined as a focal hyper-intense area detected by the DWI sequence with corresponding hypo-intensity in the apparent diffusion coefficient map in a typical vascular pattern [9]. All MRI images were analyzed independently by a certified radiologist and certified physicians blinded to this study, the clinical status and identification of the patients. A clinical neurological examination was performed on admission and the day after the ablation procedure by a certified neurologist blinded to this study.

Follow-up

Postprocedural warfarin and DOAC drugs were administered on the evening of the procedure in all patients. All patients remained on oral anticoagulation for a minimum of 3 months after the ablation procedure. A 3-month blanking period was applied such that any AF recurrences during this period were not considered as a treatment failure. Follow-up was performed by clinic visits at 1, 3, 6 and subsequently 6-month intervals with repeated 24 h Holter monitoring and event recorders. All patients had at least 6 months of follow-up. Recurrence was defined as any documented episode of AF (both symptomatic and asymptomatic) or atrial tachycardia lasting for more than 30 s. No patients were lost to follow-up.

Statistical analysis

The continuous variables are expressed as the mean ± SD, and were compared using a Student's *t*-test, and Fisher's exact test. An

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