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How to Use Novel Oral Anticoagulants during the Periprocedural Period of Atrial Fibrillation Ablation

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Abstract

Anticoagulation with novel oral anticoagulants (NOACs) for patients undergoing catheter ablation of atrial fibrillation (AF) has rapidly spread all over the world. Nevertheless, there is a lack of information on how to use the NOACs during the periprocedural period. In this review, we introduced the current trend in the way to use the NOACs during the periprocedural period of the AF ablation, and discussed its problems and future challenges.

Keywords: Ablation; Atrial fibrillation; Novel oral anticoagulants

Era of NOAC

Heparin bridging used to be a mainstream periprocedural anticoagulation strategy with warfarin at the dawn of catheter ablation of atrial fibrillation (AF). However, that was replaced by an uninterrupted warfarin strategy, because it was found to be more convenient and even safer [1]. This new strategy then reduced any cause for concern with regard to periprocedural hemorrhagic and thromboembolic complications. However, the times have changed. Novel oral anticoagulants (NOACs) without the need for laboratory monitoring have currently become available for patients with AF. Large scaled-trials have shown the non-inferiority or even a superiority of the NOACs over warfarin with regard to the occurrence of hemorrhagic or thromboembolic complications [2-5]. In response to the safety and convenience of the NOACs, they now are on track to take the place of warfarin as an anticoagulant therapy fornon-valvular AF. Thus, we cannot afford not to use NOACs during the periprocedural period of AF ablation. Studies then compared the hemorrhagic and a thromboembolic events occurring during the peri-procedural period of AF ablation between patients prescribed with an NOAC and those with warfarin. As it stands, there are 12 trials [6-17] examining the periprocedural use of NOACs for patients undergoing AF ablation. Of those, 10 trials [6-15] have compared dabigatran and warfarin. The vast majority of the studies [7-11,13-15] demonstrated a non-inferiority or superiority of dabigatran over warfarin. Out of four [18-21] currently available metaanalyses on the topic, three [18-21] reported the non-inferiority of dabigatran over warfarin. Steinberg et al. [20] however reported in their meta analysis that neurological events; ischemic strokes or transient ischemic attacks, were more frequently observed during the periprocedural period of AF ablation in the dabigatran arm as compared to the uninterrupted warfarin arm (10/1501 [0.7%] versus 4/2356 [0.2%]). This non-negligible result could be explained purely by some pharmacological difference between warfarin and dabigatran, yet importantly it may have come from a lack of familiarity with the use of NOACs during the periablation period.

How to use NOACs during the Periablation Period

What clinical electro physiologists would like to know about periablation anticoagulation with NOACs; mainly dabigatran may be summarized in the following four subjects.

(1) Dose regimen: Either a dose of 150 mg or 110 mg of dabigatran twice dailyis proposed by the manufacturers for anticoagulation in patient with AF [22]. Of the 10 studies, only two [7,8] used the low dose regimen alone for periablation anticoagulation. This trend toward the periprocedural use of 150 mg BID of dabigatran may be based on the results from the RE-LY trial in which ahigh dose of dabigatran rather than a low dose reduced the occurrence of thromboembolisms as compared to warfarin [2]. Accordingly, although the renal function, age, body weight and ethnics should be taken into account [22], a high dose of dabigatran may currently be the mainstream use for periprocedural anticoagulation during AF ablation.

(2) When to withhold and resume dabigatran: The patients were instructed to hold dabigatran the morning of the procedure in six trials [6,7,9,10,12,15]. One trial [6] reported an increase in hemorrhagic events in the dabigatran arm as compared to the uninterrupted warfarin arm, and the authors proposed an interaction between a lasting effect of dabigatran and an intraprocedural infusion of unfractionated heparin as a causal mechanism. In two trials [8,13] dabigatran was withheld the night before the procedure. As for the resumption of dabigatran, seven trials [6,8-11,13,15] restarted it by the evening of the procedure at the latest. Only one trial [14] adopted an uninterrupted dabigatran approach. Of note, only two trials [7,11] used heparin bridging, and further it was only partially applied. In summary, one dose of dabigatran was skipped before the ablation and it was restarted within a few hours after the procedure in the majority of the trials, and heparin bridging was hardly used. This trend regarding how to use dabigatran during the periablation period is based on its pharmacodynamic characteristics: a rapid onset of action and short half-life [22], and therefore may have some validity. Hawes et al. [23] concluded in their recent work that the activated clotting time (ACT) is often normal in spite of therapeutic dabigatran plasma levels. Thus, it may be dangerous to determine the degree of intraprocedural anticoagulation by measuring the ACT level alone when unfractionated heparin is used in conjunction with dabigatran. Further, to date no specific antidote against dabigatran is

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available [22]. In our opinion, thus, it is desirable as much as possible that a lasting effect of dabigatran is eliminated during the procedure. In this regard, considering dabigatran half-life of 12-14 hours [22], it may be controversial whether it is more favorable to skip one or two doses of dabigatran before the AF ablation.

(3) How much heparin is needed to achieve the target ACT?: Five [9,10,12-14] of 10 trials reported that more unfractionated heparin and much time were required to achieve an target ACT level ranging from 300-450 m/sec during the AF ablation in patients with dabigatran as compared to those receiving uninterrupted warfarin. This fact indicates that the patients with dabigatran were exposed to a lesser anticoagulated state for a longer time during the procedure, which might have contributed to the increased neurological events in the subjects with dabigatran reported by Steinberg et al [20]. Konduru et al. [24] reported an important finding that the patients with two skipped doses of dabigatran tended to require more time to achieve the target ACT level despite much greater requirement for unfractionated heparin during the procedure as compared to those with uninterrupted dabigatran. If dabigatran had an effect of preventing the ACT from prolonging when an unfractionated heparin infusion was used, the latter would have needed much more time to achieve the target ACT level than the former, because the latter must have had a greater blood level of dabigatran. However, the result was the other way around. Further, Kim et al. [13] showed that there was a lower ACT level at baseline i.e. without an unfractionated heparin infusion, in subjects with dabigatran than in those with uninterrupted warfarin. When all those findings are taken into consideration, although the mechanism is not fully elucidated, it is inferred that uninterrupted warfarin with a therapeutic INR simply has a stronger capacity to prolong the ACT than dabigatran and an additive action with unfractionated heparin on the ACT [25], and it is unlikely that dabigatran has a specific pharmacological effect to complicate the intraprocedural use of unfractionated heparin. At any rate, it is important to remember that a greater amount of unfractionated heparin should be administered during the AF ablation to minimize the risk of thromboembolisms when dabigatran is used for periablation anticoagulation than when uninterrupted warfarin is used.

(4) What is a suitable NOAC for AF ablation?: We in our recent work [16] compared the coagulable state between subjects treated with dabigatran and those receiving rivaroxaban. Although the half-life of rivaroxaban is slightly shorter than that of dabigatran, the manufacturers recommend taking it once daily rather than twice daily [26]. In this regard, we pointed out in our work a potential risk for thromboembolisms resulting from a mismatch between the half-life and dose regimen of rivaroxaban [16,27]. The study did not necessarily show any superiority of dabigatran over rivaroxaban, however, it suggested the importance of using NOACs during the periablation period based on their pharmacodynamic characteristics. The debate on what NOACs to be used for patients scheduled to undergo AF ablation has only just begun [16,17].

Future Challenge

Periablation anticoagulation with NOACs has rapidly spread all over the world. Nevertheless, almost all the recent trials examining the periablation use of NOACs have been small-scale and non-randomized ones, and thus the power of their evidence is limited. Therefore, large-scale and randomized trials on the matterare needed. However, that is not enough, and we should enter into the next stage. The evidence on the effective ways to use NOACs during the periablation period should be constructed without any delay. In particular, there is an urgent need for *in-vivo* or *in-vitro* studies clarifying whether there are any unfavorable actions of NOACs that make heparinization difficult during AF ablation, and those showing requirements of unfractionated heparin during the AF ablation according to the use of different NOACs.

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