Clinical outcomes of bridging therapy with fondaparinux versus low-molecular-weight heparin in patients undergoing atrial fibrillation ablation

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Abstract: Objective To compare the efficacy and safety of bridging therapy with fondaparinux versus low-molecular-weight heparin (LMWH) in patients undergoing radiofrequency ablation for atrial fibrillation (AF). Methods AF patients undergoing radiofrequency ablation between January, 2009 and June, 2013 in Nanfang Hospital were analyzed. The patients received subcutaneous injection of either fondaparinux or LMWH as a bridging therapy during warfarin discontinuation 5 days before the ablation until a post-ablation international normalized ratio (INR) of 2.0-3.0 was achieved. Anticoagulant-related complications, identified and classified as thromboembolic and bleeding events, were compared between the two groups. Results A total of 465 patients (68% male; mean age 52.3±15 years, range 25 to 80 years) were enrolled in the study, including 265 in fondaparinux group and 200 in LMWH group. Anticoagulation-related complications were observed in 3 patients in fondaparinux group, as compared with 13 in LMWH group (P=0.002), but the thromboembolic rate did not differ significantly between the two groups (P=0.111). Two patients in fondaparinux group and 8 in LMWH group showed bleeding complications (P=0.039). No cardiovascular death occurred in these patients during a mean follow-up period of 3 months. Conclusions Fondaparinux as the bridging therapy during catheter ablation for AF does not increase the risk of thromboembolic complications but slightly reduces the risk of bleeding compared to LMWH, suggesting its safety and effectiveness for periprocedural anticoagulation management in AF patients undergoing radiofrequency ablation.

Key words: fondaparinux; low-molecular-weight heparin; atrial fibrillation; catheter ablation; anticoagulation

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia that occurs in approximately 1% of the general population[1] and increases the risk of stroke by 5 folds [2]. Catheter ablation (CA) has proved to be an effective treatment for symptomatic AF patients who have failed drug therapy[3], but the periprocedural period carries a risk of embolic stroke in 1.1% to 7% of the patients [4, 5]. Given the importance of appropriate periprocedural anticoagulation therapy in these patients, currently there is no consensus over the optimal anticoagulation management of AF.

In patients at a high risk for thromboembolism who require chronic warfarin therapy, bridging anticoagulation reduces the time when the patients are not receiving anticoagulation and lower the risk of thrombotic events [6]. Low-molecular-weight heparin (LMWH) is recommended for bridging therapy to prevent thromboembolic complications [7, 8]. In recent years, a new antiagulant, fondaparinux, which is an indirect factor Xa inhibitor, was approved for use in providing systemic anticoagulation for venous thromboembolism [9]. However, there is currently a lack of data regarding fondaparinux bridging strategies during temporary discontinuation of warfarin. In this study, we sought to evaluate the long-term efficacy and safety of bridging therapy with fondaparinux, as compared with LMWH, during discontinuation of warfarin in patients undergoing ablation procedures for AF.

PATIENTS AND METHODS

Patient cohort

This study was conducted among consecutive patients undergoing ablation for AF between January, 2009 and June, 2013 in Nanfang Hospital (Guangzhou, China). The referral for ablation was made by electrophysiologists according to the European Society of Cardiology (ESC) 2010 Guidelines for the Management of Atrial Fibrillation [10]. The types of AF were recorded before ablation. Paroxysmal AF was defined as episodes that terminated spontaneously within 7 days or lasted for less than 48 h before electrical or pharmacologic cardioversion. Persistent AF was defined as continuous AF that was sustained beyond 7 days. Longstanding persistent AF was defined as continuous AF with a greater than 12 months’ duration.
Permanent AF was defined as failure to restore or maintain a sinus rhythm by any means. Periprocedural anticoagulation period was defined as the duration from 5 days before ablation until the patients’ international normalized ratio (INR) reaching 2.0-3.0 after ablation. The pre- and post-ablation echocardiograms were compared for the presence of effusion or significant changes in hemodynamics that indicated pericardial tamponade.

The exclusion criteria were as the following: age < 18 years; life expectancy <1 year; advanced structural heart disease including moderate-to-severe valvular stenosis or insufficiency; congenital heart disease; myocardial infarction or coronary artery bypass graft surgery within the last 3 months; left atrial thrombus; left ventricular ejection fraction <45%; creatinine clearance <20 ml/min; chronic obstructive pulmonary disease treated; severe respiratory insufficiency; known bleeding diathesis or intolerance to anticoagulant treatments; and severe comorbidities. All patients provided written informed consent, and the study was approved by the Committee on Ethics and Research of Nanfang Hospital.

**Bridging therapy**

All patients were taking warfarin for at least 1 month prior to catheter ablation and received subcutaneous injection of either LMWH (enoxaparin, 1.0 mg/kg twice daily) or fondaparinux (2.5 ml once subcutaneous injection of either LMWH (enoxaparin, 1.0 mg/kg twice daily) or fondaparinux (2.5 ml once subcutaneous injection of either LMWH (enoxaparin, 1.0 mg/kg twice daily) as a bridging therapy for warfarin discontinuation 5 days before procedure. The type of bridging therapy was at the discretion of the treating physician and was not determined by a prespecified study protocol. After the ablation procedure, warfarin therapy was resumed. We utilized CHA2DS2-VASc (Congestive heart failure, Hypertension, Age 75 years, Diabetes, previous Stroke/ TIA, Vascular disease, Age 65-74 years, and Sex category) to estimate systemic embolism and HAS-BLED risk stratification scheme to determine the risk of major bleeding in patients with AF.

**Electrophysiological study**

Spiral pulmonary vein computed tomography angiography (CTA) and transesophageal echocardiography (TEE) were performed prior operation to exclude thrombus in the atrium, especially in the left atrial appendage. All antiarrhythmic drugs, with the exception of amiodarone, were discontinued 5 half-lives before the procedure. The electrophysiological study was performed in a fasting state under mild sedation using midazolam or fentanyl, and surface ECG leads filtered at 30 to 500 Hz were recorded.

**Catheter ablation**

Multielectrode catheters were introduced percutaneously through the femoral veins. Double transeptal access was obtained via two separate puncture sites in the interatrial septum. Transseptal catheterization was performed with biplane fluoroscopy. Intracardiac echocardiography was not routinely performed in our center. After transseptal access, a single bolus of 50 IU/kg heparin was administered with repeated doses of 1000 units every 30 min to achieve and maintain an activated clotting time (ACT) of >300 s during the ablation procedure, and the ACT was recorded during the procedure. Surface ECG and endocardial electrogroms were continuously monitored and recorded for off-line analysis (Bard Electrophysiology, Lowell, Massachusetts). The left atrium was mapped using the CARTO ( Biosense Webster Inc.) mapping system. We used a 3.5-mm irrigated-tip catheter (ThermoCool, Diamond Bar, California) guided by a circular Lasso mapping catheter to ablate the ostia and posterior antra of the pulmonary veins. The pulmonary veins (PVs) were then anatomically encircled and electrically isolated using radiofrequency applications with a power of 20-35 W. The endpoint of the procedure was electrical isolation of the PV antra.

A more extensive ablation approach extending to the entire left atrial posterior wall and to complex fractionated electrogroms (CEAE5) was warranted in nonparoxysmal AF patients. At the end of the procedure, patients with sustained AF despite a complete isolation of the PVs and the administration of successive linear lesions underwent direct current cardioversion (DCCV). As the final step in the procedure, all patients underwent electrophysiology study with and without isoproterenol drug challenge. After removal of all sheaths, warfarin was reinitiated within 4 to 6 h, and LMWH or fondaparinux at the doses in bridging therapy was continued after ablation till achieving the target INR of 2-3.

**Postablation management and follow-up**

All the patients were systematically followed for 3 months after the procedure by the treating physician. Blood coagulation function test, routine transthoracic echocardiograms, and 24-hour Holter monitoring were performed at each follow-up visit. Amiodarone and warfarin were administered for 3 months after the procedure. During the follow-up, documented thrombotic events were defined as ischemic stroke, transient ischemic attack, cardiac valvular or mural thrombus, deep venous thrombosis (DVT), and pulmonary embolism (PE). Transient ischemic attack or stroke was confirmed by CT or magnetic resonance imaging. Bleeding events were defined as bleeding at any site including intracranial and retroperitoneal sources, or bleeding requiring hospitalization or surgical intervention. The complications associated with long-term anticoagulation (including death and affected quality of life) were also documented.

**Statistical analysis**

The continuous variables were expressed as Mean±
SD and were compared using Student’s t test. The categorical variables were analyzed using Fisher exact and Pearson chi-square tests. All comparisons were performed two-sided, and a P value less than 0.05 was considered to indicate a statistically significant difference. Statistical data analyses were performed using SPSS 13.0 software.

### RESULTS

#### Baseline characteristics

A total of 465 patients (68% male; mean age, 52.3±15 years; range, 25-80 years) undergoing ablation for AF were enrolled in the study, including 265 in fondaparinux group and 200 in LMWH group. The baseline characteristics of the patients are shown in Tab.1. Both groups were male-dominated. The proportion of patients with AF was different in both groups (65% vs 68%, and 35% vs 32%, P<0.05). There were 159 hypertensive patients in fondaparinux group and 140 in LMWH group, indicating the co-morbidity of AF and hypertension. There were 5 prior stroke/TIA patients in fondaparinux group and 7 in LMWH group, indicating the co-morbidity of AF and prior stroke/TIA. The CHA2DS2-VASc and HAS-BLED scores did not differ significantly between the 2 groups (1.703±1.26 vs 1.806±1.30, and 1.75±0.82 vs 1.82±0.92, P>0.05).

#### Postablation thromboembolic events and bleeding

No all-cause deaths or anticoagulation-related deaths occurred during the periprocedural period. Tab.2 lists the incidences of thromboembolic events and bleeding in the periprocedural period. Totally, 3 anticoagulation-related complications were observed in fondaparinux group, as compared with 13 in LMWH group (P=0.002), but there was no difference in the thromboembolic rate between the two groups (P=0.111). Two bleeding events in Fondaparinux group and 8 in LMWH group were recorded, showing a significant difference between the two groups (P=0.039).

In fondaparinux group, 1 patient experienced possible pulmonary embolism due to shortness of breath at 12 h after the end of ablation and elevated plasma D-Dier. He refused to receive angiography study for a definite diagnosis, but the symptom was relieved after strengthened anticoagulation; we therefore considered this a thromboembolic event. The patient reported no significant discomforts during the follow-up.

In LMWH group, 2 patients had pericardial effusion and invasive puncture to require hematoma drainage. One patient experienced a transient ischemic attack and 3 had ischemic stroke confirmed by intracranial MRI scan. Severe cerebral hemorrhage diagnosed by CT scan occurred in a low-weight female patient aged 66 years, who had a history of high blood pressure, an abnormal liver function, INR instability (1.5-4.5), and a bleeding score of 4. Reversal of hemorrhagic state was achieved with administration of intravenous fresh frozen plasma and hematoma evacuation by craniotomy decompression. The hospital stay of the patient was extended to 20 days due to surgery for this complication.

During a mean follow-up of 3 months, the recurrent rate of AF was 21% in fondaparinux group compared to 34% in LMWH group (P>0.05). No other long-term thromboembolic and bleeding events were observed in
these two groups.

**DISCUSSION**

Catheter ablation for AF carries potential periprocedural risks including thrombus formation at the catheter tip, air embolization, and dislodge of a preexisting left atrial thrombus by catheter manipulation [10-12]. To reduce the risk of thromboembolic complications during catheter ablation, the ACCP guidelines for antithrombotic and thrombolytic therapy recommend the bridging therapy with subcutaneous administration of intravenous unfractionated heparin (UFH) or LMWH. To the best of our knowledge, this is the first study investigating the replacement of LMWH with fondaparinux as a bridging strategy for warfarin prior to left atrial catheter ablation procedures. The major finding of our study was that the thrombotic complications were not significantly different between LMWH and fondaparinux groups, but LMWH was associated with a greater incidence of bleeding complications after the procedure.

The atrial endothelium has natural anticoagulant properties, and injuries of the atrial endothelium during radiofrequency ablation triggers a hypercoagulable state and increases the risk of thrombus formation [14]. Studies in experimental models support the effectiveness of fondaparinux in preventing thrombus formation on mechanical heart valves [15-17]. Fondaparinux has proved to produce a comparable effect with enoxaparin in improving the patient survival and reducing bleeding complications in patients with non-ST-segment elevation acute coronary syndromes [17]. Currently large randomized clinical trials have not been available to examine the use of fondaparinux for anticoagulation during AF ablation. In the REGIMEN registry study, Spyropoulos et al. [18] reported the clinical outcomes with unfractionated heparin or LMWH as the bridging therapy in patients on long-term oral anticoagulants. The overall adverse events, including thromboembolism and bleeding, were similar in patients treated with LMWH and unfractionated heparin.

Although bridging therapy with LMWH is widely adopted, it is associated with a high incidence of bleeding complications. In the study by Cappato et al. [19] of 16,309 patients from 182 centers who received intravenous or subcutaneous heparin or LMWH for anticoagulation after discontinuation of warfarin before catheter ablation for AF, the highest rate of complications was 4.5% (741 patients), and the most frequent complications were cardiac tamponade (1.31% ), femoral pseudoaneurysm (0.93% ), and transient ischemic attack (0.71% ). Compared with previous studies, our patient cohort showed a higher incidence of severe hemorrhages and thromboembolic complications, especially in LMWH group. Previous bridging studies revealed an increase in major bleed rates of 0.9% to 6.7% with postoperative use of treatment-dose LMWH in patients undergoing high-bleeding risk procedures [20, 21]. Some study showed that UFH and LMWH may also cause heparin-induced thrombocytopenia (HIT) [22].

Fondaparinux, which is structurally similar to heparin and LMWH, selectively binds to antithrombin and causes rapid and predictable inhibition of factor Xa. With a minimal affinity for platelet factor 4, fondaparinux is not likely to induce HIT [23], which might explain the lowered risk of bleeding events associated with fondaparinux. This suggests the safety of fondaparinux in patients with potential HIT.

Like LMWH, fondaparinux does not have an antidote when severe bleeding complication occurs, though such complications were not commonly seen in our cohort. Only two of the patients receiving fondaparinux developed invasive puncture hematoma. In patients with a hemorrhagic tendency, careful observation and dose reduction are needed, especially in those with renal dysfunction and those who are critically ill with unstable hemodynamics.

**Conclusion**

Bridging therapy with fondaparinux, as compared with LMWH, does not increase in the risk of thromboembolic complications but slightly reduces the risk of bleeding during AF catheter ablation, suggesting its safety and efficacy for periprocedural anticoagulation management in patients undergoing radiofrequency ablation for AF.

**Limitation**

In this single-center study, we did not control the choice of fondaparinux or LMWH in a randomized fashion to avoid bias in the results. Also, moderate complication related to anticoagulation may be undetectable. In addition, as the symptoms and signs of bleeding complications are more apparent than thromboembolic ones, the actual rates of complications can be underestimated, especially in terms of the thromboembolic rate.

**REFERENCES**

摘 要: 目的: 比较心房颤动射频消融术桥接使用磺达肝癸钠与低分子肝素的临床效果。 方法: 2009年1月～2013年7月接受射频消融术的房颤患者进行分析。患者在术前停用华法林1天,之后注射磺达肝癸钠或低分子肝素的桥接治疗直到至消融后国际标准化比值为2.0～3.0。对两组患者术后抗凝相关并发症进行比较。 结果: 共有465名患者,68%为男性,平均年龄52±15(25～80)岁。两组术中抗凝相关并发症发生率比较,低分子肝素组为13例(P=0.002),而磺达肝癸钠组为8例(P=0.039)。随访观察3~6月均无出血死亡病例。 结论: 平房颤患者进行射频消融术桥接治疗时,磺达肝癸钠与低分子肝素相比,两组无统计学差异,但仍需进一步研究。