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Safety of The Direct Oral Anticoagulant Edoxaban for Atrial Fibrillation After Cardiac Surgery: Pilot Study

Akira Sezai, Shunji Osaka, Hiroko Yaoita, Munehito Arimoto, Hiroaki Hata, Masashi Tanaka

Department of Cardiovascular Surgery, Nihon University School of Medicine, Itabashi, Tokyo, Japan.

Abstract

Direct oral anticoagulants have recently been recommended for non-valvular atrial fibrillation, but have rarely been studied in the field of cardiac surgery. We prospectively investigated the safety of edoxaban, a novel oral anticoagulant, for use in cardiac surgery patients with postoperative atrial fibrillation (POAF), which is the most common complication of cardiac surgery and can lead to stroke.

The subjects were adult cardiac surgery patients with POAF who received oral edoxaban for 2 months in an open-label pilot study. The primary endpoint was cerebrovascular/bleeding events up to 2 months, while the secondary endpoints were hemoglobin, prothrombin time, and activated partial thromboplastin time.

There were no cerebrovascular or bleeding events during edoxaban treatment and the test drug was not discontinued by any patient. There was no macroscopic hematuria and hemoglobin did not decrease, being significantly higher than the baseline level after 2 months. The prothrombin time was significantly prolonged from 1 week to 2 months and the activated partial thromboplastin time was significantly prolonged from 1 day to 2 months. Echocardiography detected pericardial effusion in 1 patient, but hemoglobin did not decrease and the effusion improved with diuretic therapy.

In conclusion, despite the limited sample size of this pilot study, it was demonstrated that edoxaban does not induce bleeding in patients with POAF after cardiac surgery, suggesting that it is safe to perform a large-scale efficacy study of edoxaban as anticoagulant therapy for POAF.

Introduction

Direct oral anticoagulants (DOAC) have recently been recommended for patients with non-valvular atrial fibrillation by cardiovascular guidelines.[8,9] Large-scale studies have demonstrated comparable or better efficacy of DOAC for preventing stroke with significantly less intracranial bleeding compared to conventional warfarin therapy, indicating that these agents display favorable safety and efficacy.[4,6,7,10] However, DOAC have rarely been investigated in the cardiac surgery field.

Postoperative atrial fibrillation (POAF) is the most common complication of cardiac surgery and occurs in 16-85% of patients. Many studies of pharmacological treatment to prevent POAF or restore sinus rhythm have been conducted and we have also investigated this issue.[11,12,14,15] The most important consequence of POAF is stroke, which significantly affects the prognosis. At our hospital, a total of 761 patients underwent isolated coronary artery bypass grafting (CABG), among whom POAF occurred in 24% and stroke was observed in 1.4%. All of our patients who developed postoperative stroke had POAF. Hence, it is important to start anticoagulant therapy in the early phase of POAF.[13] At our hospital, anticoagulant therapy with heparin and warfarin is initiated as soon as possible after the onset of POAF, but 1.4% of patients still developed stroke. Therefore, a more effective anticoagulant therapy would be desirable.

Since bleeding is an issue after cardiac surgery, we conducted a prospective pilot study to investigate the safety of initiating DOAC therapy immediately after the onset of POAF.

Key Words:
Edoxaban, Novel Oral Anticoagulant, Postoperative Atrial Fibrillation, Direct Oral Anticoagulation.

Disclosures:
Akira Sezai has received lecture fees from Daiichi Sankyo Company. The other authors have no conflicts of interest associated with this study.

Corresponding Author:
Akira Sezai,
Department of Cardiovascular Surgery,
Nihon University School of Medicine,
30-1 Oyaguchi-kamimachi Itabashi-ku Tokyo, 173-8610, Japan.

Methods

Study Protocol

The subjects were adult patients who developed POAF following cardiac surgery (Table 1). POAF was defined as AF that occurred after surgery and did not improve for more than 12 hours despite pharmacotherapy.

Exclusion criteria were as follows:

1. Patients with artificial heart valve(s) or rheumatic mitral stenosis because NOAC are indicated for non-valvular atrial fibrillation.

Table 1: Patients characteristics

Number	15
Age (y.o)	72.7±7.6 (58~84)
Gender (male:female)	10:5
Body weight (kg)	
>60kg	6
≤60kg	9
Main disease	
Ischemic heart disease	5
Valve disease	3
Aortic disease	7
Surgical procedure	
Isolated CABG	5
MAP	2
MAP+TAP+Maze	1
Total arch replacement	4
Ascending aorta replacement	1
Total arch replacement+CABG	2
Risk factors	
Diabetes mellitus	1
Hypertension	12
Hyperlipidemia	6
Smoking	9
Obesity	1
Cerebrovascular disease	1
Chronic heart failure	6
Chronic kidney disease (CRCL<60mL/min)	9
CRCL (mL/min)	
50<CRCL	7
15≤CRCL≤50	8
$CHADS_2$	1.9±0.8 (1~3)
CHA_2DS_2-VAS	3.6±1.5 (1~6)

CABG: coronary artery bypass grafting, MAP: mitral valve annuloplasty, TAP: tricuspid valve annuloplasty, CRCL: Creatinine clearance

2. Blood loss from the surgical drain ≥10 mL/hour.
3. Unconscious patients.
4. Inability to take oral medication.
5. Infectious endocarditis.
6. Creatinine clearance (CRCL) <15 mL/min.
7. Hepatic disease accompanied by abnormal coagulation.
8. A history of bleeding events such as gastrointestinal bleeding.
9. Patients who were unsuitable for other reasons as judged by the attending physician.

Patients were assigned to oral treatment with edoxaban (Dai-chi Sankyo Co., Ltd., Tokyo, Japan) at a dose of 60 mg/day for a body weight > 60 kg or 30 mg/day for a body weight ≤60 kg. If the CRCL at baseline was ≤50 mL/min, the dose was also reduced to 30 mg/day. Treatment was continued for 2 months.

This pilot study to investigate efficacy was conducted in an open-label manner. This study was approved by the Institutional Review Board of Nihon University Itabashi Hospital, the details of the study were explained to the subjects, and informed consent was obtained from each patient. The study was registered with the University Hospital Medical Information Network (study ID: UMIN000021138).

Endpoints: The primary endpoints were cerebrovascular events (stroke, cerebral hemorrhage, etc.) and bleeding events (major: significant bleeding events, minor: clinically significant event albeit not major by Month 2 of the study.

The secondary endpoints were as follows: hemoglobin, prothrombin time (PT), and activated partial thromboplastin time (APTT) at baseline, Day 1, Week 1, and Months 1 and 2; urinary occult blood at baseline, Week 2, and Months 1 and 2; and the presence or absence of pericardial effusion on echocardiography in Week 1. Criteria for discontinuation of treatment included the onset of bleeding events and allergy to the study medication.

Statistical Analysis

Results were expressed as the mean ± standard error. For time-course analysis, repeated measures analysis of variance (ANOVA) was used with Fisher's protected least squares difference test. In all analyses, $p<0.05$ was considered statistically significant.

Results

None of the patients died after surgery or experienced complications. POAF was detected at an average of 4.8±2.8 days (2-10 days) postoperatively. Sinus rhythm was restored in all patients by discharge.

Edoxaban was administered at a dose of 30 mg and 60 mg to 13 patients and 2 patients, respectively (Table 2). Treatment was initiated in the intensive care unit for 6 patients and on the ward for 9 patients. The surgical drain was still in place when treatment was initiated in 11 patients, but there was no increase of bleeding from the drain and it was removed on the next day or up to 2 days later. As antiplatelet therapy, aspirin was used in 9 patients and aspirin + prasugrel was given to 1 patient.

Primary Endpoints: None of the patients experienced cerebrovascular events or major or minor bleeding events by Month 2. In addition, none of the patients discontinued treatment with edoxaban.

Secondary Endpoints: Hemoglobin (Figure 1): Baseline hemoglobin was 11.4±1.4 g/dL. It did not decline after initiation of treatment and instead was significantly higher by Month 2 compared with baseline ($p=0.03$).

PT and APTT (Figure 2): PT was normal at baseline (12.7±0.8 seconds) and remained within the normal range after starting treatment. Although there was no significant difference of PT between Day 1 and baseline ($p=0.805$), it was significantly prolonged during the period from Week1 to Month 2 (Week 1: $p=0.007$, Month 1: $p=0.016$, Month 2: $p=0.011$). APTT was normal at baseline (30.4±2.4 seconds), but it was significantly prolonged from Day1 to Month 2 versus baseline (Day 1: $p=0.025$, Week 1: $p=0.001$, 1M: $p=0.012$, Month 2: $p=0.021$).

Urinary occult blood: At baseline, occult blood was 2+ in 1 patient and in 1+ in 3 patients. After the start of treatment, occult blood became negative in those patients. Among the 11 patients who had negative occult blood at baseline, 2 patients became 2+ after starting treatment. However, there was no decrease of hemoglobin and macroscopic hematuria was not observed, so treatment could be continued.

Table 2: Dose of edoxaban and the number of patients

Number	Body weight>60kg	Body weight≤60kg
CRCL>50 mL/min	2 (60mg)	5 (30mg)
15 mL/min ≤CRCL≤50 mL/min	4 (30mg)	4 (30mg)

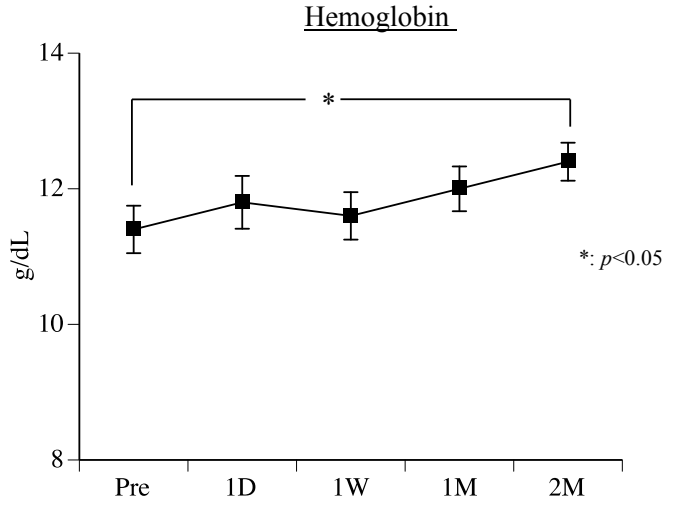
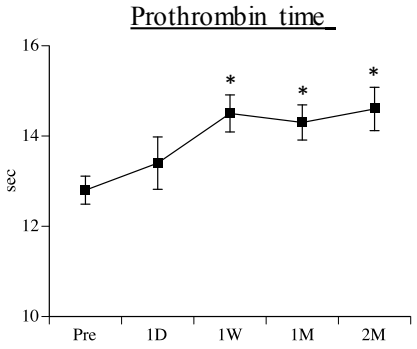


Figure 1: Change of hemoglobin

Pericardial effusion: A pericardial effusion was detected by echocardiography in 1 patient. However, it was only 8 to 11 mm and cardiac function was not affected. Moreover, there was no decrease of hemoglobin and it was considered that the possibility of bleeding was low. Treatment with a diuretic was performed and improvement was observed in Month 2.

Discussion

This pilot study demonstrated that anticoagulant therapy with edoxaban for POAF following cardiac surgery was not associated with bleeding. The most important consideration when investigating anticoagulant therapy is safety, and these findings suggested that an efficacy study of DOAC therapy after cardiac surgery could be safely initiated. It has been reported that dabigatran and rivaroxaban prolong APTT and PT, respectively, while edoxaban prolongs both



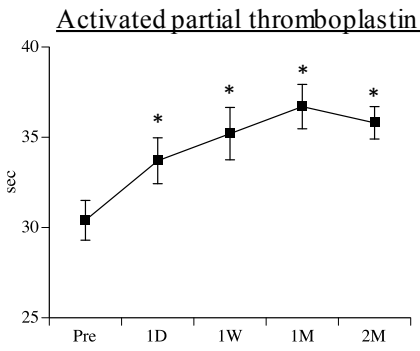


Figure 2: Changes of the prothrombin time (PT) and the activated partial thromboplastin time (APTT)

parameters. These parameters are considered to be related to the blood drug concentration and may be employed as efficacy markers. However, use of different reagents for measurement may result in variation of PT and APTT, and there are also no clear-cut criteria for clinically significant elevation of each parameter.[1] In this study, PT and APTT were prolonged during treatment with edoxaban, but excessive prolongation was not observed in any of the subjects even though they were treated during the acute postoperative period when the coagulation-fibrinolytic system is altered by the effects of surgery.

Anticoagulant therapy based on warfarin is recommended for POAF following cardiac surgery, irrespective of whether heparin bridging is performed.[5] However, it takes several days before warfarin reaches the therapeutic range. According to the results of a meta-analysis and several large-scale studies, heparin bridging is associated with a 3- to 5-fold higher incidence of bleeding compared to non-use of heparin bridging.[16,17] While anticoagulant therapy with DOAC has recently been recommended for the management of non-valvular atrial fibrillation,[8,9] there is little information available about the use of DOAC following cardiac surgery. The 2014 ESC/EACTS Guideline states that 4 weeks of treatment with heparin or DOAC is recommended for POAF that persists for 48 hours or longer, although there is no clinical evidence.[5] However, the 2014 Guideline uses the 2012 Guideline as a reference, but there is no description of DOAC therapy for POAF following heart surgery in the earlier guideline.[3] The only clinical study that we could find about DOAC therapy for POAF following cardiac surgery was a retrospective investigation performed by Anderson et al. in patients who developed POAF following isolated CABG. Warfarin (with low molecular weight heparin bridging in 27 patients) was used to treat 45 patients while DOAC (apixaban in 21 patients, dabigatran in 1 patient, and rivaroxaban in 5 patients) was used for 27 patients. There was no stroke in both groups and in hospital bleeding was not different between the two groups. However, there was no delayed major bleeding after discharge in the DOAC group, while it affected 2 patients in the warfarin group. Also, the time to reach the therapeutic range was significantly longer in the warfarin group. While drug costs were significantly higher in the DOAC group, the total anticoagulation cost (including INR tests for 30 days) was significantly higher in the warfarin group. Anderson et al. concluded that DOAC treatment provided more rapid anticoagulation and was cost-effective.[2]

Concerns with warfarin therapy include:

1. A longer time until therapeutic anticoagulation.
2. An increased incidence of bleeding if used concomitantly with heparin.
3. The effect of various foods.

Anticoagulant therapy using DOAC can address these issues related to warfarin. The present study also suggested that the risk of bleeding was not increased even when edoxaban was used in the early postoperative period.

In the future, a larger study will performed to assess the efficacy of edoxaban and identify any potential issues.

Limitations

This was a pilot study and the number of patients enrolled was too small. In addition, comparison versus warfarin was not performed. However, a future large-scale study is planned to address these limitations. In this study, CRCL >95 mL/min was not included into

the exclusion criteria. Evidence has not been obtained for Edoxaban in nonvalvular atrial fibrillation patients with CRCL >95 mL/min. Although patients at CRCL >95 mL/min were not enrolled into this study, we would like to decide if we continue to exclude CRCL >95 mL/min or include it. The duration of treatment with edoxaban was 2 months in this study. All patients achieved sinus rhythm at discharge. We will continue to study if 2 months treatment period was appropriate or 1 month is sufficient or not.

Conclusions

This pilot study demonstrated that use of edoxaban for anticoagulant therapy in patients with POAF after cardiac surgery was not likely to be associated with postoperative bleeding complications. Because the important safety concern for a large-scale study has been addressed, we are now planning an efficacy study of DOAC therapy for patients with POAF after cardiac surgery.

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