Anticoagulation Management in the Perioperative Phase of Implantable Cardioverter Defibrillator Implantation

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Background: According to the current guidelines, substitution of warfarin with heparin is recommended as perioperative management in patients with high risk of thromboembolism. Optimal management of oral anticoagulation in patients undergoing implantable cardioverter defibrillator (ICD) implantation, however, remains controversial.

Methods and Results: Bleeding complications among 273 consecutive patients undergoing initial ICD implantation were retrospectively analyzed. Patients were grouped according to medication at the time of device implantation: neither antiplatelet nor anticoagulation (N group, n=121); antiplatelet only (AP group, n=59); warfarin (W group, n=59); and heparin bridging (H group, n=34). The rate of the major bleeding complications, defined as hematoma requiring reoperation, cardiac tamponade, and pericardial effusion requiring additional hospital stay, was 1.7% in the N group, 0% in the AP group, 5.1% in the W group, and 17.6% in the H group (P<0.001, N group vs. H group). After multivariate adjustment, heparin bridging was a significant predictor of major bleeding complications (odds ratio, 7.44; 95% confidence interval: 2.06–26.89; P=0.0022). The international normalized ratio of 3 patients in the W group with major bleeding complications was 1.98±0.10, and was significantly higher than in patients without them (1.31±0.05, n=26, P<0.001).

Conclusions: Heparin bridging increased the risk of bleeding complications at the time of ICD implantation. (Circ J 2013; 77: 2003–2008)

Key Words: Anticoagulation; Bleeding complication; Heparin bridging; Implantable cardioverter defibrillator implantation

Prevention of sudden cardiac death in patients at risk of lethal ventricular tachyarrhythmias by implantable cardioverter defibrillator (ICD) has been established.1–3 In contrast, there are serious problems with ICD including perioperative complications, inappropriate discharge, infection and lead failure.4–8

Bleeding complications are a major concern in patients undergoing surgical interventions who are receiving antithrombotic agents. According to the guidelines of the Japanese Circulation Society (2009) and the American College of Chest Physicians (2008), substitution of warfarin, an oral anticoagulant agent, with heparin (ie, heparin bridging) has been recommended in such patients at high risk of thromboembolic events.9,10 Heparin, however, in combination with anti-thrombin III, is known to exert not only anticoagulant but also antiplatelet actions via anti-thrombin effect.11 The antiplatelet action of heparin may attenuate primary hemostasis due to platelet aggregation, which is essential for secondary hemostasis, thereby facilitating rebleeding. Therefore, heparin bridging may be associated with an increased risk of hematoma and other bleeding complications.12

Previous studies have confirmed these problems associated with bridging therapy. Michaud et al reported that patients receiving heparin after cardiac device implantation had a 5- or 10-fold greater risk of hematoma formation compared with those treated with warfarin alone or no anticoagulation, respectively.13 Recently, Tompkins et al and Ahmed et al showed that perioperative heparin significantly increased the risk of bleeding complications at the time of pacemaker or ICD implantation.14,15 These analyses, however, were performed in patients from Western countries including the USA, clearly different from Japanese patients. Therefore, the influence of antiplatelet or anticoagulation therapy on the risk of bleeding complications remains to be assessed in unselected Japanese patients.

The aim of the present study was to clarify the incidence of bleeding and thromboembolic complications and to assess the influence of heparin bridging on these complications at the
time of ICD implantation in Japanese patients.

**Methods**

**Subjects**

We performed a retrospective review of bleeding and thromboembolic complications in 273 consecutive patients who underwent initial ICD implantation at Hokkaido University Hospital from March 1990 to September 2010. For each patient, baseline data included (1) demography; (2) underlying heart disease; (3) clinical status; (4) indication for ICD; (5) type of ICD; (6) bleeding and thromboembolic complications during the perioperative period; (7) echocardiographic findings; and (8) anti-thrombotic treatment.

In order to clarify the effect of anti-thrombotic agents on the incidence of bleeding and thromboembolic complications, patients were classified into 4 groups according to medication at the time of device implantation: no antiplatelet or anticoagulation (N group); antiplatelet only (AP group); warfarin (W group); and heparin bridging (H group; Table 1).

In patients with heparin bridging (H group), warfarin was discontinued 3–5 days prior to implantation, and i.v. heparin (500–1,000 unit/h) was started 12 h after withholding warfarin. The dose of heparin was adjusted for activated partial thromboplastin time to reach around 60 s. I.v. heparin was withheld 4–6 h prior to the procedure, and was restarted usually 12 h after implantation. Patients in W group discontinued warfarin typically 1–2 days prior to the procedure, and restarted the day of or the next day after the implantation. When warfarin treatment or heparin bridging was performed, the patient was categorized as W group or H group even if antiplatelet drugs were ongoing. Based on the prolonged efficacy of antiplatelet drugs, their use within 5 days of the operation was considered as on-drug antiplatelet treatment. Therefore, in the AP group, the discontinuation period of aspirin and thienopyridine (either clopidogrel or ticlopidine) before the procedure was variable (ie, 0–4 days), and it was determined at the discretion of the implanting physician. The study was approved by the Ethics Committee of Hokkaido University Hospital.

**Outcome**

The status of all patients was available at least 1 month after ICD implantation. No patients died during the hospital stay for the ICD operation. The primary outcome for this study was major bleeding or thromboembolic events that occurred during or within 1 month of the implantation. Major bleeding included hematoma requiring reoperation, cardiac tamponade, pericardial effusion requiring additional hospital stay, or critical symptomatic bleeding such as intracranial hemorrhage. The major thromboembolic events were stroke and systemic embolism including acute vascular occlusion of an extremity or organs.

**Statistical Analysis**

All data are expressed as mean±SE. Simple between-group analysis were conducted using Student’s t-test. Intergroup comparisons for continuous variables were performed with the adjusted t-test within ANOVA (Bonferroni method). Categorical variables were compared using chi-square test. Logistic regression analysis were performed to estimate the predictors of major bleeding complications. Differences with P<0.05 were considered significant. Statview version 5.0 for Windows (SAS Institute, Cary, NC, USA) was used for all statistical analysis.

**Results**

**Patient Characteristics**

The present study included 273 patients with a mean age of 58±1 years, and 78% were men (Table 1). The etiology of structural heart disease was ischemic in 28% and non-ischemic in 54%. No structural heart disease were identified in 18% of patients, including primary electrical disease or coronary spas-
Heparin Bridging and ICD Implantation

The proportion of these indications did not differ between patients with or without major bleeding complications (Table 2).

Some patients had been treated with both anticoagulation and antiplatelet drugs. Among 273 patients, perioperative treatment with heparin bridging, warfarin, aspirin, and thienopyridine (either clopidogrel or ticlopidine) was performed in 34 (12%), 59 (22%), 96 (35%) and 22 (8%), respectively (Table 3).

Significant association with major bleeding complications was observed only in patients having heparin bridging treatment (Table 3).

Among 59 patients receiving warfarin (without heparin bridging) (W group), major bleeding occurred in 3 patients (5.1%): 1 hematoma, 1 cardiac tamponade, and 1 pericardial effusion. The INR on the day of or 1 day after ICD implantation was available in 29 patients (49% of W group) including all 3 patients with major bleeding complications. The INR of these 3 patients was 2.11, 2.05, and 2.03.

The rate of major bleeding complications was 4.0% (Figure 1). These consisted of hematoma requiring surgical evacuation in 6 patients (2.2%), cardiac tamponade in 3 patients (1.1%), and pericardial effusion in 2 patients (0.7%). The rate of bleeding complications was significantly higher in the H group than in the N group. In the H group, the bleeding complications included 5 cases of hematoma and one of cardiac tamponade (17.6%).

There were 2 thromboembolic complications (0.7%): 1 stroke in the N group, and 1 acute arterial occlusion of a lower extremity in the H group. These event rates did not differ between groups (Figure 1).

Ninety-three (34.1%) of 273 patients had been treated with oral anticoagulation (ie, warfarin), and they were classified into either the W group (n=59) or H group (n=34). The indications of oral anticoagulation included atrial fibrillation (AF) 17.18 in 67 patients, left ventricular thrombus or dysfunction in 17 patients, and mechanical prosthetic valve in 6 patients (Table 2).

Indication for ICD was primary prevention in 23% and secondary prevention in 77%.

Patients with any anti-thrombotic treatment (AP, W, and H groups) were significantly older and had lower LVEF. They had higher prevalence of structural heart disease, more severe heart failure symptoms (ie, high New York Heart Association [NYHA] class), and were more likely to have biventricular ICD than those without any anti-thrombotic treatment (N group; Table 1).
The optimal INR ranged from 2.0 to 3.0, and INR <2.0 steeply increased the risk of stroke in patients with AF. In contrast, low-intensity warfarin (INR 1.5–2.1) was safe and effective for secondary prevention of stroke in Japanese patients with non-valvular AF, especially in older patients. In combination with the present data, low-intensity warfarin during the perioperative period would be sufficient to reduce the likelihood of major hemorrhagic or ischemic events in Japanese patients.

Heparin bridging was originally recommended as periprocedural treatment especially in patients with acute or recurrent venous thromboembolism. The annual recurrence rate of these events is very high, reaching 15–40%, without adequate anticoagulation. In addition, surgery can induce hemostatic changes that may increase the risk of venous thromboembolism. Therefore, i.v. heparin therapy was proposed as perioperative anticoagulation in patients with high risk of venous thromboembolism, even though 2 days of such management was estimated to increase the absolute rate of major postoperative bleeding by approximately 3%.

In contrast, there is no clear evidence that surgery increases the risk of arterial embolism in patients with AF or mechanical heart valves. Moreover, the incidence of pulmonary thromboembolism and deep vein thrombosis (ie, major venous embolisms) in Japan was estimated to be one-eighth and one-fourth, respectively, that in the USA and Europe. A different periprocedural strategy might be necessary, because the indication for anticoagulation in most of the patients undergoing ICD implantation in the present study was the presence of AF and left ventricular thrombus or dysfunction (Table 2).
short-term (<5 days) interruption of warfarin therapy without heparin bridging was associated with a low risk (0.7%) of post-procedure thromboembolism within 30 days. In addition, the ACC/AHA/ESC guidelines state that, in patients with AF but no mechanical prosthetic heart valves, it is reasonable to interrupt anticoagulation for up to 1 week without substituting heparin, for surgical or diagnostic procedures that carry a risk of bleeding. Therefore, we propose the simple protocol of 1 or 2 days interruption of warfarin before device implanta-
tion and its resumption on the day of operation in patients with INR in the effective therapeutic range (2.0–3.0), thereby presumably reaching INR of around 1.3–1.7 during the perioperative period.

Several studies have reported that perioperative use of hepa-
rin at implantation of pacemaker or ICD was associated with pocket hematoma formation in 5.7–23% of patients. In contrast to the high rate of pocket hematoma in heparin bridging, continuation of warfarin (without heparin bridging) with therapeutic INR appeared to be safe and cost-effective as perioperative management in patients receiving oral anticoagu-
lation therapy in some retrospective analyses. The present study, which is the first report in Japanese patients, is in agreement with those studies, and emphasizes the increased risk of bleeding complications with heparin bridging after ICD implantation.

Two prospective randomized trials assessed the management strategy of oral anticoagulation in patients undergoing pacemaker or ICD implantation. In contrast to the retrospective studies, a prospective study showed that development of pocket hematoma after implanting/replacing a pacemaker or ICD was observed in 7.8% of patients treated with heparin bridging, and in 8.0% of those with oral anticoagu-
lation who maintained an INR of 2.0±0.3. In another prospective study, there was a trend toward reduced complications in patients with warfarin continuation, but the results were not statistically significant, possibly due to the small number of patients (n=7) randomized to heparin bridging. A large randomized controlled trial to compare the 2 strategies (heparin bridging vs. continuation of oral anticoagulation), in patients undergoing pacemaker or ICD implantation is now under way in North America.

In the present study, discontinuation of warfarin was made typically 1–2 days prior to operation, thereby maintaining some anticoagulant effects (INR 1.4±0.3, n=29; which was lower than that in the prospective randomized trial by Tolosana et al., INR 2.0±0.3, n=50). In the Tolosana et al study, the rate of bleeding complication was not different between the 2 perioperative strategies, maintenance of oral anticoagulation and heparin bridging. The lower incidence of bleeding complications without increase of thromboembolic events in the present W group compared to the H group (Figure 1) may have resulted from short-term interruption of warfarin.

There are several limitations to be considered in this study. First, hematomas without surgical evacuation were not included as bleeding complications. We thus could not evaluate the precise number of all pocket hematomas that might be consid-
ered as bleeding complications. Second, perioperative man-
agement of anticoagulation was dependent on the decision by each doctor. Moreover, as was evident in Figure 2, INR on or 1 day after ICD implantation in the W group was variable and less than optimal (ie, 2.0–3.0) in most patients. This is because there were no predetermined protocols of continuation of war-
farin (without heparin bridging). Third, due to the definition of ongoing antiplatelet treatment (within 5 days of operation), heterogeneous patients in terms of antiplatelet potency may have been included in the AP group. A recent study reported that clopidogrel significantly increased the risk of pocket he-
matoma at the time of pacemaker or ICD implantation, and that its discontinuation >4 days before device implantation prevented development of hematoma. The present study, how-
ever, highlights the perioperative management of anticoagu-
lation, which seems to have more impact on major bleeding complications compared to antiplatelet therapy in patients un-
dergoing ICD implantation (Table 3).

Conclusion

Heparin bridging increased the risk of bleeding complications in patients undergoing initial ICD implantation.

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Heparin Bridging and ICD Implantation

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