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Antithrombotic or Anti-Platelet Agents in Patients Undergoing Permanent Pacemaker Implantation

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Background and Objectives: The growing implantations of electrophysiological devices in the context of increasing rates of chronic antithrombotic therapy in cardiovascular disease patients underscore the importance of an effective periprocedural prophylactic strategy for prevention of bleeding complications. We assessed the risk of significant bleeding complications in patients receiving anti-platelet agents or anticoagulants at the time of permanent pacemaker (PPM) implantation.

Subjects and Methods: We reviewed bleeding complications in patients undergoing PPM implantation. The use of aspirin or clopidogrel was defined as having taking drugs within 5 days of the procedure and warfarin was changed to heparin before the procedure. A significant bleeding complication was defined as a bleeding incident requiring pocket exploration or blood transfusion.

Results: Permanent pacemaker implantations were performed in 164 men and 96 women. The mean patient age was 73±11 years old. Among the 260 patients, 14 patients took warfarin (in all of them, warfarin was changed to heparin at least 3 days before procedure), 54 patients took aspirin, 4 patients took clopidogrel, and 25 patients took both. Significant bleeding complications occurred in 8 patients (3.1%), all of them were patients with heparin bridging ($p<0.0001$). Heparin bridging markedly increased the length of required hospital stay when compare with other groups and the 4 patients (1.5%) that underwent the pocket revision for treatment of hematoma.

Conclusion: This study suggests that hematoma formation after PPM implantation was rare, even among those who had taken the anti-platelet agents. The significant bleeding complications frequently occurred in patients with heparin bridging therapy. Therefore, heparin bridging therapy was deemed as high risk for significant bleeding complication in PPM implantation. **(Korean Circ J 2012;42:538-542)**

KEY WORDS: Aspirin; Clopidogrel; Warfarin; Hematoma.

Introduction

More than 50 years after the first permanent pacemaker (PPM) implantation, we witness the continuous development and growing clinical application of implantable devices in a wide range of heart rhythm disorders. Apart from the conventional use of PPMs for management of bradycardia, more sophisticated devices are used increasingly for cardiac re-synchronization therapy in heart failure, while the implantable cardioverter-defibrillator (ICD) has become established as the most effective therapy against malignant arrhythmia and sudden cardiac death.[1] Electrophysiological device (EPD) implantation requires minor surgical procedures, but needs special consideration. The need of venous access for lead manipulation and placement is the main characteristic distinguishing these procedures from other 'minor' surgical operations. The new indications for EPD in association with the standard PPM implantation have led to a significant increase of implantation cases in the ultrasonography and around the world.[2-4] The majority of patients referred for EPD implantation are taking some form of anti-platelet agent or oral anticoagulant (OAC). Common indications for warfarin therapy include atrial fibrillation (AF), mechanical prosthetic valves, cerebrovascular disease, and deep venous thrombosis (DVT) or pulmonary thromboembolism. Patients are often taking anti-platelet agents, such as aspirin and/or clopidogrel for primary or secondary prevention of co-

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ronary artery disease, particularly after percutaneous coronary interventions (PCIs). The most common hemorrhagic complication after EPD implantation is pocket hematoma. The overall incidence of pocket hematoma has been published in a series of PPM or ICD implantation that may reach and exceed the level of 5%.[5] Despite differences in the definition, 'clinically significant pocket hematoma' has been associated with local pain and patient discomfort, prolonged hospital stay, and increased follow-up visits, and in some cases with a need of reoperation to perform a surgical evacuation and/or pocket revision; in some of these cases, a blood transfusion may be required. Although pocket hematoma has been suggested as a risk factor for EPD-related infections, current data challenge this association.[5][6] Apart from the pocket hematoma, intra-operative hemorrhage is potentially relevant to prolonged procedural time and increased infection risk. We reviewed data from our institution to look at the rate of bleeding complications in patients having received PPM implantation with continuous antithrombotic agents, such as aspirin, clopidogrel, both, or heparin bridging instead of warfarin, at the time of device implantation. One common practice in patients with warfarin use is to temporarily discontinue the medication for 3 to 4 days in order to achieve a target international normalized ratio (INR) of 1.5. "Heparin bridging" is then instituted in patients deemed at high risk for thromboembolic events.[7] The purpose of this study was to investigate the influence of anti-platelet agents or OAC on the risk of significant bleeding complications after PPM implantation. We hypothesized that dual anti-platelet therapy and heparin bridging increase the risk of significant bleeding complications after PPM implantation.

Subjects and Methods

We reviewed data from PPM implantation performed at Gangneung Asan hospital using a charts review. Exclusion criteria included "known coagulation or bleeding disorders", "thrombocytopenia (defined as platelet count, 50000/mm^3)". This retrospective study was approved by Human Ethics Committee of our hospital. We included elective presentations for PPM implantation in our hospital. Patients were divided into 4 groups according to medications taken at the time of device implantation. Hospital records, including administration records were reviewed to determine bleeding complication and medications taken before and after device implantation. Medical records from the index hospitalization and clinic notes within 6 weeks of the procedure were reviewed for documentation of procedure-related complications. A significant bleeding complication was defined as the need for pocket exploration due to increasing size despite of compression dressing or a blood transfusion of more than 2 pints because of a decreased hemoglobin >2 g/dL after a procedure or a change in vital signs.

Devices implant procedures

The PPM implantation or exchanges of generator was performed according to the standard technique described in the literature. In all new implants, access was achieved with a first rib approach under fluoroscopic guidance to the extra-thoracic portion of the subclavian vein. In patients using wafarin, our institutional protocol is to hold the medication for 3 to 4 days in order to achieve an INR of 1.5. Heparin bridging is then instituted in patients deemed at high risk for thromboembolic events. Intravenous heparin infusion was stopped 8 hours before implantation and restarted 6 hours after the procedure. However, we did continue the use of aspirin, clopidogrel, or dual anti-platelet agents (DAPT) before the implantation.

Statistical analysis

Data were summarized as frequencies and percentages of categorical variables. Normally distributed continuous variables were presented as the mean and standard deviation. Differences in proportions were analyzed using the chi-square or Fisher's exact test as appropriate. Proportional variables were assessed using chi-square statistics and continuous variables with 1-way analysis of variance, expressed as mean±SD. A p of 0.05 was considered statistically significant. Logistic regression analysis was used to estimate the magnitude of association (i.e., odds ratios) between the use of anticoagulation or anti-platelet agents and the risk of developing the primary composite end point.

Results

A total of 260 patients were identified and included in the present analysis. The patients were composed of 164 men and the average age of those was 73±11 years old. We divided 260 patients into 4 groups according to medications taken before the procedure; 14 patients took warfarin (for all of these patients, the medication was changed to heparin at least 3 to 4 days before procedure; 2 patients with dual valve replacements, 2 patients with AF and stroke, 1 patent with mitral valve replacement, 1 patient with DVT, and 8 patients with AF), 54 patients were taking aspirin, 4 patients were taking clopidogrel, and 25 patients were taking DAPT (Fig. 1). Table 1 outlines the baseline characteristics for the entire cohort. Significant bleeding complications occurred in 8 patients (3.1%), all of them were receiving heparin bridging during procedure (p<0.0001) and all patients with significant bleeding complication had normal range of INR before procedure. There was no significant difference of baseline characteristics between patients with and without complications. But none of them had any infection sign. Most of them

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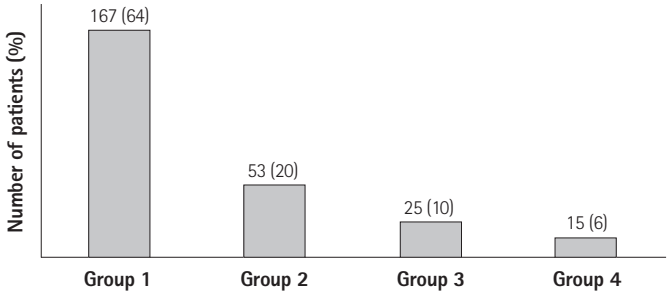

Fig. 1. Distribution of patients between groups. Group 1: none, Group 2: aspirin or clopidogrel, Group 3: dual antiplatelet agents, Group 4: temporary interruption of warfarin with switching to unfractionated heparin in peri-procedural period.

Table 1. Baseline characteristics

Variable	Group 1	Group 2	Group 3	Group 4	p
Male (%)	54 (32.3)	25 (47.2)	12 (48.8)	5 (33.3)	0.150
Type (%)					0.193
AAI	2 (1.2)	1 (1.9)	0 (0.0)	0 (0.0)	
AAIR	4 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	
DDD	101 (60.5)	22 (41.5)	16 (64.0)	9 (60.05)	
DDDR	14 (8.4)	5 (9.4)	1 (4.0)	0 (0.0)	
VDD	27 (16.2)	9 (17.0)	4 (16.0)	1 (6.7)	
VVI	19 (11.4)	16 (30.2)	4 (16.0)	5 (33.3)	
DM (%)	31 (18.6)	8 (15.1)	9 (36.0)	0 (0.0)	0.031
HF (%)	6 (3.6)	5 (6.4)	1 (4.0)	3 (20.0)	0.037
HTN (%)	121 (72.5)	40 (75.5)	22 (88.0)	7 (46.7)	0.040
CRF (%)	3 (1.8)	1 (1.9)	1 (4.0)	1 (6.7)	0.611
VHD (%)	0 (0.0)	0 (0.0)	0 (0.0)	5 (33.3)	0.001

Group 1 (none), Group 2 (Aspirin or Clopidogrel) Group3 (dual anti-platelet agents), Group 4 (heparin bridging). DM: diabetus meellitus, HF: heart failure, CRF: chronic renal failure, VHD: valvular heart disease

had use of intravenous heparin for preventing embolic strokes without abnormally prolonged activated partial thromboplastin time. Among them, three patients had the mechanical prosthetic cardiac valves (two patients with double valve replacement and one with mitral valve replacement) and one patient had the AF with history of stroke. Another patient had a DVT. Four patients (1.5%) underwent the pocket revision to treat their hematoma and others had been taken the dressing with compression and change of medications. Group 4 patients had markedly increased hospital stay when compared with other groups (10.36±0.41 days vs. 3.53±2.28 days; p=0.004). There were no significant differences in hospital stay between patients taking aspirin, clopidogrel, or DAPT and without any drugs (Fig. 2). In multivariate analysis, the heparin bridging was independent predictor of hospital stay (Table 2).

Discussion

Discontinuation of antithrombotic therapy before the implantation of EPD devices may increase the thromboembolic risk. The assessment of this risk in every particular patient usually guides the therapeutic strategy. For example, conditions such as the presence of a prosthetic aortic valve, or AF with a low thromboembolic risk score are considered low-risk procedures and therefore cessation of anticoagulation in the perioperative period is not a risky strategy. On the other hand, conditions, such as AF with high thromboembolic risk score, mechanical mitral, tricuspid, or pulmonic valves, recent PCI associated with stent implantation, or recent DVT with or without pulmonary embolism are considered high-risk. Contemporary experts opinion regarding non-cardiac surgery patients with high thromboembolic risk suggests bridging with heparin for those on chronic anticoagulation, and continuation of DAPT therapy if someone had a bare metal stent implanted within the past 6 weeks

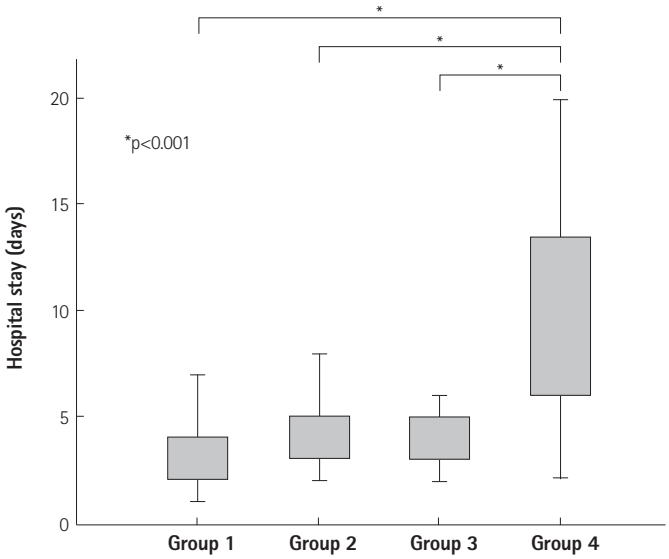

Fig. 2. Hospital stay between groups.

Table 2. Independent factors for hospital delay by regression model

Variables	Odds	CI (95%)	p
Female	0.327	-0.296 - 0.950	0.302
Age	0.008	-0.021 - 0.038	0.569
DM	0.177	-0.604 - 0.958	0.656
Hypertension	-0.830	-1.553 - -0.107	0.025
Heart failure	2.684	1.358 - 4.010	<0.001
CRF	2.960	0.984 - 4.936	0.003
Valvular heart disease	8.113	5.710 - 10.516	<0.001
Atrial fibrillation	0.970	0.244 - 1.696	0.009
Pacemarker type	-0.375	-1.520 - 0.771	0.520
Aspirin use	-0.455	-1.254 - 0.343	0.262
Clopidogrel use	-0.164	-2.551 - 2.222	0.892
Dual antiplatelet use	0.357	-2.323 - 3.038	0.793
Heparin use	2.964	1.977 - 3.950	<0.001

CI: confidence interval, DM: diabetes mellitus, CRF: chronic renal failure

or a drug eluting stent implanted within the previous 12 months.[8)9)] However, there are data suggesting that the actual risk of short-term interruption of anticoagulation is very low, even in high thromboembolic risk patients.[10)]

We reported the relationship between hematoma formation and heparin bridging, particularly with the use of bridging therapy with intravenous heparin at therapeutic dosages. Marquie et al.[11)] suggested that patients receiving heparin after pacemaker implantation were at high risk for severe adverse effects. This increased morbidity and directly caused by the use of heparin. Our study was similar with previous studies in that heparin bridging increased the bleeding complications. Our study did not consistent with it because previous study included the patients with ICD implantation and ICD was markedly bigger than PPM. In case of Medtronic company, the dimension {height×width×thickness (mm)} of the ICD is 64×51×15 mm and that of PPM is 44.7×47.9×7.5 mm. Goldstein et al.[12)] was among the first to report their implanting devices in 37 patients continued on warfarin. They found no difference in wound-related or wound-unrelated complications between patients receiving warfarin and patients not receiving anticoagulation medications. They assessed the risk of major bleeding complications in 1025 patients referred for pacemaker or ICD implantation, 470 of whom were continued on warfarin therapy (mean INR 2.5, range 1.5 to 7.5). They found similar complication rates between patients continued on warfarin therapy and patients with a normal INR while warfarin was held. We have to acknowledge that the majority of studies are observational, while there are small numbers of randomized clinical trials but with a limited study population. Of note, current data challenge the practice of heparin (unfractionated or low-molecular weight) bridging in high risk patients who are on chronic anticoagulation. Most of the studies have demonstrated that bridging with heparin is associated with an increased risk of bleeding complications compared with warfarin continuation.[13)14)] Discontinuation of the OAC therapy may cause a hyper-coagulation state or a thrombotic rebound phenomenon[15)] although, as mentioned before, short-term interruption does not seem to cause clinically significant thromboembolic events. This assumption is supported by the very low incidence of thromboembolic events in the studies regarding EPD implantation.

Another important finding is that DAPT therapy does not significantly increase the bleeding risk after PPM implantation. Regarding DAPT therapy the reported bleeding risk varies between 0.7 and 24%.[16)17)] This great variability is due to differences in the definition of bleeding complications, and patient and procedural disparities.

It would be noted that even clopidogrel alone significantly increases the risk of pocket haematoma.[18)] On the contrary, aspirin monotherapy does not seem to have a significant impact on bleeding complications.[16)18)] Withholding clopidogrel 5-7 days before the operation and continuing aspirin significantly reduces bleeding risk. DAPT therapy prevents stent thrombosis which is a devastating complication with a high mortality. On the contrary, Dreger et al.[17)] did not demonstrate increased bleeding complications in DAPT therapy patients but in this study a vacuum drainage system was applied to all patients. Tompkins et al.[19)] reported dual DAPT and peri-procedural heparin significantly increased the risk of bleeding complications at the time of pacemaker or ICD implantation. Patients receiving DAPT at the time of device implantation were at a 2-fold increased risk of reaching the primary end point as compared with patients taking aspirin only (7.2% vs. 3.9%, respectively), and 5-fold greater risk when compared with patients taking no medications (7.2% vs. 1.6%, respectively).[19)] As mentioned before, a recent coronary stent implantation (≤30 days) represents a particular problem since DAPT therapy should not be safely interrupted, even for a short-time period.[20)] However, we have to acknowledge that specific data on stent thrombosis in patients with a recent PCI undergoing EPD implantation are lacking. With regard to triple antithrombotic therapy (OAC+aspirin+clopidogrel), there are limited data in the medical literature.

Normal hemostasis involves a series of complex, well regulated interactions between the vascular wall, platelets, and coagulation cascade intended to reduce bleeding and promote vascular repair after injury.[21)] Primary hemostasis involves interactions between the vascular wall and platelets, leading to formation of platelet plug. aspirin and clopidogrel affect the development of the primary hemostatic plug by disrupting platelet adhesion and aggregation.[5)22)] In contrast to heparin, warfarin does not specifically inhibit platelet function. Secondary hemostasis involves reinforcement of the platelet plug by fibrin cross-linking. Both warfarin and heparin exhibit their anticoagulation effect by disrupting the formation of fibrin and, thus, platelet plug reinforcement.[23)]

Our study suggested heparin bridging was associated with increase of significant bleeding complication compared with patients receiving aspirin or DAPT. Importantly, the use of DAPT was not a predictor of significant bleeding complications. This might be reassuring in those patients with coronary disease, including those with deployed coronary stents in whom cessation of anti-platelet agents is problematic. But physicians hesitate to suggest withholding these medications after placement of drug-eluting stents, particularly in the light of enhanced awareness of both early and late in-stent thrombosis.[24)]

In this study, we found that DAPT did not significantly increase bleeding risk after PPM implantation. Appropriate peri-procedural management requires a thorough understanding of indications for anti-platelet agents or OAC and assessing the risks of thromboem-

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bolic vs. bleeding complications. In summary, patients who receive heparin after pacemaker implantation were at high risk for development of significant bleeding complication. The use of heparin around the time of device implantation was the risk factor for the development of bleeding complications, but there was no development of complicated hematoma in patients that were taking aspirin or DAPT.

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