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Dual antiplatelet therapy increases pocket hematoma complications in Chinese patients with pacemaker implantation

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Abstract

Objective To assess the prevalence of the bleeding complications in pacemaker implanted patients receiving different antiplatelet regimens, and the influence of each regimen on hospital stays after device implantation. **Methods** We prospectively enrolled 364 patients receiving the cardiac rhythm device implantations in Fuwai Hospital from July 2012 to December 2013. Bleeding complications including pocket hematoma, hemothorax, cardiac tamponade and blood transfusion requirement were measured as endpoints. Post operation hospital stay was also included in the endpoints. **Results** Bleeding complications were detected in 15 patients (14 with hematoma, one with hemothorax) out of all 364 patients (4.12%). Dual antiplatelet therapy (DAT) significantly increased hematoma (19.3%) compared with aspirin treatment (ASA) (3.2%, $P = 0.001$) and no antiplatelet therapy (1.9%, $P < 0.001$). There was no significant difference in incidence of pocket hematoma between the ASA group and the control group ($P = 0.45$). The post procedure hospital stay was longer in DAT group (5.45 ± 2.01 days) compared to those in the ASA group (3.65 ± 1.37 days, $P < 0.05$) or control group (3.99 ± 2.27 days, $P < 0.05$). Pocket hematoma was considered an independent predictor of hospital stay prolongation (OR: 5.26; 95% CI: 1.56–16.64; $P = 0.007$). **Conclusions** Among the Chinese patients undergoing device implantation in this study, the use of dual antiplatelet agents significantly increased the risk of pocket hematoma complications and led to a longer hospital stay. Use of aspirin alone did not increase the risk.

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Keywords: Complication; Dual antiplatelet therapy; Hematoma; Pacemaker

1 Introduction

An increasing number of patients suffering from cardiovascular diseases are treated with antiplatelet drugs. The main indication for dual antiplatelet therapy (DAT), i.e., aspirin and clopidogrel, is percutaneous coronary intervention (PCI), with placement of stents. According to the contemporary guidelines, the majority of patients with acute coronary syndromes (ACS) also require DAT. DAT significantly reduces the risk of in-stent thrombosis, and premature discontinuation of clopidogrel treatment in these patients is strongly associated with serious events, including myocardial infarction and death.[1–3]

Many patients referred for a heart rhythm device are treated with antiplatelet drugs. Pocket hematoma and other bleeding complications occur and are potentially dangerous after implantation.[4] Unfortunately, there are no guidelines dealing specifically with the optimal strategy in the setting of device procedures. The peri-procedural bleeding risk has to be weighed against the risk of thrombotic complications.

Current data regarding the effect of antiplatelet treatment on the pocket hematoma were mostly analyzed in Caucasian.[4–8] There is only one study by Chen focusing on Chinese patients,[9] which is also a retrospective study. To our knowledge, the pharmacogenetics of clopidogrel has been shown to be different in terms of metabolizing status between Asian and Caucasian populations.[10] This prospective observational study was carried out to assess: (1) the prevalence of the bleeding complications in Chinese patients receiving DAT in comparison with patients with no antiplatelet treatment, as well as patients with only aspirin treatment (ASA); and (2) The influence of each regimens on hospital stays after device implantation.

2 Methods

2.1 Study population

A total of 426 patients was enrolled according to the fol-

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lowing inclusion criteria as below: gender, male or female; ethnic, Chinese patients; age, at any age; receiving pacemaker implantation in Fuwai Hospital from July 2012 to December 2013. A total of 62 out of the 426 patients were excluded according to the exclusion criteria as below: (1) Patients treated with oral anticoagulants or anticoagulants combined with antiplatelet drugs; (2) Patients having undergone cardiac resynchronization therapy (CRT) or implantable cardioverter-defibrillator (ICD) implantation; (3) Patients with severe thrombocytopenia (platelet count < 50,000/μL); (4) Patients with a known history of coagulation disorder; and (5) Patients with other than pre-pectoral pockets. At last, 364 patients were selected for analysis.

The antiplatelet therapy strategy for each patient was made at the discretion of the physician based on the patient's physical condition. All patients were divided into three groups according to the medications prescribed applied at the time of device implantation: Control group (n = 209), patients with no antiplatelet and other anticoagulation treatment at least one week before the procedure and thereafter; ASA only group (n = 124), patients treated with aspirin only; DAT group (n = 31), patients with dual antiplatelet treatment (aspirin and clopidogrel). Aspirin was given in a daily dose of 100 mg, and Clopidogrel was given in a standard dose of 75 mg once daily.

2.2 Implantation procedure

The study was approved by THE Institutional Review Committee at Fuwai Hospital, and written informed consent was obtained from the patients prior to initiation of the study specific procedures. All procedures were performed under local anesthesia by experienced cardiac electrophysiologists. The major approach for leading insertion was via the subclavian vein (over 90%). The other venous access such as cephalic or axillary vein was only taken when the subclavian vein was not available. The pacemakers were placed in the pre-pectoral pocket in all patients. The prophylactic antibiotic cefamezine was administered intravenously at one-half to one hour before procedure and at 48 h post procedure. After completion of the operation, hand pressure hemostasis for 5–10 min was only performed if the wound was still bleeding. Pressure dressing for 12–24 h was performed for all patients.

2.3 Post implantation follow-up

After implantation, the patients were asked to lie still for 12–24 h before they were allowed to return to their normal activities. The patients were assessed 24–48 h after implantation and the stitches were removed in seven days at which time the follow-up duration ended.

2.4 Bleeding complications and other endpoints

Bleeding complications included pocket hematoma, hemothorax, cardiac tamponade and blood transfusion requirement. Pocket hematoma was defined as swelling and a painful mass with ecchymosis formation extending the margin of generators. Pressure bandaging was used if pocket hematoma occurred. Surgical revision was recommended only if the pocket pressure increased or a serious symptom occurred. Antibiotics administration was not routinely prolonged for infection prophylaxis. Post operation hospital stay was also included in the endpoints.

2.5 Statistical analysis

Statistical analysis was performed using SPSS 17.0. Data were reported as mean ± SD and percentages as appropriate. The continuous variables were analyzed by independent samples t test or one-way ANOVA followed by Student-Newman-Keuls test. The categorical variables were compared using χ^2 test. Factors associated with complications were determined using standard logistic regression. Variables reaching a significance level $P < 0.15$ on univariate correlation analysis were entered into a multivariate logistic regression analysis. Results of multivariate analysis were reported as OR with 95% CI and $P < 0.05$ were considered statistically significant.

3 Results

Out of the 426 consecutive patients undergoing cardiac implantable electronic device (CIED) implantation in Fuwai Hospital during the period of 18 months, 364 were selected for the study. Clinical characteristics of the patients are shown in Table 1. Among this population, 31 patients were treated with DAT, representing 8.5% of selected patients undergoing CIED implantation in the indicated period. The main indication of DAT was recent coronary stent implantation (n = 18, 58.1%). The other indications of DAT among the patients without previous coronary stent implantation were acute myocardial infarction (AMI) (n = 6), severe coronary artery disease (n = 5), suspected ACS (n = 1) and history of jugular artery stent (n = 1).

There were no significant differences within the three groups with regard to gender, obesity, renal function, heart function, platelet count and international normalized ratio value. Compared to those in the control group, patients were older in the ASA only group or DAT group. There were significantly more patients with diagnosed hypertension, diabetes, coronary artery disease and atrial fibrillation in the DAT group or ASA group compared to that in the control

Table 1. The clinical characteristics in all groups.

	Control (n = 209)	ASA only (n = 124)	DAT (n = 31)
Age[#], yr	62 ± 14	69 ± 9	67 ± 11
Male	98 (47)	66 (53)	17 (55)
Hypertension[#]	106 (51)	94 (76)	27 (87)
Diabetes[*]	30 (14)	23 (18)	11 (36)
Coronary artery disease[#]	11 (5)	30 (24)	30 (96.8)
Atrial fibrillation[#]	49 (23)	62 (50)	10 (32)
Renal insufficiency	7 (3)	3 (2)	1 (3)
Obesity	16 (8)	9 (7)	1 (3)
NYHA II-IV	26 (12)	23 (19)	10 (32)
Platelet count, $\times 10^9$/L	191 ± 50	189 ± 48	200 ± 66
INR	1.01 ± 0.10	1.00 ± 0.08	1.01 ± 0.08
Procedure			
New implant*	168 (80)	91 (73)	29 (93)
Replacement*	41 (20)	33 (27)	2 (7)

Data are presented as mean ± SD or n (%). [*]$P < 0.05$, [#]$P < 0.001$, when compared among groups. ASA: aspirin treatment; DAT: dual anti-platelet therapy; INR: international normalized ratio; NYHA: New York Heart Association heart functional class.

group. More new implantation occurred in the DAT group compared to that in the ASA or control group.

In this series, a total of 15 patients had bleeding complication (4.12%), 14 with hematoma among all three groups, one with hemothorax in the control group because of artery damage during the procedure (Table 2). Although there were more patients requiring pressure hemostasis in the procedure in the ASA only group compared to those in the control group (14.5% *vs*. 2.4%, $P < 0.001$), there were no significant differences in bleeding complication between these two groups (3.2% *vs*. 2.4%, $P > 0.05$). However, the rates of in-procedure pressing and bleeding complication were significantly higher in patients receiving DAT compared to those in patients in the ASA only and or control group (as shown in Table 2).

Table 2. Morbidity associated with different antiplatelet therapy.

	Control (n = 209)	ASA only (n = 124)	DAT (n = 31)
Bleeding complication after	5 (2.4)	4 (3.2)	6 (19.3)[*†]
Pocket hematoma	4 (1.9)	4 (3.2)	6 (19.3)[*†]
Hemothorax	1 (0.5)	0 (0)	0 (0)
In-procedure pressure	5 (2.4)	18 (14.5)[*]	9 (29)[*†]
Post procedure hospital stay, day	3.99 ± 2.27	3.65 ± 1.37	5.45 ± 2.0[*†]

Data are presented as mean ± SD or n (%). [*]$P < 0.05$, in comparison with the control group; [†]$P < 0.05$, in comparison with the ASA only group. ASA: only aspirin treatment; DAT: dual antiplatelet therapy.

In the entire cohort, pocket hematoma occurred in 14 patients (3.8%). The incidence of hematoma was significantly greater among patients receiving DAT (19.3%) compared with those treated with ASA (3.2%, $P = 0.001$) and those without antiplatelet therapy (1.9%, $P < 0.001$), as shown in Figure 1. No patients required surgical revision of the pocket. The post procedure hospital stay was longer in the DAT group compared to that in the ASA only or control group (Table 2). DAT was identified by univariate analysis as a factor associated with hematoma (OR 9.75, 95% CI 3.137–30.403, $P < 0.001$), whereas platelet count tend to be associated with hematoma ($P = 0.08$) (Table 3). As a result of multivariate analysis, that only DAT was identified an independent predictors of hematoma complication, with an OR of 3.70 (95% CI 1.66–8.26; $P = 0.01$).

Patients with pocket hematoma had significantly longer post procedure hospital stays compared to those without

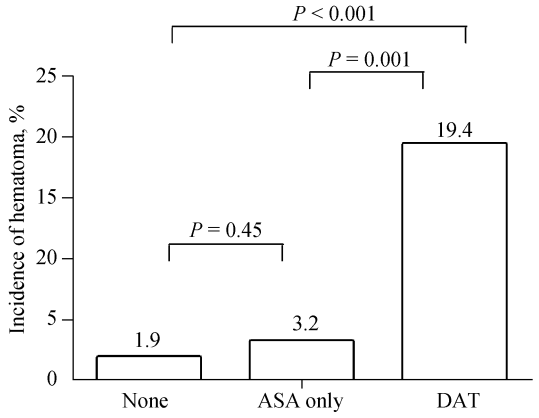

Figure 1. Pocket hematoma incidence (in percentages) among patients with different anti-platelet regimens. ASA: aspirin treatment; DAT: dual antiplatelet therapy; None: no antiplatelet drugs.

Table 3. Univariate analysis of pocket hematoma in the population sample.

	OR value	*P* value	95% CI
Age	1.036	0.18	0.984–1.089
Male	0.733	0.57	0.249–2.157
BMI	0.965	0.60	0.844–1.103
NYHA II-IV	2.145	0.21	0.650–7.086
Procedure	1.035	0.96	0.281–3.806
Platelet count	0.989	0.08	0.978–1.001
INR	4.093	0.40	0.158–105.929
DAT	9.750	< 0.001	3.137–30.403

BMI: body mass index; DAT: dual antiplatelet therapy; INR: international normalized ratio; NYHA: New York Heart Association heart functional class.

hematoma (mean hospital stay 5.38 ± 1.71 days in patients with hematoma *vs*. 3.95 ± 2.01 days in patients without hematoma, $P = 0.012$). Three predictors of over four days post procedure hospital stays were indicated by univariate analysis: heart dysfunction [New York Heart Association (NYHA) functional class II-IV], structural heart disease and pocket hematoma. However, in the multivariate analysis, only heart functional class and hematoma were identified as independent predictors of hospital stay prolongation, with an OR of hematoma of 5.26 (95% CI: 1.56–16.64, $P = 0.007$) (Table 4).

Table 4. Multivariate analysis of over four days post procedure hospital stay in the population sample.

	OR value	*P* value	95% CI
Age	0.997	0.763	0.97–1.02
[a]Structural heart disease	0.71	0.310	0.37–1.38
Procedure	1.81	0.146	0.82–3.99
NYHA class I *vs*. II–IV	0.35	0.004	0.17–0.72
Pocket hematoma	5.26	0.007	1.56–16.64

[a]including coronary artery disease, cardiomyopathy, valvular heart disease. NYHA: New York Heart Association functional class.

4 Discussion

The results of this prospective, observational study indicate that dual antiplatelet therapy (aspirin plus clopidogrel) significantly increase the pocket hematoma incidence at the time of pacemaker implantation, and prolong the post procedure hospital stay. Furthermore, dual antiplatelet therapy is an independent risk factor of pocket hematoma in patients with pacemaker implantation.

A long term dual antiplatelet therapy is recommended for almost all patients after stent implantation or presenting with ACS. For example, DAT should be administered for 12 months in patients who have received a drug-eluting stent and for 12 months in patients with ACS.[1–3] At the same time, the number of patients requiring CIED, including a pacemaker, also increased significantly during the years encompassed by the study. Although the consequences of bleeding complications are lower after pacemaker implantation than those associated with other cardiosurgery, such as coronary artery bypass grafting, pocket bleeding may increase the risk of pocket infection or even bacterial endocarditis. On the other hand, since a majority of CIED implantations are potentially life-saving, they cannot be postponed until the completion of DAT therapy. In fact, the number of patient receiving DAT at the time of CIED implantation has not been well assessed in this era, but what we know is that the number is increasing. For example, in a single-center study on 3,164 patients receiving CIED implantation in the years from 1990 to 2002, only 0.7% accepted DAT.[4] In our study, 8.4% of Chinese patients received DAT, which is quite similar to the results from a prospective two-center registry study including 626 patients published in 2010.[5]

Previous studies in Caucasian patients showed that continuing dual antiplatelet treatment during the perioperational period of the CIED implantation was associated with a high risk of bleeding complications ranging from 7.2% to 24.2%.[4–8] The difference of the bleeding complication rate can possibly be attributed to the difference of study design (e.g., retrospective or prospective), clinical characteristics of the respective patients, and also the definition of endpoints. In a retrospective chart review of bleeding complications in patients undergoing ICD or pacemaker implantation, Tompkins, *et al*.[7] found that patients treated with DAT presented a five-fold increased risk of significant bleeding complications as compared with patients taking no antiplatelet medication (7.2% *vs*. 1.6%), and a two-fold increased risk as compared with those taking aspirin only (7.2% *vs*. 3.9%). In a prospective registry study, Przybylaki, *et al*.[5] had not observed an increased risk of major bleeding complications as a result of device implantation in patients under DAT, but minor bleeding complications (subcutaneous hematoma) were more frequent in these patients compared with those taking ASA only (24.5% *vs*. 11.3%). Additionally, the large scale retrospective study of Chen, *et al*.[9] found that DAT Chinese population group had a significantly higher incidence of pocket hematoma than the no-antithrombotic group (16.2% *vs*. 2.1%, $P < 0.001$). The main risk of bleeding complication of antiplatelet therapy is pocket hematoma. Several studies reported that the incidence of pocket hematoma in patients with device implantation under DAT was 13.3%–24.5%.[5,8,9] In our patients, the incidence of hematoma complication is 19.4% in DAT group, which is significantly increased compared with both no-antiplatelet treatment and the ASA only group. This confirms the results of previous studies. The cohort of patients enrolled in this study differs from the aforementioned studies with respect to the type of implanted devices and the study population. As mentioned above, this is a prospective study in Chinese patients. Our results refer to a homogenous study population because we enrolled only patients who received pacemaker device.

Previous studies found that single, oral antiplatelet agent use (aspirin mostly) did not increase bleeding complications and pocket hematoma.[5,7–9] In our study, patients on aspirin alone experience a low incidence of pocket hematoma, similar to those in the control group (3.2% *vs*. 1.9%). How-

ever, there were more patients in ASA treatment requiring pressure hemostasis during the procedure compared to those in the control group, which perhaps, indicated that pressure hemostasis during the operation may have some effects on the reduction of hematoma formation.

According to the results from this study, DAT significantly increase the risks of hematoma and is associated with longer hospital stays. There were two other studies assessing the relationship between antiplatelet therapy and hematoma as well as hospital stay. In a retrospective case-control study consisted of 202 patients, Boule, *et al*.[11] found clopidogrel treatment at the time of device procedure significantly increased pocket hematoma (9.9% *vs*. 3.0%), and hematoma related prolonged hospitalization. In another prospective observational study conducted by Cano, *et al*.[8] patients with pocket hematoma had significantly longer hospital stays than those without pocket related complications (7.9 ± 7.3 *vs*. 2.6 ± 4.5 days), and the mean hospital stay for patients on dual antiplatelet therapy tended to be longer but did not reach statistical significance. In our study, the hospital stay after procedure was longer in the DAT group compared to those in the ASA only or control group. Although all hematoma complications did not require surgical revision, they did increase the post procedure hospital stay (5.38 ± 1.71 days in patients with hematoma *vs*. 3.95 ± 2.01 days in patients without hematoma, $P = 0.012$). Multivariate analysis also showed pocket hematoma is an independent predictor of hospital stay prolongation besides NYHA functional class.

There are limitations to this study. The study represented a single-center experience. The sample size was relatively small, especially in the DAT group, so definitive conclusions should be taken with caution. The investigators were not blinded to the anti-aggregant state of the patients, therefore, we considered that investigator bias was possible and, since we did not have a uniform protocol for antiplatelet management in this study, different operators may have had preference for different strategies. Finally, the effects of new antiplatelet drugs (e.g., prasugrel or ticagrelor) were not included in this study.

In conclusion, among Chinese patients undergoing device implantation, use of dual antiplatelet agents significantly increased the risk of pocket hematoma complications and prolonged hospital stays. Use of aspirin alone did not increase the risk.

References

1 Silber S, Albertsson P, Aviles FF, *et al*. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J* 2005; 26: 804–847.

2 Van de Werf F, Bax J, Betriu A, *et al*. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2008; 29: 2909–2945.

3 Ho PM, Spertus JA, Masoudi FA, *et al*. Impact of medication therapy discontinuation on mortality after myocardial infarction. *Arch Intern Med* 2006; 166: 1842–1847.

4 Wiegand UK, LeJeune D, Boguschewski F, *et al*. Pocket hematoma after pacemaker or implantable cardioverter defibrillator surgery: influence of patient morbidity, operation strategy, and perioperative antiplatelet/anticoagulation therapy. *Chest* 2004; 126: 1177–1186.

5 Przybylski A, Derejko P, Kwasniewski W, *et al*. Bleeding complications after pacemaker or cardioverter-defibrillator implantation in patients receiving dual antiplatelet therapy: results of a prospective, two-centre registry. *Neth Heart J* 2010; 18: 230–235.

6 Kutinsky IB, Jarandilla R, Jewett M, *et al*. Risk of hematoma complications after device implant in the clopidogrel era. *Circ Arrhythm Electrophysiol* 2010; 3: 312–318.

7 Tompkins C, Cheng A, Dalal D, *et al*. Dual antiplatelet therapy and heparin "bridging" significantly increase the risk of bleeding complications after pacemaker or implantable cardioverter-defibrillator device implantation. *J Am Coll Cardiol* 2010; 55: 2376–2382.

8 Cano O, Osca J, Sancho-Tello MJ, *et al*. Morbidity associated with three different antiplatelet regimens in patients undergoing implantation of cardiac rhythm management devices. *Europace* 2011; 13: 395–401.

9 Chen HC, Chen YL, Guo BF, *et al*. Thrombocytopenia, dual antiplatelet therapy, and heparin bridging strategy increase pocket hematoma complications in patients undergoing cardiac rhythm device implantation. *Can J Cardiol* 2013; 29: 1110–1117.

10 Sawada T, Shinke T, Shite J, *et al*. Impact of cytochrome P450 2C19*2 polymorphism on intra-stent thrombus after drug-eluting stent implantation in Japanese patients receiving clopidogrel. *Circ J* 2011; 75: 99–105.

11 Boule S, Marquie C, Vanesson-Bricout C, *et al*. Clopidogrel increases bleeding complications in patients undergoing heart rhythm device procedures. *Pacing Clin Electrophysiol* 2012; 35: 605–611.