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Incidence of pocket hematoma after electrophysiological device placement: dual antiplatelet therapy versus low-molecular-weight heparin regimen

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Abstract

Background Given the increasing number of patients who require dual antiplatelet (DAP) therapy and electrophysiological device (EPD) placement, perioperative antiplatelet management is a current challenge. In this study, we investigated the incidence of pocket hematoma formation after EPD placement in patients undergoing DAP therapy or an alternative low-molecular-weight heparin (LMWH) regimen. **Methods** This clinical observational study was performed from July 2010 to July 2012. In total, 171 patients were enrolled in the analysis after meeting the inclusion criteria. These patients were divided into two groups: 86 patients were treated with DAP therapy at the time of device implantation, and the DAP therapy was discontinued for 5 to 7 days and replaced with enoxaparin before device implantation in the other 85 patients. Adenosine phosphate (ADP)-mediated platelet aggregation and arachidonic acid-induced platelet aggregation were tested preoperatively. We compared the incidence of pocket hematoma between the two groups and the association of pocket hematoma development with ADP-mediated platelet aggregation and arachidonic acid-induced platelet aggregation. **Results** The incidence of pocket hematoma in the patients who continued DAP was lower than that in the patients who replaced the dual antiplatelet regimen with LMWH (3.49% *vs*. 16.47%, respectively; $X^2 = 6.66$, $P < 0.01$). Among the patients who continued DAP therapies, the rate of ADP-mediated platelet aggregation inhibition in patients with pocket hematomas was higher than that in patients without pocket hematomas. None of the patients undergoing DAP or enoxaparin therapy developed pocket infection, thromboembolic events, or other serious complications. Multiple logistic regression analysis revealed that LMWH therapy was an independent risk factor for the development of pocket hematoma (RR = 0.054, 95%CI = 0.012–0.251). Furthermore, patients undergoing LMWH therapy were 5.1-fold more likely to develop pocket hematomas than were DAP-treated individuals. **Conclusion** Continuance of DAP therapy does not increase the risk of pocket hematoma formation after EPD placement.

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Keywords: Antiplatelet drug; Hematoma; Low-molecular-weight heparin; Electrophysiological device

1 Introduction

With technical developments in the treatment of cardiovascular disease, increasingly more patients are undergoing electrophysiological device (EPD) placement. In addition, the number of cardiovascular events increases along with the number of patients who undergo long-term dual antiplatelet (DAP) therapy for secondary prevention of cerebrovascular events.[1–4] The most common antiplatelet therapy drugs are acetylsalicylic acid and clopidogrel, both of which are recommended to be continued for at least one year in patients undergoing drug-eluting stent placement.[2,3] The perioperative management of antiplatelet therapy in patients undergoing EPD implantation remains a controversial issue, and the effects of platelet aggregation indices on the development of pocket hematomas have not been prospectively analyzed on a large scale.[1] Retrospective investigations have shown that 90% of surgeons favor DAP therapy discontinuation with alternative low-molecular-weight heparin (LMWH) therapy,[5–9] because even short-term withdrawal of DAP medications is associated with a significantly increased risk of major cardiac adverse events, including stent thrombosis and fatal myocardial infarction.[10] Moreover, EPD implantation procedures cannot

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always be delayed to allow for adjustments in antiplatelet treatment.[11–13] Perioperative antithrombotic treatment strategies vary among different heart centers, and there is little consensus regarding the perioperative management of DAP therapy. The development of suitable therapeutic strategies to simultaneously avoid pocket hematoma formation and reduce thrombosis after device implantation is becoming increasingly more important.[5] The purpose of our study was to explore whether the continuation of DAP therapy increases the risk of pocket hematoma in patients undergoing EPD.

2 Methods

2.1 Patient characteristics

Only patients who underwent surgery involving an electrophysiological device, including placement of a permanent pacemaker or implantable cardioverter defibrillator, cardiac resynchronization therapy device placement, or generator replacement and who received a DAP medication were enrolled in this analysis during the 2-year period from July 2010 to July 2012. The inclusion criteria were: (1) an indication for DAP therapy because of recent drug-eluting stent placement, secondary prevention of coronary heart disease or stroke, or recent transcatheter aortic valve implantation; and (2) EPD procedures including new implants, generator replacements, and upgrading. The control group comprised patients not undergoing antiplatelet or anticoagulant therapy and individually matched 1: 1 with respect to age (± 5 years), sex, device, type of procedure, and number of leads implanted.[4] The exclusion criteria included a recent history of bleeding, LMWH drug allergy, hepatic dysfunction, and renal failure.

2.2 Laboratory assays

All patients underwent preoperative analysis of routine blood parameters, liver and renal function, the adenosine phosphate (ADP)-mediated platelet aggregation inhibition index, and rate of platelet aggregation induced by arachidonic acid. The last two parameters were analyzed by thromboelastography.

2.3 Therapeutic strategies

Patients undergoing EPD procedures were classified into two groups according to their perioperative management regimen: In the DAP therapy group, patients underwent continuing DAP therapy (aspirin 100 mg/d + thienopyridine 75 mg/d), whereas in the LMWH group, the DAP therapy was discontinued and temporary replaced by LMWH (enoxaparin, 1 mg/kg per 12 h) 5 to 7 days before implantation. Enoxaparin was withdrawn 12 h before the procedure and usually restarted 24 h after the implantation, then continued for 48 h.

2.4 Surgical technique

All procedures were performed by experienced surgeons (> 100 implants per year) under local anesthesia. In each patient, the device was implanted in a subcutaneous prepectoral pocket. The pocket was then pressed with 20 layers of sterile surgical gauze and one kilogram of sandbags for 8 h. Finally, the wound was covered with sterile gauze for 24 h and the patient was monitored for 48 h by the treating physician. The study investigators examined the pocket daily for hematoma development.

2.5 Pocket hematoma

The development of pocket hematoma was determined by the operators. We monitored the occurrence of pocket hematoma with a standardized form throughout the study course. A pocket hematoma was defined as a palpable mass protruding > 2 cm past the anterior margin of the pulse generator. The criteria for surgical drainage were progressive enlargement that could not be resolved with conservative treatment and the presence of tense swelling that caused poor capillary perfusion and/or severe pain.[14,15]

2.6 Definition of thromboembolic events

Thromboembolic events were defined as stent thrombosis, myocardial infarction, cerebral thrombosis, deep venous thrombosis, and pulmonary embolism.

2.7 Clinical follow-up

Follow-up interviews were performed six months after discharge, and procedure-related complications were recorded by the same operators and investigators via telephone calls and outpatient clinic visits.

2.8 Statistical analysis

SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA) was applied by a professional statistician to complete the analyses. Continuous variables are expressed as mean ± SD. Comparisons between continuous variables were performed using the *t* test or one-way analysis of variance (ANOVA) as appropriate. Categorical variables are expressed as frequency and percentage. Comparisons between categorical variables were performed using the X^2 test or Fisher's exact test. Multiple logistic regression analysis identified risk factors for pocket hematoma. $P \leq 0.05$ was considered statistically significant.

3 Results

A total of 171 patients met the inclusion criteria and were enrolled in the study; 86 patients comprised the DAP therapy continuation group at the time of device implantation, and 85 patients with interrupted DAP therapy and temporary replacement of DAP therapy by enoxaparin therapy five to seven days before device implantation comprised the LMWH therapy group. Only three pocket hematomas were documented among the 86 patients [3.49% (3/86)] of the DAP continuation therapy group, whereas 14 pocket hematomas developed in the 85 patients [16.47% (14/85)] of the LMWH therapy group. The incidence of pocket hematomas in patients who were not taking antiplatelet or anticoagulant agents (control group) was 1.17% (2/171). The incidence of pocket hematomas was not similar between patients on DAP therapy and those in the control group (P = 0.338). The incidence of pocket hematomas in the LMWH therapy group was significantly higher than that in the DAP continuation therapy group (16.47% *vs*. 3.49%, respectively; P = 0.010). The baseline characteristics of the study groups are presented in Table 1. There were no significant differences between the groups.

Table 2 shows the correlation between pocket hematoma development and the type of implanted device in the two groups. There was no statistical difference in the risk of pocket hematoma development between the groups.

Table 3 shows the relationship between platelet function indices on pocket hematoma development in the two groups. In the DAP therapy group, the ADP-mediated platelet aggregation inhibition rates in patients with pocket hematomas were significantly different from those of patients without pocket hematomas (P < 0.01), indicating an association between ADP values and pocket hematomas in patients on DAP therapy. In contrast, the occurrence of pocket hematomas was not associated with ADP values in the LMWH group (P = 0.139). In both the DAP and the LMWH groups, the arachidonic acid-mediated platelet aggregation inhibition rates were not associated with the development of pocket hematomas (P = 0.634 and 0.527, respectively).

The risk factors for pocket hematoma development and their significance are listed in Table 4. Multiple logistic regression analysis using a forward stepwise (conditional) method revealed that LMWH therapy is an independent risk factor for the development of pocket hematoma (RR = 0.054, 95% CI = 0.012–0.251). Patients on LMWH treatment were

Table 1. Baseline demographic characteristics of the patients.

Variables	Dual antiplatelet group (n = 86)	LMWH group (n = 85)	Control group (n = 171)	P value
Age, yrs	69.81 ± 8.57	70.38 ± 7.36	71.74 ± 7.99	0.372
Male	47 (54.65)	36 (42.35)	83 (48.54)	0.274
BMI, kg/m^2	24.04 ± 2.59	24.09 ± 2.56	23.99 ± 2.38	0.091
Smoking	67 (77.91)	64 (75.29)	128 (74.85)	0.860
Alcohol	39 (45.35)	41 (48.24)	81 (47.37)	0.926
Hypertension	76 (88.37)	73 (85.88)	143 (83.63)	0.590
Hemorrhagic/ischemic stroke	23 (26.74)	27 (31.76)	51 (29.82)	0.950
COPD	26 (30.23)	21 (24.71)	43 (25.15)	0.633
Diabetes	43 (50.00)	31 (36.47)	69 (40.35)	0.172
CRE, μmol/L	67.71 ± 15.90	69.32 ± 14.51	68.07 ± 15.06	0.339
HGB, g/L	125.3 ± 9.8	123.7 ± 10.3	120.64 ± 13.83	0.576
ALT, μ/L	22.32 ± 7.16	22.31 ± 7.08	22.30 ± 7.05	0.452
PLT, ×10^9/L	233.13 ± 30.42	230.23 ± 30.01	232.75 ± 43.01	0.538
EF	55.96% ± 6.20%	55.74% ± 6.01%	55.87% ± 5.98%	0.739
LDL-C, mmol/L	2.77 ± 0.34	2.68 ± 0.33	2.76 ± 0.39	0.079
Device				0.846
PM	79 (91.86)	80 (94.12)	159 (92.98)	
CRT/ICD	7 (8.14)	5 (5.88)	12 (7.02)	

Data are presented as mean ± SD or n (%). ALT: alanine aminotransferase; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRE: serum creatinine; CRT/ICD: cardiac resynchronization therapy device/implantable cardioverter defibrillator; EF: left ventricular ejection fraction; HGB: hemoglobin; LDL-C: low-density lipoprotein-cholesterol; LMWH: low-molecular-weight heparin; PLT: platelets; PM: permanent pacemaker.

Table 2. Correlation between pocket hematoma formation and type of implanted device.

Variables	Pocket hematoma	No pocket hematoma
Dual antiplatelet group, *n* = 86		
PM	1 (1.63)	78 (90.7.)
ICD	2 (2.33)	3 (3.49)
CRT	0 (0.00)	2 (2.33)
LMWH bridging group, *n* = 85		
PM	13 (15.29)	67 (78.82)
ICD	0 (0.00)	2 (2.35)
CRT	1 (1.18)	2 (2.35)
Control group, *n* = 171		
PM	2 (1.17)	157 (91.81)
ICD	0 (0.00)	9 (5.26)
CRT	0 (0.00)	3 (1.75)

Data are presented as *n* (%). CRT: cardiac resynchronization therapy; ICD: implantable cardioverter defibrillator; LMWH: low-molecular-weight heparin; PM: permanent pacemaker;

Table 3. Correlation between incidence of pocket hematomas and ADP/AA-mediated platelet aggregation inhibition indices.

Variables	Pocket hematoma	No pocket hematoma	*P* value
ADP			
Dual antiplatelet	83.33 ± 2.11	54.01 ± 10.96	0.000
LMWH bridging	28.16 ± 11.28	33.14 ± 11.41	0.139
AA			
Dual antiplatelet	67.47 ± 3.54	70.23 ± 9.95	0.634
LMWH bridging	68.21 ± 6.93	66.76 ± 10.81	0.527

Data are presented as mean ± SD. AA: arachidonic acid; ADP: adenosine phosphate; LMWH: low-molecular-weight heparin.

Table 4. Risk factors for pocket hematoma formation.

Variables	*P*	RR	95%CI
Age	0.672	1.253	0.442–3.547
Sex	0.275	1.795	0.628–5.134
Obesity	0.832	1.118	0.400–3.121
Hypertension	0.252	0.294	0.036–2.387
Dyslipidemia	0.129	2.389	0.776–7.358
Smoking	0.499	0.622	0.157–2.467
Alcohol	0.580	0.746	0.263–2.111
Diabetes	0.224	0.527	0.188–1.479
Dual antiplatelet therapy	0.217	0.316	0.051–1.968
LMWH therapy	0.000	0.054	0.012–0.251

LMWH: low-molecular-weight heparin.

5-fold (3.49% *vs*. 16.47%) more likely to develop pocket hematomas than were patients on continuing DAP therapy. Pocket hematomas were not associated with age, sex, diabetes, obesity, hypertension, hyperlipidemia, smoking, alcohol, or diabetes.

4 Discussion

Pocket hematoma is a common complication after implantation of permanent pacemakers, cardiac resynchronization therapy devices, and implantable cardioverter defibrillators and can cause local discomfort, pocket infection, and extended hospitalization. We have addressed potential strategies for minimizing the risk of pocket hematoma and thrombosis events. Neither cephalic vein cutdown nor direct subclavian puncture for perioperative device implantation has a significant influence on the risk of pocket hematoma formation.[15,16] Additionally, the type of implanted device does not affect the incidence of pocket hematoma.[13,17]

Among patients undergoing interventional surgical procedures, those with indications for the use of antiplatelet agents will require interruption of antiplatelet therapy and replacement with LMWH.[18] However, in the present study, we maintained DAP therapy in 86 patients, and only three developed pocket hematomas [(3/86), 3.49%]. In contrast, the incidence rate of pocket hematomas among patients medicated with a LMWH regimen [(14/85), 16.47%] was 5-fold higher than that of patients receiving DAP. At present, the reported occurrence of pocket hematoma formation in patients undergoing a heparin strategy ranges from 7.5% to 25.0%,[14,15,19,20] which is in agreement with our data in the LMWH group of patients. In contrast, the incidence of pocket hematoma formation after EPD implantation in our patients undergoing DAP continuation therapy was lower than the 25.0%, 15.0%, and 7.2% previously reported in the literature.[1,13,21] In our study, the proportion of pocket hematomas was effectively reduced by strengthening bandages, and our perioperative therapy management regimen was simple, convenient, and feasible. Lockhart, *et al*.[22] pointed out that once an initial clot has formed, the event of bleeding is unlikely to occur. The mechanisms involved in the more frequent occurrence of pocket hematomas in the LMWH group are unclear. A possible explanation for this may be associated with the potent inhibition of one or more elements of the coagulation cascade and the prevention of a clot/thrombus from the synergistic action of LMWH.[23] Activation of thrombosis is a major factor involved in the development of thrombosis; LWMH with a significant amount of antithrombin factor Xa cannot only inhibit the activation of thrombin and aggregation of blood platelets, but also decrease the transformation of permanent platelet–fibrin clots from temporary platelet clots and change the

hemorheology properties. With the exception of the effect of antithrombin factor Xa and antithrombin factor 2a, LWMH has some non-anticoagulant properties including the release of tissue factor pathway inhibitor and tissue-type plasminogen activator. Medium that promotes fibrinolytic and antithrombotic activity could limit the release of von Willebrand factor and pro-inflammatory cytokines from the vessel wall, and even affect the hemorheology properties and interaction between platelets and leukocytes. The mechanism of action is usually more complicated than that of antiplatelet drugs.[24,25]

In our study, DAP did not increase the risk of pocket hematoma development. Thus, we suggest that operators do not choose a DAP discontinuation therapy for the following reasons: (1) Compared with aspirin alone or aspirin plus warfarin, DAP therapy with aspirin and thienopyridine dramatically decreases the risk of stent thrombosis, myocardial infarction, and death after stent placement. Spertus, *et al*.[26] reported that suspending DAP after positioning of drug-eluting stents may endanger patients with antiarrhythmic devices because of in-stent thrombosis. (2) Drug-eluting stents can lead to late stent thrombosis, even after years of stent implantation.[26–28] As an independent predictive factor of stent thrombosis, even temporarily, premature cessation of thienopyridine obviously increases the occurrence of stent thrombosis.[11] (3) DAP should not be withdrawn for minor surgery,[29] and compared with major surgery such as cardiac surgery, EPD implantation is a minor operation and we can take local measures during the operation to decrease pocket bleeding.

Otherwise, in the current literature, some studies have reported that pocket hematoma formation in patients on DAP therapy was related to clopidogrel.[13] Clopidogrel prevents platelet activation by inhibiting ADP receptors. The ADP-mediated platelet aggregation index is a common indicator for the evaluation of platelet aggregation in clinical practice and an important indicator in assessing the effect of clopidogrel. Clinically, whether the ADP-mediated platelet aggregation rate decreases by > 50% is one of the most important indices with which to evaluate the platelet aggregation efficiency of clopidogrel.[30] The use of thromboelastography to test the ADP-mediated platelet aggregation rate has important practical value in the clinical environment because it is simple to perform, easy to develop, and inexpensive.[31–33] In our study, in the patients undergoing continued DAP therapy, the ADP-mediated platelet value in patients with pocket hematomas was higher than that in patients without pocket hematomas. This finding indicates that a higher ADP-mediated platelet aggregation inhibition rate leads to pocket hemorrhage, which may explain the variability in pocket hematoma formation among patients undergoing DAP therapy because of different ADP-mediated platelet aggregation rates. We suggest that the risk of pocket hemorrhage in patients on DAP therapy might be estimated by ADP-mediated platelet aggregation rate analysis and might be adjusted to values beyond the critical range before EPD implantation.

In conclusion, continuing DAP therapy does not increase the risk of pocket hematoma formation in patients undergoing EPD placement. Within six months of follow-up, we found no major bleeding events in the two patient groups. None of the patients undergoing DAP or enoxaparin therapy developed pocket infections, stent thrombosis, myocardial infarction, cerebral thrombosis, deep venous thrombosis, pulmonary embolism, or other complications. Continuing pre-established DAP therapy is superior to perioperative LMWH treatment in terms of reducing pocket hematoma formation after anti-arrhythmic device placement.

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