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ORIGINAL ARTICLE

Predictors of pocket hematoma in patients on antithrombotic therapy undergoing cardiac rhythm device implantation: insights from the FinPAC trial

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Background. **The FinPAC trial showed that the strategy of uninterrupted oral anticoagulation (OAC) was non-inferior to interrupted OAC for the primary outcome of bleeding and thromboembolic complications in patients undergoing cardiac rhythm management device (CRMD) implantation.**

Methods. **We conducted a *post hoc* analysis of the FinPAC data to explore the incidence and predictors of significant (> 100 cm^2) pocket hematoma after CRMD implantation among the study population ($n = 447$). A total of 213 patients were on OAC, 128 were on aspirin, and 106 on no antithrombotic therapy.**

Results. **The incidence of significant pocket hematoma during hospital stay was significantly higher among patients using OAC (5.6%) and aspirin (5.5%) than in those with no antithrombotic medications (0.9%), but only one patient (0.8%) in the aspirin group needed revision of hematoma. Two patients (0.9%) in the OAC group and one (0.8%) in the aspirin group needed blood products. In multivariable regression analysis, no pre-procedural features predicted the significant hematoma in any of the groups.**

Conclusions. **Clinically significant pocket hematoma is a rare complication after CRMD implantation in patients with ongoing therapeutic OAC. The incidence of significant pocket hematoma formation is similar in patients using OAC and those using aspirin.**

Key words: Cardiac rhythm management, oral anticoagulation, pocket hematoma

Key messages

- Significant pocket hematomas are rare after pacing device implantation performed during therapeutic oral anticoagulation.
- The bleeding risk of therapeutic peri-procedural anticoagulation is similar to that of aspirin therapy.
- Patients at a moderate-to-high risk of thromboembolism should undergo cardiac rhythm management device implantation without interruption of oral anticoagulation.

Introduction

Many patients (12%–45%) undergoing implantation of cardiac rhythm management device (CRMD) use long-term oral anticoagulation (OAC) (1,2). The optimal strategy for perioperative management of OAC therapy is controversial. The current practice guidelines recommend transient discontinuation of OAC and 'bridging' with heparin in patients at moderate-to-high risk of thromboembolic events before surgical procedures (3). Accordingly, heparin bridging is the standard-of-care for CRMD implantation in many centers. However, several reports indicate that compared with uninterrupted OAC, the strategy of heparin bridging may increase rather than decrease the risk of pocket hematoma and other perioperative bleeding complications in patients undergoing CRMD implantation (1,4–7).

The result of the multicenter randomized FinPAC trial showed that the strategy of uninterrupted OAC was non-inferior to interrupted OAC without heparin bridging for the primary outcome of any pocket hematoma in patients undergoing CRMD implantation (8). We conducted a *post hoc* analysis of the FinPAC data to explore the predictors of significant pocket hematoma formation after CRMD implantation in patients with an indication for long-term anticoagulation therapy. In addition, we compared the incidence of complications to control groups with ongoing aspirin treatment or no antithrombotic treatment during implantation.

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Material and methods

Patient selection and study design

The FinPAC trial is a part of an ongoing study program in Western Finland assessing thrombotic and bleeding complications associated with various cardiac procedures in patients using long-term OAC (9–11). The FinPAC trial was aimed to evaluate the safety of uninterrupted antithrombotic therapy in patients undergoing CRMD implantation. The inclusion and exclusion criteria of the trial have been previously described in detail (8). In short, we excluded patients with known coagulation disorder or bleeding diathesis, mechanical heart valves or other absolute contraindication to interrupt warfarin, international normalized ratio (INR) not in therapeutic range at randomization, and significant anemia (hemoglobin $<$ 100 gm/L). The main study group comprised 213 patients on long-term chronic OAC, who were randomized on a 1:1 basis in two groups. In the first group, no pause in the OAC was used, whereas in the other group OAC was discontinued 2 days before the CRMD implantation (with no heparin bridging). In addition to the main study group, we enrolled 128 patients on long-term aspirin and 106 patients with no antithrombotic therapy during the same study period at the same centers, in order to compare the magnitude of complications in these three patient groups. Patients in the aspirin group continued on aspirin (dose 100 mg daily in 116 patients) throughout the peri-procedural period. CHA_2DS_2VASc and HAS BLED scores were calculated to evaluate the individual risks for thromboembolic and bleeding events, respectively.

Device implantation and perioperative management

All devices were implanted according to the current clinical practice guidelines (12). After prophylactic antibiotic, an incision was made and dissected down to the fascia of the pectoral muscle under local anesthesia. Leads were implanted under fluoroscopic guidance via subclavian or axillary vein puncture, or cephalic vein cut-down. The pocket was expanded with blunt dissection. Electrocautery was used when necessary to ensure adequate hemostasis. All devices were implanted above the pectoral muscle fascia.

Ethical issues

This investigator-driven study was conducted according to the guidelines of the 1964 Declaration of Helsinki, as revised in 2002. The study protocol was approved by the ethics committees of the participating centers. Informed written consent was obtained from every patient after full explanation of the study protocol. The FinPAC trial is registered with ClinicalTrials.gov under the identifier: NCT00479362.

Study definitions and end-points

All patients were evaluated at discharge and 1 month after the index procedure. The primary outcome measure of this substudy was the formation of a significant pocket hematoma ($>$ 100 cm^2 in area) and other bleeding complications. Major bleeding was defined as any bleeding or pocket hematoma that required an additional intervention. Pocket exploration was performed if the hematoma progressively enlarged causing pain or threat to the suture line.

Statistical analysis

Continuous variables were reported as the mean $\pm$ standard deviation. Categorical variables were described with absolute and relative (percentage) frequencies. Baseline clinical, procedural, and laboratory measures were tested for correlation with the occurrence of a significant pocket hematoma in univariate analyses. Multivariable regression analysis was performed to identify the independent predictors of a significant pocket hematoma in patients on long-term OAC and in those on aspirin. Significant pocket hematoma was entered as the dependent variable, and those variables correlating with significant pocket hematoma in univariate analyses were entered as the covariates. Statistical analysis was performed using SPSS statistical software (SPSS v. 17.0.1, SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

The baseline clinical, procedural, and laboratory data of the three groups are shown in Tables I and II. The main indication for OAC was atrial fibrillation. The HAS BLED score was higher in patients using aspirin, compared with those using OAC (1.9 ± 0.9 versus 1.4 ± 0.8, respectively); yet, the CHA_2DS_2VASc score was comparable in these two groups. The route of access was comparable between the three groups. Patients using OAC were more likely to undergo cardiac resynchronization therapy ($P = 0.013$); however, patients using aspirin had more leads inserted during the procedure ($P < 0.001$).

The incidence of significant pocket hematoma

Significant hematomas and other bleeding complications are summarized in Table III. There was no significant difference in the incidence of significant pocket hematoma between patients using OAC and those using aspirin; 12 out of 213 patients on long-term OAC (5.6%) and 7 out of 128 (5.5%) on long-term aspirin had significant pocket hematoma. In contrast, only 1 out of 106 patients (0.9%) with no antithrombotic medications had significant pocket hematoma. One patient (0.8%) in the aspirin group needed revision of hematoma, whereas in the OAC and control group no revisions were needed. Blood product transfusion was needed by two patients (0.9%) in the OAC group, one (0.8%) in the aspirin group, while no patient in the control group needed blood products. The lowest post-operative hemoglobin level was 88 g/L in the OAC group, 99 g/L in the aspirin group, and 96 g/L in patients with no antithrombotics. One patient with OAC had a stroke 3 days after the procedure (Table III). His INR was 1.7 at the time of the stroke. No mortality was observed in the three groups during 30-day follow-up. Hospital stay was comparable among all patient groups, and only a minority of patients were treated as out-patients.

Predictors of significant pocket hematoma

In patients on long-term OAC, post-procedural INR ($P = 0.04$) and implantable cardioverter defibrillator (ICD) device ($P = 0.04$) correlated with significant pocket hematoma in the univariate analyses, and clopidogrel use showed a trend to correlation ($P = 0.09$). In the multivariable logistic regression analysis, the only independent predictor of significant pocket hematoma was post-procedural INR (HR 2.6, 95% CI 1.0–6.6, $P = 0.045$) (Figure 1). In patients on long-term aspirin, the only independent predictor of significant pocket hematoma in the multivariable logistic regression analysis was the duration of the procedure (HR 1.01, 95% CI 1.00–1.03, $P = 0.05$). Of note, HAS BLED score, access vein, or use of hemostatic agents did not predict incidence of significant pocket hematoma among patients treated with OAC or aspirin.

Table I. Baseline clinical and procedural characteristics of the study groups.

	OAC group $n = 213$	Aspirin group $n = 128$	Control group $n = 106$	*P* value
Age (y)	72.2 ± 8.7	72 ± 10.7	64.3 ± 15.2	< 0.001
Male gender	131 (61.5)	70 (54.7)	59 (55.7)	0.39
Atrial fibrillation	200 (93.9)	37 (28.9)	13 (12.3)	< 0.001
Diabetes	38 (21.2)	32 (31.7)	14 (15.9)	0.028
Hypertension	81 (43.8)	63 (57.8)	40 (41.7)	0.031
Heart failure	45 (24.9)	19 (20.2)	7 (8.3)	0.007
Prior stroke	28 (13.1)	10 (7.8)	5 (4.7)	0.013
Renal failure	7 (3.3)	4 (3.1)	1 (0.9)	0.091
CHA_2DS_2VASc score	3.1 ± 1.7	3.1 ± 1.7	1.8 ± 1.4	< 0.001
HAS BLED score	1.4 ± 0.8	1.9 ± 0.9	0.9 ± 0.8	< 0.001
HAS BLED score ≥ 3	17 (9.2)	36 (28.8)	2 (2.4)	< 0.001
Aspirin use	6 (2.8)	127 (99.2)	0 (0)	< 0.001
Clopidogrel use	4 (1.9)	7 (5.5)	0 (0)	0.027
Venous access route				
Cephalic vein	95 (44.8)	67 (52.8)	55 (52.9)	0.559
Axillary vein	89 (42.0)	44 (34.6)	37 (35.6)	
Subclavian vein	28 (13.2)	16 (12.6)	12 (11.5)	
Device implanted				
ICD	19 (8.9)	18 (14.1)	13 (12.3)	0.318
CRT	28 (13.1)	7 (5.5)	3 (2.8)	0.013
Number of leads	1.5 ± 0.6	1.7 ± 0.5	1.8 ± 0.4	< 0.001
Duration of operation (min)	65 ± 43	76 ± 44	68 ± 37	0.085
Hemostatic use	11 (5.2)	4 (3.1)	1 (0.9)	0.298
Out-patient operations	13 (6.1)	7 (5.5)	5 (4.7)	0.695
Hospital stay (days)	2.3 ± 2.5	3.1 ± 3.8	2.5 ± 2.3	0.078

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are presented as frequency (percentage).
CRT = cardiac resynchronization therapy; ICD = implantable cardioverter defibrillator; OAC = oral anticoagulation.

Discussion

The main finding of our study is that the risk of clinically relevant pocket hematoma and other bleeding complications in patients undergoing CRMD implantation during therapeutic OAC without heparin bridging is low and similar to that during ongoing aspirin therapy. The risk of significant pocket hematoma was only weakly associated with higher post-procedural INR, but not with the estimated bleeding risk assessed by the HAS BLED score. Most importantly, the only stroke occurred in a patient with a low INR level due to warfarin pause, supporting the view that therapeutic OAC should be maintained during the whole perioperative period.

Antithrombotic management during CRMD implantation

Pocket hematoma formation is the most common complication of CRMD implantation. Its incidence in patients on long-term OAC has been 5%–8% (5,13–15). Management of antithrombotic therapy during CRMD implantation in patients on long-term OAC is controversial. The options are either to stop temporarily OAC and start low-molecular-weight heparin a few days before the procedure ('heparin bridging'), to interrupt OAC with no heparin bridging, or to perform the procedure under therapeutic OAC (16). The goal of heparin bridging is to reduce the frequency of bleeding complications without predisposing the patient to thromboembolic events. According to multiple retrospective observational studies, the risk of bleeding complications was higher with heparin bridging than with uninterrupted OAC (1,4–6,17,18). Importantly, one recent randomized trial was terminated prematurely because of a marked reduction of clinically significant pocket hematoma with the strategy of uninterrupted OAC versus heparin bridging in patients undergoing CRMD implantation (7). Moreover, two prospective randomized trials showed comparable rates of bleeding complications between the strategy of uninterrupted and that of interrupted OAC in patients undergoing CRMD implantation (8,19).

Risk factors of hematoma formation during CRMD implantation

Our data show that the level of peri-procedural OAC has minor effect on hematoma formation, although post-procedural INR was weakly associated with significant pocket hematoma. The clinical value of this finding is limited, since it cannot be

Table II. Laboratory data of the study groups.

	OAC group $n = 213$	Aspirin group $n = 128$	Control group $n = 106$	*P* value
Preoperative hemoglobin (g/L)	139 ± 16	138 ± 14	136 ± 20	0.534
Postoperative hemoglobin (g/L)	135 ± 17	133 ± 15	134 ± 16	0.427
Platelet count ($\times 10^3$)	217 ± 68	236 ± 81	232 ± 69	0.038
Creatinine (μmol/L)	90 ± 24	87 ± 27	82 ± 20	0.048
Preoperative INR	2.1 ± 0.5	1.1 ± 0.3	1.0 ± 0.1	< 0.001
Postoperative INR	1.9 ± 0.6	1.3 ± 0.4	1.1 ± 0.1	< 0.001

Variables are presented as mean ± standard deviation.
INR = international normalized ratio; OAC = oral anticoagulation.

Table III. Significant hematoma and other bleeding complications.

	OAC $n = 213$	Aspirin $n = 128$	Controls $n = 106$	*P* value
Any pocket hematoma/bruise	78 (36.6)	31 (24.2)	25 (23.6)	0.014
Significant hematoma (> 100 cm^2)	12 (5.6)	7 (5.5)	1 (0.9)	0.131
Operative bleeding	19 (8.9)	9 (7.0)	3 (2.8)	0.044
Revision of pocket hematoma	0 (0)	1 (0.8)	0 (0)	0.363
Pocket infection	1 (0.5)	0 (0)	0 (0)	0.577
Blood products	2 (0.9)	1 (0.8)	0 (0)	0.616
Thromboembolic events	1 (0.5)	0 (0)	0 (0)	0.464

Variables are presented as frequency (percentage).
OAC = oral anticoagulation.

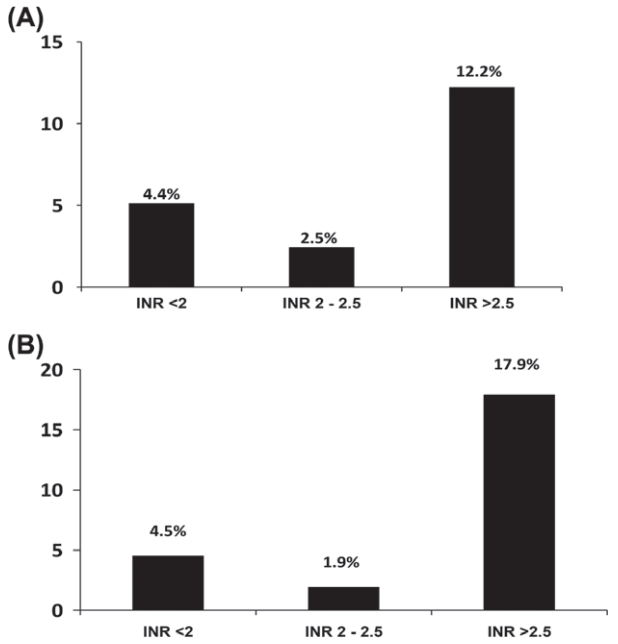

Figure 1. The incidence of clinically significant pocket hematoma classified according to the level of pre-procedural INR (A) ($P = 0.06$), and post-procedural INR (B) ($P = 0.009$) (INR = international normalized ratio).

used to predict pocket hematoma before the procedure. Similarly, HAS BLED score, introduced to classify the risk of bleeding during long-term OAC, did not predict the occurrence of significant pocket hematoma in our cohort. Implantation of ICD was weakly associated with increased risk of significant pocket hematoma, but as in some prior studies (20,21) the type of the implanted device was not an independent predictor of a significant pocket hematoma. A potential bias in this finding is that most of the ICDs were implanted by an experienced operator, which may carry a lower risk of hematoma than the procedures performed by trainees (13,15,21). In our study, however, operation by a trainee was only weakly associated with significant pocket hematoma and only in patients on long-term aspirin. Longer duration of the procedure was an independent predictor of significant pocket hematoma in patients using aspirin in line with a previous study (5). In a recent registry, procedures including lead revisions and device upgrades were associated with more frequent hematoma formation (22). Consistent with our results, previous studies have shown no advantage of the cephalic vein approach in terms of bleeding complications (1,13,20,23). There were more patients with atrial fibrillation in the OAC group, explaining the lower number of pacemaker leads in this group, which may reduce the bleeding risk (17), but this was counterbalanced by the fact that the number of patients who received cardiac resynchronization therapy devices was higher in the OAC group. Finally, the use of clopidogrel and dual antiplatelet therapy has been reported to increase the incidence of hematoma formation (5,23). In our study, the use of clopidogrel was very rare and only weakly associated with significant pocket hematoma in patients on long-term OAC.

Limitations of the study

The statistical power of the current analysis is limited by the infrequent occurrence of significant complications. The results may have been affected by the fact that the patients were treated according to our routine clinical practice by cardiologists and trainees, and that various techniques were employed for venous access (e.g. subclavian or axillary vein puncture, and cephalic vein cut-down). It should also be emphasized that in this study most of the INR values in patients on long-term OAC were at subtherapeutic or low therapeutic level. Therefore, caution is needed when extrapolating these results to patients with higher INR values. Moreover, baseline characteristics were heterogeneous among the three groups, reflecting the healthier state of the controls. These differences may contribute to the lower rate of pocket hematoma in the control group, but show the level of bleeding complications in low-risk patients referred for CRMD implantation.

Conclusion

In patients undergoing CRMD implantation during OAC therapy, the incidence of significant pocket hematomas was low and comparable to that during ongoing aspirin therapy. Peri-procedural INR had little effect on the incidence of significant pocket hematoma formation. Hence, patients at moderate-to-high risk of thromboembolism should undergo CRMD implantation without interruption of OAC.

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