Interrupted versus uninterrupted NOAC peri-implantation of cardiac device: a single-centre randomised prospective pilot trial

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Abstract

Background. Many patients requiring cardiac implantable electronic device (CIED) implantation are on long-term oral anticoagulant therapy. While continuation of warfarin has been shown to be safe and reduce bleeding complications compared to interruption of warfarin therapy and heparin bridging, it is not known which novel oral anticoagulants (NOAC) regimen (interrupted vs. uninterrupted) is better in this setting.

Methods. One-hundred and one patients were randomized to receive CIED implantation with either interrupted or uninterrupted/continuous NOAC therapy before surgery. No heparin was used in either treatment arm. The primary end-point was the presence of a clinically significant pocket haematoma after CIED implantation. The secondary end-point was a composite of other major bleeding events,

device-related infection, thrombotic events and device-related admission length post device implantation.

Results. Both treatment groups were equally balanced for baseline variables and concomitant medications. One clinically significant pocket haematoma occurred in the uninterrupted NOAC group and none in the interrupted group (p= 0.320). There was no difference in other bleeding complications. No thrombotic events were observed in either of the two groups.

Conclusions. Despite the paucity of bleeding events, data from this pilot study suggest that uninterrupted NOAC therapy for CIED implantation appears to be as safe as NOAC interruption and does not increase bleeding complications.

Key-words: anticoagulants; bleed; complications; pacemakers; defibrillators.

Introduction

Each year, more than 1 million pacemakers and 400,000 implantable-cardioverter defibrillators (ICDs) are implanted worldwide [1]. Many patients requiring cardiac implantable electronic device (CIED) implantation or replacement are on long-term oral anticoagulation [2]. In patients undergoing CIED implantation, the benefit of uninterrupted/continuous warfarin therapy, compared to warfarin interruption and heparin bridging, has been clearly demonstrated in randomised trials and has become part of routine clinical practice. Heparin bridging has been associated with increased bleeding complications, which present most commonly with pocket haematoma formation [3]. Novel oral anticoagulants (NOACs) have only recently emerged as efficacious and practical alternatives to warfarin for patients requiring oral anticoagulation, and thus the most effective peri-procedural management of patients anticoagulated with NOACs is yet to be determined. Currently, interruption of NOAC therapy is recommended, even before procedures with a low bleeding risk, such as

pacemaker and ICD implantation [4]. Data on the efficacy and safety of uninterrupted NOACs in this setting are currently scarce.

Methods

Study design

This was a prospective, open-label, randomised controlled single blind pilot trial (1:1 randomisation). The local ethical committee approved the study. All patients gave informed consent. Between January 2015 and April 2017, we enrolled 101 consecutive patients already on treatment with dabigatran, apixaban or rivaroxaban (edoxaban was still not available at the time of the study design) and undergoing elective implant/replacement of a cardiac pacemaker, ICD or cardiac resynchronisation therapy (CRT) device in our centre. Each patient had been on NOAC treatment for at least 7 days before the procedure. Patients were either on a high (dabigatran 150 mg bd, apixaban 5 mg bd or rivaroxaban 20 mg od) or low (dabigatran 110 mg bd, apixaban 2.5 mg bd or rivaroxaban 15 mg od) dose anticoagulant regime as per approved manufacturer recommendations. Patients with a creatinine clearance (CrCl) $\leq$ 30 ml/min were excluded from the study. Three days before the CIED implantation, each patient was randomised to either interrupt/withhold (group 1) or to continue NOAC treatment (group 2). Closed envelope method was used for randomization. The timing of NOAC interruption in group 1 varied among the different drugs and occurred in accordance with EHRA recommendations for low risk bleeding procedures [4]. Rivaroxaban and apixaban were held for 24 hours before the implantation, while dabigatran was held between 24 and 48 hours as per CrCl, ($\geq$ 24 hours for CrCl $\geq$ 80 ml/min, $\geq$ 36 hours for CrCl 50-80 ml/min and $\geq$ 48 hours for CrCl 30-50 ml/min). The NOAC was then restarted at least 24 hours after the procedure. NOAC therapy was continued in group 2 as per usual, and administered on the same day of CIED implantation. Antiplatelet therapy was not suspended in any patients. Two experienced cardiologists performed the

device implantation using either cephalic or subclavian vein access. All the CIEDs were positioned in a pre-pectoral subcutaneous pocket. Diathermy was used for haemostasis as per routine practice in our centre. Patients were discharged after 24 hours, and had their first postoperative clinical follow-up 2-3 weeks after the procedure, and a second follow-up 2 to 3 months later. In the ward and in the outpatient device clinic, the wounds and potential bleeding complications were assessed by one of three cardiologists part of the endpoint adjudication committee, who were blind to treatment allocation. A pocket haematoma was defined as any palpable mass that protruded > 1 cm anteriorly or laterally to the pulse generator. A clinically significant haematoma was defined as any haematoma requiring further surgery, and/or resulting in prolongation of hospitalisation or requiring rehospitalisation for at least 24 hours after index surgery and/or requiring interruption of the anticoagulant therapy. A haematoma requiring further surgery was defined as a haematoma causing prolonged pain, that continued to expand or was causing imminent skin necrosis/perforation. A haematoma requiring interruption of the anticoagulant therapy was defined as withholding of the all the anticoagulants for at least 24 hours in response to wound haematoma. Other major bleeding events were defined as any bleeding complications requiring pericardiocentesis or surgical intervention (e.g. cardiac tamponade or hemothorax), a newly diagnosed pericardial effusion (> 1 cm) not causing tamponade or any bleeding requiring a blood transfusion. Thrombotic events were defined as a stroke, transient ischaemic attack, myocardial infarction, pulmonary embolism or deep vein thrombosis.

Study end-points

The primary end-point of this study was the presence of a clinically significant pocket haematoma after CIED implantation. The secondary end-point was a composite of other major bleeding events, device-related infection, thrombotic events and device-related admission lengthening after implant. Other secondary end-points included the evaluation of the bleeding and thrombotic outcomes according to the anticoagulant type and dosing regimen (low or high).

Statistical analysis

Chi-square test was used for comparison of nominal variables. The Student t-test, one-way ANOVA, or their non-parametric equivalents, Mann–Whitney and Kruskall–Wallis when appropriate, were used for comparison of continuous variables; Levene's test was used to check the homogeneity of variance. Results with $P \leq 0.05$ were regarded as significant. Descriptive statistics and all aforementioned inferential statistics were performed using IBM SPSS Statistics, Version 19.0.

Results

A total of 101 consecutive patients (mean age 76 ± 8, 65.3% men) were enrolled in this study. The clinical characteristics of the cohort are described in Table 1, there were no differences between the two groups. Thirty-seven patients (36.6%) were on dabigatran, 33 (32.7%) on rivaroxaban and 31 (30.7%) on apixaban. Forty-six patients (45.5%) were on a low dose NOAC regimen. Sixteen patients (16%) were also on aspirin, 6 (5.9%) on clopidogrel and 3 (3%) on both antiplatelet agents. Sixty patients (59.4%) had pacemaker, 23 (2.8%) had a CRT device and 28 (27.7%) an ICD implanted. Seventy patients (69.3%) had a de-novo implant. Fifty-one patients (50.5%) were assigned to interruption of NOAC therapy before device implantation, while 50 patients (49.5%) were randomised to uninterrupted NOAC therapy. Overall, four patients (4%) had a pocket haematoma (two in the group 1 and two in the group 2, $p = 0.984$). Among the patients who had pocket haematoma, two were in dual antiplatelet therapy (one in the group 1 and one in the group 2) and one, in the uninterrupted NOAC group, was on clopidogrel. A clinically significant haematoma occurred in only one patient (1%) in the uninterrupted NOAC group (this patient was not on any antiplatelet therapy) and in none of the patients in the interrupted group ($p = 0.320$). The same patient had a pocket infection that was treated successfully with antibiotics and did not require surgery. No other

major bleeding complications or thrombotic events were reported in either of the interrupted or uninterrupted group. There was no significant difference in the incidence of the primary and secondary end-points between the two groups (Table 2). There was no difference among dabigatran, rivaroxaban and apixaban; or among the high or low dose regimes in the primary and secondary end-points (Table 3).

Discussion

Between 23-34% of patients requiring CIED implantation are on long-term oral anticoagulation, most commonly for stroke prophylaxis in the presence of underlying atrial fibrillation [5-8]. Many studies have demonstrated that CIED implantation with uninterrupted warfarin therapy is safe and reduces bleeding events compared to heparin bridging [9]. The BRUISE CONTROL trial [3] did show that a strategy of continuing warfarin at the time of CIED surgery significantly reduced the incidence of clinically significant device-pocket haematomas compared to heparin bridging. Continuation of warfarin, with a a target international normalized ratio (INR) on the day of surgery less than or equal to the upper limit of the patient's prescribed therapeutic range, has since been suggested by international guidelines, especially in patients with a high annual thromboembolic risk (≥ 5%) [4, 10]. NOACs have emerged over the last few years and are now largely used as first line therapy in patients with atrial fibrillation, requiring stroke prophylaxis, or as treatment for a deep vein thrombosis or pulmonary embolism. Interruption of NOAC therapy without heparin bridging is currently recommended before device surgery [4]. In a subgroup of patients undergoing CIED surgery in the RE-LY trial, interruption of dabigatran was associated with similar incidence of pocket haematoma compared with interruption of warfarin [11]. Routine discontinuation of NOAC therapy is currently a common practice in most centres, and was demonstrated by the recent European Snapshot Survey on Procedural Routines for Electronic Device Implantation (ESS-PREDI) in which NOAC therapy was interrupted in 88.7% of patients before CIED implant [12]. Jennings et al demonstrated the safety of

uninterrupted dabigatran therapy prior to CIED implantation in a small retrospective study involving 14 patients [13]. These findings were confirmed in a prospective observational trial involving 25 patients on dabigatran, who underwent CIED implantation. Dabigatran therapy was continued in 11 patients and there was no difference in major bleeding/thrombotic complications when compared to those whose dabigatran therapy was interrupted [14]. The recently presented, but not yet published, data from the BRUISE-2 trial [15, 16] failed to demonstrate superiority of non-interrupted NOAC strategy compared to NOAC interruption before CIED implant, but did prove the safety of NOAC continuation in this setting.

Our data are consistent to the results of the BRUISE-2 trial and confirm that a non-interrupted NOAC strategy appears to be safe and not associated with an increased risk of complications compared to interrupted NOAC therapy. The overall rate of bleeding events in both groups was low and similar to that shown in previous studies evaluating CIED implantation in patients on anticoagulation. Furthermore, there was no difference in the incidence of pocket haematoma formation between the two groups. A pocket haematoma is a serious complication of CIED implantation. It often requires reoperation, with prolonging hospitalisation and increased healthcare costs [9, 17]. Moreover, pocket haematomas often result in prolonged interruption of anticoagulation, and a consequently increased risk of thrombotic events. Pocket haematomas are also associated with a 15-fold higher risk of device infection, which carries a significantly higher risk of morbidity and mortality [12, 17-18]. Implantation of a CIED without interruption of NOAC therapy may reduce the risk of thromboembolic events in those with underlying atrial fibrillation. Furthermore, regular discontinuation of NOAC therapy can cause prolonged hospitalisation, particularly in non-elective patients whereby CIED implantation is commonly postponed for 24-48 hours prior to the operation, to allow reversal of the anticoagulant effects. The possibility of performing the CIED implant safely without interruption of NOACs may reduce hospitalization duration and overall healthcare costs.

The main limitation of this pilot study is the limited number of patients and the single centre design. This trial is underpowered to detect bleeding difference in the two groups.

Conclusion

Data from this pilot study suggest that uninterrupted NOAC therapy for CIED implantation appears to be as safe as NOAC interruption and does not increase bleeding complications compared to conventional interrupted NOAC therapy.

Author contribution: concept/design: AC, DR; data analysis/interpretation: AC, DR, RP; drafting article: AC; critical revision of article: DR, RP, AI, GDS, VC; approval of article: AC, DR, RP, VC, AI, GDS, IC, FP, DS, LR; statistics: RP; data collection: AC, DR, IC, VC, FP, DS, LR.

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Table 1 – Baselines

	Total (n=101)	Uninterrupted (n=50)	Interrupted (n=51)	P
Age	76.0±8.8	75.9±9.4	76.1±8.4	N.S.
Men	65.3% (66)	64.0% (32)	66.7% (34)	N.S.
Diabetes	26.7% (27)	18.0% (9)	35.3% (18)	N.S.
Coronary artery disease	27.7% (28)	34.0% (17)	21.6% (11)	N.S.
Hypertension	77.2% (78)	72.0% (36)	82.4% (42)	N.S.
Creatinine	1.01±0.24	1.04±0.24	0.97±0.24	N.S.
CHA2DS2VASc	3.1±.0	3.2±1.0	3.1±1.0	N.S.
BBlockers	68.3% (69)	70.0% (35)	66.7% (34)	N.S.
ACEi	85.1% (86)	88.0% (44)	82.4% (42)	N.S.

Diuretics	63.4% (64)	74.0% (37)	52.9% (27)	N.S.
Dabigatran	36.6% (37)	30.0% (15)	43.1% (22)	N.S.
Rivaroxaban	32.7% (33)	36.0% (18)	29.4% (15)	
Apixaban	30.7% (31)	34.0% (17)	27.5% (14)	
Low dose NOAC	45.5% (46)	46.0% (23)	45.1% (23)	N.S.
Aspirin	15.8% (16)	18.0% (9)	13.7% (7)	N.S.
Clopidogrel	5.9% (6)	8.0% (4)	3.9% (2)	N.S.
Dual antiplatelet therapy	3.0% (3)	4.0% (2)	2.0% (1)	N.S.
Procedural duration (min)	53.8±12.1	51.4±2.8	56.2±10.9	N.S.
PPM	59.4% (60)	58.0% (29)	60.8% (31)	N.S.
CRT	22.8% (23)	24.0% (12)	21.6% (11)	N.S.
ICD	27.7% (28)	32.0% (16)	23.5% (12)	N.S.
De novo implant	69.3% (70)	60.0% (30)	78.4% (40)	N.S.
Box change	22.8% (23)	28.0% (14)	17.6% (9)	N.S.
Upgrade	8.9% (9)	14.0% (7)	3.9% (2)	N.S.
Sub-pectoral implant	0% (0)	0% (0)	0% (0)	N.A.

N.S.: non-significant. N.A.: non-applicable.

Table 2 – Outcomes

	Total (n=101)	Uninterrupted (n=50)	Interrupted (n=51)	P
Haematoma	4.0% (4)	4.0% (2)	3.9% (2)	0.984
Clinical significant haematoma	1.0% (1)	0% (0)	2.0% (1)	0.320
Loss of >2g Hgbl	7.9% (8)	6.0% (3)	9.8% (5)	0.479
Pocket infection	1.0% (1)	0% (0)	2.0% (1)	0.320
Infection requiring explant	0% (0)	0% (0)	0% (0)	N.A.
Admission length (days)	2.2±0.9	2.1±0.6	2.3±1.1	0.505
Bleeding <30days	0% (0)	0% (0)	0% (0)	N.A.
Stroke <30days	0% (0)	0% (0)	0% (0)	N.A.
Rehospitalisation <30days	1.0% (1)	0% (0)	2.0% (1)	0.320
Mortality <30days	0% (0)	0% (0)	0% (0)	N.A.

N.A.: non-applicable.

Table 3 – Outcomes according to anticoagulant and dose regimen

	Dabigatran (n=37)	Rivaroxaban (n=33)	Apixaban (n=31)	P	Normal dose (n=55)	Low dose (n=46)	P
Haematoma	5.4% (2)	3.0% (1)	3.2% (1)	0.851	1.8% (1)	6.5% (3)	0.227
Clinical significant haematoma	2.7% (1)*	0% (0)	0% (0)	0.417	1.8% (1)*	0% (0)	0.358
Loss of >2g Hgbl	10.8% (4)	6.1% (2)	6.5% (2)	0.715	5.5% (3)	10.9% (5)	0.316
Pocket infection	2.7% (1)*	0% (0)	0% (0)	0.417	1.8% (1)*	0% (0)	0.358
Rehospitalization <30days	2.7% (1)*	0% (0)	0% (0)	0.417	1.8% (1)*	0% (0)	0.358

Note: * Same patient