Europace (2006) **8**, 283–287
doi:10.1093/europace/eul011

Post-operative use of heparin increases morbidity of pacemaker implantation

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Received 23 January 2004; accepted after revision 3 January 2006; online publish-ahead-of-print 16 March 2006

KEYWORDS
Pacemaker implantation;
Heparin;
Mechanical heart valves;
Atrial fibrillation;
Haemorrhage;
Thrombo-embolism;
Adverse events

Aims The objective of this study is to characterize the incidence of peri-operative severe adverse events (AEs) related to the post-operative use of heparin in patients undergoing pacemaker surgery.
Methods and results We retrospectively compared the outcome of 38 patients with mechanical valves (MVs) and 76 patients with atrial fibrillation (AF) with control cases matched for gender, age, and surgical details. Heparin was systematically used post-operatively in MV patients, but left to clinical judgment in AF patients. The relative risk for severe haemorrhagic AEs was 11 (CI 1.5–81.1, $P < 0.01$) in the MV group when compared with matched controls and 8 (CI 1.0–62.5, $P < 0.05$) in the AF group. Overall, the relative risk of heparin use in the post-operative period was 14 (CI 1.88–104, $P = 0.0006$) and the post-operative stay was prolonged from 7 days in this group when compared with control cases ($P < 0.0001$).The variables associated with haemorrhage were the delay to restart heparin after surgery and the presence of an MV.
Conclusion Post-operative use of heparin increases morbidity of pacemaker implantation. A different approach to management of these patients is possible.

Introduction

Complications have been reported in up to 5% or even 10% of patients undergoing pacemaker implantation.[1,2] Haemorrhagic manifestations occur in 1.5% of these patients.[2,3] Some of them chronically treated by oral anticoagulation drugs are asked to discontinue this therapy before surgery, and if anticoagulation is still needed (patients with MV or AF), heparin may be substituted and restarted after surgery.

These patients are threatened with thrombo-embolic or haemorrhagic complication after surgery.[4] Paradoxically, there is no consensus on management of oral anticoagulation during this type of surgery. The incidence of peri-operative adverse events (AEs) related to this management remains scarcely documented.[5,6]

We sought after severe AEs occurring peri-operatively in a retrospective case-control study to compare patients with atrial fibrillation (AF) or mechanical valve (MV) undergoing pacemaker surgery. As a secondary objective, we also aimed at identifying pre-disposing factors for bleeding in this population.

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Methods

Population studied

This retrospective case–control study was conducted over a period of 3 years from January 1998 until December 2001. Overall, 921 patients were admitted for pacemaker implantation or replacement with electrode insertion when appropriate. Among these patients, 114 received oral anticoagulant drug therapy for a minimum of 1 month before referral: 76 for AF group and 38 for MV group. These patients were matched with 114 controls (C group, Cmv for the control patients of the MV group, and Caf for the control patients of the AF group). Each patient receiving anticoagulation therapy was matched with a control patient for age, gender, type of surgery (first implant or replacement), type of venous access (subclavian or cephalic vein), number of leads, and year of surgery. The study complies with the declaration of Helsinki and all patients gave written and informed consent before pacemaker surgery.

Exclusion criteria

These criteria were age below 18 years, ticlopidine or clopidogrel therapy, bi-atrial or bi-ventricular pacing systems, and documented disorders of haemostasis.

Heparin management in the MV group

In the MV group, our management, following the European Guidelines,[7] was to suspend oral anticoagulation 3 days

(acenocoumarol) or 4 days (warfarin, fluindione, and phenindione) before admission and to substitute it with heparin until 5 h prior to surgery. Heparin was given intravenously with a target aPTT of 60 s. Patients were eligible for surgery when pre-operative INR and aPTT, assessed 1 h before surgery, were below 1.2 and 45 s, respectively. Intravenous (IV) heparin was re-initiated post-operatively in all patients with a target aPTT of 60 s. No recommendation was given to re-initiate oral anticoagulant drug therapy. aPTT was controlled on a daily basis while the patient received heparin. INR was assessed according to the type of antivitamin K used. The final target INR followed the established recommendations depending on the type of prosthetic valve.[7] Patients were discharged only when the target INR was reached.

Heparin management in the AF group

In these patients, the substitution with heparin was made according to referring physician preference. When this substitution was made on an ambulatory basis, subcutaneous (SC) heparin was used by the general practitioner. The minimum delay allowed between the last SC injection and surgery was 12 h. Post-operatively, anticoagulant drug management was left to the operator.

In both groups, the use of wound drainage was also left to the operator. Electrocautery was systematically used to perform incisions before lead and pulse generator insertion.

Definitions

An AE was defined as any undesirable and unexpected clinical occurrence. However, a pre-existing condition resolved by hospitalization after enrolment was considered an AE. All AEs occurring within 30 days after surgery were collected, and then submitted to a committee of three independent physicians for analysis. AEs were classified as haemorrhagic or not, procedure-related or not, and severe or not. AEs causing or prolonging hospitalization, leading to another surgical procedure or fatal, were considered as severe AEs. Procedure-related AEs were defined by the presence of a direct causative link between AE and invasive/surgical procedure even if late after implantation (e.g. a pocket haematoma 10 days after surgery) and whatever the nature of the AE was. Haemorrhagic AEs were defined as events related to external or internal bleeding or haematomas including bloody effusions in pericardium or pleural space. Blood transfusions were also considered as haemorrhagic AEs. Heparin overdose was considered when aPTT was found to be above 100 s.

Follow-up

Its duration was 30 days post-surgery. All patients underwent a telephonic interview. In the case of admission to another institution, data were obtained from the patient's files or through the general practitioner. AEs were collected from these interviews.

Data collection

Data were collected retrospectively from medical and nursing observations and from medical reports in the case of re-admission to a different hospital after discharge from our institution. In addition to information pertaining to AEs, the following information was collected: a history of diabetes, the indication for oral anticoagulation therapy, aspirin therapy, pre- and post-operative INR and aPTT values, and complete blood cell counts including platelets, routine serum chemistry, technical surgical details (i.e. venous access, procedure duration, and use of wound drainage), and details of management of anticoagulation (i.e. delay between wound closure and IV or SC heparin restart and delay before antivitamin K restart).

Statistical analysis

Univariate statistical analysis including Student's *t*-test and Fisher's exact test was conducted with the Insat software package (GraphPad, USA). Relative risks were computed with Katz approximation. Logistic regression analysis was performed with the SPSS software. Data were expressed as mean $\pm$ standard deviation. Comparisons were two-tailed and a *P*-value <0.05 was considered significant.

Results

MV group

Characteristics of the MV group

Patient characteristics are presented in *Table 1*. This MV subgroup comprised 8 patients with mitral valve prosthesis and 21 with aortic and 9 patients with both aortic and mitral valve prostheses. The vast majority of these patients received fluindione ($n = 31$), five patients received acenocoumarol, two received phenindione, and no patients warfarin. Heparin was stopped 6.6 ± 2.9 h prior to surgery. All pre-operative aPTT and INR assays were below 45 s and 1.2. Regarding the post-operative anticoagulation management, all patients were treated with IV heparin, which was restarted 3.3 ± 2.9 h after wound closure. The minimum delay for heparin restart after surgery was 1 h, the maximum 14 h, and the median 3 h. The mean delay for oral anticoagulant drug therapy restart was 3.3 ± 3 days. Wound drainage was used in 31 patients (81%) compared with no patient in the Cmv group ($P < 0.0001$).

Morbidity analysis

Hospital stay was 17.3 ± 6.2 days for MV patients compared with 7.4 ± 3.9 days in the Cmv group ($P < 0.0001$), which was caused by a longer post-operative stay: 11.6 ± 6.3 vs. 4.7 ± 2.6 days ($P < 0.0001$).

A total of 16 severe AEs were observed in 15 patients of the MV group, whereas only 5 severe AEs occurred in control patients ($P < 0.02$, relative risk 4.3, CI 1.4–13.5).

As indicated in *Table 2*, among these 16 severe AEs, 3 were procedure related but non-haemorrhagic, 1 was haemorrhagic but not procedure related, and 12 were severe bleeding manifestations related to surgery. In comparison, only one event among the five severe AEs reported in the Cmv group was haemorrhagic and procedure related ($P < 0.05$)

Table 1 Characteristics of the MV group

Group	Mechanical valve (MV)	Controls (Cmv)
n	38	38
Age (years)	68 ± 10	68 ± 9
Men/women	17/21	17/21
Body weight (kg)	68 ± 10	69 ± 9
One/two leads insertion	6/21	6/21
Pacemaker replacement only	11	11
Cephalic/subclavian vein access	20/7	20/7
Wound drainage	31*	0
Diabetes	7	5
Aspirin therapy	0	5

*$P < 0.0001$.

Table 2 Severe AEs observed in the MV group and their matched controls

	MV group	Controls (Cmv)
Non-procedure-related AEs	Abdominal haematoma and transfusion ($n = 1$)	Acute coronary syndrome ($n = 1$)
Non-haemorrhagic but procedure-related AEs	Lead dislodgment ($n = 2$) Lead infection ($n = 1$)	Pneumothorax ($n = 3$)
Haemorrhagic and procedure-related AEs	Pocket haematoma requiring surgery ($n = 5$) Pocket haematoma not requiring surgery ($n = 5$) Pocket haematoma requiring surgery, cardiogenic shock, and death ($n = 1 + 1$)	Pocket haematoma requiring surgery ($n = 1$)

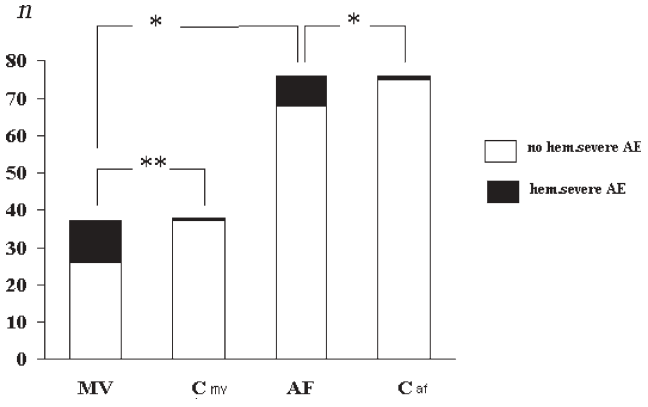

Figure 1 Incidence of severe haemorrhagic AEs in 38 patients with MV prosthesis (MV subgroup) and their 38 controls and in 76 patients with AF subgroup and their respective controls. $^{*}P < 0.05$; $^{**}P < 0.01$.

(*Figure 1*). Overall, the relative risk for severe haemorrhagic AEs was 11 (CI 1.5–81.1, $P < 0.01$) in MV patients compared with matched controls. When analyzing the 11 patients (29%) of this group in whom haemorrhagic AEs occurred, we found earlier IV heparin restart compared with the 27 without bleeding (2.1 ± 1.4 vs. 3.8 ± 3.3 h, $P = 0.03$).

AF group

Characteristics of the AF group

Patient characteristics are presented in *Table 3*. All pre-operative aPTT and INR assays were below 45 s and 1.2. Twenty-five patients did not received heparin post-operatively, 30 were treated with IV heparin, and 21 with SC low molecular weight heparin.

Morbidity analysis

Hospital stay was prolonged compared with the respective controls: 11.0 ± 6.0 vs. 7.5 ± 4.0 days ($P < 0.001$), which was here again caused by a longer post-operative stay: 6.0 ± 3.3 vs. 4.9 ± 2.9 days ($P < 0.05$). We observed 10 severe AEs in the AF group compared with 5 in the Caf group ($P =$ ns, *Table 4*).

In this group, eight patients had severe haemorrhagic AEs compared with one patient in the Caf group ($P < 0.05$) (*Figure 1*). In this group, the relative risk for severe haemorrhagic AEs was 8 (CI 1.0–62.5, $P < 0.05$), compared with matched controls.

Table 3 Characteristics of the AF group

Group	AF	Control (Caf)
n	76	76
Age (years)	72 ± 8	72 ± 8
Men/women	42/34	41/35
Body weight (kg)	71 ± 13	69 ± 10
One/two leads insertion	25/33	25/33
Pacemaker replacement only	18	18
Cephalic/subclavian vein access	27/31	28/30
Wound drainage	9	8
Diabetes	12	13
Aspirin therapy	4	5

Impact of heparin use

Overall, 89 patients from both groups receiving heparin in the post-operative period were pooled and compared with their respective controls (38 patients in the MV group and 51 patients in the AF group). A total of 21 patients presented severe AEs compared with 7 in the controls (RR = 3, CI 1.3–6.7, $P = 0.007$). Fourteen of these 21 patients had severe haemorrhagic events related to the procedure compared with a single patient among the controls. The relative risk of haemorrhagic AEs linked to heparin use was 14 (CI 1.88–104, $P = 0.0006$). Hospital stay was 14.0 ± 6.6 days in patients with heparin compared with 7.3 ± 3.9 in the controls ($P < 0.0001$). Surprisingly, no thrombotic or embolic event resulting in a severe AE was noted. We did not find any case of heparin-induced thrombocytopenia.

As detailed in *Table 5*, the delay in heparin restart in the post-operative period and the presence of an MV were the sole independent factors identified, which were associated with the risk of bleeding.

Mortality analysis

A single fatal event was observed in this study. This patient had an aortic valve prosthesis and presented a pocket haematoma that required re-operation 8 days after surgery. He died from cardiogenic shock 19 days post-pacemaker surgery with no echographic evidence of valve thrombosis and no recurrent bleeding. Autopsy was not performed.

Discussion

The main finding of this study is that patients who receive heparin post-operatively have a 14-fold increased risk of

Table 4 Nature of the severe AEs observed in the population studied

Group	AF group	Control (Caf)
Non-procedure-related AEs	Pre-existing anaemia ($n = 1$)	Acute coronary syndrome ($n = 1$)
Non-haemorrhagic but procedure-related AEs	Lead dislodgment ($n = 1$)	Lead dislodgment ($n = 1$) Pneumothorax ($n = 2$)
Haemorrhagic and procedure-related AEs	Pocket haematoma requiring surgery ($n = 2$) Haemopericardium ($n = 2$) Blood transfusion ($n = 2$) Pocket haematoma not requiring surgery ($n = 1$) Intramediastinal bleeding ($n = 1$)	Blood transfusion ($n = 1$)

Table 5 Factors associated with the occurrence of severe bleeding in patients who received heparin post-operatively

	Severe haemorrhagic AEs	No severe haemorrhagic AEs
n	14	75
Age (years)	70.4 ± 6.9	69 ± 9
Men/women	7/7	37/38
Body weight (kg)	65 ± 10	71 ± 12
Diabetes	2	12
Aspirin therapy	0	3
Two leads inserted	5	40
Subclavian vein access	3	24
Mechanical valve prothesis	11*	27
Operation duration	50 ± 24	62 ± 32
Post-operative heparin delay (h)	2.14 ± 1.4**	5 ± 3.8
Post-operative heparin overdose	8	31

*$P = 0.006$.
**$P < 0.0001$.

haemorrhagic severe AEs in comparison with control patients. This accounts for a mean prolongation of hospital stay of 7 days.

The only predictive factors identified for this increased morbidity were the presence of an MV prosthesis and a short time before restarting heparin after surgery.

Substitution of oral anticoagulation by IV heparin was not responsible for any observable thrombo-embolic event, neither in MV patients nor in AF patients. The observed increased morbidity, at least in the MV subgroup, can be interpreted as a direct consequence of the systematic use of IV heparin in the post-operative period. The haemorrhagic risk related to heparin use has been previously emphasized in the available literature.[5]

Unlike non-cardiac surgery,[4,8–10]reports are scarce of anticoagulant drug management in patients with MVs undergoing pacemaker surgery. A major concern is the occurrence of valve thrombosis, justifying in some cases pre-operative substitution with heparin. This risk is estimated at 4 per 100 patients-years in patients who are not given any anticoagulant therapy.[11] Whether oral anticoagulant therapy should be withheld in all patients and all types of surgery are still a matter of debate. Some recommendations suggest that the risk of embolism is not high enough to warrant either pre- or post-operative therapy with IV heparin in the vast majority of these patients.[4] Other reports recommend systematic use of IV heparin after admission until 5 h before surgery when the MV is a mitral prosthesis.[12] Some experts suggest a patient-based analysis of the pros and cons of heparin substitution and recommend reserving heparin for patients with recent embolism (<1 year), for those with thrombotic problems when previously off therapy or those with Björk–Shiley MVs. Other patients with prosthetic valves should receive heparin only in the presence of additional risk factors including AF, left ventricular dysfunction, or mitral location of the prosthesis.[13] European guidelines, followed in the present study, are much more stringent, as they recommend systematic discontinuation of oral anticoagulation with interim heparin at a dose prolonging aPTT to 60 s in the case of non-cardiac surgery.[7]

The requirement of aPPT and INR values below 45 s and 1.2, 1 h before surgery, seems to be valid in the light of our results with the absence of any thrombo-embolism. These pre-operative thresholds are somewhat different from those usually recommended in the US guidelines (INR $\leq$ 1.3 or 1.5) before non-cardiac surgery or before cardiac catheterization.[12,13]

Post-operatively, we describe a 31% rate of severe haemorrhagic events in MV patients, which is similar to that reported in non-cardiac surgery.[14] Therefore, because of this high risk, pacemaker surgery cannot be considered any longer as a minor operative modality in this population. This result makes highly questionable the systematic use of IV heparin in the post-operative management of these patients.

Three strategies, not tested in the present study, could be proposed for pacemaker surgery: implantation without reversal of oral anticoagulation therapy,[15,16] implantation without reversal but with a low INR value,[17,18] or implantation with delayed anticoagulation restart.[4] These options should be considered taking the balance between the risk of thrombo-embolism, especially acute valve thrombosis, and the risk of bleeding. Haemorrhagic events complicating pacemaker surgery may be life threatening by themselves (e.g. haemopericardium) or by inducing new AEs due to re-operation or the development of septic complications.[19,20]

Owing to the risk of insufficient anticoagulation potentially leading to valve thrombosis, operators in the present study have probably been inclined toward high heparin dosage. This can be derived from the observation of a high incidence (39/114) of post-operative heparin overdose, especially in the MV subgroup where this incidence reached 70%. This observation which is probably a

consequence of an overestimation of the thrombo-embolic risk has been already described.[14]

In patients with AF, the use of pre or post-operative IV heparin or SC low molecular weight heparin was left open.[12] Clinical judgment was required from the operator to determine which patients were at high risk (approximately one-third) and required IV heparin until oral anticoagulation could be re-instated.[21,22] Patients judged at low embolic risk represented another one-third of the subgroup; they did not receive any type of heparin, in that case, oral anticoagulation was re-instated post-operatively as previously described.[23]

Nonetheless, despite this tailored approach, the relative risk for severe bleeding was eight-fold higher compared with matched controls. In this population, at lower risk, and because of the risk of heparin use in the post-operative period, we propose that oral anticoagulation should be re-initiated without heparin use.

In summary, following current European guidelines, patients who receive heparin after pacemaker implantation are at high risk for severe AEs. This increased morbidity is haemorrhagic in nature and directly caused by the use of heparin. As expected, patients with MVs are those at highest risk. The optimal management of these patients deserves further controlled studies and a re-appraisal of the guidelines should be undertaken.

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