

REVIEW ARTICLE

Perioperative anticoagulation in patients having implantation of a cardiac pacemaker or defibrillator: a systematic review and practical management guide

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Summary. *Background:* The perioperative management of anticoagulation in patients who are having implantation of a pacemaker or implantable cardioverter defibrillator (ICD) is a common clinical problem in which best clinical practise is not established. *Methods:* We performed a systematic review of the literature to assess the safety (pocket hematoma risk) and efficacy (thromboembolism risk) of different management strategies. We included studies involving patients who were having pacemaker or ICD implantation whenever a portion of these patients were receiving a coumarin and also assessed pocket hematoma or thromboembolism. *Results:* We identified eight studies that assessed two strategies used for perioperative anticoagulation management: interruption of a coumarin and use of bridging anticoagulation with a short-acting heparin; and perioperative continuation of a coumarin. A strategy involving bridging anticoagulation with therapeutic-dose heparin was associated with an incidence of pocket hematoma of 12–20%. A strategy involving perioperative continuation of a coumarin was associated with an incidence of pocket bleeding of 1.9–6.6%. The incidence of thromboembolic events was 0–1%, irrespective of the perioperative anticoagulation strategy used. *Conclusion:* The perioperative anticoagulation management of patients who require pacemaker or ICD implantation is not established but a strategy involving postoperative bridging with intravenous heparin confers a high risk for bleeding whereas perioperative continuation of a coumarin appears to confer a lower risk for bleeding.

Keywords: anticoagulation, bleeding, implantable cardioverter defibrillator, pacemaker, pacemaker pocket hematoma.

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Introduction

Approximately 176 000 patients undergo surgery for a permanent pacemaker or implantable cardioverter defibrillator (ICD) annually in North America [1], and up to 45% of such patients are receiving a coumarin because of atrial fibrillation or a mechanical heart valve [2]. The perioperative anticoagulant management of such patients is challenging because interruption of coumarin therapy may increase the risk for embolic stroke, which can be fatal or associated with major disability in 70% of patients [3]. Patients who have pacemaker or ICD implantation are susceptible to bleeding within the pacemaker pocket because the fascial layers are not sutured and remain unopposed. Pocket hematomas can become infected, increase the risk of bacterial endocarditis and may require surgical drainage [4,5].

In managing the perioperative anticoagulation of patients who are having pacemaker or ICD implantation, one approach is to stop the coumarin approximately 5 days before surgery and to administer bridging anticoagulation with intravenous heparin or low-molecular-weight heparin (LMWH) before and after surgery when the international normalized ratio (INR) is sub-therapeutic [6]. This approach aims to minimize the time patients are not therapeutically anticoagulated and the risk for thromboembolism. Another approach is to continue the coumarin during the perioperative period, thereby mitigating the risk for thromboembolism, and provide close attention to local hemostasis. Although minor procedures, such as dental extractions, can be safely carried out in anticoagulated patients [7], the safety of this approach in patients is not established for surgical procedures. We systematically reviewed studies assessing perioperative anticoagulation of patients requiring pacemaker or ICD implantation. We aimed to assess the safety (pocket hematoma and non-pocket bleeding risk) and efficacy (thromboembolism risk) of different management strategies and, based on this evidence, to provide practical guidelines for the perioperative anticoagulation management of such patients.

Methods

Data sources

We identified all English language articles that assessed perioperative anticoagulation management in patients having pacemaker or ICD implantation. Databases used were MEDLINE (1966–April 2008, week 4), EMBASE (1997–2008, week 18) and the Cochrane Library (1999–2008, issue 2). The search strategy is detailed in Appendix 1. In addition, reference lists were reviewed by a manual search.

Study selection

A study was included if it assessed patients who were having pacemaker or ICD implantation and if at least a portion of these patients were receiving a coumarin. Included studies also assessed at least one of these outcomes: pocket hematoma; thromboembolism. Case reports and commentaries were excluded.

Data extraction

Due to the heterogeneity of study outcomes, pooling of data was not possible, thereby precluding any statistical analyses. Instead, our findings are presented in a narrative format. The outcomes of interest were: pocket hematoma bleeding and thromboembolic events.

Results

Study selection

A search of the MEDLINE database identified 288 potentially relevant articles, of which eight satisfied our selection criteria and were included in this review [8–15]. Manual searches of reference lists yielded no additional studies. Searches of the EMBASE and Cochrane databases did not yield any additional articles.

Data extraction

The characteristics of included studies and the incidence of clinical outcomes associated with different perioperative anticoagulation strategies are shown in Table 1.

Perioperative anticoagulation strategies

In the articles that satisfied the study selection criteria, we identified two strategies used for perioperative anticoagulation management: (i) interruption of the coumarin and use of bridging anticoagulation, either with intravenous heparin or subcutaneous LMWH [8–11]; and (ii) continuation of the coumarin in the perioperative period [12–15]. We did not identify any studies assessing perioperative management with partial anticoagulation (INR 1.5–1.9) at the time of pacemaker or ICD implantation.

Perioperative interruption of the coumarin and use of bridging anticoagulation Wiegand *et al.* [8], in a retrospective cohort study, assessed the incidence of pocket hematoma in 3164 patients who had pacemaker implantation, which included 1069 phenprocoumon-treated patients. Phenprocoumon was stopped 1–5 days before surgery and bridging with therapeutic-dose heparin or LMWH was administered when the INR was <2.0. After surgery, bridging was resumed at a dose determined by patients' thromboembolic risk. This study included a comparator group involving patients who were not receiving phenprocoumon but who received low-dose subcutaneous heparin (5000 IU twice-daily) after surgery. Patients who received bridging with therapeutic-dose intravenous heparin after surgery had a lower incidence of venous thrombosis than those who did not receive such treatment (0.09% vs. 0.60%; $P = 0.04$). However, bridging with intravenous heparin did not confer a lower incidence of arterial thromboembolism within the first month after surgery (0.18% vs. 0.21%; $P = \text{NS}$), and was associated with a higher incidence of pocket hematoma (12.2% vs. 2.5%; hazard ratio, 5.43; 95% CI, 3.23–9.13).

Michaud *et al.* [9] assessed pacemaker hematoma in three patient groups who were undergoing pacemaker implantation: a cohort of warfarin-treated patients who received bridging with intravenous heparin after warfarin interruption; a cohort of warfarin-treated patients who did not receive bridging after warfarin interruption; and a third cohort consisting of patients who were not receiving warfarin. Within the cohort of patients who were to receive bridging after warfarin interruption, they were randomly allocated to resume heparin either 6 or 24 h after surgery. In patients who received bridging with heparin, the overall incidence of pocket hematoma was 20% (the incidence was 23% and 17% in patients who received heparin 6 and 24 h after surgery, respectively). The overall incidence of hematoma was significantly higher in the bridging group than in the no bridging group (4%) and the cohort that was not receiving warfarin (2%). However, there was one thromboembolic event (stroke) in the no bridging group, for an incidence of 0.5%.

Using a case-control design, Marquie *et al.* [10] assessed 114 patients who were receiving a coumarin because of atrial fibrillation or a mechanical heart valve and 114 matched controls who were not receiving a coumarin. Patients with a mechanical heart valve stopped the coumarin 3–4 days before surgery and received pre- and post-operative bridging with intravenous unfractionated heparin; patients with atrial fibrillation stopped the coumarin 4–5 days before surgery and some (51 of 76) received perioperative low-dose heparin (5000 IU twice-daily), which was given at the discretion of the treating physician. Pocket hematoma occurred in 11 of 38 (29%) patients who received intravenous heparin, in three of 76 (4%) patients who received low-dose heparin, and in one of 114 (1%) controls who did not receive perioperative heparin. Postoperative use of heparin, of any type, conferred a 14-fold increased risk for pocket hematoma (OR = 14.0; 95% CI, 1.9–104).

Table 1 Studies evaluating pacemaker or ICD implantation using various anticoagulation strategies

Author (year)	Study design	Recruitment	Patient population and sub-groups studied	Perioperative anticoagulation	Mean INR*	Follow-up	Pocket hematoma n, %	Thromboembolic events	All-cause mortality
Perioperative interruption of the coumarin and use of bridging anticoagulation									
Wiegand <i>et al.</i> [8]	Retrospective cohort	1990–2002	1069 patients requiring VKA (mean age, 72 years): 67% AF, 16% MHV, 14% ventricular dysfunction, 2% prior DVT Group A: 1069 Group B: 765 controls	A: VKA stopped, bridging with IV or SC UFH B: no VKA; low-dose UFH post-op	<2.0	3 months	A: 70, 12.2% B: 19, 2.5%	CVA: 0.2% suspected CVA: 0.1% DVT: 0.2% (1 fatal PE)	0.16%
Michaud <i>et al.</i> [9]	RCT + cohort	1997–1998	192 patients requiring VKA (mean age, 64 years): 61% AF, 37% MHV, 2% prior DVT Group A: 49 Group B: 28 Group C: 115 controls	A: VKA stopped; bridging with IV UFH (started 6 or 24 h post-op) B: VKA stopped, restarted after surgery C: no VKA	<1.5	2 months	A: 10, 20% B: 1, 4% C: 2, 2%	stroke: 0.5% (1 patient in group B)	0.5% (1 patient in group C)
Marquie <i>et al.</i> [10]	Case-control	1998–2001	114 patients requiring VKA: 38 MHV group (mean age, 68 years); 76 AF (mean age, 72 years) Group A: 38 Group B: 76 Group C: 114 controls	A: VKA stopped; bridging with IV UFH B: VKA stopped; low-dose UFH pre- and post-op at discretion of physician C: no VKA	<1.2	1 month	A: 11, 29% B: 3, 4% C: 1, 1%	Not reported	0.9%
Hammerstingl <i>et al.</i> [11]	Subset of prospective case series	2000 onwards	116 patients with MHV requiring VKA (mean age, 71 years) Group A: 21	A: VKA stopped, bridging with SC LMWH	<1.5	1 month	A: 0%	None	None
Perioperative continuation of the coumarin									
Al-Khadra [12]	Retrospective cohort	2001	Group A: 47 patients (mean age, 56 years) requiring VKA: 70% AF; 23% MHV; 2% DVT; 2% atrial thrombus; 2% MI; 2% stroke	A: VKA continued (unless INR ≥ 3.5)	2.3	6 weeks	A: 1, 2%	None	None

Table 1 (Continued)

Author (year)	Study design	Recruit-ment	Patient population and sub-groups studied	Perioperative anticoagulation	Mean INR*	Follow-up	Pocket hematoma n, %	Thromboembolic events	All-cause mortality
Giudici <i>et al.</i> [13]	Retrospective cohort	1996–2002	Group A: INR ≥ 1.5 , 470 patients (mean age, 72 years) Group B: INR < 1.5 , 555 patients (mean age, 72 years) – included patients whose VKA was stopped and those not taking warfarin)	A: VKA continued B: VKA stopped	A: 2.6 B: 1.1	2 weeks	A: 12, 2.6% B: 12, 2.2%	A: 0% B: 0.2%	None
Goldstein <i>et al.</i> [14]	Retrospective cohort	1994–1997	Group A: warfarin group, 37 patients (mean age, 69 years) Group B: no warfarin group, 113 patients (mean age, 64 years) (within control group)	A: uninterrupted warfarin B: no perioperative anticoagulation	A: 2.5 B: 1.1	1 week	None [†]	0%	None
Milic [‡] <i>et al.</i> [15]	Sub-group of RCT	2002–2004	Group A: 20 patients Group B: 21 patients 89% AF; 6% MHV; 5% DVT	Group A: Perioperative heparin Group B: Uninterrupted warfarin	A: & B: 2.7	2–27 months	A: 5, 25% B: 5, 23.8%	Treatment: tx: 0% Controls: 1.2%	None

*Day of surgery unless otherwise indicated. † based on 576 patients who received high dose heparin. ‡ Outcome measured was 'wound related complications', which included bloody or serious wound drainage, difference between groups not significant. † Patients randomized to a fibrin sealant during surgery (treatment group) or no sealant (controls); none in the sealant group developed hematoma. ICD, implantable cardioverter defibrillator; AF, atrial fibrillation; MHV, mechanical heart valve; CVA, cerebrovascular accident; DVT, deep vein thrombosis; MI, myocardial infarction; PE, pulmonary embolism; RCT, randomized controlled trial; UFH, unfractionated heparin.

In a prospective case series of patients anticoagulated due to mechanical heart valves, Hammerstingl *et al.* [11] included 21 patients who were undergoing pacemaker implantation. These patients followed a standardized bridging protocol involving cessation of phenprocoumon 4–6 days pre-procedure followed by subcutaneous enoxaparin twice daily once the INR fell below 2.0. Therapeutic-dose LMWH was restarted at least 24 h after the procedure along with phenprocoumon until the INR became therapeutic. All procedures were performed with an INR <1.5, and no bleeding or thromboembolic events were observed among this subset of patients.

Perioperative continuation of the coumarin In a retrospective cohort study, Al-Khadra *et al.* [12] assessed 47 patients who continued warfarin in the perioperative period and had a mean INR of 2.3 (range 1.5–3.1) on the day of surgery. This approach was associated with no (0%) pocket hematomas that required evacuation, although one patient (2%) developed a hematoma that resolved spontaneously. There were no (0%) thromboembolic events observed.

Giudici *et al.* [13], in a retrospective cohort study, assessed the incidence of perioperative complications in 470 warfarin-treated patients having pacemaker or ICD implantation with warfarin continued perioperatively and in 555 controls, who were either not receiving warfarin or had warfarin stopped before surgery. On the day of surgery, the mean INR in the warfarin continuation group and the control group was 2.6 (range 1.5–6.9) and 1.1 (range 0.9–1.4), respectively. The incidence of hemorrhagic complications was 2.8% (12 pocket hematomas) in the warfarin group and 2.2% (12 pocket hematomas) in the control group, which was not significantly different. The mean INR in warfarin-treated patients who developed pocket hematoma was 3.0 (range: 2.0–6.9). There was one thromboembolic complication, one stroke (0.2%) in the control group.

In another retrospective cohort study, Goldstein *et al.* [14] assessed 150 patients who had pacemaker or ICD implantation, 37 of whom were receiving warfarin that was continued around the time of surgery and the remainder were controls who were not receiving warfarin. On the day of surgery, the mean INR in the warfarin continuation group and control group was 2.5 and 1.1, respectively. The incidence of complications was 5.4% in the warfarin continuation group (one patient with bloody wound drainage, one patient with serous wound drainage) and 1.8% in the control group (two patients with bloody wound drainage), which was not significantly different. There were no thromboembolic events observed in either group.

Finally, Milic *et al.* [15] did a randomized trial to compare the use of a fibrin sealant (vs. no sealant) in 81 patients having pacemaker implantation. In the sub-group of 41 patients randomized to the no sealant arm, who are comparable with other patients in this review, five of 20 (25%) patients who received perioperative bridging with intravenous UFH developed pocket hematoma and five of 21 (24%) who continued

warfarin (INR 1.8–3.8 at time of surgery) developed pocket hematoma. One (1%) patient suffered a stroke.

Discussion

Literature review

There are two main findings from our review of studies evaluating the safety and efficacy of different perioperative anticoagulation strategies in patients having pacemaker or ICD implantation. First, there is a lack of good quality evidence as to the optimal management strategy. All studies had one or more major methodological limitations. Most studies were retrospective and, therefore, subject to patient selection bias, with the potential to provide skewed outcome rates. Each study was done at a single institution and centre-specific factors, such as surgical technique, may have influenced observed outcome rates. Finally, there was no uniform definition of pocket hematoma, which, for example, was described as 'exceeding the size of the generator' in one study [8] and based on quantitative criteria in two other studies [13,15]. This limited the ability to reliably determine rates of pocket hematoma. The only randomized trial that was included assessed resumption of heparin bridging at 6 or 24 h after surgery [9]. However, no trial compared a continuation of a coumarin approach with that of interrupting the coumarin and using bridging anticoagulation.

Second, the dominant finding from the available evidence is that a perioperative anticoagulation strategy that involves intravenous heparin use is associated with a high risk for bleeding whereas a promising, and possibly safer, alternative strategy involves perioperative continuation of the coumarin. Thus, in studies that assessed patients who stopped the coumarin and received bridging anticoagulation with intravenous heparin, rates of pocket hematoma were high, between 12% and 29% [8–10]. On the other hand, in patients who did not stop the coumarin, the rates of pocket or other non-pocket bleeding were between 1.9% and 6.6% in four studies totaling 611 patients [12–14], although it was 24% in a small study involving 21 patients whose INR at the time of surgery was 1.8–3.8 [15].

The explanation for the apparently lower risk for bleeding with perioperative continuation of a coumarin is not clear. It is possible that acute administration of intravenous heparin in close proximity *after* surgery may precipitate new bleeding that was not observed *during* surgery and managed with local hemostatic measures such as cautery or blood vessel ligation. Indeed, in patients undergoing major orthopedic surgery, the incidence of bleeding is lower if anticoagulants are administered before surgery than 4–6 h after surgery [16]. On the other hand, if patients undergo surgery while anticoagulated, any excessive bleeding may be detectable at an earlier stage and would prompt hemostatic measures. Though continuation of a coumarin without dose reduction conferred a lower risk for pocket hematoma than perioperative use of intravenous heparin, it is plausible that a lower perioperative intensity of

anticoagulation, with partial interruption of the coumarin, would further reduce the risk for pocket hematoma. In support of this contention, studies involving patients who had surgery in association with lower intensity anticoagulation (INR <2.0 at the time of surgery) showed a lower risk for bleeding than patients who received higher-intensity perioperative anticoagulation (INR 2.0–3.5) [17,18].

Practical guide to perioperative anticoagulation

Based on the findings from our review, coupled with our experience in the perioperative management of patients who are receiving warfarin and require pacemaker or ICD insertion, we have attempted to provide a sensible approach to perioperative anticoagulation, which is shown in Fig. 1. Our suggested management algorithm is anchored on patients' risk for arterial thromboembolism. Thus, patients at high risk can be managed with an approach that involves stopping warfarin and administering bridging anticoagulation in the pre- and post-operative periods or an approach that involves continuing warfarin without a dose reduction. Both strategies aim to minimize the time patients are not therapeutically anticoagulated. Based on the findings from our review, if a 'bridging anticoagulation' strategy is chosen, we suggest avoiding the use of intravenous heparin in the

postoperative period. To simplify perioperative management, subcutaneous LMWH can be substituted for unfractionated heparin and, to mitigate the risk for pocket hematoma, LMWH can be resumed 48–72 h after surgery. The development of a bleed will necessitate reversal and extended interruption of anticoagulation, which is counter to the management objectives. If a continuation of warfarin strategy is used, we suggest ensuring the INR is <3.0 on the day of surgery and, ideally, between 2.0 and 2.5.

In patients at moderate to low risk for thromboembolism, in whom maintenance of therapeutic anticoagulation is a lesser priority, the aim is to minimize risk for bleeding. This would entail simply stopping warfarin approximately 5 days before the procedure and resuming treatment on the day after the procedure. A novel alternative strategy that can be considered, which we have used in our practise, is one where warfarin is continued in the perioperative period but at a reduced intensity of anticoagulation. With this admittedly empiric approach, 50% of patients' usual dose of warfarin is administered before surgery, aiming for an INR of 1.5–2.0 at the time of surgery. The initiation of this reduced dose approach will depend on patients' baseline INR, which is typically measured 7–10 days before surgery when patients are assessed for perioperative anticoagulation.

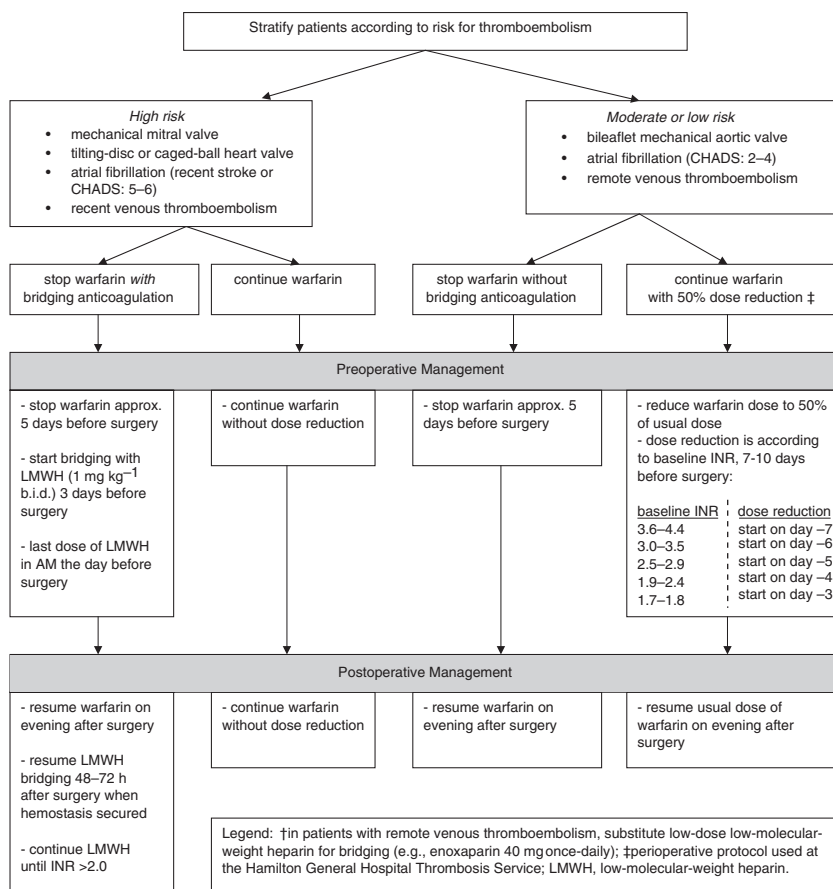


Fig. 1. Suggested perioperative anticoagulant management for patients having pacemaker or ICD implantation.

Conclusion

The optimal perioperative anticoagulation management of patients who require pacemaker or ICD implantation is not established but a strategy involving bridging with intravenous heparin is associated with a high risk for bleeding, whereas perioperative continuation of warfarin appears to confer a lower risk for bleeding. Randomized trials are needed to compare the efficacy and safety of different perioperative anticoagulation strategies in the increasing number of patients who require a pacemaker or ICD.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interests.

Appendix. Literature search strategy

A search of the Cochrane Collection using the following search terms resulted in two Cochrane reviews.

1. anticoagulation [search all text]

AND

2. pacemaker [search all text]

AND

3. perioperative [search all text]

A further search of all EBM reviews (ACP Journal Club, DARE, and CCTR) through OVID did not yield any more reviews.

A search of MEDLINE from 1966 to April, Week 4, 2008 was limited to English language articles and used the following keywords and associated subject headings:

1. venous thromboembolism.mp

a. Subject headings: pulmonary embolism, thromboembolism, venous thrombosis,

2. perioperative anticoagulation.mp

a. Subject headings: anticoagulants, perioperative care, warfarin, heparin

3. pacemaker implantation.mp

a. Subject headings: "pacemaker, artificial," "cardiac pacing, artificial"

This yielded 288 results.

The addition of "pocket hematoma.mp" alone yielded 18 results (no new ones) and a combination of the four searches yielded 0 results.

A subsequent identical search of EMBASE from 1996–2008 Week 18 yielded 296 results but no new articles.

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