Pacemaker and Implantable Cardioverter-Defibrillator Implantation During Chronic Anticoagulation: Continuation of Warfarin versus Bridging with Heparin

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ABSTRACT. Patients chronically anticoagulated often require implantation of permanent pacemakers (PPMs) or implantable cardioverter-defibrillators (ICDs). Many are high risk for interrupting anticoagulation. We evaluated the safety of different anticoagulation strategies. We performed a retrospective study of 962 consecutive patients undergoing initial device implantation (102 were bridged with heparin products while 76 had a therapeutic international normalized ratio (INR) at the time of implantation) and compared bleeding complication rates. Post-procedural length of stay and cost were also compared. Preprocedural INR was not a predictor of bleeding complications. The use of a heparin product or dual antiplatelet therapy was associated with increased bleeding risk (p < 0.001). When bleeding complications did occur, the mean length of stay more than doubled (5.2 ± 3.8 days versus 2.3 ± 3.3 days, p = 0.01) and the cost of hospitalization increased 62% ($15,019 ± 8663 versus $9,266 ± 7517, p = 0.01). In patients at increased risk for thromboembolism, a strategy of proceeding with a therapeutic INR at the time of device implantation appears safer and is associated with reduced hospital length of stay and costs in comparison to bridging with heparin products.

KEYWORDS. anticoagulation, pacemaker, implantable cardioverter-defibrillator, bleeding, complications.

Introduction

An estimated two million Americans are chronically anticoagulated for the treatment or prophylaxis of thromboembolic events, and up to 25% of patients undergoing implantable cardioverter-defibrillator (ICD) or permanent pacemaker (PPM) implantation are on oral anticoagulation therapy. In many low-risk patients it is safe to temporarily interrupt warfarin and allow the international normalized ratio (INR) to normalize prior to proceeding with device implantation. However, in some patients who are considered high risk for thromboembolism (including mechanical cardiac valves, recent conversion of atrial fibrillation, history of embolic stroke, recent deep venous thrombosis, pulmonary embolism, or certain clotting disorders), interruption of anticoagulation, even for a short time, is often high risk. Studies have demonstrated that using heparin products to bridge anticoagulated patients is generally safe, and current guidelines recommend temporarily stopping warfarin and recommend bridging with heparin products in this patient population. However, it is unclear if this is the best strategy, as the early use of therapeutic heparin after device implantation has been associated with an increased risk of bleeding complications. The use of periprocedural anticoagulation has also been implicated in increasing the post-procedural length of stay and cost in elective surgeries. Several studies have suggested that device implantation with therapeutic INR is likely safe.

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maintenance of oral anticoagulation at time of device implant as well as decreased length of stay. Our study builds on this growing body of evidence and adds additional cost and length of stay comparison.

In this study, we retrospectively reviewed two different anticoagulation strategies and compared the bleeding complication rates, hospital length of stay, and costs associated with each strategy in patients undergoing de novo device implantation.

**Methods**

**Patient population**

A total of 962 consecutive patients undergoing initial PPM or ICD implantation with known INR values between October 2007 and December 2008 were included for review (42 patients did not have a documented INR at the time of implantation and were excluded from the study). All patients were treated at the Ohio State University Medical Center. Patients undergoing a PPM or ICD generator change out, system revision, or lead extraction were excluded as these procedures have different complication profiles from initial lead and device implantation.

**Anticoagulation management**

Anticoagulation guidelines were developed by a consensus among the practicing electrophysiologists at our institution to guide patient care at the time of device implantation. These guidelines were revised in June 2008. This change in the guidelines allowed us to compare two different periprocedural management strategies for the highest-risk patients.

**Bridging group (October 2007 to May 2008)**

Warfarin was discontinued several days prior to the planned procedure, with bridging IV heparin or subcutaneous enoxaparin when the INR fell below 2.0. Device implant was scheduled when the INR was below 1.8. IV heparin was stopped 6 h prior to device implantation and restarted 24 h after device implantation (without bolus). If enoxaparin was used, the last dose was no less than 12 h prior to device implantation, and reinstituted 24 h after surgery. Warfarin was restarted the evening of device implantation. Bridging was continued until a therapeutic INR was achieved.

**Therapeutic INR group (June 2008 to December 2008)**

Warfarin therapy was continued to maintain a therapeutic INR (2.0–3.0) throughout the perioperative period. For the lower-risk patients on warfarin, the warfarin was withheld, and the INR was allowed to drift below 1.8 prior to device implantation, without heparin bridging (INR drift group). There was also a large number of patients who were not anticoagulated at any time (control group).

**Cost data**

Direct cost data for the procedure and hospitalization were obtained from the hospital-based cost-tracking database. The total hospital direct cost (procedure plus hospitalization) less the device cost was used for comparison between patient groups.

**Definitions**

Bleeding complications included any of the following: hematoma requiring directed therapy or prolonged hospitalization, hemoglobin drop of ≥3 g or requiring blood transfusion, clinically significant pericardial effusion, hemothorax, or death. Complications were recorded at the time of the procedure or post-procedure by our institution’s quality assurance team. The quality assurance team follows all cardiac patients post-procedure to record procedure-related complications.

**Statistical analysis**

All statistical analyses were conducted using SPSS Statistical Version 17.0 (SPSS, Inc. Chicago, IL). Categorical data were evaluated using the chi-squared or Fisher’s exact test. Continuous data were analyzed via the t-test. A logistical regression model was utilized to assess for predictors of complications. Variables included in the model are as follows: use of aspirin, use of clopidogrel, INR value, periprocedural enoxaparin, periprocedural heparin, or any heparin product (unfractionated heparin (UFH) plus low molecular weight heparin (LMWH)). A two-tailed p value ≤0.05 was considered statistically significant.

**Results**

**Bleeding complications**

Of the 962 patients included in the analysis, 680 (71%) had an INR less than 1.4 and did not receive any periprocedural systemic anticoagulation (control group), 102 had an INR <2.0 and received heparin bridging (bridging group), 104 had an INR of 1.2–1.9 and did not receive any heparin products (INR drift group), and 76 had a therapeutic INR at the time of device implantation (therapeutic INR group). The baseline characteristics of the patients are listed in Table 1.

The overall bleeding complication rate for the entire population was 1.7% (16/962). The complication rate was 0.8% (5/680) in the control group, 7.8% (8/102) in the bridging group (p = 0.001), 2.9% (3/104) in the INR drift group (p = 0.08), and 0.0% (0/76) in the therapeutic INR group. Nine of the 16 complications were hematomas (56%), five (31%) were clinically significant pericardial effusions (three of which had tamponade and required pericardiotesis), and two (12.5%) had a hemothorax. Half (8/16) of these complications required a blood transfusion. There were no deaths.
Approximately half of the patients who had a complication (7/16; 44%) received periprocedural IV UFH or LMWH. When the INR was evaluated as an independent predictor of complication, it was non-significant (p = 0.71).

In direct comparison of patients on systemic anticoagulation, the bridging group had a significantly higher risk of bleeding complication than the therapeutic INR group (7.8% compared with 0.0%; p = 0.01). There was a trend toward a higher complication rate when LMWH (14%) was used compared with IV heparin (4%, p = 0.1); however, this was not statistically significant due to the small sample size in the LMWH group.

A comparison of the patients with complications versus those without is shown in Table 2.

**Thrombotic/embolic complications**

There were no thrombotic or embolic complications recorded in any of the patients in this study.

**Antiplatelet therapy**

Patients receiving single antiplatelet therapy (aspirin or clopidogrel) did not have an increased risk of bleeding complications (6 of 556, 1.1%; p = 0.39). However, patients on dual antiplatelet therapy (aspirin and clopidogrel) did have an increased risk of complication (8 of 263, 3.0%; p = 0.05) compared with those not on antiplatelet therapy. There was a total of 40 patients receiving “triple therapy” (dual antiplatelet therapy with either a therapeutic INR (n = 13) or bridged with heparin (n = 27)), with four complications (10%). In comparison to patients on dual antiplatelet therapy, the complication rate in all patients on triple therapy was not statistically significant (p = 0.058), although it was significant when comparing those on dual antiplatelet therapy plus bridging with heparin and those just on dual antiplatelet therapy (15% compared with 3%, p = 0.028).

**Hospital costs and length of stay**

In patients who developed a bleeding complication, there was a significant increase in the hospital length of stay and the direct hospital cost (less device cost). The length of stay was 5.2 ± 3.8 days versus 2.3 ± 3.3 days (p = 0.01) and the direct cost was $15,019 ± 8663 versus $9,266 ± 7517 (p = 0.01) for those with a complication versus those without, respectively. It was also noted that even in patients who did not have a complication, the strategy of holding warfarin and bridging with periprocedural heparin resulted in a significant increase in the

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**Table 1:** Baseline characteristics. Asterisks indicate a statistically significant difference from control (p < 0.05)

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Control group</th>
<th>INR drift group</th>
<th>Therapeutic INR group</th>
<th>Bridging group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>65.7 ± 14.4</td>
<td>64.8 ± 14.6</td>
<td>70 ± 13.3*</td>
<td>67.5 ± 12.4</td>
<td>66.5 ± 14.6</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>65.3</td>
<td>66.5</td>
<td>65.4</td>
<td>67.1</td>
<td>63.2</td>
</tr>
<tr>
<td>INR (mean ± SD)</td>
<td>1.28 ± 0.36</td>
<td>1.11 ± 0.09</td>
<td>1.6 ± 0.18*</td>
<td>2.29 ± 0.24*</td>
<td>1.4 ± 0.3*</td>
</tr>
<tr>
<td>Platelets K/μL (mean ± SD)</td>
<td>216 ± 102</td>
<td>221 ± 73</td>
<td>201 ± 73*</td>
<td>210 ± 79</td>
<td>207 ± 92</td>
</tr>
<tr>
<td>Aspirin (% pts)</td>
<td>82.4</td>
<td>83.8</td>
<td>76.9</td>
<td>69.7*</td>
<td>85.5</td>
</tr>
<tr>
<td>Clopidogrel (% pts)</td>
<td>29.8</td>
<td>33.6</td>
<td>17.3*</td>
<td>18.4*</td>
<td>24.8</td>
</tr>
<tr>
<td>Heparin (% pts receiving therapeutic IV UFH)</td>
<td>10.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>85.5*</td>
</tr>
<tr>
<td>Enoxaparin (% pts receiving therapeutic LMWH)</td>
<td>2.2</td>
<td>0</td>
<td>0</td>
<td>17.1*</td>
<td></td>
</tr>
</tbody>
</table>

INR: international normalized ratio; LMWH: low molecular weight heparin; UFH: unfractionated heparin.

**Table 2:** Comparison of patients with and without complications

<table>
<thead>
<tr>
<th></th>
<th>Without complications</th>
<th>With complications</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>65.7 ± 14.4</td>
<td>72.3 ± 12.8</td>
<td>0.067</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>66.6</td>
<td>55.0</td>
<td>0.164</td>
</tr>
<tr>
<td>INR (mean ± SD)</td>
<td>1.28 ± 0.36</td>
<td>1.3 ± 0.32</td>
<td>0.71</td>
</tr>
<tr>
<td>Platelets K/μL (mean ± SD)</td>
<td>215 ± 79</td>
<td>188 ± 79</td>
<td>0.177</td>
</tr>
<tr>
<td>Device (% ICD)</td>
<td>58</td>
<td>70.0</td>
<td>0.36</td>
</tr>
<tr>
<td>% of number of leads implanted (1/2/3)</td>
<td>9.6/72.6/17.8 mean=2.08 (0.5)</td>
<td>10.0/55.0/35.0 mean=2.31 (0.7)</td>
<td>1.00/0.13/0.07 p=0.213</td>
</tr>
<tr>
<td>Aspirin (% pts)</td>
<td>82.4</td>
<td>85.0</td>
<td>0.591</td>
</tr>
<tr>
<td>Clopidogrel (% pts)</td>
<td>29.5</td>
<td>50.0</td>
<td>0.08</td>
</tr>
<tr>
<td>Heparin (% pts receiving therapeutic IV UFH)</td>
<td>10.1</td>
<td>25.0</td>
<td>0.054</td>
</tr>
<tr>
<td>Enoxaparin (% pts receiving therapeutic LMWH)</td>
<td>1.9</td>
<td>18.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any therapeutic heparin or enoxaparin (% pts)</td>
<td>11.6</td>
<td>43.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LMWH: low molecular weight heparin; UFH: unfractionated heparin.
hospital length of stay. The length of stay was 2.7 ± 2.0 days versus 1.6 ± 1.2 days (p < 0.0001) for those bridged with heparin products versus those continued on warfarin.

Discussion

The current guidelines recommend bridging anticoagulation around the time of device implantation with heparin products rather than continuing warfarin. However, a randomized controlled trial comparing therapeutic INR versus heparin bridging demonstrated no difference in outcomes, and previous studies have demonstrated that the practice of using heparin products post device implant increases the bleeding risk, and therefore this brings into question the utility of the current guidelines. Further, several recent studies have demonstrated that perhaps device implant with a therapeutic INR is preferred. This apparent contradiction has resulted in confusion regarding the best anticoagulation strategy as well as wide variability in physician anticoagulation management, highlighted in a recent survey of electrophysiologists in Canada regarding the use of periprocedural anticoagulation around the time of device implant.

Our study further adds to the growing evidence that patients who are at high risk for thromboembolic events can be continued on warfarin and can safely undergo device implantation at therapeutic INR values. In fact, this strategy appears to be safer and more time- and cost-efficient than a strategy of bridging. In addition, our study demonstrates the cost-effectiveness of proceeding with a therapeutic INR versus a bridging strategy. It should be noted that these findings apply only to patients undergoing primary device implant and should not be extrapolated to patients undergoing lead extractions or extensive device revisions, as these may be associated with additional bleeding risks. It also should be noted that no patient had a thrombotic or embolic adverse event during this study, regardless of the anticoagulation management.

Previous data have suggested that antiplatelet therapy increases the risk of hematoma formation after device implantation, especially in concert with bridging with heparin. In this study, neither the use of aspirin nor the use of clopidogrel alone increased the complication risk. However, dual antiplatelet therapy did significantly increase the periprocedural risk. There were only 40 patients on “triple therapy” (dual antiplatelet with a therapeutic INR or bridging heparin), making it difficult to make broad statements about this patient population, but it does appear that the complication risk does increase in this subset, especially when a bridging strategy is used.

The occurrence of bleeding complications led to a significant increase in the overall length of stay and patient care costs. The average duration of hospitalization for a patient with a complication was over twice that of a patient without a complication, and the occurrence of a complication increased the average direct hospital cost by 60%. Even in patients who did not have a complication, the use of bridging heparin products was associated with an increase in the overall hospital length of stay, attributable to the need for inpatient monitoring of IV heparin.

Limitations

The major limitation of this study is the retrospective design and the associated shortcomings, such as the different antiplatelet therapies possibly acting as confounders. Nonetheless, the data were accurately collected in a prospective manner and maintained for all patients. Also, these results reflect clinical practice at a single center with a large device volume. Finally, although a large data set, only 76 patients had therapeutic INRs at the time of the procedure (although the fact that none had complications makes the data more compelling).

Conclusions

The findings of this study add to the growing body of evidence that a strategy of continuing warfarin with a therapeutic INR at the time of device implantation is a safer approach than bridging. This approach is also associated with reduced hospital length of stay and costs compared with bridging with heparin products. Dual antiplatelet therapy also appears to increase complication risk with de novo device implantation. The ongoing randomized controlled trial will hopefully clarify these important clinical issues, but until these results are available, the best strategy appears to be device implantation with a therapeutic INR in the high-risk population.

References

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