Warfarin Cessation Before Cardiopulmonary Bypass: Lessons Learned from a Randomized Controlled Trial of Oral Vitamin K

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Background. No standard protocol of warfarin cessation and bridging for cardiac surgery exists. This study examined a single institution’s protocol with respect to timing of cessation and low molecular weight heparin bridging. The recovery of vitamin K–dependent factors and the effects of cardiopulmonary bypass on coagulation factors were explored. Administration of preoperative oral vitamin K was investigated in a randomized, placebo-controlled trial. A post hoc analysis examined residual anti-Xa activity of enoxaparin bridging.

Methods. Forty patients on warfarin undergoing cardiopulmonary bypass were randomized to receive 5 mg of oral vitamin K or placebo 6 days before surgery. Blood samples were acquired at six times and assayed for prothrombin time, anti-Xa activity, and functional levels of factors II, V, VII, and IX and of protein C. Measures of bleeding and transfusion were also collected.

Results. No difference in bleeding or transfusion was observed between the treatment groups. Appropriate recovery of coagulation factors was observed with warfarin cessation irrespective of treatment group. The coagulation factors decreased by an average of 0.36 units/mL during the period of surgery. Enoxaparin 1 mg/kg until the evening before surgery resulted in 70% of patients entering the operating room with therapeutic anti-Xa activity (0.6 ± 0.3 units/mL).

Conclusions. The cessation of warfarin 6 days preoperatively is sufficient for functional recovery of vitamin K–dependent factors, which undergo significant changes during the operative course. A 5-mg dose of vitamin K with warfarin discontinuation did not enhance recovery of vitamin K–dependent factors and is unnecessary. With the observation that enoxaparin up until the night before surgery resulted in high residual anti-Xa levels in the operating room, our center now administers the last dose of enoxaparin 24 hours before surgery.

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Ann Thorac Surg 2007;84:103–9
the risk of warfarin-associated hemorrhage, it is standard at our center to discontinue warfarin approximately 5 days before open heart surgery and bridge with the low molecular weight heparin (LMWH) enoxaparin with the last dose given the evening before surgery. Enoxaparin is thought to mitigate the risk of thrombosis and, as a result of its short half-life, without increasing the risk of operative bleeding. Again, the evidence to support this approach is scarce.

We undertook a randomized controlled trial of perioperative warfarin management in patients undergoing CPB. This study had several aims: (1) to describe the levels of coagulation factors in patients electively discontinuing warfarin who did or did not receive vitamin K; (2) to monitor the levels of coagulation factors before, during, and after CPB; and (3) to examine residual anti-Xa activity of LMWH on entry into the operating room. We hypothesized that patients who are receiving warfarin are relatively deficient in the VKD coagulation factors when entering the operating room despite normalization of their international normalized ratios (INRs). We further hypothesized that significant dilution and consumption of these factors occur during CPB, which could exacerbate these deficiencies, leading to increased intraoperative and postoperative bleeding and blood product utilization. Oral vitamin K at the time of warfarin cessation would accelerate factor recovery, reducing the risk of VKD coagulation factor deficiency. Finally, many patients bridged with LMWH may have detectable anticoagulant effects at the time of operation, and this anticoagulant state may predispose to bleeding.

**Patient Population**

The study considered adult patients undergoing cardiac surgery with the use of CPB who had been on warfarin therapy with a goal INR greater than or equal to 2 for at least 6 months. The patients’ warfarin had to be stopped within 6 days of anticipated surgery, and the patients were required to be bridged with therapeutic dose LMWH. The last dose of LMWH (enoxaparin 1 mg/kg twice daily) was given the night before surgery. Exclusion criteria were known hepatic dysfunction, serious bleeding disorder, platelet defect, or coagulation disorder not attributable to medications. Additional patients were, by necessity, excluded from analysis if their surgery did not occur as planned within 5 to 7 days of discontinuation of warfarin. All patients provided written informed consent, and the study was approved by the local institutional review board and was in accordance with the Helsinki declaration of 1975.

**Study Design**

Participants were enrolled at a single center (The Hamilton Health Sciences Corporation—Hamilton General Campus, Hamilton, Ontario, Canada). Patients were randomly assigned to receive 5 mg of liquid vitamin K (phytonadione, Baxter Corp, Mississauga, Canada) given orally (20 patients) or normal saline placebo (20 patients) mixed in orange juice on the day of warfarin cessation. The randomization sequence was generated using a standard random number table. A single clinic nurse who was not otherwise involved in the patients’ care performed randomization by opening sequentially numbered sealed opaque envelopes. The patients, clinical staff, laboratory technologists, and the members of the research teams were blinded to treatment allocation. Data analysis was performed after unmasking of the codes.

Blood samples were drawn from all patients at 6 points (Table 1). Samples were drawn from an antecubital vein using standard technique (points 1, 2, and 6) and from an indwelling arterial catheter with care to avoid heparin contamination (points 3, 4, and 5). Samples were immediately transported to the hospital core laboratory where platelet-poor plasma was prepared by double centrifugation at 4,000 rpm. The plasma was then aliquoted, snap-frozen, and stored at −70°C until batch analysis. Samples were analyzed by means of commercially available kits for prothrombin time (PT) and functional levels of factors II (prothrombin), VII, IX, and V, protein C, and anti-Xa levels. Heparin neutralization was performed when appropriate. Functional levels are expressed as units per milliliter (1 unit/mL = 100%). Anti-Xa heparin levels were measured using a Stachrom Heparin kit from Diagnostica Stago. (Asnieres-Sur-Seine, France) on an AMAX 190 (Trinity BioTech, Bray, Ireland). Plasma was diluted in an antithrombin buffer mix and incubated with an excess concentration of Xa. After a fixed period, an Xa-specific chromogenic substrate was added and the release of para-nitroaniline (PNA) was measured. The amount of heparin present was inversely related to the concentration of PNA released. A reference curve using World Health Organization unfractionated heparin was prepared in pooled normal human platelet-poor plasma.

**Clinical Data**

Baseline demographic data was collected on all patients. Intraoperative and postoperative variables including surgical times, blood products administered (homologous red blood cells, fresh-frozen plasma, platelets, or cryoprecipitate), and chest tube output were also collected. All patients received antifibrinolytics at the time of operation.

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**Table 1. Points of Blood Sampling**

<table>
<thead>
<tr>
<th>Point</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Baseline</td>
<td>Just before study medication administration</td>
</tr>
<tr>
<td>2. PreO</td>
<td>The morning of surgery</td>
</tr>
<tr>
<td>3. B4</td>
<td>Just before CPB initiation</td>
</tr>
<tr>
<td>4. 10 min</td>
<td>After 10 minutes on CPB</td>
</tr>
<tr>
<td>5. ICU admit</td>
<td>With ICU admission bloodwork</td>
</tr>
<tr>
<td>6. Postop 5</td>
<td>Postoperative day 5</td>
</tr>
</tbody>
</table>

CPB = cardiopulmonary bypass; ICU = intensive care unit.
Statistical Analysis

SAMPLE SIZE. The sample size of this study was one of convenience; to our knowledge there are no data that described the response of the VKD coagulation factor levels to vitamin K administration, and thus we elected arbitrarily to enroll 20 patients per arm into the study.

BASELINE AND CLINICAL VARIABLES. Categorical variables are reported as percentages and are compared using a chi-squared analysis or Fisher’s exact test as appropriate. The means of continuous variables were compared by the Student’s t test. Nonnormally distributed continuous variables were compared by the nonparametric Mann-Whitney U test. Significance was established at a value of p less than 0.05.

COAGULATION FACTOR MEASURES. Coagulation factor changes with time were compared between groups by repeated measures analysis of covariance as well as multilevel modeling (a variation of regression analysis that avoids incorrect statistical inferences when dealing with cluster sampling or repeated measures). For multilevel modeling, two levels within the hierarchy were used. The behavior of the level 1 outcome factor level was examined as a function of the level 2 predictor individual and other level 1 predictors. Criteria for entry of a predictor into the model were a significant (p < 0.05) change in the -2loglikelihood based on maximum likelihood estimate, or a significant (p < 0.05) parameter estimate.

Clinically sensible fixed and random effects were tested. Normality and homoscedascity of the residuals from the final model were confirmed. Pearson correlation coefficient between predicted and observed level was assessed. Postoperative day 5 was not used in the analyses of VKD factors because of variability in restarting warfarin.

The study was analyzed as per protocol; patients who did not either stop warfarin, receive bridging with LMWH, or had failed to undergo CPB within 5 to 7 days were excluded from the analysis because the required blood samples and clinical data were not available for these patients.

ANTI-XA LEVELS. Anti-Xa heparin activity was measured at points 3 and 5. To assess the impact on bleeding or transfusion outcomes, we used linear and logistic regression, respectively. Variables known to affect these out-

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Table 2. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vitamin K Group (n = 20)</th>
<th>Control Group (n = 20)</th>
<th>As Per Protocol Vitamin K Group (n = 12)</th>
<th>As Per Protocol Control Group (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y ± SD</td>
<td>69 ± 10</td>
<td>66 ± 10</td>
<td>69 ± 12</td>
<td>66 ± 6</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>16 (80)</td>
<td>13 (65)</td>
<td>11 (92)</td>
<td>13 (81)</td>
</tr>
<tr>
<td>Warfarin indication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A fib, n (%)</td>
<td>18 (90)</td>
<td>16 (80)</td>
<td>10 (83)</td>
<td>13 (81)</td>
</tr>
<tr>
<td>Prosthetic valve, n (%)</td>
<td>0</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mural thrombus, n (%)</td>
<td>2 (10)</td>
<td>2 (10)</td>
<td>2 (17)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>TIA, n (%)</td>
<td>0</td>
<td>1 (5)</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Surgery type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td>7 (35)</td>
<td>7 (35)</td>
<td>5 (42)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Single value, n (%)</td>
<td>5 (25)</td>
<td>4 (20)</td>
<td>4 (33)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Complex, n (%)</td>
<td>8 (40)</td>
<td>9 (40)</td>
<td>3 (25)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Redo, n (%)</td>
<td>3 (15)</td>
<td>2 (10)</td>
<td>2 (17)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Preoperative antiplatelets, n (%)</td>
<td>7 (35)</td>
<td>3 (15)</td>
<td>5 (42)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time, min ± SD</td>
<td>137 ± 63</td>
<td>127 ± 53</td>
<td>116 ± 77</td>
<td>96 ± 40</td>
</tr>
</tbody>
</table>

A fib = atrial fibrillation; CABG = coronary artery bypass grafting; SID = standard deviation; TIA = transient ischemic attack.
comes including age, total pump time, surgery type, reoperation, and preoperative antiplatelet use were adjusted for.

Results

Forty eligible, consenting patients were recruited from April 2003 to February 2004. Twelve of the 40 patients did not undergo planned surgery within the allowable time; thus 28 patients (16 in the control group) were included in the analysis of the as per protocol patients. Table 2 summarizes the characteristics of patients enrolled in the two study groups as well as the patients analyzed as per protocol.

Clinical Outcomes by Treatment Group

Two participants within the study died, both in the vitamin K group. The first patient had an unrecognized abdominal aortic aneurysm that ruptured on postoperative day 5. The second died of sepsis on day 92 in the intensive care unit. None of the 40 patients recruited for the study experienced preoperative bleeding or had identifiable perioperative thromboembolic events. Postoperative blood loss was non-Gaussian in distribution, and no significant difference was found between the group medians (vitamin K, 560 mL versus control, 575 mL; \( p = 0.80 \)). Further, no difference was observed in the proportion of participants transfused (vitamin K, 67\% versus control, 63\%; \( p = 0.82 \)). There was no difference in the use of aprotinin between the groups (vitamin K, 17\% versus control, 6\%; \( p = 0.56 \)).

Coagulation Factor Activities

Patients stopped their warfarin on average 6.2 ± 1.3 days before surgery (vitamin K, 6.0 ± 1.4 days versus placebo, 6.3 ± 1.3 days; \( p = 0.66 \)). Multilevel modeling as well as repeated measures analysis of covariance demonstrated no significant difference in the levels of these factors irrespective of whether patients received vitamin K or placebo at any point. There did appear a trend for the patients who had received vitamin K to have higher VKD coagulation factor levels on the morning of surgery, but the clinical significance is questionable given the results at the other points.

Predictor variables of factor activity tested within the multilevel models included point, time between measures in units of days, units of fresh-frozen plasma administered, patient age, patient sex, and vitamin K administration. Multilevel modeling of factor V activity demonstrated that significant (\( p < 0.05 \)) predictors of functional levels include “point,” “time between measures,” and their interaction (Fig 1). Modeling of the other factors demonstrated only “point” to be a significant predictor, yielding little clinical relevance. Figure 2 demonstrates the typical model for the VKD factors using factor II as the example.

With no difference in coagulation factor level by vitamin K treatment, the groups were combined. Table 3 summarizes the coagulation factor levels for each point analyzed with a one-way analysis of variance. All coagulation factors changed significantly during the points measured. Before warfarin cessation, all VKD factors were appropriately suppressed and the levels of factor V

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Table 3. Factor Mean Functional Level by Point*  

<table>
<thead>
<tr>
<th>Factor</th>
<th>Baseline</th>
<th>PreO</th>
<th>B4</th>
<th>10 min</th>
<th>ICU admit</th>
<th>Postop 5</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>0.38 (0.19)</td>
<td>0.84 (0.21)</td>
<td>0.71 (0.19)</td>
<td>0.44 (0.10)</td>
<td>0.50 (0.14)</td>
<td>0.67 (0.30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VII</td>
<td>0.36 (0.18)</td>
<td>0.82 (0.21)</td>
<td>0.70 (0.19)</td>
<td>0.45 (0.13)</td>
<td>0.60 (0.16)</td>
<td>0.47 (0.31)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IX</td>
<td>0.70 (0.20)</td>
<td>1.08 (0.19)</td>
<td>0.92 (0.17)</td>
<td>0.69 (0.17)</td>
<td>0.80 (0.18)</td>
<td>0.99 (0.35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prot C</td>
<td>0.33 (0.25)</td>
<td>0.94 (0.24)</td>
<td>0.87 (0.27)</td>
<td>0.73 (0.29)</td>
<td>0.65 (0.15)</td>
<td>0.36 (0.24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>V</td>
<td>0.88 (0.17)</td>
<td>0.86 (0.19)</td>
<td>0.64 (0.28)</td>
<td>0.43 (0.12)</td>
<td>0.69 (0.23)</td>
<td>0.86 (0.20)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Units/mL (SD).

B4 = just before initiation of cardiopulmonary bypass; ICU = intensive care unit; Postop 5 = postoperative day 5; PreO = morning of operation; Prot C = protein C.
(which is not suppressed by warfarin) were normal. This was reflected by the baseline INR of 2.2 ± 0.7. As expected, warfarin withdrawal resulted in a statistically significant increase in the levels of the VKD coagulation factors seen in both groups by the morning of surgery. The mean INR of all patients at this point was 1.2 ± 0.1. With initiation of surgery there was an average decline of 0.14 units/mL of factors by CPB initiation, with a further fall during the period of initiation of CPB of 0.22 units/mL. By the time of intensive care unit admission, there had been some recovery of factor activity with an average increase of activity by 0.08 units/mL. Postoperative day 5 had the greatest variance in activity levels, with factor V returning to normal levels (0.86 ± 0.20 units/mL) and the VKD factors ranging from severely depressed (0.36 units/mL) to normal (0.99 units/mL).

**Anti-Xa Residual Activity**

The residual anti-Xa activity could be determined for 27 patients; one sample had required all of its volume for coagulation factor measures. The anti-Xa activity was found to be 0.6 ± 0.3 units/mL and 0.2 ± 0.1 units/mL on the morning of surgery and at intensive care unit admission, respectively. After adjusting for age, surgical complexity, preoperative antiplatelet use, reoperation, and total CPB time, we failed to identify any association between anti-Xa levels and bleeding or transfusion of any blood product.

**Comment**

It was our practice to stop warfarin 5 to 6 days preoperatively and bridge with enoxaparin until the night before surgery. With this protocol, we would observe a normal INR by the day of operation. However, given that only 30% functional levels of the coagulation factors are necessary to have a normal INR, we thought it was important to demonstrate full recovery of the factors themselves. This study demonstrates that the functional levels of the coagulation factors change significantly during the perioperative course with CPB having a large impact. Therefore, starting the operation with a relative factor deficiency would be problematic. This was not the case. From this prospective randomized trial of preoperative warfarin cessation protocols, we found that cessation of warfarin 6 days preoperatively is sufficient for VKD coagulation factor recovery. Further, we did not observe an enhanced recovery of VKD coagulation factors in patients who received a single 5-mg dose of oral vitamin K at the time of warfarin discontinuation.

In a post hoc analysis we made the somewhat surprising and likely clinically important observation that 19 of 27 patients (70%) entered the operating room with therapeutic levels of LMWH, all of who had received bridging enoxaparin 1 mg/kg given up to the evening before surgery. However, the study was underpowered to detect even large differences in bleeding by anti-Xa level. The lack of an association between an anti-Xa level within the therapeutic range and bleeding is not biologically plausible and likely represents a type 2 statistical error. The anti-Xa activity of LMWH is poorly reversible with protamine [11], and thus our center has changed its bridging protocol. We now administer the last dose of enoxaparin on the morning of the day before surgery, ie, no LMWH within 24 hours of surgery. The biochemical results of this study suggest the need for a sufficiently powered trial addressing the appropriate time to stop LMWH before surgery.

This study had several significant limitations. First, the study enrolled 40 patients of whom 12 were excluded from the analysis. All of the study patients were booked as elective cases with 30% of their first booking being canceled, most commonly for more urgent cases. Second, the population studied in this trial was extremely heterogeneous with respect to complexity of surgery. Surgery types ranged from isolated CABG to complex reoperations involving CABG as well as ascending aorta and arch replacement. This heterogeneity led to large variation in the clinical variables, as depicted by the skewed data of postoperative hemorrhage, making comparison between the two groups more challenging. Either stricter inclusion criteria, which would greatly delay recruitment, or a larger sample size is necessary to examine the clinical variables appropriately.

Our results are likely to be valid. Patients were identified and enrolled prospectively at the time of their preoperative assessment. Vitamin K administration was done in a blinded fashion and study personnel unaware of treatment assignment performed both subsequent laboratory evaluations and outcome assessments. The preparation of low-dose oral vitamin K used in this study has been demonstrated to effectively reverse warfarin anticoagulation in previous studies [12, 13]. Laboratory measurements were performed using standardized, commercial assays in batch at the end of the study. Thus, the study design was rigorous.

In conclusion, the management of warfarin before cardiac surgery has not been standardized. Cessation of warfarin 6 days before cardiac surgery requiring CPB appears to ensure recovery of warfarin-associated depletion in the levels of the VKD coagulation factors. We did not observe enhanced coagulation factor recovery in patients allocated to receive vitamin K, suggesting that this therapy is unnecessary. Use of preoperative enoxaparin at a dose of 1 mg/kg given up to the evening before surgery resulted in a high proportion of patients having clinically important elevations in their residual anti-Xa on entry into the operating room. Although the study was underpowered to detect bleeding associated with this unexpected anticoagulant effect, other literature does support an association between elevated anti-Xa heparin levels with LMWHs and bleeding risk [14, 15]. These observations contributed to a change in our institutional protocol for preoperative warfarin cessation. A standardized, well-studied protocol will be helpful in determining optimal perioperative management of anticoagulation in patients receiving preoperative warfarin.
The authors thank the cardiac surgeons, anesthetists, and perfusionists of HHSC, Alexander G. G. Turpie, MD and the thrombosis unit nurses, and Marilyn Johnson and the Hemostasis Reference Laboratory. This work was supported by a grant from McMaster University Department of Surgery.

References


INVITED COMMENTARY

Whitlock and colleagues [1] give us concrete evidence to back up clinical impressions of bleeding in cardiac surgical patients. The authors report a randomized, controlled trial of perioperative warfarin management in patients undergoing cardiopulmonary bypass (CPB). The aim of the study was threefold: (1) to describe the levels of vitamin K-dependent coagulation factor (VKDCF) in patients electively discontinuing warfarin who did or did not receive vitamin K, (2) to monitor the levels of VKDCF during and after CPB, and (3) to determine the residual anti-Xa activity after preoperative administration of a low molecular weight heparin (enoxaparin).

Decreased functional levels of factors II, VII, IX, and V were found at baseline. Warfarin was discontinued 5 to 6 days before surgery, and by the day of surgery these levels of factors were approaching normal with or without administration of vitamin K. Crowther and colleagues [2] had previously reported the normalization of the international normalized ratio within 24 to 48 hours after the administration of low-dose vitamin K. Therefore the findings in this study are not unexpected. Unfortunately in this study the authors do not explore the time course for recovery of the factors between preoperative day 6 and the day of surgery. This information would be particularly helpful in determining whether vitamin K administration would be of use if warfarin cessation were delayed for 2 to 3 days.

The authors go on to report that VKDCFs declined through the period of CPB, and in fact are only approaching normal by postoperative day 5. The 50% decrease in factor levels is more than would be expected secondary to hemodilution alone. Brister and colleagues [3] have reported ongoing thrombin generation through cardiac surgery. With increasing duration of surgery, thrombin generation increased. The additional decrease of VKDCF levels seen in this study may be related to consumption during surgery. Regardless of the cause, the decrease in factor levels may contribute to postoperative bleeding.

Other authors have reported an increased incidence of postoperative bleeding associated with the preoperative administration of low molecular weight heparin. Suggested times for discontinuation range from 12 to 24 hours preoperatively [4, 5]. Whitlock and colleagues [1] report that when enoxaparin was discontinued the night before surgery, residual anti-X activity was 0.6 ± 0.3 μU/mL. Similar results have been reported by O’Donnel and colleagues [6]. Therapeutic levels of anti-X activity for treatment of deep venous thrombosis are in the range of 0.4 to 0.69 IU/mL. Anti-Xa levels greater than 1 IU/mL are associated with increased bleeding in nonsurgical patients [7]. In all probability an anti-X activity level of 0.6 μU/mL would increase the risk of bleeding in a cardiac surgical patient.

In conclusion, bleeding remains a significant problem in cardiac surgery. More studies similar to that of Whitlock and colleagues [1] are required. These studies will