Complications of Perioperative Warfarin Therapy in Total Knee Arthroplasty

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Abstract:

Patients presenting for knee replacement on warfarin for medical reasons often require higher levels of anticoagulation peri-operatively than primary thromboprophylaxis and may require bridging therapy with heparin. We performed a retrospective case control study on 149 consecutive primary knee arthroplasty patients to investigate whether anti-coagulation affected short-term outcomes.

Specific outcome measures indicated significant increases in prolonged wound drainage (26.8% of cases vs 7.3% of controls, p<0.001); superficial infection (16.8% vs 3.3%, p<0.001); deep infection (6.0% vs 0%, p<0.001); return-to-theatre for washout (4.7% vs 0.7%, p=0.004); and revision (4.7% vs 0.3%, p=0.001).

Management of patients on long-term warfarin therapy following TKR is particularly challenging, as the surgeon must balance risk of thromboembolism against post-operative complications on an individual patient basis in order to optimise outcomes.
Introduction:

Although the use and choice of pharmacologic anticoagulant for prophylaxis against venous thromboembolism (VTE) or pulmonary embolism (PE) in lower extremity arthroplasty is an area of ongoing discussion and controversy [1-4], it is no doubt the case that management of arthroplasty patients who are already on therapeutic anticoagulation therapy in the perioperative period presents a plethora of clinical challenges: the decision to maintain, modify or discontinue the oral anticoagulant, or whether to bridge with heparin, is a common, but fraught one, with the surgeon balancing the risk of haemorrhagic complication against the risk of thromboembolism in the context of invasive surgery.

While in general there is evidence to support an association between use of thromboprophylaxis and a reduction in deep-vein thrombosis (DVT), there has been no reduction in the incidence of fatal pulmonary embolism, and there is, in fact, increasing evidence to support a potential increase in localised wound complications, bleeding problems, infection and ultimately, an increased all-cause mortality [2, 5, 6].

In most parts of the world, warfarin has traditionally been used as a first-line thromboprophylactic agent, and in low doses has been shown to be as effective as other forms of pharmacologic anticoagulation in preventing VTE, with a low incidence of complications [7, 8]. However, some patients require warfarin perioperatively to address medical issues such as atrial fibrillation, prosthetic heart valve, previous thromboembolism or a pro-coagulant disorder. In these patients, the
target International Normalised Ratio (INR) is frequently, and necessarily, higher than that traditionally used for primary thromboprophlaxis. Therefore, the concern is raised that the incidence of post-operative complications could be correspondingly higher.

To mitigate this potential risk, a significant number of these patients will have their warfarin discontinued prior to surgery, and will be treated with some form of bridging heparin therapy. Traditionally, intravenous unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) have been used as the bridging agents, but there are concerns that the rate of bleeding complications is particularly high in this group, especially within the first week after surgery[9].

This study aims to assess the incidence of complications in patients undergoing primary knee arthroplasty who require therapeutic warfarin (or bridging heparin) in the perioperative period. Primary outcome measures include evidence of significant extra-articular bleeding, superficial or deep infection, excessive wound drainage or haematoma, return to theatre for washout, or revision of the joint during the study period.

Patients & Methods:

Relevant ethical approval for this study was obtained from the regional Human Research Ethics Committee at The Prince Charles Hospital and relevant data obtained from the Orthopaedic Research and Data Management Unit, where operation details are routinely recorded.
We extracted computerised records from the prospective arthroplasty database at our institution to identify 1625 patients undergoing primary total knee arthroplasty (TKA) between 2004 and 2008. Computerised pathology results were examined for this group and all patients who had abnormal coagulation profiles peri-operatively were initially identified. A review of the case notes confirmed 149 patients were on warfarin within 30 days of surgery, which made up the study group. A subset of this group (32 patients) required bridging IV heparinisation perioperatively because of the inherent risks of their co-morbid conditions.

The case subjects were age and gender matched in a 1:2 ratio with a control group of TKA patients who did not require therapeutic anticoagulation. The study group consisted of 63 males and 79 females with a mean age of 70.8 [range, 43 to 89 years; SD 8.0], (seven of the cases were bilateral); the control group consisted of 126 males and 160 females, mean age 71.0 [range, 41 to 92 years; SD 8.0], (14 bilateral).

The following data were collected for each patient:

- Indication for warfarinisation
- Pre- and post-operative coagulation parameters
- Details of thromboprophylaxis (in both the study and control groups)
- Details of bridging anticoagulation, including therapeutic INR value
- Evidence of significant extra-articular bleeding
• Evidence of superficial infection (defined as positive microbiology from a wound swab, with subsequent initiation of antibiotics by the treating orthopaedic team)\(^1\)
• Evidence of deep infection (defined as positive microbiology from operative tissue specimens or joint aspirate)
• Evidence of excessive wound drainage or haematoma (defined as case note documentation within 48 hours of surgery)
• Documentation of return to theatre for washout during original admission
• Documentation of revision for any cause during the study period
• History of diabetes

Because the 32 study patients who required bridging anticoagulation with IV heparin in the perioperative period were hypothesised to be of particularly high risk for complications, they were analysed as an additional sub-group.

In the study group as a whole, there was marked heterogeneity of the choice and dosage of agents provided, (detailed in Table 1). In the IV heparin group the target APTT across the group was standardised at 65-100 seconds (1.5 - 2 times the upper value of the reference range).

Following current best-practise recommendations, all patients in the control group (except one) underwent primary chemical thromboprophylaxis in the immediate post-operative period. Warfarin was not used prophylactically in this group. Of the 300 controls, 222 (74.0%) were given aspirin 150mg or 300mg PO OD; 58 (19.3%)...
had UFH 5000 units TID; 19 (6.3%) received LMWH (enoxaparin, 40 mg SC); and one patient received no thromboprophylaxis. All patients also routinely used mechanical methods of thromboprophylaxis.

Statistical analysis was performed by a biostatistician, using SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL). Frequencies were compared, using chi-squared or Fisher’s exact test, as appropriate. Bonferroni’s correction was applied to adjust for multiple testing, which set the p-value for statistical significance at 5% to p=0.01.

Results:

Analysis of data from the 449 patients in the study indicates there were significantly more complications (mean per patient) in the group of patients on perioperative, therapeutic anticoagulation [0.9, (95% CI: 0.66 to 1.05)] as compared to the control group [0.3, (95% CI: 0.23 to 0.36), p<0.001], with the bridged group at particularly high all-cause risk [1.8, (95% CI: 1.15 to 2.35), p<0.001]. Figure 1 illustrates the specific outcome measures, indicating significant increases in prolonged wound drainage (26.8% of cases vs 7.3% of controls, p<0.001); superficial infection (16.8% vs 3.3%, p<0.001); deep infection (6.0% vs 0%, p<0.001); return-to-theatre for washout (4.7% vs 0.7%, p=0.004); and eventual revision within the period under investigation (4.7% vs 0.3%, p=0.001).

The most common indication for warfarinisation in patients in the study group was previous venous thromboembolism, followed by history of atrial fibrillation. Seventeen patients received warfarin for a suspected or confirmed post-operative venous thromboembolism, which represented an overall incidence of venous
thromboembolic events of 1% for patients undergoing knee replacement during the five-year period. A summary of the various rationales for prescription of perioperative warfarin is displayed in Table 2.

Thirty-two patients of the study group required bridging IV heparin perioperatively. Almost half of these patients (15) had prosthetic heart valves. Compared to the rest of the study group, incidence of complication among this sub-group was significantly higher across the categories, as indicated in Figure 2. Significantly, two-thirds of this sub-group (21 patients) had their heparin started on the day of surgery.

Post-operatively, the seven surgeons in the study considered a variety of measures to determine when and at what level to restart their patients on therapeutic warfarin. However, achieving the desired level of anticoagulation appeared to be problematic. For example, 21 of the 149 case patients (14%) had post-operative INRs above the upper therapeutic limit for their condition. And, of the subset of 32 patients who needed bridging IV heparin, 23 (72%) had post-operative APTT levels above the upper therapeutic limit for the protocol target of 65-100 seconds. In fact, 14 of the 32 bridged patients (44%) had APTTs that were more than double the upper therapeutic post-operative parameter. A sub-analysis on the effects of excessive anticoagulation did not reveal any effect of a high INR or supratherapeutic APTT on complication rates either on an individual complication basis or when all complications were grouped together.
In the control group there were no significant differences in the frequencies of complications between the different pharmaceutical modalities used for thromboprophylaxis.

There was no statistically significant difference between the prevalence of diabetes between the study group (16 [10.7%]) and the control group (36 [12.0%]) (p=0.69).

**Discussion:**

Much of the literature surrounding the use of anticoagulants in total joint arthroplasty relates to the pharmacologic prophylaxis of venous thromboembolism, and its most frightening consequence: pulmonary embolism. This subject remains the subject of considerable debate and evokes strong opinions across the medical fraternity. Warfarin has been shown to be an effective thromboprophylactic agent in numerous studies for both hip and knee replacement [7, 10-12]. In these studies, the primary focus has been on the prevention of venographically-confirmed deep vein thrombosis or pulmonary embolus detected by ventilation/perfusion scan. Regarding safety, there is considerable information on major extra-articular bleeding (retroperitoneal, intraocular or cerebral), but little data on the presence of persistent or excessive wound discharge, and superficial or deep infection. Persistent wound discharge has been shown to correlate with an increased risk of superficial and deep infection in arthroplasty patients [13].

Fitzgerald and colleagues [11] showed a clinically significant rate of haemorrhage in 23% of patients undergoing primary knee replacement while on warfarin prophylaxis (target INR 2-3). Their study found major haemorrhage in 2.3% of the TKA patients,
clinically important operative-site haemorrhage in 3.4%, and minor haemorrhage in 21% of the patients. Leclerc, et al. [12] reported clinically overt bleeding in 26.6% of the 211 knee replacements on warfarin in their series with a 1.8% major haemorrhage rate (target INR 2-3). None of these studies looked at superficial or deep infections as end-points. Sachs [2] found a superficial infection rate of 0.3% and a deep infection rate of 0.6% in the 957 knee replacements who underwent knee replacement on low dose warfarin (target INR 1.6-2.2).

In our study, the incidence of excessive wound discharge, superficial and deep infection in the study group were significantly higher than in the controls, while the incidence of superficial and deep infection in the control group (3.3% and 0) were similar to other studies published in the literature [13-15]. However, the finding of no deep infections in our control group is probably artificially low and may represent an inadvertent bias during the matching process. The rates we found in the study group are higher than those reported elsewhere in the literature, but if the subgroup of patients treated with bridging heparin is removed, results become far more comparable.

Patterson and colleagues described a 30% bleeding-related complication rate in 112 patients who were treated for thromboembolism with IV heparin following hip or knee arthroplasty [9]. They found that the prevalence jumped to 45% if the heparin was started within six days of surgery, and dropped to 15% if it was started more than six days post-operatively. This study did not look at the incidence of infection however, and was descriptive only, with no control group. Bicalho et al. [16] reported a complication rate of 11% in 28 patients who received IV heparin for post-
arthroplasty pulmonary embolism, although only one of these complications was bleeding-related, and 20 of the Bicalho cohort began their heparin a week or more following surgery. In a retrospective case-control study, Della Valle et al. [17] looked at 44 consecutive hip or knee replacement patients who were managed with IV unfractionated heparin for post-operative thromboembolism. This study found a post-operative bleeding complication rate of 9%, which was not significantly different to that encountered in the control group, which was on LMWH enoxaparin. Heparin therapy was begun at a mean of 5 days post-op, and the target therapeutic level was 1.5 times the normal APTT.

In our bridging IV heparin sub-group, there were no major extra-articular bleeding complications, but the rate of other complications was strikingly significant: more than half of the patients developed significant postoperative wound drainage, more than a quarter developed superficial infection and a fifth of the sub-group developed deep infection. Of note, we also observed a high rate of over-anticoagulation, with just over 70% of patients experiencing an APTT greater than the upper therapeutic limit. The difficulty of maintaining serum anticoagulation levels within a “relatively narrow therapeutic range” has recently been highlighted in a systematic review by Krishnaswamy [18].

The stress on homeostasis brought about by both prolonged or excessive wound drainage and localised bleeding complications stems from an imbalance in total blood volume, haemoglobin, hematocrit and platelet counts. We have used prolonged or excessive wound drainage as a surrogate for localised bleeding complications, enabling us to more directly compare our study’s primary outcomes
with those described above. For example, our cohort started their bridging IV heparin much earlier in the post-operative period, with 21 of 32 starting within 6 hours, quite possibly in response to the high prevalence of patients with prosthetic heart valves in our study.

Another point of variance arises when comparing Della Valle’s group to our more aggressively anti-coagulated patients, a difference that highlights two potentially important points: Firstly, the timing of the introduction of bridging heparin after surgery may be critical; initiation of IV heparin within the first 6 hours post-op was associated with the highest risk of complications. Secondly, the ideal degree to which patients are anti-coagulated would appear to fall within a relatively narrow therapeutic window. Both our study and that by Patterson et al. (in which the target APTT was around twice the normal), were associated with much higher complication rates than those found in Della Valle’s study, in which the target APTT was only 1.5 times the normal value. We were not able to demonstrate a difference in complication rates between those who had an APPT within the therapeutic range and those who were excessively anticoagulated. However, this may have been due to the small numbers involved in the analysis at this stage.

Finally, the high incidence of superficial and deep infection in our study is concerning, particularly with regard to the sub-group bridged with intravenous heparin. In our series, these infections significantly added to the patients’ revision burden, with implications for both patient morbidity and cost.
The vast majority of patients in our study were being treated with warfarin either for atrial fibrillation or a previous VTE. In the case of atrial fibrillation, there is a wealth of data regarding the serious annual risk of embolic stroke in AF patients who are not treated with warfarin. Evidence from the Framingham studies found a 28.2% risk of stroke for isolated AF over an 11-year period [19]. Patients with a previous history of transient ischaemic attack, diabetes or ischaemic heart disease have an even higher risk of stroke [20]. Nevertheless, the American College of Cardiology has recommended that warfarin may be discontinued in patients for up to a week for procedures which carry a bleeding risk without bridging with heparin [21]. Of course, the body does encourage individual risk stratification assessment, as do many in the orthopaedic field itself [22]. In the context of this study, the automatic initiation or continuation of traditional anticoagulation protocols without the benefit of such individualised assessment may be called into question among orthopaedic surgeons.

Moving forward, the challenge for surgeons and physicians alike will be to identify which patients on chronic warfarin treatment can do without therapeutic anticoagulation perioperatively. In those who clearly require some form of cover, such as patients with prosthetic valves or pro-coagulant disorders, the goal will be to identify the optimum method of balancing the risks of thrombosis with the bleeding and infection risks of surgery. This may mean using low-molecular weight heparin instead of IV heparin. General guidelines on optimal anti-coagulation protocols do exist. The British Committee for Standards in Haematology and the American College of Chest Physicians (23, 24) currently recommend that bridging therapy should not be instituted for a minimum of 48 hrs post-op after high bleeding risk surgery. For
patients with uncomplicated AF (no prior stroke or TIA) or an aortic bileaflet mechanical valve with no other risk factors, no bridging therapy is recommended. If a patient has had a venous thromboembolus in the last 3 months, has complicated AF or has a mitral mechanical heart valve, bridging therapy is recommended. At present there are 2 large multi-centre randomised trials –

clinicaltrials.gov/ct2/show/NCT00432796 and

clinicaltrials.gov/ct2/show/NCT007864740 – in progress which are examining the safety and efficacy of bridging therapy with LMWH in high risk patients and lower risk patients respectively. The results are due for publication in 2013 and will hopefully provide the medical community with more concrete evidence upon which to base these difficult decisions.

One of the limitations of our study stems from the fact that we only matched for gender and age with our control group. Had this not been a retrospective study, the pairing of additional parameters such as the presence of diabetes, the type of thromboprophylaxis in the control group, the use of tourniquets and drains, and use of a uniform transfusion protocol ideally would have been controlled for, helping to reduce theoretical selection bias even more. Additionally, we were unable to comment upon the number of patients who may have been treated for infection or had their TKAs revised at other institutions.

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2 Although diabetes was not matched for, the difference in prevalence between the study group and the controls was not significant (10.7% v 12.0%, p=0.69).
In conclusion, this study contributes to the core of literature addressing the
challenge of managing patients on long term anticoagulation therapy when they
present for total knee arthroplasty. The study confirms the hypothesis that patients
who require warfarin perioperatively for medical co-morbidities are at increased risk
of post-operative complications, including superficial and deep infections and
localised wound problems. They also appear to add to the revision burden and the
need to return to theatre in the immediate perioperative period. Patients who
require bridging with IV heparin are at particularly high risk especially if their anti-
coagulation is commenced in the early post-operative period. It is therefore
incumbent upon the orthopaedic surgeon, in conjunction with medical colleagues, to
weigh up the risk of thrombosis versus bleeding and infection complications for each
patient in order to determine the optimal perioperative anticoagulant regimen.
References:

Figure 1: Frequency of complications comparing case and control groups (%)
Figure 2: Frequency of complications comparing IV heparin bridged patients and perioperatively warfainised patients (%)
Table 1. Bridging Agents Used in Subjects Requiring Anticoagulation (combined with warfarin)

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Dosage</th>
<th># of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Low-dose” unfractionated heparin (UHF)</td>
<td>5000 units SC daily or BD</td>
<td>18</td>
</tr>
<tr>
<td>“High-dose” unfractionated heparin (UHF)</td>
<td>5000 units SC TDS or QID</td>
<td>43</td>
</tr>
<tr>
<td>“Low-dose” low molecular weight heparin (LMWH)</td>
<td>Enoxaparin sodium 20mg SC TDS</td>
<td>11</td>
</tr>
<tr>
<td>“High-dose” low molecular weight heparin (LMWH)</td>
<td>Enoxaparin sodium ≥40mg SC</td>
<td>6</td>
</tr>
<tr>
<td>IV heparin</td>
<td>5000 units IV loading dose followed by continuous infusion adjusted to APTT</td>
<td>32</td>
</tr>
<tr>
<td>Aspirin</td>
<td>300mg Daily</td>
<td>14</td>
</tr>
<tr>
<td>Nothing</td>
<td></td>
<td>25</td>
</tr>
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</table>
Table 2. Frequency distribution of indications for warfarinisation

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number (%) of Study Group</th>
<th>Number (%) of bridging IV heparin sub-group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous venous thromboembolism</td>
<td>50 (33.6)</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>48 (32.2)</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>Post-operative venous thromboembolism</td>
<td>20 (13.4)</td>
<td>9 (28.1)</td>
</tr>
<tr>
<td>Mechanical valve</td>
<td>19 (12.8)</td>
<td>15 (46.9)</td>
</tr>
<tr>
<td>Procoagulant disorder</td>
<td>5 (3.4)</td>
<td>0</td>
</tr>
<tr>
<td>Unclear</td>
<td>7 (4.7)</td>
<td>0</td>
</tr>
</tbody>
</table>