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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.

Although the use and choice of pharmacologic anticoagulant for prophylaxis against venous thromboembolism (VTE) or pulmonary embolism (PE) in lower extremity arthroplasty are areas 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 thromboprophylaxis. 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.

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Patients and 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-operative 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 h 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 s (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 150 mg or 300 mg PO OD; 58 (19.3%) had UFH 5000 U 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.

[1] Patients commenced on antibiotics by a general practitioner were excluded from this study.

Table 1
Bridging Agents Used in Subjects Requiring Anticoagulation (Combined With Warfarin).

Anticoagulant	Dosage	# of Patients
"Low-dose" unfractionated heparin (UHF)	5000 U SC daily or BD	18
"High-dose" unfractionated heparin (UHF)	5000 U SC TDS or QID	43
"Low-dose" low molecular weight heparin (LMWH)	Enoxaparin sodium 20 mg SC TDS	11
"High-dose" low molecular weight heparin (LMWH)	Enoxaparin sodium ≥40 mg SC	6
IV heparin	5000 U IV loading dose followed by continuous infusion adjusted to APTT	32
Aspirin	300 mg Daily	14
Nothing		25

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), $P<0.001$]. Fig. 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.

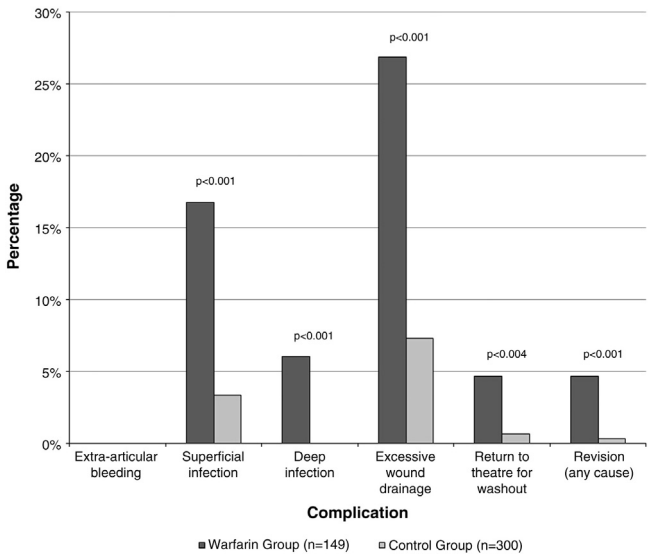

Fig. 1. Frequency of complications comparing case and control groups (%).