*Clinical Study*

# Management of Warfarin Anticoagulation in Patients with Fractured Neck of Femur

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*Background.* Most orthopaedic units do not have a policy for reversal of anticoagulation in patients with hip fractures. The aim of this study was to examine the current practice in a district general hospital and determine difference in the time to surgery, if any, with cessation of warfarin versus cessation and treatment with vitamin K. *Methods.* A retrospective review of the case notes between January 2005 and December 2008 identified 1797 patients with fracture neck of femur. Fifty seven (3.2%) patients were on warfarin at the time of admission. Patients were divided into 2 groups (A and B). Group A patients (16/57; 28%) were treated with cessation of warfarin only and group B patients (41; 72%) received pharmacological therapy in addition to stopping warfarin. Time to surgery between the two groups was compared. *Results.* The mean INR on admission was 2.9 (range 1.7–6.5) and prior to surgery 1.4 (range 1.0–2.1). Thirty eight patients received vitamin K only and 3 patients received fresh frozen plasma and vitamin K. The average time to surgery was 4.4 days in group A and 2.4 days in group B. The difference was statistically significant ($P < .01$). *Conclusion.* Reversal of high INR is important to avoid significant delay in surgery. There is a need for a national policy for reversing warfarin anticoagulation in patients with hip fractures requiring surgery. Vitamin K is safe and effective for anticoagulation reversal in hip fracture patients.

## 1. Introduction

Approximately 1% of the UK population is on oral anticoagulation with vitamin K antagonists [1]. Warfarin therapy is commonly administered to elderly patients for conditions such as atrial fibrillation, prosthetic heart valves, and thromboembolic disorders [2]. This population group is prone to osteoporotic fractures, such as fracture neck of femur. Current recommendations state that surgery for hip fractures following patient optimisation should be undertaken early, ideally within 24–48 hours [3–8]. This has created a challenge for orthopaedic surgeons as warfarin anticoagulation can cause significant delay in the surgical management of these patients [9]. Reversal of anticoagulation to prevent excessive bleeding at the time of hip surgery is required. This, however, carries a risk of thromboembolism that is further superimposed by immobility and hip surgery itself [10–12]. On the other hand, delaying surgery results in increased morbidity and mortality [7]. Complications of recumbency include pneumonia, pressure sores, muscle wasting, and urinary tract infections [13].

In order to reverse anticoagulation, one can "wait and watch" for INR to correct itself by stopping warfarin only, or actively reverse anticoagulation using pharmacologic means. These include vitamin K, fresh frozen plasma, clotting factor concentrates, or a combination of these [14]. Studies have shown that it may take up to 4 days for INR to reach acceptable levels for surgery [15]. There is a lack of local and national guidelines for reversal of anticoagulation in patients with a hip fracture [16, 17]. This study examines the current practice of perioperative management of anticoagulation in hip fracture patients in a district general hospital setting.

## 2. Patients and Methods

We retrospectively reviewed case notes of patients who underwent surgery for fracture neck of femur between January 2005 and December 2008 at our unit. Patients on warfarin were identified and evaluated. The clinical indication for warfarin therapy, INR on admission and prior to surgery were documented. Patients were divided into two groups. Group A patients were treated with cessation of warfarin only, and group B patients received pharmacological therapy in addition to stopping warfarin. Time to surgery (excluding any other reason for delay) between the two groups was compared. Statistical analysis was done using one-way analysis of variance (ANOVA) test.

## 3. Results

Between January 2005 and December 2008, 1797 patients with fracture neck of femur underwent hip surgery in our unit. Fifty-seven (3.2%) of these patients were on warfarin therapy at the time of admission. The mean age was 79.3 years (range 58–99), and 34 (59.6%) were females. The indications for warfarin treatment were as follows:

   (i) atrial fibrillation (AF), 40 patients (70.1%)

   (ii) thromboembolism, 12 patients (21.1%)

   (iii) prosthetic heart valves, 5 patients (8.8%).

The mean INR on admission was 2.9 (range 1.7–6.5) and prior to surgery 1.4 (range 1.0–2.1). Thirty patients (52.6%) had an extracapsular fracture; 28 were treated with a dynamic hip screw (DHS) and 2 with an intramedullary hip screw (IMHS). Twenty-seven patients (47.4%) had intracapsular fracture neck of femur; 24 were treated with a hemiarthroplasty and 3 with cannulated screws. The method of anticoagulation reversal (watchful waiting or pharmacologic) was decided by the admitting doctor, the Orthopaedic Consultant, or following discussion with the Haematology Consultant. High INR was managed by watchful waiting in 16 (28.1%) and pharmacologic therapy in 41 (71.9%) patients. Despite cessation of warfarin in the watchful waiting group, INR initially increased in 5 patients (8.8%). In the pharmacologic reversal group, 38 patients received intravenous (IV) vitamin K (5–10 mg) only, and 3 patients received fresh frozen plasma (FFP) and IV vitamin K (5–10 mg). Three patients who received FFP and vitamin K had high INR values (5.2, 5.5, 6.5) on admission and were discussed with the Haematology Consultant.

Reasons for surgical delay in warfarinised hip fracture patients, other than INR, were obtained from the notes. Seven patients in total had surgery delayed due to reasons other than high INR. These included medically unwell patients requiring optimization (4 patients); awaiting echocardiogram (1 patients); awaiting pacemaker check (1 patient); awaiting further imaging to confirm fracture (1 patient). These patients were excluded from our study. The average time to surgery from admission in patients not given pharmacologic treatment was 4.4 days (range 1–8 days).

The average time to surgery from admission in patients given pharmacologic treatment was 2.4 days (range 1–5 days). The difference between the 2 groups is statistically significant ($P < .01$).

## 4. Discussion

Most of the patients (71.9%) were managed using vitamin K and waiting for the INR to reach acceptable levels for anaesthesia and surgery. Warfarin was stopped on admission for all patients. A watch and wait policy was used for 16 patients (28.1%). The lack of standard protocol resulted in patients being given variable treatments to reverse anticoagulation. The decision was generally dependent upon the INR level, the indication for warfarin, and the urgency for surgery.

An interesting finding in 5 of our patients in the "watch and wait" group was an increase in INR value one day after admission. This was also observed in a study investigating surgical delay in patients on warfarin [14]. The erratic increase in INR was thought to be secondary to posttraumatic stress responses, immobilization, and long periods of fasting in surgical patients [14]. The additive effect of these factors on the anticoagulation effect of warfarin has also been demonstrated in an experimental study [18].

The mean INR on admission for our patients was 2.9 (range 1.7–6.5) and prior to surgery 1.4 (range 1.0–2.1). There is a consensus that performing surgery in anticoagulated patients will increase the risk of intra- and post operative bleeding despite adequate surgical technique [19–21]. Current guidelines recommend an INR of less than 1.5 before any major surgery [22]. However, some surgeons and anaesthetists still undertook hip fracture surgery with a slightly higher level. Three patients were operated with INR > 1.5, and two of them received intraoperative FFP. INR of greater than 1.5 exposes surgical patients to increased risks of intra- and post operative bleeding complications [19, 23, 24]. In addition, the type of anaesthesia may be affected by anticoagulation. Bleeding and neurological dysfunction may occur during the insertion or removal of a spinal or epidural catheter in an anticoagulated patient [25–27]. Warfarin therapy is a contraindication for regional anaesthesia, such as spinal and epidural [12].

The thromboembolic risk after discontinuing warfarin should also be taken into consideration. This depends on the clinical indication for warfarin, the period the patient remains without anticoagulation therapy, the degree of anticoagulation reversal, and the type of surgical procedure undertaken [23, 24]. There are specific clinical indications that entail a high risk for thrombosis. These include mechanical prosthetic heart valves and chronic atrial fibrillation in association with other stroke risk factors. The high-risk group also includes patients with recent venous or arterial thromboembolism within the preceding 3 weeks [28]. Lower risk patients are those with AF without additional risk factors for stroke patients with deep vein thrombosis treated for more than six months after the acute event and patients with a hypercoagulable state without a thrombotic complication [28]. In the high-risk group, the absolute risk of thromboembolism in a 6–8-day perioperative period when warfarin

is interrupted is approximately 0.3%. This corresponds to approximately 0.03% in the low-risk group [28].

The average time to surgery from admission in patients in the "watch and wait" group was 4.4 days (range 1–8 days). The average time to surgery from admission in patients given pharmacologic treatment was 2.4 days (range 1–5 days). The difference between the 2 groups is statistically significant ($P < .01$). These results have reinforced data obtained from previous studies [9, 13, 14, 17, 29–31]. The findings of this study revealed little evidence to support watchful waiting as the best strategy in preventing delay for semiurgent surgery. It is clear that pharmacologic reversal of warfarin anticoagulation facilitates earlier surgery in patients with hip fractures. It is costeffective, as it decreases hospital inpatient stay [9]. There were no side effects of pharmacologic reversal in our study. Risks of intravenous and subcutaneous vitamin K include anaphylactoid and cutaneous reactions respectively. Recent studies have recommended oral vitamin K for warfarin reversal [17, 29, 32, 33]. There is minimal difference in postsurgery rewarfarinisation time following low dose vitamin K administration in hip fracture patients compared to "watch and wait" patients. This indicates few discharge delays due to postsurgery rewarfarinisation [9, 29].

There are no clear guidelines in the literature for anticoagulation reversal in hip fracture patients. For elective hip operations, most surgeons adopt a "wait and watch policy." Warfarin is generally discontinued 5 days prior to the elective procedure for INR to become subtherapeutic [34]. In emergencies, such as young patients with hip fractures, a rapid correction of INR is required. Available options include vitamin K, infusion of fresh frozen plasma, or prothrombin complex concentrate. This depends on the INR level and the urgency of surgical intervention. Warfarin acts as a vitamin K antagonist and inhibits $\gamma$-carboxylation of coagulation factors II, V, IX, and X, protein C, and protein S [35]. It has a half-life of approximately 40 h, and this may be further increased in the elderly. In most patients with INR 2.0–3.0, the level falls to less than 1.5 within 96–115 h after the last warfarin dose [15]. However, if the steady state of INR is greater than 3.0, or the patient is elderly, more time is required for the level to fall to less than 1.5 [23].

Overanticoagulation can result from a multitude of factors. These include administration of inappropriately high warfarin doses, altered protein binding, decreased vitamin K intake, reduced vitamin K synthesis, and increased clearance of vitamin K-dependent clotting factors. Elderly hip fracture patients are frequently on other medications. Drugs that alter liver enzyme activity or compete with warfarin for protein binding will also affect the level of anticoagulation [36]. In addition, anticoagulant responses can be affected by various factors such as age, body weight, gender, and ethnicity [37].

Vitamin K therapy alone is inappropriate if immediate normalisation of the INR is required in hip fracture or actively bleeding patients. This is because the onset of action is 4–6 h after intravenous administration and at least 24 h after oral administration [34, 38]. High doses will not further shorten the time to anticoagulation reversal. However, high doses may lower INR more than is necessary and cause warfarin resistance that persists for up to 1 week

[39]. Some authorities, such as the American College of Cardiology/American Heart Association, suggest avoidance of Vitamin K for patients with mechanical valves for fear of valve thrombosis [40].

Fresh frozen plasma can reverse anticoagulation immediately without causing any later resistance to warfarin or heparin [41]. However, its effect dissipates within 8–12 h and is optimally administered within 4 h of the procedure [42]. Risks include anaphylactoid reactions, alloimmunisation, excessive intravascular volume [42], and transmission of infection [21]. In addition, it also must be thawed before use, which can delay treatment.

Prothrombin complex concentrates (PCCs) contain high concentrations of the coagulation factors inactivated by warfarin, namely, factors II, VII, IX, and X, and can be rapidly administered. There are no studies evaluating the use of PCCs in hip fracture patients requiring anticoagulation reversal. A major advantage of PCCs over FFP is that smaller volumes of PCCs are required to reverse anticoagulation [37]. PCCs are also quicker to prepare than FFP [38]. The time required for INR correction was reported to be five times more rapid with PCCs than FFP [43]. One important consideration is the association of FFP with a risk of transfusion-related acute lung injury, which has not been documented as a safety concern with PCCs [44]. However, the primary safety concern with PCCs has been their association with thrombogenic events such as stroke, myocardial infarction, pulmonary embolism, disseminated intravascular coagulation, and deep vein thrombosis [45]. The majority of hip fracture patients do not require immediate surgery. Therefore, the risks of administering PCCs to reverse anticoagulation generally outweigh the benefits. Surgeons should, however, be aware of the availability of PCCs for rapid anticoagulation reversal.

There are no guidelines for perioperative bridging therapy for patients on long-term warfarin requiring surgery. However, it is advocated that most patients except those at the highest risk of thromboembolism, while off warfarin, do not need bridging therapy. High-risk patients (e.g., with mechanical prosthetic valves) are recommended to receive unfractionated heparin whilst the INR is subtherapeutic [46]. Discussion with the haematology and cardiology departments is mandatory in this group of patients in order to carefully manage their anticoagulation.

There were limitations of our study. Patients who were not local to our area could not be included. This was due to the fact that GP anticoagulation records were not available. Therefore, not all warfarinised patients undergoing hip fracture surgery in our unit were included. As previously mentioned, not all surgeons and anaesthetists in our unit required the INR to be strictly less than 1.5 before undertaking the procedure. Another limitation is the lack of randomisation and the retrospective analysis which make this study liable for selection bias.

Previous studies have reported similar experience with hip fracture patients on warfarin [9, 13, 14, 17]. Al-Rashid et al. reviewed the literature and recommended that hip fracture patients should be stratified into high- or low-risk categories based on clinical indication for warfarin

and comorbidities [13]. Low-risk patients can be given intravenous or oral Vitamin K until INR is below 1.5. For high-risk patients requiring surgery immediately or on the same day, fresh frozen plasma should be considered. Bridging therapy with low molecular heparin should be used for high risk patients for the duration of the subtherapeutic INR.

## 5. Conclusion

This study confirms the variation in practice for management of hip fracture patients on warfarin needing semi-urgent surgery. Reversal of warfarin anticoagulation facilitated earlier surgery. Patients on warfarin admitted with hip fractures should have their anticoagulation reversed to avoid significant delays in surgery. Further prospective studies are needed to assess the best management of warfarin anticoagulation in acute preoperative admissions through a combined effort from surgeons, haematologists, and cardiologists. A national policy should be developed for reversing warfarin anticoagulation in patients with hip fractures requiring surgery. Current evidence favours the use of oral vitamin K for anticoagulation reversal in hip fracture patients.

## Conflicts of Interest

The authors declare that there are no conflict of interest.

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