

Treatment with Vitamin K in Hip Fracture Patients Receiving Warfarin

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ABSTRACT: **Background:** Hip fractures are common in the elderly population, but surgical treatment of these fractures within the first 48 hours decreases morbidity and mortality. The management of patients with hip fracture requiring surgery who are taking warfarin anticoagulation is unclear.

Objectives: To determine the effect of vitamin K on hip fracture patients treated with warfarin.

Methods: We retrospectively examined the management of 21 patients with hip fractures who were being treated with warfarin at the time of admission. Vitamin K was given to 11 of the 21 patients. A third group, which served as a control, consisting of 35 hip fracture patients who were not being treated with anticoagulants was also evaluated.

Results: Patients who received vitamin K took fewer days to reach target international normalized ratio (INR) (1.73 ± 0.90 vs. 4.30 ± 1.89 , $P < 0.001$) and had less preoperative time (2.64 ± 1.12 vs. 5.10 ± 2.42 days, $P < 0.008$) when compared with patients who did not receive vitamin K. In addition, these patients had statistically significantly shorter hospitalization stays (9.4 ± 1.9 and 13.2 ± 4.9 days, one-sided $P < 0.06$). There was no difference in the amount of blood found in the wound drains (111.8 ± 68.5 vs. 103.0 ± 69.4 ml) or the number of blood units administered (1.45 ± 1.29 vs. 2.00 ± 2.75 units).

Conclusions: Treatment with vitamin K for hip fracture patients who receive warfarin shortens preoperative time, reduces the length of hospitalization and probably reduces morbidity and mortality.

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ture patients who are treated with warfarin at presentation and have a high level of international normalized ratio, which must be normalized prior to their surgery [7].

Normal INR in patients receiving warfarin can be achieved by various methods: “watch and wait” [7], oral or intravenous vitamin K [8,9], or fresh frozen plasma administration. Fresh frozen plasma is reserved only for cases necessitating emergency surgical intervention due to the potential hazards, high cost, and the additional requirement for continuous vitamin K administration to maintain the low INR [10]. The strategy of “watch and wait” is problematic in these patients. White et al. [7] found that for the INR level to be less than 1.2 prior to surgery, warfarin must be withheld for 96 to 115 hours in patients with INR levels between 2.0 and 3.0.

The purpose of this study was to evaluate the efficacy of vitamin K administration in order to alter the INR from a therapeutic to an operable range. There is insufficient information on this issue in the literature.

PATIENTS AND METHODS

We reviewed the medical charts of all patients who were admitted to our department with hip fractures from 1 January 2007 to 31 August 2008. We included hip fracture patients who were receiving warfarin therapy at admission for atrial fibrillation and divided them into two groups according to the treatment protocols (“watch and wait” and vitamin K) for those with an elevated INR. These two treatment strategies were implemented after our department changed the protocol from “watch and wait” to active reversal with warfarin. The active reversal was performed immediately after admission from the emergency department to the orthopedic department, with vitamin K at a single dose of 10 mg given orally or intravenously. We included a third consecutive group of hip fracture patients who were not receiving any anticoagulation therapy as a control group. All patients received bridging therapy of antithrombotic prophylaxis treatment with a daily single dose of 40 mg enoxaparin subcutaneously. The warfarin was resumed 12–24 hours after surgery.

Hip fractures are common in the elderly population. It has been shown that surgical treatment of these fractures within the first 48 hours decreases the morbidity and mortality rates in this group [1-3]. In recent years, warfarin has been used increasingly as a preventive measure of thromboembolic events mainly in atrial fibrillation and prosthetic heart valve patients [4-6]. This has led to a growing number of hip frac-

*The first two authors contributed equally to this study

INR = international normalized ratio

Table 1. Demographic and clinical data by treatment and patient group

	Warfarin			Control				
	Vitamin K (n=11)	None (n=10)	P	All warfarin (n=21)	Control (n=35)	All P	Vit K P	None P
Age (yr)	81.1 ± 7.5	82.2 ± 5.2	NS	81.6 ± 6.4	80.1 ± 6.5	NS	NS	NS
No. of females (% females)	10 (90.9%)	6 (60.0%)	NS	16 (76.2%)	22 (62.9%)	NS	NS	NS
INR at reception	2.35 ± 0.68	2.69 ± 0.73	NS	2.51 ± 0.71	–	–	–	–
Time to reach target INR (days)	1.73 ± 0.90	4.30 ± 1.89	0.001	2.95 ± 1.94	–	–	–	–
Time until operation (days)	2.64 ± 1.12	5.10 ± 2.42	0.008	3.81 ± 2.20	0.69 ± 0.83	0.0001	0.0001	0.0001
Units of blood before the operation	0.18 ± 0.40	1.10 ± 1.97	NS	0.62 ± 1.43	0.06 ± 0.24	0.09	NS	NS
Units of blood after the operation	1.27 ± 1.10	0.90 ± 1.10	NS	1.10 ± 1.30	1.17 ± 1.01	NS	NS	NS
Total units of blood	1.45 ± 1.29	2.00 ± 2.75	NS	1.71 ± 2.08	1.23 ± 1.11	NS	NS	0.09
Amount of blood in drain (ml)	111.8 ± 68.5	103.0 ± 69.4	NS	107.6 ± 67.4	75.9 ± 79.3	NS	0.05	NS
Length of hospitalization (days)	9.4 ± 1.9	13.2 ± 4.9	0.06	11.2 ± 4.1	7.3 ± 2.4	0.0001	0.004	0.0001

Demographic data included age and gender. Clinical data included admission INR levels, days required to achieve target INR (1.2), the number of inpatient days prior to surgery, blood transfusions administered before and after surgery, the amount of blood found in the drain during the first 48 hours following surgery, and total hospitalization time.

STATISTICAL ANALYSIS

Independent *t*-tests or Wilcoxon two-sample tests in the case of non-normally distributed data were used to compare the age and clinical data between the two warfarin-treated groups and between the two warfarin groups and the control group. Chi-square tests were used to compare the gender distribution between the groups. A *P* value ≤ 0.05 was considered statistically significant.

RESULTS

Twenty-one hip fracture patients receiving warfarin treatment upon admission were eligible for the study. Ten of these were managed by “watch and wait” while the other 11 patients received a single dose of 10 mg vitamin K (3 oral and 8 intravenous). A control group of 35 consecutive hip fracture patients not receiving any anticoagulation therapy was also evaluated. The three groups were of similar age and gender. The two groups of patients treated with warfarin also had the same INR levels at admission [Table 1]. No complications were recorded regarding stopping the warfarin.

VITAMIN K AND NON-VITAMIN K GROUP

The patients who received vitamin K took fewer days to reach target INR levels (1.73 ± 0.90 vs. 4.30 ± 1.89, *P* < 0.001) [Figure 1] with shorter inpatient preoperative time (2.64 ± 1.12 vs. 5.10 ± 2.42, *P* < 0.008) [Figure 2] as compared to the patients who did not receive vitamin K. In addition, these

Figure 1. Time to reach target INR

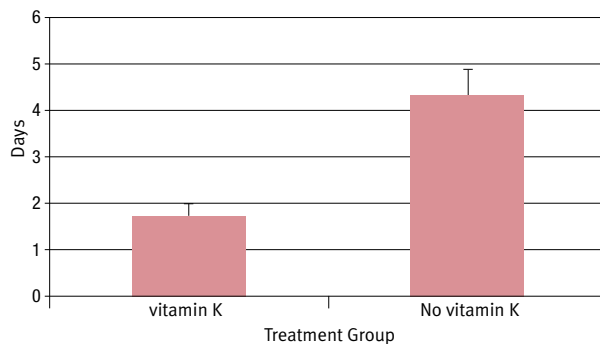
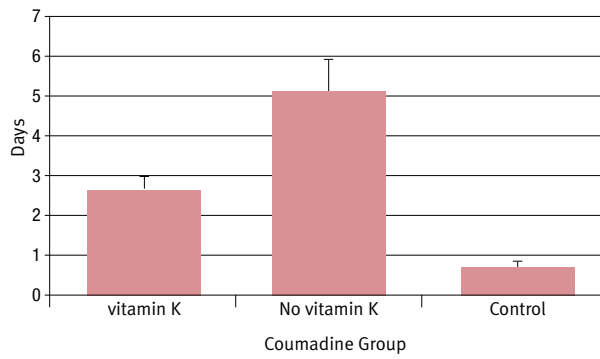
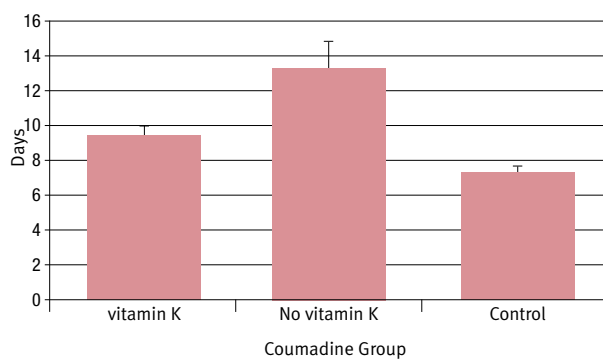


Figure 2. Days until surgery



patients had statistically significantly shorter hospitalization stays (9.4 ± 1.9 and 13.2 ± 4.9 days, one-sided *P* < 0.06) [Figure 3]. There were no statistically significant differences in the amount of blood seen in the drains (111.8 ± 68.5 vs. 103.0 ± 69.4 ml) or the total number of blood units administered (1.45 ± 1.29 vs. 2.00 ± 2.75 units).

Figure 3. Length of hospitalization**VITAMIN K AND THE CONTROL GROUP**

Comparison between the group that received vitamin K and the control patients showed more inpatient days prior to the operation (2.64 ± 1.12 vs. 0.69 ± 0.83 , $P < 0.0001$) [Figure 2] and an overall longer hospitalization period (9.4 ± 1.9 vs. 7.3 ± 2.4 days, $P < 0.004$) [Figure 3] in the vitamin K group. The group that received vitamin K had significantly more blood collected in the drains (warfarin with vitamin K 111.8 ± 68.5 vs. control 75.9 ± 79.3 m, $P < 0.05$), but there was no difference in the total amount of blood units administered (1.45 ± 1.29 vs. 1.23 ± 1.11 units).

NON-VITAMIN K GROUP AND CONTROL GROUP

The patients who did not receive vitamin K were admitted for a longer period prior to the operation (5.10 ± 2.42 vs. 0.69 ± 0.83 , $P < 0.0001$) [Figure 2], with a longer overall hospitalization period (13 ± 5 vs. 7 ± 2 days, $P < 0.0001$) [Figure 3], and received more units of blood than the control group (2.00 ± 2.75 vs. 1.23 ± 1.11 , $P < 0.09$). There was no difference in the blood obtained in the drains (warfarin without vitamin K 103.0 ± 69.4 as compared to control 75.9 ± 79.3 ml).

DISCUSSION

This study demonstrates the efficacy of vitamin K therapy in reversing the effect of warfarin treatment. This intervention reduced inpatient time preoperatively and, as a consequence, reduced the total hospitalization time. Three other papers have addressed this subject: Al-Rashid et al. [11] studied 33 hip fracture patients of whom only 4 were treated with vitamin K, while 9 received fresh frozen plasma and their target INR was 2.2. Eleven patients were treated with a “watch and wait” method. Of the four patients who received vitamin K, three were initially treated with “watch and wait” but eventually were treated with vitamin K when a delay in the INR fall rate was observed. Commenting on the lack of evidence-based protocols for urgent turnover of INR in warfarin patients, the

authors suggest dividing the patients into low and high risk patients. For low risk patients they recommend low dose intravenous or oral vitamin K, and fresh frozen plasma for high risk patients who require urgent surgery. Tharmarajah and collaborators [12] studied 48 patients who underwent several types of orthopedic surgeries in various joints, including knees, ankles and shoulders, and even fasciectomy. Since some of the patients received several doses of vitamin K it is difficult to compare their results to ours. The authors concluded that warfarin reversal with vitamin K was successful, facilitating more rapid surgery in all patients, that it was cost-effective and had no side effects. Bhatia et al. [13] studied 90 patients who received warfarin and required hip fracture surgery urgently. The patients were divided into two groups of 45 patients each. The first was treated by withholding warfarin therapy alone and the second was given one intravenous dose of 1 mg vitamin K. Their results were similar to ours. Time until target INR in the “watch and wait” group was 91 hours as compared to 102 hours in our study. Time until operation in the “watch and wait” group was 158 hours (vs. 122 hours in our study), time until target INR in the vitamin K group was 38 hours (vs. 41.5 hours in our study), and time until operation in the vitamin K group was 67 hours (vs. 63 hours in our study). However, there were some differences: their target INR was 1.5 as compared to 1.2 in our study and they administered only 1 mg vitamin K and only intravenously, whereas in our study 10 mg of vitamin K was given either orally or intravenously.

The only possible adverse effect in our study was that more blood was collected in the drains (not statistically proven). Crowther et al. [14] found that low dose oral vitamin K (1.25 mg) did not alter bleeding in warfarin recipients with INRs of 4.5 to 10.0. This issue should be further investigated.

Three of the 11 patients treated with vitamin K were given 10 mg orally, while 8 received 10 mg intravenously. Tharmarajah et al. [12] administered vitamin K intravenously only, as did Bhatia et al. [13]. Intravenous administration of vitamin K has been associated with possible allergic reactions, although Shields and team [15] found that only 2 of 105 patients who received intravenous vitamin K suffered from an adverse effect of dyspnea and chest tightness. None of our patients suffered any adverse effect during vitamin K administration. Lubetsky et al. [16] conducted a prospective randomized control trial on the difference between oral and intravenous administration of vitamin K in patients receiving warfarin. They randomly divided 47 patients receiving warfarin with an INR higher than 6 and no active bleeding into two groups. The first 24 patients were treated with intravenous vitamin K and the other 23 with oral vitamin K. In patients with baseline INR 6–10 the response to intravenous vitamin K was more rapid than in the oral group, and the proportion of patients reaching therapeutic range INR at 6 hours (11/24 vs. 0/23) and at 12 hours (16/24 vs 8/23) was significantly higher.

However, mean INR values were similar for both groups at 24 hours (2.9 ± 0.8 vs. 2.6 ± 0.8). In patients with baseline INR values > 10 , efficacy and safety were comparable for both methods of administration. Their conclusion was that oral and intravenous administration of vitamin K had similar efficacy and safety and may be suitable for treatment of patients with excessive anticoagulation rates.

The recommendations published in *Chest* [17] appeared after completion of our study. These recommendations suggest that a patient who requires urgent surgery should receive a single dose of vitamin K of up to 5 mg orally, and if the INR does not return to normal range within 24 hours another dose of 1–2 mg vitamin K should be given orally. These recommendations are of Grade 2C basis only. The problem of applying these recommendations in our patients is that they are based on studies that evaluate non-urgent reversal of therapeutic INR to a therapeutic range [18-20].

The main limitations of our study were the small number of patients and its retrospective nature. The small number of patients prevented us from proving statistically that patients receiving vitamin K required fewer blood transfusion units, especially prior to surgery, although we concluded from the results that this is true.

Our study emphasizes the need for large randomized controlled trials and well-designed prospective studies to investigate the efficacy and safety of different preoperative anticoagulation strategies, although it seems clear to us that an active reversal protocol should be generally applied.

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“My pain may be the reason for somebody's laugh. But my laugh must never be the reason for somebody's pain”

Charlie Chaplin (1889–1977), English comic actor and filmmaker who became a worldwide icon through his screen persona “the Tramp.” His films are characterized by slapstick combined with pathos, and often feature the Tramp struggling against adversity. Many contain social and political themes, with *The Gold Rush*, *City Lights*, *Modern Times*, and *The Great Dictator* often ranked among the greatest films of all time

“Human kindness has never weakened the stamina or softened the fiber of a free people. A nation does not have to be cruel to be tough”

Franklin D. Roosevelt (1882-1945), 32nd American President and central figure in world events during the mid-20th century, leading the United States during a time of worldwide economic depression and total war