

Oral Vitamin K Lowers the International Normalized Ratio More Rapidly Than Subcutaneous Vitamin K in the Treatment of Warfarin-Associated Coagulopathy

A Randomized, Controlled Trial

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Background: Excessive anticoagulation due to warfarin use is associated with hemorrhage. Subcutaneously administered vitamin K has not been evaluated for the treatment of warfarin-associated coagulopathy, yet it is widely used.

Objective: To show that oral vitamin K is more effective than subcutaneous vitamin K in the treatment of warfarin-associated coagulopathy.

Design: Randomized, controlled trial.

Setting: Two teaching hospitals.

Patients: Patients with an international normalized ratio (INR) between 4.5 and 10.0.

Intervention: Warfarin therapy was withheld, and 1 mg of vitamin K was given orally or subcutaneously.

Measurements: The primary outcome measure was the INR on the day after administration of vitamin K. Secondary outcome measures were hemorrhage and thrombosis during a 1-month follow-up period.

Results: 15 of 26 patients receiving oral vitamin K and 6 of 25 patients receiving subcutaneous vitamin K had therapeutic INRs on the day after study drug administration ($P = 0.015$; odds ratio, 4.32 [95% CI, 1.13 to 17.44]).

Conclusion: Oral vitamin K lowers INR more rapidly than subcutaneous vitamin K in asymptomatic patients who have supra-therapeutic INR values while receiving warfarin.

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Warfarin-associated coagulopathy, characterized by excessive prolongation of the international normalized ratio (INR), is clinically important because of its associated risk for life-threatening bleeding complications (1, 2). Compared with the simple withholding of warfarin, use of low-dose oral vitamin K has been shown to produce a faster reduction in an elevated INR and a potential reduction in risk for bleeding (3–5). These observations, coupled with the high rate of major or fatal hemorrhage in patients presenting with INRs greater than 6.0 (1), has led to increased use of vitamin K for the treatment of warfarin-associated coagulopathy. In North America, subcutaneous administration is most common (6). However, preliminary evidence suggests that oral vitamin K is more effective than subcutaneous vitamin K (3, 7).

We did a randomized, controlled trial to compare the efficacy of 1 mg of vitamin K administered orally and 1 mg of vitamin K administered subcutaneously for the treatment of asymptomatic patients with warfarin-associated coagulopathy. Our hypothesis was that oral vitamin K is more effective than subcutaneous vitamin K.

METHODS

Study Design

This multicenter, randomized, open-label, controlled trial involved patients who were receiving warfarin, were asymptomatic, and presented with an INR between 4.5 and 10. Eligible patients stopped receiving warfarin for at

least 1 day and were randomly assigned to receive 1 mg of vitamin K either orally or subcutaneously. Warfarin therapy was restarted at the discretion of the treating physician when the INR had decreased into the therapeutic range. We chose the INR range for study inclusion (4.5 to 10) by surveying thrombosis experts and health care providers who frequently prescribe warfarin. The consensus was that risk for hemorrhage in patients with an INR less than 4.5 was low enough that such patients did not mandate intervention, but there was concern about the safety of giving only 1 mg of vitamin K to patients with an INR greater than 10.

Patients

Patients were identified at two teaching hospitals, one in Hamilton, Ontario, Canada, and one in Varese, Italy. The study was approved by the Institutional Review Boards of each center, and all patients provided written informed consent (Appendix Figure, available at www.annals.org). Inclusion and exclusion criteria were identical to those in our previous studies (3). Briefly, eligible patients were those receiving warfarin with a target INR of 2.0 to 3.0 who presented with single INRs of 4.5 to 10.0 and did not require immediate normalization of their INR, have current hemorrhage, or have a high risk for hemorrhage.

Randomization and Intervention

Sealed, sequentially numbered, opaque envelopes were used to randomly assign eligible, consenting patients to

Context

Giving vitamin K when stopping warfarin increases the rate at which the international normalized ratio (INR) returns to normal. Although many clinicians give vitamin K subcutaneously, it appears that oral vitamin K reduces INR more rapidly.

Contribution

This randomized, controlled trial compared oral with subcutaneous vitamin K for patients receiving warfarin who had an INR of 4.5 to 10.0 but no bleeding. Oral administration normalized the INR faster than the subcutaneous route.

Clinical Implications

Clinicians should consider oral administration when prescribing vitamin K for patients who become overanticoagulated while receiving warfarin.

This study had limited power to evaluate bleeding or thrombotic episodes and did not include a group that simply discontinued warfarin.

—The Editors

receive oral or subcutaneous vitamin K. The randomization sequence was generated from a random number table, was stratified by center, and was block randomized in groups of four. Subcutaneous vitamin K was given by injection in the abdominal wall, and oral vitamin K was given under observation. In Canada, vitamin K1 in liquid form (phytonadione for intravenous injection [Abbot, Montreal, Canada]) was used for both oral and subcutaneous administration. In Italy, oral phytomenadione liquid (Konakion, Roche, Milan) was given to patients assigned to oral therapy; the subcutaneous form was diluted to a concentration of 1 mg/mL.

Outcomes

International normalized ratio testing was mandated on the day after study drug administration and was optional thereafter. In Canada, INR testing was done by using Thromborel S (Dade-Behring, Mississauga, Canada) with instrument-specific International Sensitivity Index values of 1.23 to 1.28. In Italy, INR testing was done by using Innovin (Dade-Behring, Milan, Italy) with an instrument-specific International Sensitivity Index value of 1.03. Patients were evaluated by telephone or at a clinic visit 1 month after study enrollment to determine whether thromboembolic or bleeding events had occurred. Major bleeding was defined as bleeding that required a blood transfusion or hospitalization; all other bleeding events were classified as minor. All thromboembolic events required objective confirmation.

Statistical Analysis

The primary analysis was a comparison of the proportion of patients in each study group with INRs between

1.8 and 3.2 on the day after study drug administration; all patients were analyzed in the group to which they were assigned. This range of INRs was chosen because it is a range within which most physicians would be comfortable restarting warfarin therapy. Our a priori assumption was a success rate of 60% in patients assigned to receive oral vitamin K and a success rate of 20% in patients assigned to receive subcutaneous vitamin K (3, 7–9). With an α error set at 0.05 and a power of 80%, we needed 54 patients to complete the study. The effectiveness of oral vitamin K compared with subcutaneous vitamin K was expressed by an odds ratio with a 95% CI. The numbers of clinical events were compared by using the Fisher exact test.

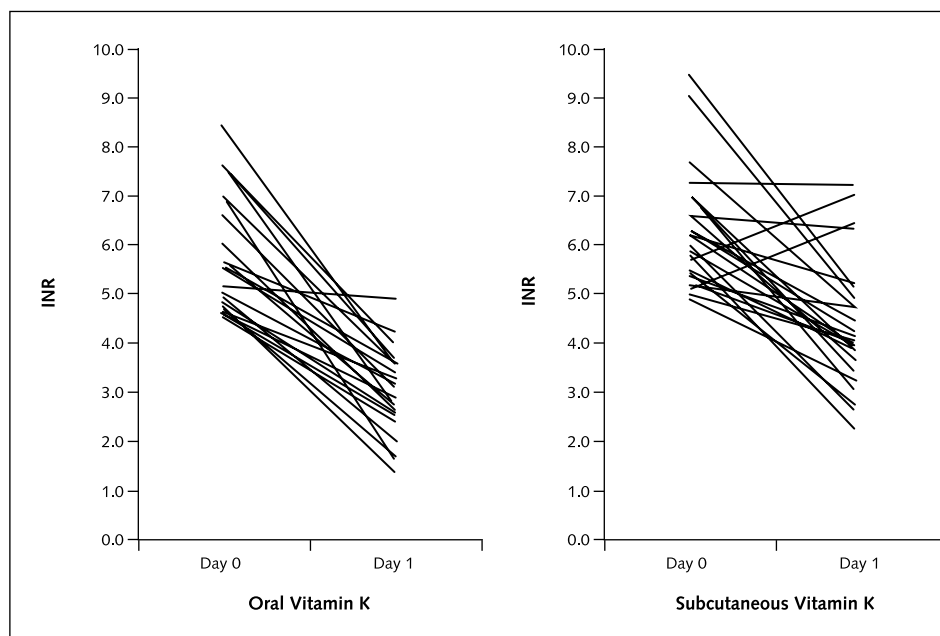
RESULTS**Patients**

Patient enrollment began in April 2000 and was completed in February 2001. Fifty-one patients were screened for study enrollment; all were eligible, and all provided written informed consent. We did not achieve our a priori sample size of 54 patients; only after closing the study did we determine that we had enrolled only 51 patients. The 26 patients assigned to the oral vitamin K group had a mean age (\pm SD) of 73 ± 14 years. Fifty-eight percent were women, 8% had received warfarin therapy for fewer than 7 days, and 38% were inpatients at the time of enrollment. The mean INR on day 0 was 5.8 (range, 4.5 to 7.6). Nineteen (73%) were enrolled in Canada, and 7 (27%) were enrolled in Italy. The 25 patients in the subcutaneous vitamin K group had a mean age (\pm SD) of 67 ± 15 years. Forty-eight percent were women, 20% had received warfarin for less than 7 days, and 20% were inpatients at the time of enrollment. The mean INR on day 0 was 6.2 (range, 4.8 to 9.0). Seventeen patients (68%) were enrolled in Canada, and 8 patients (32%) were enrolled in Italy. This study was done without external funding from peer-review agencies or pharmaceutical companies, and the authors maintained complete control of all aspects of the investigation throughout its course.

Outcomes

All 51 patients had INR testing done on the day after study drug administration. No patients were excluded from the primary analysis. Fifteen of 26 patients (58%) who received oral vitamin K and 6 of 25 patients (24%) who received subcutaneous vitamin K had INRs of 1.8 to 3.2 on the day after study drug administration (odds ratio, 4.32 [95% CI, 1.13 to 17.44]; $P = 0.015$; number needed to treat for benefit, 3) (Figure). No patient who received oral vitamin K and 2 patients (8%) who received subcutaneous vitamin K had an increased INR on the day after study drug administration (the INR increased from 5.0 to 6.3 and from 5.6 to 6.9 in the 2 patients). Three patients (12%) who received oral vitamin K and no patients who received subcutaneous vitamin K had an INR less than 1.8 on the day after study drug administration ($P > 0.2$). The

Figure. International normalized ratio (INR) of patients receiving oral (left) and subcutaneous (right) vitamin K.



More patients who received oral vitamin K than those who received subcutaneous vitamin K had INR values in the range of 1.8 to 3.2. In addition, 1 mg of oral vitamin K lowers the INR more rapidly than does subcutaneous vitamin K.

mean INRs were higher in the subcutaneous vitamin K group than in the oral vitamin K group on the second and third days after study drug administration (Table).

No statistically significant difference was seen in the proportion of patients in Italy (3 of 7 [43%]) and Canada (12 of 19 [63%]) who achieved an INR of 1.8 to 3.2 on the day after oral vitamin K administration (relative risk, 1.26 [CI, 0.75 to 2.10]). In the subcutaneous vitamin K group, a trend was seen in favor of increased efficacy in the patients randomly assigned to study groups in Italy. Thus, 2 of 17 patients (12%) compared with 4 of 8 patients (50%) achieved the target INR (relative risk, 0.42 [CI, 0.13 to 1.34]).

During the 1-month follow-up period, no episodes of

thromboembolism or bleeding occurred. Five patients, all receiving oral vitamin K, died ($P = 0.05$). Three died of cancer, one died of progressive lung disease, and one died of unknown causes.

DISCUSSION

This study provides evidence that oral vitamin K may be more effective than subcutaneous vitamin K in reestablishing a therapeutic INR in asymptomatic patients with warfarin-associated coagulopathy and an INR between 4.5 and 10. This observation is supported by an extensive body of literature suggesting that 1) oral vitamin K is effective for the treatment of warfarin-associated coagulopathy and

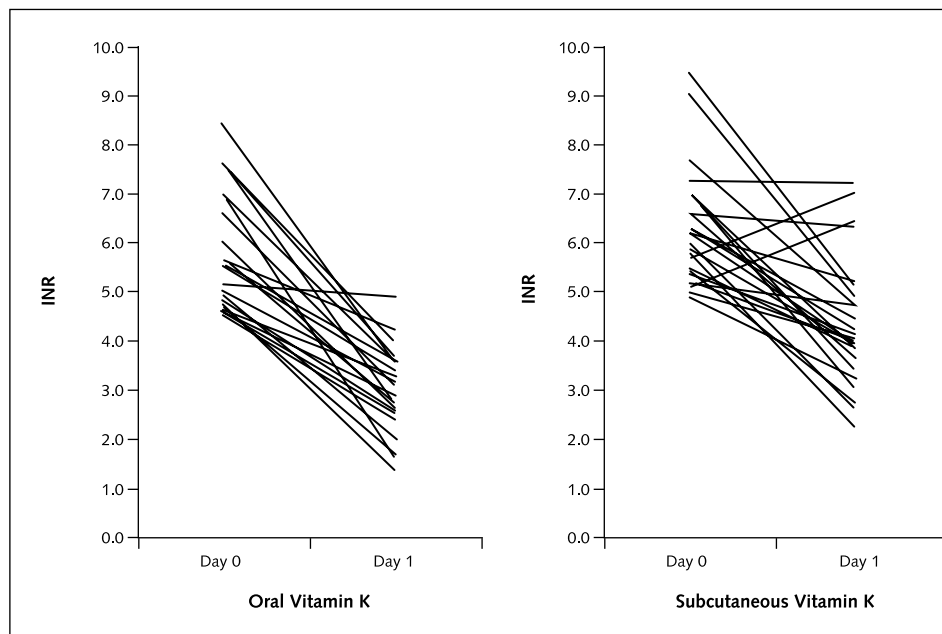
Table. International Normalized Ratios*

Value	Day 0	Day 1	Day 2	Day 3
Oral vitamin K group				
Patients having blood drawn, <i>n</i>	26	26	10	9
Mean INR ± SD	5.8 ± 1.2	2.9 ± 0.8	2.2 ± 0.9	2.7 ± 0.9
Patients with an INR <1.8, <i>n</i>	0	3	3	2
Patients with an INR >3.2, <i>n</i>	26	8	3	1
Patients restarting warfarin therapy, <i>n</i>		16	7	1†
Subcutaneous vitamin K group				
Patients having blood drawn, <i>n</i>	25	25	8	5
Mean INR ± SD	6.2 ± 1.2	4.2 ± 1.3	3.1 ± 1.4	2.8 ± 1.1
Patients with an INR <1.8, <i>n</i>	0	0	1	1
Patients with an INR >3.2, <i>n</i>	25	19	3	1
Patients restarting warfarin therapy, <i>n</i>		7	7	2

* INR = international normalized ratio.

† One patient receiving oral vitamin K restarted warfarin therapy on day 5 after study drug administration. In the group receiving subcutaneous vitamin K, 4 patients restarted warfarin therapy on day 4 after study drug administration, 1 patient restarted warfarin therapy on day 5 after study drug administration, and 5 patients had not restarted warfarin within 5 days after study drug administration.

Appendix Figure. Flow of patients through the study.



INR = international normalized ratio.

2) subcutaneous vitamin K does not produce reliable, rapid reductions in the INR (3, 4, 7–9).

Our findings are likely to be valid because our study was randomized, no patients were excluded after enrollment, the primary outcome was available for all patients, the primary outcome was not subject to observer interpretation, and the results were both statistically significant and consistent with our previous results (3, 7). The results are probably generalizable. The inclusion criteria captured a representative population, and the primary outcome was chosen because it is an INR range (that is, 1.8 to 3.2) within which most clinicians would be comfortable restarting warfarin therapy.

One potential limitation of our study is that the INR is a surrogate marker for bleeding and, thus, our findings cannot address whether low-dose oral vitamin K reduces risk for hemorrhage. However, the INR is a widely accepted and validated surrogate for bleeding and thrombotic risk in patients receiving oral anticoagulants. Another potential limitation is that a trend was seen toward increased efficacy of subcutaneous vitamin K in patients enrolled in Italy compared with patients enrolled in Canada.

The increase in the number of deaths in patients assigned to receive oral vitamin K is noteworthy. Although this increase was marginally significant, its biological rationale is difficult to explain, and we did not see an increased risk for death in our previous studies (3, 7). Thus, this finding may be due to chance.

Our results are clinically important. Currently, it is common practice not to treat patients receiving warfarin who present with excessively increased INRs, in part because of the perception that these patients have a low risk

for hemorrhage (6, 10, 11). However, this risk has probably been underestimated. For example, Hylek and associates (1) found that 4% of patients (5 of 114) with an INR greater than 6.0 developed major bleeding. These authors concluded that bleeding might have been prevented by timely correction of the INR. Another reason cited for not treating patients with elevated INRs is the risk for “over-correction” of the INR. Indeed, we found that 3 patients assigned to receive oral vitamin K and no patients assigned to receive subcutaneous vitamin K had INRs less than 1.8 on the day after study drug administration. The clinical significance of this observation is unclear because no patient developed thrombosis.

In summary, 1 mg of oral vitamin K decreases the INR faster than does 1 mg of subcutaneous vitamin K in asymptomatic patients with supratherapeutic INR values while receiving warfarin. The results of this study, combined with our previous work in this area (3, 7), suggest that to reduce risk for hemorrhage, use of 1 mg of oral vitamin K should be considered for asymptomatic patients who are receiving warfarin and present with an INR of 4.5 to 10. Additional studies are needed to quantify the clinical effect of low-dose oral vitamin K in these patients and to determine whether low-dose oral vitamin K is effective in the management of patients with INRs greater than 10 and patients with target INR ranges other than 2.0 to 3.0.

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