Vitamin K lowered the international normalized ratio into the therapeutic range in patients receiving warfarin

Crowther MA, Julian J, McCarty D, et al. **Treatment of warfarin-associated coagulopathy with oral vitamin K: a randomised controlled trial.** Lancet. 2000 Nov 4;356:1551-3.

QUESTION

In patients who are receiving warfarin and have an international normalized ratio (INR) value between 4.5 and 10.0, does low-dose vitamin K lower the INR better than placebo?

DESIGN

Randomized (allocation concealed*), blinded {patients, clinicians, and outcome assessors}†,* placebo-controlled trial with 3-month follow-up.

SETTING

5 thromboembolism services at teaching hospitals in London and Hamilton, Ontario, Canada.

PATIENTS

92 patients (mean age 65 y, 53% women) who were receiving warfarin and had an INR value between 4.5 and 10.0. Exclusion criteria were INR determined > 12 hours before screening, life expectancy < 10 days, need for immediate normalization of INR, severe liver disease, major bleeding in the previous month, allergy to vitamin K, bleeding diathesis or thrombolytic therapy within 48 hours of screening, inability to take oral medications, platelet count < 50×10^9/L, or geographic inaccessibility. 89 patients (97%) completed the trial and were analyzed.

INTERVENTION

Patients were allocated to 1 mg of oral vitamin K (Abbott Laboratories, Montreal, Quebec, Canada) (n = 46) or to placebo (n = 46).

MAIN OUTCOME MEASURES

Proportion of patients with an INR value between 1.8 and 3.2 the day after the intervention. Patients were assessed for thrombotic and hemorrhagic events at 1 and 3 months after enrollment.

MAIN RESULTS

More patients who received vitamin K than patients who received placebo had INR values between 1.8 and 3.2 the day after the intervention (P = 0.001) (Table). No vitamin K–group patients and 4 placebo-group patients (9%) had an increase in INR values the day after treatment (P = 0.056). An INR value of < 1.8 occurred in 7 vitamin K–group patients (16%) and no placebo-group patients (P = 0.012). After the second day posttreatment, the INR values were similar in the 2 groups. At 3 months, fewer patients receiving vitamin K had bleeding episodes than did patients receiving placebo (4% vs 17%, P < 0.05).

CONCLUSION

In patients who are receiving warfarin and have an international normalized ratio (INR) value between 4.5 and 10.0, low-dose vitamin K lowered the INR to between 1.8 and 3.2 the day after administration.

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For correspondence: Dr. M.A. Crowther, Room L208, St. Joseph's Hospital, Hamilton, Ontario L8N 4A6, Canada. FAX 905-521-6034. ■

*See Glossary.

†Information provided by author.

Vitamin K vs placebo for lowering the international normalized ratio (INR) to the therapeutic range 1 day after the intervention‡

Outcome	Vitamin K	Placebo	RBI (95% CI)	NNT (CI)
INR value between 1.8 and 3.2	56%	20%	272% (49 to 421)	3 (2 to 7)

‡Abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article.

COMMENTARY

In the United States, more than 1 million people per year receive anticoagulation therapy to treat or prevent various thromboembolic complications. Of those receiving such therapy, the INR values will be > 3.9 approximately 8% to 9% of the time (1). The risk for substantial bleeding increases progressively with every 1-point increment of INR above 4.0 (2). For patients with serious bleeding, transfusion with fresh frozen plasma or prothrombin concentrate is the appropriate intervention. In asymptomatic patients, reduction of the INR can be achieved passively by withholding therapy or actively by administering vitamin K. Is active treatment more safe and effective than passive withholding? A recent review of the literature identified the need for large, well-designed, randomized controlled trials to answer this question (3).

A previous prospective cohort study by Crowther and colleagues (4) suggested that 1 mg of oral vitamin K was safe and effective in reversing anticoagulation for most patients within 16 hours of treatment. The current study by Crowther and colleagues provides additional insight into optimal therapy. Oral vitamin K in asymptomatic patients without an overt bleeding risk produces a clinically important increase in the proportion of target-range INR values. For unclear reasons, the intervention group had fewer bleeding episodes during the 3-month follow-up period. Active oral treatment appears to be safe and effective, but it is also unclear whether additional benefit and equivalent safety exist using intravenous or subcutaneous vitamin K administration.

Brian P. Schmitt, MD, MPH
Northwestern University Medical School
Chicago, Illinois, USA

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