

Treatment of Excessive Anticoagulation With Phytonadione (Vitamin K)

A Meta-analysis

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Background: Patients taking oral anticoagulants with an international normalized ratio (INR) greater than 4.0 are at increased risk for bleeding. We performed a meta-analysis to determine the effectiveness of phytonadione (vitamin K) in treating excessive anticoagulation.

Methods: The MEDLINE, EMBASE, and Cochrane Library databases were searched (without language restrictions) for articles published between January 1985 and September 2004. Randomized controlled trials or prospective, nonrandomized trials that used vitamin K to treat patients without major hemorrhage with an INR greater than 4.0 due to oral anticoagulant use were included. The primary outcome was achievement of the target INR (1.8-4.0) at 24 hours after vitamin K administration. Summary estimates were calculated using a random effects model.

Results: Twenty-one studies (10 randomized and 11 prospective trials) were included. Among oral vitamin K treatment arms (4, n=75), the proportion with a target INR

at 24 hours was 82% (95% confidence interval [CI], 70%-93%), which was similar to intravenous vitamin K treatment arms (6, n=69; target INR, 77%; 95% CI, 60%-95%). Treatment arms of subcutaneous vitamin K (3, n=58; 31%; 95% CI, 7%-55%) and placebo/observation (2, n=27; 20%; 95% CI, 0%-47%) were less likely to achieve target INR at 24 hours. Only 1 of 21 trials appropriately assessed for adverse events, so a summary estimate for bleeding risk could not be generated.

Conclusions: Limited evidence suggests that oral and intravenous vitamin K are equivalent and more effective for excessive anticoagulation than simply withholding warfarin sodium. Subcutaneous vitamin K, however, is inferior to oral and intravenous vitamin K for this indication and is similar to placebo. Whether treatment with vitamin K decreases hemorrhagic events cannot be determined from the published literature.

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ORAL ANTICOAGULANTS ARE commonly used in many settings to prevent thrombosis.¹ Excessive anticoagulation also is common, with 1 article's results showing that 27% of patients had an international normalized ratio (INR) greater than 6.0 across 5 years.² When the INR is greater than 4.5 or greater than 6.0, patients are more likely to have bleeding complications.^{3,4} One study's results showed that patients with an INR greater than 6.0 who were treated only by discontinuation of warfarin sodium had a rate of minor and major bleeding events during the next 2 weeks of 8.8% and 4.4%, respectively.⁴

Researchers in several trials evaluated phytonadione (vitamin K) administration to treat excessive anticoagulation. In these trials, different doses and adminis-

tration routes of vitamin K, including oral, intravenous (IV), and subcutaneous (SC), were used. None of these trials was powered adequately to determine if treatment with vitamin K reduced hemorrhagic events. We performed a meta-analysis to address whether patients with excessive anticoagulation (INR >4.0) with oral agents and without symptoms of major bleeding benefit from administration of vitamin K. We attempted to determine (1) if vitamin K administration results in a therapeutic INR (or target INR) sooner than with simply discontinuing the anticoagulant, (2) the optimal dose and route of administration, (3) if vitamin K administration results in fewer adverse outcomes (bleeding, thrombosis, anaphylaxis, or death) than discontinuing the anticoagulant alone, and (4) whether *warfarin resistance* actually exists.

METHODS

STUDY IDENTIFICATION AND SELECTION

We conducted a systematic search of the literature, without language restrictions, using MEDLINE, EMBASE, and the Cochrane Library (Issue 3, 2004; Oxford: Update Software). Our search strategy used exploded medical subject heading terms *anticoagulants* and *vitamin K*, combined with a separate search of *vitamin K* and *INR*. Both searches were limited to humans and publication years January 1, 1985, through September 1, 2004 (the INR was not used before 1985). The references of relevant review articles and all articles meeting inclusion criteria also were screened. All potential articles were reviewed independently by 2 of us (N.M.S. and K.J.D.). Studies were included if they were randomized controlled trials (RCTs) or prospective, nonrandomized trials in which vitamin K was used to treat patients without major hemorrhage with an INR greater than 4.0 because of oral anticoagulant use. All discrepancies for inclusion, quality ratings, and data abstraction were resolved by means of consensus.

STUDY QUALITY

Included articles were reviewed independently by 2 of us (K.J.D. and K.M.D.) for quality using validated instruments for RCTs⁵ and nonrandomized trials.⁶ Agreement was assessed using a quadratic κ statistic. In addition, the adequacy of adverse event reporting in each article was described independently using the following criteria: (1) whether a systematic method was described to assess for adverse events, (2) length of follow-up for adverse events, and (3) number of withdrawals during follow-up (adequate being <10%). We considered 2 weeks the minimum length of follow-up to detect adverse events, on the basis of the work by Hylek and colleagues.⁴ Because major hemorrhage is a rare event (<5%) and missing just 1 event could affect the results, we required all 3 components to meet our standard for a study to be pooled into a summary estimate for adverse effects.

DATA ABSTRACTION

Included articles were reviewed independently by 2 of us (K.J.D. for all, P.G.O. for nonrandomized trials, and W.T.S. for RCTs) for data abstraction using standardized forms. We abstracted the characteristics of the study (year, country, financial support, randomized [yes/no], blinding), patient characteristics (age, sex,

indication for anticoagulation, INR goal of treatment), drug used (warfarin, acenocoumarol, phenprocoumon), route of administration (oral, IV, or SC), vitamin K dose, warfarin resistance definition, and number of patients with warfarin resistance. We defined warfarin resistance as a prolonged period of subtherapeutic INR, despite warfarin administration, after a dose of vitamin K.¹ As described, we abstracted the method of assessing for side effects, follow-up for side effects, and percentage of withdrawals during follow-up.

For INR outcomes, we stratified the abstraction according to baseline INR (INR at study entry) from 4.0 to 10.0 vs greater than 10.0 because many of the studies reported their results in this manner. We were able to abstract INR outcomes only for the 24-hour INR (INR 24 hours after placebo or vitamin K administration) because study reporting was too incomplete and heterogeneous after 24 hours for meaningful analysis. We abstracted the mean, standard deviation, and total number of patients in the study arm, as well as proportion with an INR less than 1.5 (overcorrection), INR 1.8 through 4.0 (target INR), and INR greater than 4.0 (ineffective). We chose the range of 1.8 through 4.0 because we were able to classify nearly all studies with this scheme and it is clinically meaningful across different indications for anticoagulation and associated target ranges. The INR data were abstracted from tables when possible or graphs when necessary. Last, for adverse outcomes, we abstracted the number of minor/major bleeding events (as defined by the study), thrombosis, anaphylaxis, and deaths due to vitamin K (as defined by the study).

STATISTICAL ANALYSIS

For 24-hour INR outcomes, we analyzed RCTs separately from nonrandomized trials and patients with a baseline INR between 4.0 and 10.0 separately from those with a baseline INR greater than 10.0. Because we were able to abstract 24-hour INR outcomes for only 50% of the treatment arms in nonrandomized trials, we abandoned this approach and summarized the data only from RCTs. Because of the various vitamin K doses and routes of administration compared, often without placebo, we elected to use the study arm rather than the entire study as the unit of analysis. Because few studies report the standard deviation of the mean change in INR, we could not statistically combine this outcome but instead present this data qualitatively.

We summarized the data according to the proportions from each study arm

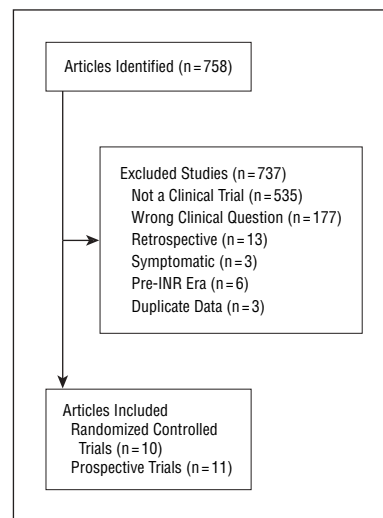


Figure 1. Map of the literature search and selection process. INR indicates international normalized ratio.

reaching each INR range (INR <1.5, INR 1.8-4.0, INR >4.0) at 24 hours after vitamin K or placebo administration. We calculated confidence intervals (CIs) for each proportion using the exact binomial method. Pooled effects for each of the 3 abstracted proportions were calculated using these CIs with a random effects model. We assessed for heterogeneity using the I^2 statistic, which estimates the proportion of variability due to heterogeneity rather than chance and is based on the traditional Cochrane Q statistic.⁷ When heterogeneity was present, we searched for explanations based on certain study design characteristics, primarily the route of administration and oral anticoagulant used. We performed all calculations using Stata software (version 8.0; Stata Corp, College Station, Tex).

RESULTS

LITERATURE SEARCH

The search identified 758 articles, summarized in **Figure 1**. We included 10 RCTs (**Table 1**)⁸⁻¹⁷ and 11 nonrandomized prospective trials (**Table 2**)¹⁸⁻²⁸ in the analysis. These trials were typically small and of limited duration. Most trials did not mandate follow-up beyond 24 hours. Of the RCTs, warfarin was used in 8 and acenocoumarol was used in 2.

QUALITY ASSESSMENT OF THE INCLUDED STUDIES

The quality of the studies was fair to poor. Scores for all studies ranged

Table 1. Characteristics of the 10 Randomized Controlled Trials

Source	No. of Patients	Jadad Score*	Downs Score†	Oral Agent	Vitamin K Route and Dose, mg‡	Baseline INR§	Decrease in INR by 24 h§
Lubetsky et al, ¹³ 2003	66	4	19	Warfarin	Oral, 2.5 and 5 IV, 0.5 and 1	7.8 7.5	4.9 4.9
Crowther et al, ¹⁰ 2002	51	5	22	Warfarin	Oral, 1 SC, 1	5.8 6.2	2.92 2
Agno et al, ⁸ 2002	60	3	23	Acenocoumarol	Oral, 1		
Fondevila et al, ¹¹ 2001	109	2	26	Acenocoumarol	Oral, 1		
Crowther et al, ⁹ 2000	92	4	28	Warfarin	Oral, 1 Placebo	5.4 5.9	2.8 1
Hung et al, ¹² 2000	24	1	9	Warfarin	IV, 0.5 IV, 1 IV, 2	7.8 7.5 8	4.7 4.5 4.6
Patel et al, ¹⁵ 2000	30	7	24	Warfarin	Oral, 2.5 Placebo	7.2 7	4.8 1.6
Nee et al, ¹⁴ 1999	57	4	21	Warfarin	IV, 0.5 and 3 SC, 0.5 and 3	7.3 7.5	3.4 1.9
Raj et al, ¹⁷ 1999	22	4	17	Warfarin	IV, 1 SC, 1	6.8 6.9	3.9 2.7
Pengo et al, ¹⁶ 1993	23	0	11	Warfarin	Oral, 2 Observation	5.8 6.1	2.6 1

Abbreviations: INR, international normalized ratio; IV, intravenous; SC, subcutaneous.

*Jadad refers to the quality score, range 0 through 8.⁵

†Downs refers to the quality score, range 0 through 31.⁶

‡Vitamin K was given as phytonadione.

§Includes only the patients with a baseline INR less than 10.0. Decrease in INR means that amount the INR decreased in 24 h.

||Dose used only for INR greater than 10.0. Not used in the calculation of the decrease in INR.

Table 2. Characteristics of the 11 Nonrandomized, Prospective Clinical Trials

Source	No. of Patients	Jadad Score*	Downs Score†	Oral Agent	Vitamin K Route‡	Vitamin K Dose, mg‡
Poli et al, ²¹ 2003	141	0	10	Warfarin, acenocoumarol	Oral	2
Watson et al, ¹⁹ 2001	64	1	11	Warfarin	Oral IV	1, 2, 5 2
Pendry et al, ²³ 2001	30	1	13	Warfarin	Oral	1
Byrd et al, ²⁷ 1999	21	3	15	Warfarin	SC	1, 2
Penning-van Beest et al, ²² 1999	24	0	12	Phenprocoumon	Oral	1, 2, 2.5
Crowther et al, ²⁶ 1998	62	2	14	Warfarin	Oral	1
Wentzien et al, ¹⁸ 1998	21	2	20	Warfarin	Oral	Varied
Duong et al, ²⁵ 1998	14	3	15	Warfarin	Oral	2.5
Brophy et al, ²⁸ 1997	23	1	8	Warfarin	IV	0.1, 0.5, 1
Fetrow et al, ²⁴ 1997	18	2	12	Warfarin	SC	Varied
Shetty et al, ²⁰ 1992	31	1	9	Warfarin	IV	0.5, 1

Abbreviations: IV, intravenous; SC, subcutaneous.

*Jadad refers to the quality score, range 0 through 8.⁵

†Downs refers to the quality score, range 0 through 31.⁶

‡Vitamin K was given as phytonadione.

from 0 to 7 (maximum possible score, 8) with the Jadad instrument and from 8 to 28 (maximum possible score, 31) with the Downs instrument. As expected, quality of the RCTs was better than the nonrandomized trials. The mean Jadad score for the RCTs was 3.4, compared with 1.5 for the nonrandomized trials ($P=.02$, Mann-Whitney test). Likewise, the mean Downs score for RCTs was 20, compared to

13 for the nonrandomized trials ($P=.01$, Mann-Whitney test). Interrater agreement was high for the Jadad ($\kappa=0.83$) and Downs ($\kappa=0.88$) instruments.

ORAL ANTICOAGULANTS OTHER THAN WARFARIN IN RCTs

Acenocoumarol was the only non-warfarin oral anticoagulant studied

in RCTs. In these 2 trials,^{8,11} oral vitamin K (1 mg) was compared with withholding acenocoumarol and had similar results. Those treated with vitamin K were associated with the same proportion of patients in the target range (INR, 1.8-4.0) at 24 hours as those treated by withholding acenocoumarol (pooled relative risk, 0.9; 95% CI, 0.7-1.1, $P=.48$). However, in both studies, vitamin K administration was associ-

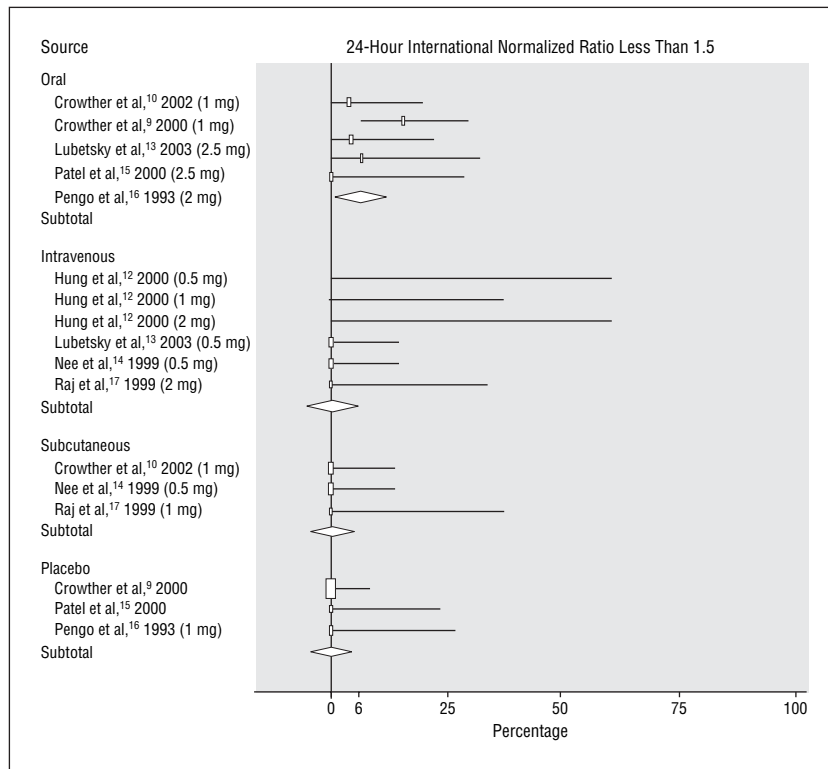


Figure 2. Percentage of patients achieving an international normalized ratio less than 1.5 (overcorrection) 24 hours after phytanadione (vitamin K) (or placebo) was administered. Only patients with baseline international normalized ratio less than 10.0 in a randomized controlled trial using warfarin are included. Each box represents 1 study arm. Study arms are sorted and subtotaled according to route of vitamin K administration. The diamond shapes represent the 95% confidence interval for the route of administration.

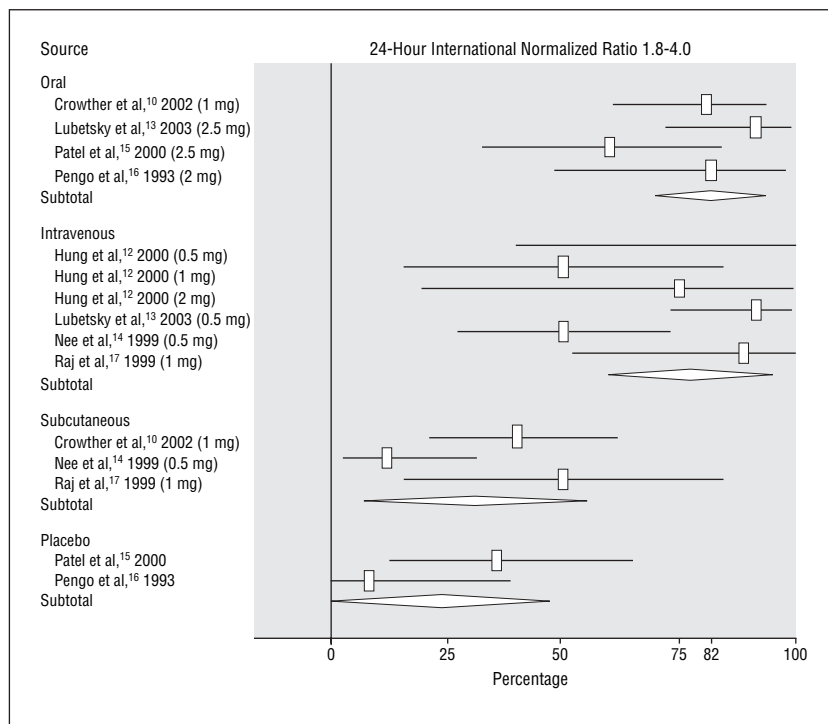


Figure 3. Percentage of patients achieving an international normalized ratio of 1.8 through 4.0 (the target international normalized ratio) 24 hours after phytanadione (vitamin K) (or placebo) was administered. Only patients with baseline international normalized ratio less than 10.0 in a randomized controlled trial using warfarin are included. Each box represents 1 study arm. Study arms are sorted and subtotaled according to route of vitamin K administration. The diamond shapes represent the 95% confidence interval for the route of administration.

ated with an increased risk for a subtherapeutic INR (pooled relative risk, 5.7; 95% CI, 2.3-14.0, $P < .001$). Therefore, researchers in both trials concluded that vitamin K administration was unnecessary in patients taking acenocoumarol.^{8,11}

WARFARIN PATIENTS WITH A BASELINE INR OF 4.0 THROUGH 10.0

Eight trials were included in this analysis, 3 of which were placebo (or observation) controlled. These trials included 321 patients with a baseline INR less than 10.0. Oral vitamin K arms had the most patients (121 patients in 5 trials), followed by placebo/observation (73 patients, all compared with oral vitamin K), IV (69 patients in 4 trials), and SC (58 patients in 3 trials). Baseline and 24 INR means are qualitatively summarized in Table 1. Several oral vitamin K trials had a lower mean baseline INR, and all SC treatment arms had smaller reductions than any oral or IV treatment arms.

Pooled estimates for the proportion of 24-hour INRs less than 1.5, 1.8 to 4.0, and greater than 4.0 are shown in **Figures 2, 3, and 4**. Most patients who received oral (82%; 95% CI, 70%-93%) and IV (77%; 95% CI, 60%-95%) vitamin K achieved an INR of 1.8 to 4.0 (Figure 3). In contrast, SC (31%; 95% CI, 7%-55%) was similar to placebo (20%; 95% CI, 0%-47%) for this outcome. This same pattern was repeated for INR greater than 4.0 (Figure 4). Only oral vitamin K was associated with an INR of less than 1.5 (6%; 95% CI, 0%-12%) (Figure 2). There was significant heterogeneity in the analysis ($P < .001$). Some of this heterogeneity was explained by stratifying the analysis according to administration route, as described. However, within each stratum, heterogeneity was still present (range I^2 , 0%-72%).

WARFARIN PATIENTS WITH A BASELINE INR OF GREATER THAN 10.0

Most trials contained small numbers of patients with a baseline INR greater than 10.0 and were qualitatively heterogeneous, so we were un-

able to combine data in these patients statistically. There were 105 patients in total: 42 patients in 4 RCTs and 63 patients in 5 nonrandomized trials. Both RCTs and nonrandomized trials had oral, IV, and SC treatment arms, with doses ranging from 0.1 mg IV to 5 mg oral vitamin K. Only 6 patients received no vitamin K.

Most patients who received vitamin K (52%) had an INR between 1.8 and 4.0 at 24 hours, with most of the remainder (43%) still having an INR greater than 4.0. Remarkably, only a single patient had an INR less than 1.5. Again, it appeared that SC administration was less effective because 71% (17/24) of patients still had an INR greater than 4.0 at 24 hours. Fewer than half of patients receiving oral (10 [48%] of 21) and IV (16 [30%] of 54) vitamin K had an INR greater than 4.0 at 24 hours.

ADVERSE EVENTS

We were unable to calculate a summary estimate of adverse events because of lack of adequate methods in the studies. Only a single trial⁹ met all 3 of our quality criteria. Most (71%) followed up patients for less than 2 weeks. A similar amount (76%) did not report the number of participants lost to follow-up during the study. Only 5 trials (23%) had an explicit method of following up patients for adverse outcomes.

WARFARIN RESISTANCE

We were unable to summarize the risk of developing warfarin resistance primarily for 2 reasons. First, researchers in only 2 studies^{13,15} defined warfarin resistance. Second, most trials did not require follow-up beyond 24 hours, which prevented these trials from finding patients with warfarin resistance. Of the 2 trials in which the problem was defined, 1 had no patients (0/15) with warfarin resistance,¹⁵ and the other had 2 (2 of 61 [3%]), both of whom had received IV vitamin K.¹³ In no other trial were qualitative comments consistent with warfarin resistance made.

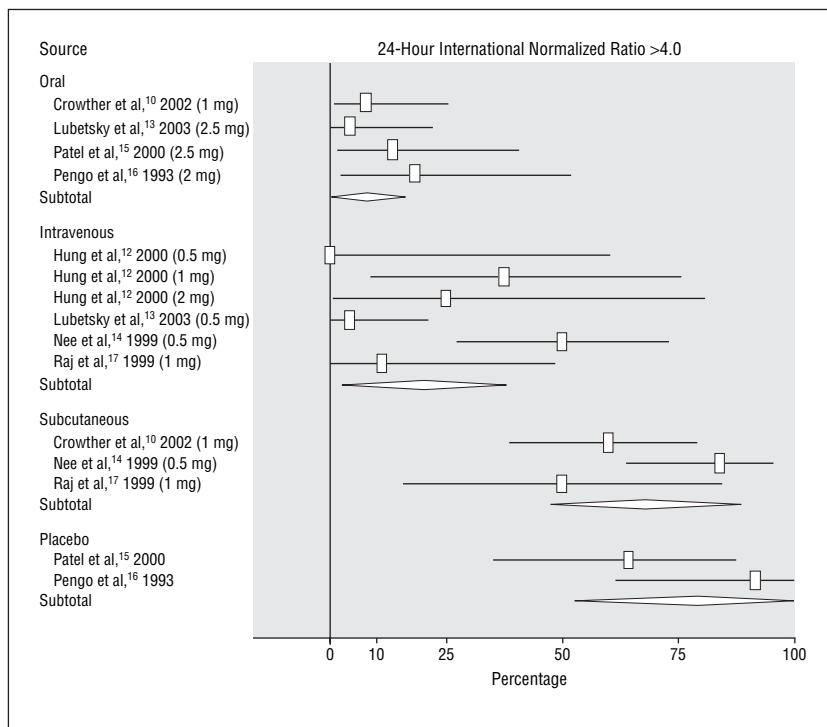


Figure 4. Percentage of patients achieving an international normalized ratio greater than 4.0 (ineffective) 24 hours after phytonadione (vitamin K) (or placebo) was administered. Only patients with baseline international normalized ratio less than 10.0 in a randomized controlled trial using warfarin are included. Each box represents 1 study arm. Study arms are sorted and subtotaled according to route of vitamin K administration. The diamond shapes represent the 95% confidence interval for the route of administration.

SENSITIVITY ANALYSIS

Other than analyzing the effects according to drug administration route and type of oral anticoagulant, we were not able to perform a sensitivity analysis for any other factors, including study quality, because of the small number of RCTs. The small number of RCTs also precluded statistical assessment for publication bias.

COMMENT

Our results showed that oral and IV vitamin K effectively reduce the 24-hour INR to less than 4.0 in about three quarters of patients with excessive anticoagulation (INR <10.0) who are receiving warfarin. However, vitamin K was ineffective for this indication when administered subcutaneously or if the patient was taking an oral anticoagulant other than warfarin. Whether this treatment affects a patient's bleeding risk remains unanswered.

The results from these trials suggest that oral and IV vitamin K are equivalent at 24 hours. However, only

oral vitamin K was associated with severe overcorrection (INR <1.5). Closer analysis of these trials shows that patients receiving oral vitamin K had lower baseline INRs (>4.5) compared with those receiving IV vitamin K (>6.0). It is not clear from the studies if these patients in the lower INR range (4.5-6.0) at baseline were the ones accounting for a higher risk of INR of less than 1.5. What is clear from other literature is that IV vitamin K has been associated with fatal anaphylaxis.²⁹ Given this risk of a fatal outcome with IV vitamin K, oral vitamin K should be preferred. Whether the threshold for vitamin K should be an INR greater than 4.0 or greater than 6.0 remains unanswered from the literature. The Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy recommends considering oral vitamin K, starting at an INR of 5.0.¹

Subcutaneous vitamin K appears to be inferior to oral and IV vitamin K for this indication at the currently studied doses. All 3 RCTs in which SC vitamin K was used had INRs similar to those seen with pla-

cebo at 24 hours and had statistically significantly worse outcomes than the comparative regimen.^{10,14,17} One prospective trial of relatively poor methodologic quality (Downs score 12) concluded that SC vitamin K was superior to withholding warfarin.²⁴ Our search strategy identified 2 other articles in which SC vitamin K was compared with another treatment in adults receiving anticoagulant therapy. Researchers in 1 trial concluded that low-dose SC vitamin K was modestly superior to withholding warfarin in postoperative orthopedic patients (in whom the target INR was <2.5) who were starting warfarin and had an INR less than 3.0.³⁰ Researchers in another trial retrospectively compared oral, IV, and SC vitamin K for excessive anticoagulation and found that SC was the least effective therapy.³¹ Thus, the published literature has yet to show that SC vitamin K is equivalent to either oral or IV vitamin K in any type of study, nor has there been an RCT that shows that SC vitamin K is superior to withholding warfarin. We conclude on the basis of the current evidence that SC vitamin K should not be used for excessive anticoagulation.

Most RCTs and prospective trials contained only a small number of patients with an INR greater than 10.0, which precluded statistical analysis. However, oral and IV again appeared to be superior to SC administration. Our search strategy also identified 1 relatively large retrospective analysis of patients with an INR greater than 10.0.³² Investigators gave 2 mg of oral vitamin K to 45 nonbleeding patients with an INR greater than 10.0 and found that 89% had an INR less than 5.0 at 72 hours, compared with 53% of 15 patients who were not given vitamin K.³² These retrospective trial findings support those of this review that oral vitamin K may be used to treat patients with an INR greater than 10.0.

Given the small numbers of trials in which each type of administration route was used, we were unable to calculate an optimal dose. Oral vitamin K doses ranging from 1 to 2.5 mg and IV doses from 0.5 to 3 mg were used successfully. In the United States, oral vitamin K is currently

available in a 5-mg tablet, which is scored to allow a dose of 2.5 mg. To achieve a reliable dose of 1 mg, Crowther and colleagues^{9,10,26} simply give 1 mg of the IV preparation by mouth. Further trials are needed to determine the optimal dose.

Unfortunately, these trials do not allow a determination of the effect of vitamin K on adverse outcomes. Only a single study provided sufficient information to reliably report adverse outcomes. If we are to use vitamin K, then we must accept the assumption that treating the number (lowering the INR by administering vitamin K) also treats the patient (reduces the risk of bleeding without increasing the risk of thrombosis). Of course, one might suggest that a prospective, placebo-controlled RCT be performed to answer this question. However, using standard assumptions ($\alpha = .05$, $\beta = .20$), a trial to show a reduction of major bleeding from 4% to 1% would require at least 1000 patients.

Likewise, the topic of warfarin resistance was inadequately addressed by available studies. The 2 trials that defined and reported outcomes of warfarin resistance, however, suggest this phenomenon is rare, occurring in 0% and 3% of patients.^{13,15}

This synthesis has several limitations. The trials were small, and multiple doses and administration routes were used, with clear heterogeneity among administration routes. The small numbers of heterogeneous trials prevented us from adequately evaluating for publication bias or sources of heterogeneity other than administration route and type of oral anticoagulant. We also did not search for articles before 1985. However, the bibliographies of other review articles reference 6 pre-1985 articles, none of which were RCTs.³³⁻³⁸ Given our search methods, it is unlikely that important articles were missed. It is also possible that the trial investigators used adequate methods to collect adverse events, but this information was not included in the published articles. However, given that only 1 of 21 trials met our standard, any synthesis of adverse events would come nearly entirely from

outside the peer-review process and therefore be subject to bias.

Limited evidence suggests that oral and IV vitamin K are more effective treatment for excessive anticoagulation than simply withholding warfarin, but SC vitamin K is not in the currently studied doses. It cannot be determined from the published literature whether treatment with vitamin K results in fewer hemorrhagic events or more thrombosis among these patients. Because of the risk of anaphylaxis with IV vitamin K, oral administration should be preferred. Providers should consider administering 1 to 2.5 mg of oral vitamin K in patients receiving warfarin with an INR greater than 6.0 and no clinical considerations preventing its use.

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