Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis
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CRD summary
This review examined the efficacy of vitamin K in treating excessive anticoagulation. The authors concluded that the limited evidence available suggests that oral or intravenous, but not subcutaneous, vitamin K are more effective than withholding anticoagulation therapy. The methods employed to combine the studies were inappropriate, thus it is impossible to determine whether these conclusions are reliable.

Authors' objectives
To determine the effectiveness of vitamin K in the treatment of excessive anticoagulation in patients taking oral anticoagulants.

Searching
The authors searched MEDLINE and EMBASE from January 1985 to September 2004, and the Cochrane Library (Issue 3, 2004); the search terms were reported. The references of included studies and relevant review articles were also screened. There were no language restrictions.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and prospective non-randomised trials were included in the review.

Specific interventions included in the review
Studies of vitamin K administration were eligible for inclusion. The included studies used oral, intravenous and subcutaneous methods: the doses for each method ranged from 1 to 5 mg, 0.5 to 3 mg, and 0.5 to 3 mg, respectively. Comparison groups were treated by alternative methods of administration or by placebo (including withholding oral anticoagulant therapy).

Participants included in the review
Studies of patients without major haemorrhage, and with an international normalised ratio (INR) greater than 4.0 because of oral anticoagulant use, were eligible for inclusion. The oral anticoagulants used in the included studies were warfarin, acenocoumarol and phenprocoumon. The mean baseline INRs ranged from 5.4 to 8.0; patients with an INR greater than 10.0 were excluded.

Outcomes assessed in the review
The primary outcome of interest was the achievement of the target INR of 1.8 to 4.0, 24 hours after the administration of vitamin K. The secondary outcomes were adverse events and the development of warfarin resistance.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed all studies for inclusion in the review. Any disagreements were resolved by consensus.

Assessment of study quality
The quality of both the RCTs and the non-randomised trials was assessed using the Jadad scale (applying the following criteria: randomisation, allocation concealment, blinding, and the treatment of withdrawals and drop-outs) and the Downs scale. The Downs scale is designed for the assessment of both types of studies. Two reviewers independently assessed the quality of all studies. Kappa statistics were calculated to assess agreement between the reviewers. Any disagreements were resolved by consensus.
Data extraction
Two reviewers extracted the data independently. Any disagreements were resolved by consensus. Patient characteristics, along with details of anticoagulant drug used, mode of vitamin K intervention, and warfarin resistance, where available, were extracted. For each trial arm, the mean, standard deviation, number of patients, and the proportions of patients with an INR below 1.5 (over-correction), between 1.8 and 4.0 (effective), and greater than 4.0 (ineffective) were extracted. Relative risks (RRs) were calculated for the proportion of patients in each category, along with the 95% confidence interval (CI). Particular types of adverse events were also extracted.

Methods of synthesis
How were the studies combined?
The RRs for percentages of patients with INRs within a given range in each study arm of the RCTs were pooled for the primary outcome of INR level 24 hours after administration. A random-effects model was used. A narrative synthesis was provided where this pooling was not considered possible. In order for data on adverse events to be pooled, the study had to meet three criteria: use of a systematic assessment method, follow-up for a minimum of 2 weeks, and withdrawals of less than 10% of the study population. It was not possible to assess publication bias because of the small number of RCTs.

How were differences between studies investigated?
Heterogeneity was assessed using the I-squared statistic. A subgroup analysis was carried out for the different oral anticoagulants used in the studies. The study arms were analysed according to different methods of administration or control employed. Patients were stratified by whether their baseline INR was between 4.0 and 10.0, or greater than 10.

Results of the review
Twenty-one studies with 983 patients were included in the review: 10 RCTs (534 patients) and 11 non-randomised prospective studies (449 patients).

The Jadad scores for all studies ranged from 0 to 7 out of a possible 8. The mean score was 3.4 for RCTs and 1.5 for non-randomised trials. The Downs scores for all studies ranged from 8 to 28 out of a possible 31. The mean score was 20 for RCTs and 13 for non-randomised trials.

Trials of patients taking acenocoumarol (2 trials, n=169).
When oral vitamin K (1 mg) was compared with withholding acenocoumarol, there was no difference between the treatments in the proportion of patients in the target range at 24 hours post-treatment (INR between 1.8 and 4.0) (pooled RR 0.9, 95% CI: 0.7, 1.1, P=0.48). Significantly more patients in the vitamin K groups had a sub-therapeutic INR less than 1.5 (pooled RR 5.7, 95% CI: 2.3, 14.0, P<0.001).

Trials of patients taking warfarin (8 trials, n=363).
Patients with a baseline INR of between 4.0 and 10.0 (n=321): the proportions of patients achieving an INR of 1.8 to 4.0 at 24 hours post-treatment was high at 82% (95% CI: 70, 93) for oral vitamin K, and was 77% (95% CI: 60, 95) for intravenous vitamin K. Patients receiving the intervention subcutaneously and those receiving placebo or observation were less likely to achieve the target INR at 24 hours: 31% (95% CI: 7, 55) and 20% (95% CI: 0, 47), respectively. A similar pattern of results was obtained for INR greater than 4.0 at 24 hours, where a much lower percentage of patients treated with oral and intravenous vitamin K had an INR in this range compared with groups given subcutaneous treatment or placebo. Only in patients given oral therapy did a significant number of patients have an INR less than 1.5: 6% (95% CI: 0, 12). Significant heterogeneity was observed in this analysis (I-squared range: 0% to 72%, P<0.001).

Patients with a baseline INR of greater than 10.0 (n=105, 42 in RCTs): 52% of patients who received vitamin K had an INR of between 1.8 and 4.0 at 24 hours, whereas 43% had an INR greater than 4.0; only 1 patient had an INR less than 1.5. Seventy-one per cent of patients given subcutaneous vitamin K had an INR greater than 4.0, compared with 48% of patients given oral therapy and 30% given intravenous treatment.

No information was available on adverse events and warfarin resistance.
Authors' conclusions
The limited evidence available suggests that oral and intravenous vitamin K are equivalent and are more effective for excessive anticoagulation than withholding warfarin sodium. Subcutaneous vitamin K is inferior to oral or intravenous vitamin K for excessive anticoagulation, but performs similarly to placebo. It is not possible to determine whether vitamin K decreases haemorrhagic events.

CRD commentary
The review question and the inclusion criteria were specific and clear. The authors searched a number of relevant sources but did not appear to search for unpublished studies, which might have introduced publication bias into the review. The potential for language bias was appropriately addressed. The authors used appropriate methods to minimise bias and error in the study selection, validity assessment and data extraction processes. However, although the authors stated that data on patient characteristics were extracted, these were not reported in the paper. The use of the Jadad scale to assess the validity of non-randomised trials as well as RCTs is unlikely to provide an adequate assessment of their quality. The decision to use the trial arm, rather than the randomised trial, as the unit for analysis was inappropriate as this method discards the benefits of a randomised comparison. Consequently, it is not possible to determine if the authors' conclusions accurately reflect the evidence contained in the review, or whether they are reliable.

Implications of the review for practice and research
Practice: The authors stated that providers should consider administering 1 to 2.5 mg of oral vitamin K to patients with an INR greater than 6.0 who are receiving warfarin and have no clinical considerations preventing its use.

Research: The authors stated that further research is necessary. However, they also noted that a future placebo-controlled RCT would require at least 1,000 patients to assess whether vitamin K produces a reduction of 3% in the proportion of patients experiencing major bleeding.

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