Management of coumarin-associated coagulopathy in the non-bleeding patient: a systematic review

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A B S T R A C T

Background and Objectives. Excessive anticoagulation is a frequent complication of anticoagulant therapy. The risk of hemorrhage approximately doubles for each one point increase in the International Normalized Ratio (INR) above 3.0. Reducing a prolonged INR to within the desired therapeutic range requires that oral anticoagulants be withheld. In addition, vitamin K may be administered. Since this latter treatment can produce rapid reductions in the INR, it must be carefully tailored to meet individual needs, balancing the risk of bleeding against the potential risk of causing thromboembolism.

Methods. To review available literature on the management of coumarin-associated coagulopathy in asymptomatic patients, a Medline search was carried out and papers published in English from 1966 and 2003 were identified. All available information on the management of asymptomatic patients presenting with coumarin-associated coagulopathy was analyzed.

Results. Following the results of clinical studies that only used an elevated INR as a surrogate end-point for the risk of bleeding, low dose oral vitamin K appears as the preferable strategy for rapidly restoring therapeutic INR levels in asymptomatic patients who present with an excessively prolonged INR due to warfarin therapy. For the treatment of patients with asymptomatic acenocoumarol-induced coagulopathy, vitamin K does not add any benefit to the strategy of simply withholding oral anticoagulant treatment.

Interpretation and Conclusions. Large randomized trials using clinical end-points are now required to provide evidence-based treatment recommendations for patients with coumarin-associated coagulopathy.

Key words: vitamin K, warfarin, acenocoumarol, coagulopathy.

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Excessively prolonged International Normalized Ratio (INR) values are an independent predictor for major bleeding,[1-3] and the risk of hemorrhage approximately doubles for each one point increase in the INR above 3.0.[4] In a recent study, Hylek and associates[5] reported that 5 of 114 (4%) asymptomatic patients with an INR more than 6.0 who were only managed with temporary warfarin withdrawal developed major or life-threatening bleeding within 2 weeks of their elevated INR value being recorded. This evidence supports the need to examine the optimal method for returning prolonged INR values towards the desired therapeutic range.

The objectives of treatment for non-bleeding patients with an excessively prolonged INR value are to limit the risk of bleeding complications by reducing the time the INR is elevated, while not producing a sub-therapeutic INR which could be associated with either thrombosis or subsequent resistance to re-anticoagulation. Two treatment strategies are available: withholding oral anticoagulants and allowing the INR level to return to within the therapeutic range, or withholding oral anticoagulants and administering vitamin K.[6] A third option, withholding oral anticoagulants, administering vitamin K and administering fresh frozen plasma or coagulation factor concentrates, should not be used because of the risks and costs associated with prophylactic administration of coagulation factor concentrates except in patients who are at the highest risk of hemorrhage.

Vitamin K is a specific pharmacologic antagonist to coumarin drugs and one form of vitamin K, phytonadione or vitamin K1, is available for clinical use.

Vitamin K can be administered by intravenous, sub-cutaneous or oral routes and can produce rapid reductions in the INR. This is why its use requires careful tailoring to meet individual needs, balancing the risk of bleeding against the potential risk of causing thromboembolism. According to the results of two physician surveys that were carried out to assess the use of vitamin K in patients with warfarin-associated coagulopathy,[7,8] even in non-bleeding patients with markedly prolonged INR values most physicians would not administer vitamin K. In the survey carried out in the USA, Libby and Garcia[8] reported that as many as 86% of contacted physicians would not give vitamin K to asymptomatic patients presenting with an INR greater than 6.0 and no evident risk of bleeding, and that 25% of contacted physicians would not administer vitamin K even to a similar patient considered to be at high risk of bleeding.

To assess available evidence on the efficacy and safety of different managements of coumarin-associated coagulopathy and on the efficacy and safety of the different routes of administration and doses of vitamin K used, we performed a systematic review of the literature.

Design and Methods

A series of Medline searches were conducted in the database from 1966 to December 2003. All searches were carried out without mapping search terms to subject headings. In the first search, terms included *vitamin K*, *phylloquinone*, *phytonadione*, and excluded *infant*, *newborn*, *fetus*, *seizure* or *chemotherapy*. The results of this search were combined with the results of a second search (using the AND function), in which terms included *warfarin*, *acenocoumarol*, *vitamin K antagonist*, *coumarin* or *oral anticoagulant*. The results of the combined search were limited to *human*, and *English language*. This strategy was refined by combining the results, using the AND function, with the results of a search including the terms *treatment* or *intervention* or *correction*. Papers whose titles or abstracts suggested they presented either prospective cohort studies, randomized trials, or academic reviews were selected for detailed review. Additional papers meeting these inclusion criteria were selected for review from the authors' libraries, and from consideration of the reference lists of those articles selected for detailed review. Studies conducted on non-bleeding patients presenting with coumarin-associated coagulopathy were selected for the purpose of this review. This search strategy produced 18 relevant articles.[5,9-17,20-27]

Results

Withholding treatment

Simply withholding oral anticoagulants and allowing the INR to fall into the therapeutic range is a widely used approach. Two large case-series examined the safety of this approach[9,10] and both concluded that conservative treatment of non-bleeding over-anticoagulated patients is safe. In these investigations, a total of 352 INR values above 6.0 occurred in 299 patients and only 2 patients (0.6%) suffered hemorrhage after temporary discontinuation of their anticoagulants. One of these studies suggested that simply withholding warfarin was more cost-effective than administering vitamin K.[10] Concerns about these studies include retrospective data collection, lack of uniform outcome assessment, and lack of prospectively defined outcome measures. More recently, Hylek and colleagues[5] prospectively compared 114 patients with INR levels greater than 6.0 with 268 patients with INR levels in the target range. All patients in the former group were managed by simply withholding warfarin treatment. After a 2-week follow up, 10 (8.8%) patients with elevated INR values reported abnormal bleeding, and 5 (4.4%) of them had experienced a major hemorrhage whereas none of the patients with an in-range INR had done so. Of interest, only 33% of patients with an INR greater than 6.0 had an INR less than 4.0 within 24 hours, and 55% within 48 hours.

Intravenous vitamin K₁

Two studies[11,12] have compared different doses of vitamin K administered intravenously in patients presenting with warfarin-associated coagulopathy and concluded that 0.5 mg was the optimal dosage if the therapeutic intent was to return the INR to within the usual therapeutic range. In the study by Shetty and colleagues,[11] 50% of patients with an INR greater than 5.0 who were treated with 1 mg of intravenous vitamin K had a subtherapeutic INR (lower than 2.0) after 24 hours, whereas none of the patients who received 0.5 mg had INR values lower than 2.0. Only 4 out of 21 patients who received 0.5 mg of intravenous vitamin K had an INR greater than 4.0 at 24 hours. Similar results were observed by Hung and colleagues[12] in a randomized controlled trial that compared 3 doses of intravenous vitamin K: 2.0 mg, 1.0 mg, and 0.5 mg. The two higher doses were effective but led to an excessive rate of subtherapeutic INR. In a third study, Andersen *et al.*[13] reported that administering 1.0 mg of intravenous vitamin K without withholding warfarin was more effective than simply withholding warfarin.

A potential concern with the use of the intravenous route of administering vitamin K is the risk of ana-

phylactoid reactions. Although frequently reported, and likely more common in patients who receive large intravenous doses administered rapidly, the true frequency of this complication is probably very low. Apparently, micelle preparations of vitamin K are less allergenic than castor oil preparations and should, therefore, be preferred when commercially available. An additional strategy to reduce the risk of anaphylactoid reactions consists in increasing the time of administration of intravenous vitamin K by giving it in a slow infusion over 15 to 30 minutes. Another concern is the potential to cause resistance to coumarin drugs. The frequency with which this complication develops is unknown.

Subcutaneous vitamin K₁

Although used to treat warfarin-associated coagulopathy,[7,8] subcutaneous vitamin K appears to be relatively ineffective. After the positive results of a small prospective cohort study conducted on 17 patients with INR levels between 8.0 and 14.0 who safely and effectively received 1.0 mg of subcutaneous vitamin K and 4 patients with an INR between 14.0 and 20.0 who received 2.0 mg of subcutaneous vitamin K,[14] Nee et al.[15] performed a randomized, clinical trial in which patients with INR values between 6.0 and 20.0 received either subcutaneous or intravenous vitamin K.

Independently of the route of administration, patients with INR values between 6 and 10 received 0.5 mg of vitamin K, while those with values between 10 and 20 received 3 mg of vitamin K. Thirty-three patients were randomized to receive subcutaneous vitamin K, while 22 patients received intravenous vitamin K. Twenty-four hours following administration of the study drug, 45% of patients in the subcutaneous group had an INR less than 4.5, compared with 95% of patients in the intravenous group. Surprisingly, after 72 hours, over-correction of the INR occurred more frequently in the subcutaneous group (42%) than in the intravenous group (23%). Similarly, Raj et al.[16] performed a single blind, randomized trial that enrolled non-bleeding patients with INR values greater than 6.0 to receive either 1 mg of intravenous or subcutaneous vitamin K. Eight hours after administration of the study drug, 9% of patients in the subcutaneous group, and 82% of patients in the intravenous group had an INR less than 5.0. At 24 hours, 64% of the patients in the subcutaneous group, and 82% of the patients in the intravenous group had an INR value of less than 5.0. Taken together, these studies support the contention that if rapid reductions in INR are desired, vitamin K administered by the intravenous route is the treatment of choice because it begins to reduce the INR within 8 hours.

Oral vitamin K₁

There is increasing interest in the use of oral vitamin K for the treatment of coumarin-associated coagulopathy. When used in doses of 1 to 2.5 mg, oral vitamin K does not appear to produce warfarin resistance, and its use has not been associated with anaphylactoid or skin reactions.[17-20] Furthermore, the oral administration of vitamin K has the potential to simplify the out-of-hospital management of asymptomatic coumarin-associated coagulopathy by obviating the need for such patients to visit a health care facility to receive parenteral vitamin K. The first randomized trial of oral vitamin K was performed by Pengo et al.[21] Twenty-three asymptomatic patients presenting with an INR > 5.0 were randomized to have their warfarin withheld for one day or to receive 2 mg of oral vitamin K and to continue on warfarin. After 24 hours, five out of twelve patients in the former group and none in the latter group still had an INR > 5.0. Subsequently, Weibert and colleagues[22] carried out a prospective cohort study in which 81 non-bleeding patients with INR levels > 5.0 received 2.5 mg of oral vitamin K and abstained from taking warfarin for 1 or 2 days. After 24 hours the INR was safely lowered to < 5.0 in 96% of the patients. Crowther et al.[20] carried out a randomized trial in which 92 patients with INR values of 4.5 to 10.0 were randomly allocated to receive 1 mg of oral vitamin K, or placebo. The primary endpoint was the proportion of patients with an INR value of 1.8 to 3.2 on the day following the study drug. Twenty-five of 45 patients (56%) who received vitamin K and 9 of 44 (20%) patients who received placebo had INR values of 1.8 to 3.2 on the day following study drug administration (p=0.001; OR 0.21, 95% CI: 0.07,0.57). No patient who received vitamin K and 4 patients (9%) who received placebo had an increase in their INR values on the day following study drug administration (p=0.056). Seven patients (16%) who received vitamin K and none who received placebo, had an INR value of less than 1.8 on the day following study drug administration (p=0.012). INR values were significantly higher in the placebo group than in the vitamin K group on both the first and second study days but were comparable thereafter. Similar results were reported by Patel and colleagues[23] in a study of 30 patients with an INR between 6.0 and 10.0 who were randomized to receive 2.5 mg of oral vitamin K or placebo. Oral vitamin K significantly reduced the time to achieve an INR of less than 4.0, the primary endpoint of the study.

Oral versus subcutaneous or intravenous vitamin K₁

A randomized controlled trial[17] was performed to compare the efficacy of 1 mg oral compared to 1 mg

subcutaneous vitamin K for the treatment of patients with asymptomatic warfarin-associated coagulopathy who presented with an INR between 4.5 and 10. The study clearly demonstrated that low dose oral vitamin K is more effective than low dose subcutaneous vitamin K in re-establishing a therapeutic INR level within 24 hours: 15 of 26 patients (58%) who received oral vitamin K and 6 of 25 (24%) patients who received subcutaneous vitamin K had INR values of 1.8 to 3.2 on the day following study drug administration (OR = 4.32; 95% CI: 1.13, 17.44, p=0.015). In a recent randomized, controlled trial[24] 44 patients with an INR between 6.0 and 10.0 received 0.5 mg intravenous vitamin K or 2.5 mg oral vitamin K and 17 patients with an INR greater than 10.0 received 1mg or 5 mg, respectively. Although the response to intravenous vitamin K was more rapid than the response to oral vitamin K, as assessed by INR levels at 6 and 12 hours, there was no difference between the two groups after 24 hours, with mean INR levels of 2.9 and 2.6, respectively. Moreover, a higher percentage of patients treated with intravenous vitamin K had INR levels < 2.0 than did patients treated with oral vitamin K. Findings were similar in the two groups with baseline INR levels lower than 10.0 or greater than 10.0.

Use of vitamin K₁ in patients treated with acenocoumarol

Most of the available evidence on the safety and efficacy of the different strategies proposed to manage asymptomatic patients presenting with coumarin-associated coagulopathy has been obtained from studies conducted on patients treated with warfarin. However, many patients in Europe and other countries are treated with acenocoumarol or phenprocoumon, rather than warfarin. Because these compounds have different pharmacokinetic properties than warfarin, which may result in different responses to vitamin K treatment, the results of these studies should not be extrapolated to all patients receiving oral anticoagulant therapy. Few studies have been conducted on patients treated with acenocoumarol. Our group[25] recently compared the effect of withholding acenocoumarol and administering 1 mg oral vitamin K with the effect of simply withholding acenocoumarol in asymptomatic patients with INR values between 4.5 and 10.0. We found that patients receiving oral vitamin K had more sub-therapeutic INR levels than did controls (36.6% and 13.3%, respectively; RR 1.83, 95% confidence interval 1.16, 2.89) and a lower (but not significantly so) proportion of INR values in range (50% and 66.6%, respectively) on the day following randomization. This study suggested that low dose oral vitamin K does not add any benefit to the strategy of simply withholding oral anticoagulant treatment for the immediate reversal of asymptomatic acenocoumarol-induced coagulopathy. These results are consistent with those of a previous randomized trial by Fondevila and colleagues[26] and of a recent, prospective cohort study by Poli and colleagues.[27] In the study by Fondevila,[26] conducted on 109 patients treated with acenocoumarol who presented with a baseline INR equal to or greater than 6.0, the administration of 1 mg oral vitamin K offered no advantage over the simple discontinuation of acenocoumarol, and also exposed more than one third of patients to excessive reversal of anticoagulant treatment. In the study by Poli and colleagues,[27] both patients treated with warfarin and patients treated with acenocoumarol presenting with an INR greater than 7.0 received 2 mg oral vitamin K. The authors observed that INR values a mean of 1.5 days after study drug administration were significantly lower in the group of patients treated with acenocoumarol and that, in this group of patients, all INR values were subtherapeutic.

Discussion

There are currently no published data which support the hypothesis that a rapid return of a prolonged INR to within the desired range is associated with a reduction in clinical bleeding events. Available evidence on the best management of non-bleeding patients presenting with coumarin-associated coagulopathy is based on the results of studies that used the elevated INR as a surrogate marker for the risk of bleeding. However, there is more than sufficient evidence to support the belief that excessively prolonged INR values are an independent predictor of major bleeding.[1-3] Most of these studies had a small sample size, used different baseline INR values to include the patients, used different outcomes, and used different doses of vitamin K. However, until strong clinical evidence becomes available, we can conclude that there are sufficient data based on surrogate outcomes to justify the routine use of oral vitamin K in patients presenting with warfarin-associated coagulopathy. A summary of the main findings is reported in Tables 1 and 2.

Oral vitamin K has been consistently proven more effective than simply withholding warfarin in restoring therapeutic INR levels in patients presenting with INR values greater than 4.5 without causing excessive reversal. Oral vitamin K has also been proven more effective than subcutaneous vitamin K and equally effective to intravenous vitamin K. Compared to this last treatment, oral vitamin K has a more convenient route of administration and causes less subtherapeutic INR. Doses from 1 mg to 2.5 mg appear

Table 1. Summary of the results of the randomized controlled trials in patients treated with warfarin: comparison of the different routes of administration.

Hung et al.[12]	0.5 mg, 1.0 mg, 2.0 mg intravenous vitamin K equally effective in reducing INR values 1.0 mg and 2.0 mg produced excessive reversal
Nee et al.[15]	0.5 mg intravenous vitamin K more effective than 0.5 mg subcutaneous vitamin K
Raj et al.[16]	1.0 mg intravenous vitamin K more effective than 1.0 mg subcutaneous vitamin K
Lubetsky et al.[24]	0.5 mg intravenous vitamin K and 2.5 mg oral vitamin K equally effective 0.5 mg intravenous vitamin K produced excessive reversal
Pengo et al.[21]	2.0 mg oral vitamin K more effective than withholding warfarin
Crowther et al.[20]	1.0 mg oral vitamin K more effective than withholding warfarin
Patel et al.[23]	2.5 mg oral vitamin K more effective than withholding warfarin
Crowther et al.[17]	1.0 mg oral vitamin K more effective than 1.0 mg subcutaneous vitamin K

Table 2. Summary of the results of the randomized controlled trials in patients treated with acenocoumarol.

Ageno et al.[25]	1 mg oral vitamin K equivalent to withholding acenocoumarol in reducing INR values. Oral vitamin K produced excessive reversal
Fondevila et al.[26]	1 mg oral vitamin K equivalent to withholding acenocoumarol. Oral vitamin K produced excessive reversal

similarly effective, although no direct comparisons are available. Indirect comparisons are strongly limited by the different study designs, because warfarin administration was stopped in some studies and continued in others, because different cut-offs for INR values were used as inclusion criteria, and because of different definitions of therapeutic success. It is likely that to optimize the efficacy and safety of the treatment the dosage should be adjusted according to the baseline INR value. An oral preparation of vita-

min K is not available in some countries. In this case, oral administration of the intravenous preparation is a possible option, as was done in many clinical studies. When this is done, the 1 mg/mL preparation should be used in preference to the 10 mg/mL preparation as it is easier to measure accurately.

For patients treated with acenocoumarol the use of oral vitamin K seems not to offer additional benefit to that from simply withholding the oral anticoagulant and seems to produce an excessive rate of subtherapeutic INR. Simply omitting one dose of acenocoumarol is associated with a return of the INR to the usual therapeutic range within 24 hours in most patients and it is likely to be the best therapeutic option.

Patients with mechanical heart valves are a particular therapeutic challenge, because there is concern that using vitamin K may over-correct the INR, with the potential to cause valve thrombosis or systemic embolization. Although there are no case reports of this complication developing, pending the results of ongoing studies there is no evidence to support the use of vitamin K or a more conservative strategy.

Conclusion

Based on the available evidence, the following recommendations can be offered. When a patient presents with an excessively prolonged INR, the cause of the prolongation, including the use of concomitant drugs and the patient's compliance, should be identified. For patients on warfarin therapy whose therapeutic INR range is between 2.0 and 3.0, oral vitamin K is the treatment of choice when the INR exceeds 4.5. We suggest withholding warfarin, administering 1 mg of oral vitamin K and restarting warfarin when the INR has returned to the desired therapeutic range (usually the day following the administration of vitamin K). To prevent recurrent excessive prolongation of the INR, the dose of warfarin should be reduced unless the cause of the prolongation can be safely eliminated. Higher doses of oral vitamin K (2.5 to 5 mg) should be considered in patients with INR values of more than 10.0, although there is, at present, no clinical evidence to support any particular intervention in this group of patients. For patients on acenocoumarol treatment, we suggest withholding acenocoumarol and restarting acenocoumarol when the INR has returned to within the therapeutic range. Oral vitamin K could be considered in patients with INR values of more than 10.0, although there is no evidence to support this strategy.

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