Vitamin K May Be A-OK, in Kids and Cholestatic Patients

To the Editor:

We would like to thank the authors of the article “Routine Use of Vitamin K in the Treatment of Cirrhosis-Related Coagulopathy: Is it A-O-K? Maybe Not, We Say,” published in the March 2019 issue, for discussing this very interesting subject. However, we wish to share some concerns about the very strong message sent by this article against vitamin K administration in cirrhotic patients. In our opinion, the evidence presented is insufficient to draw such conclusions.

First, the clinical cases lack some critical information in order for readers to understand if the elevated international normalized ratio (INR) at baseline was related to vitamin K deficiency, and if this potential deficit was secondary to impaired liver function and/or cholestasis. It would have been useful to dose PIVKA-II and vitamin K-dependent coagulation factor levels at baseline and after vitamin K administration, as well as factor V and direct bilirubin levels at baseline.

Although the cases presented involved adult patients, no distinction was made between adult and pediatric patients. However, articles on the pediatric population are cited. Mager et al.’s work, described in the paper, showed that there is a deficit of vitamin K in pediatric cholestatic liver diseases. Strople et al. also provided evidence that all of their cholestatic adult and pediatric patients with elevated INR showed an associated vitamin K deficit. This deficit was not corrected by oral vitamin K administration because intestinal absorption is compromised in cholestasis, but intravenous vitamin K administration was not investigated in this study. Both studies suggested a correlation between vitamin K deficit and disease severity. Takahashi et al. recently highlighted the prevalence of intracranial hemorrhage in young patients (aged 0–3 months) in biliary atresia as a result of vitamin K deficiency related to cholestasis. They emphasize the importance of intramuscular vitamin K injection to avoid this severe bleeding complication.

Concerning the use of vitamin K in cirrhosis, the authors cite Shah et al., who still recommend the preventive use of the vitamin in liver disease despite its lack of impact on clinical outcome, because of the prevalence of vitamin K deficiency in this population. They also cite the work of Saja et al., which indicated an improved prothrombin time 72 hours after subcutaneous vitamin K administration, regardless of the fact that no vitamin K deficiency was indicated at baseline. On the other hand, Blanchard et al. did not show any decrease in prothrombin time after vitamin K administration, but the route of administration is not specified and the observation includes only seven patients with cirrhosis (and no specifications about cholestasis). Finally, they cite Feldshon et al., who did not show any improvement in coagulation parameters after vitamin K administration; no information is provided about the number of patients and disease, or about the administration regimen.

The authors also discuss the fact that elevated INR does not distinguish between adult and pediatric patients. However, articles on the pediatric population are cited. Mager et al.’s work, described in the paper, showed that there is a deficit of vitamin K in pediatric cholestatic liver diseases. Strople et al. also provided evidence that all of their cholestatic adult and pediatric patients with elevated INR showed an associated vitamin K deficit. This deficit was not corrected by oral vitamin K administration because intestinal absorption is compromised in cholestasis, but intravenous vitamin K administration was not investigated in this study. Both studies suggested a correlation between vitamin K deficit and disease severity. Takahashi et al. recently highlighted the prevalence of intracranial hemorrhage in young patients (aged 0–3 months) in biliary atresia as a result of vitamin K deficiency related to cholestasis. They emphasize the importance of intramuscular vitamin K injection to avoid this severe bleeding complication.

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The authors also discuss the fact that elevated INR does not protect against venous thromboembolic risk and that adult patients with cirrhosis are at greater risk of venous thromboembolism than the general population, as confirmed in a recent meta-analysis by Ambrosino et al. However, thrombotic complications are not common in pediatric patients, and no study is cited about the potential prothrombotic effect of vitamin K.

The authors conclude that the routine use of vitamin K should be avoided in liver cirrhosis in the absence of active bleeding as it has no demonstrated benefits on clinical outcome and could potentially have prothrombotic effects.

In light of the information given, it seems clear that the prevalence of vitamin K deficiency is high in chronic liver disease, and even higher in cholestatic liver disease. The administration of vitamin K has no demonstrated beneficial impact on clinical outcome, but does seem to improve coagulation parameters in some studies. In addition, the potential prothrombotic effect of vitamin K administration has not been demonstrated or even investigated to date.

We believe that avoiding the routine use of vitamin K could be harmful for certain patients, especially pediatric and cholestatic ones. We agree with the authors that further studies are needed to assess the safety, efficacy, and impact on clinical outcome. We thank you for your attention and are at your disposal for any further discussion on this topic.

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REFERENCES


Authors’ Response

We thank Jannone and colleagues for their thoughtful critique of our article, as well as the informative reflections that followed. On the charge that we completely omitted the pediatric population from our discussion, we are guilty beyond a reasonable doubt!

Our narrative was based upon our experiences with adult inpatients admitted to the University of Michigan Hospital on either our Medicine Gastroenterology or General Medicine services. As we have no experience in pediatric medicine, we thought it would have been disingenuous to include this population in the narrative. That said, your letter helps expand the topic to a wider population demographic.

To clarify our messaging, it’s important to repeat the basic tenets of our review. In an effort to sound less dogmatic, please note the word “maybe” in the title. We stated that we recommended against the routine use of vitamin K for adults admitted with cirrhosis and elevated INRs. Patients with cholestatic disease are not specifically included in this recommendation. In our conclusion, we stated that an exception could certainly be made for those admitted with active bleeding.
Among our inpatient adult population, about 90% of our cirrhosis patients qualify as “decompensated,” and are generally in Child-Pugh Turcotte Classes B and C. Therefore, most of those patients have clinically significant impaired protein synthetic capabilities. Even if they were given vitamin K, as our unpublished study quoted below implies, INRs will usually not improve to a clinically significant degree. This is because with hepatic cirrhosis, they lack the circulating inactive protein precursors which vitamin K helps activate.1

As vitamin K is routinely given to most of our cirrhosis patients with abnormal INR who are admitted to the above-mentioned services, we decided to do a retrospective analysis quantifying the INR changes that actually occur before and after the completion of a regimen of one to three days. (Although the study is not yet published, the manuscript is currently being prepared for peer-review journal submission.)

There were 100 inpatients with documented cirrhosis included in the analysis; 90 were “decompensated” (with ascites and/or hx variceal bleeds, and/or hx hepatic encephalopathy) and 10 were “compensated” (absence of all three complications). One baseline INR was measured on admission before vitamin K. This was compared with the lowest INR, which was measured within seven days post-vitamin K administration. In all 100 patients, we found the mean baseline INR to be 1.79, and after one to three doses of vitamin K, the nadir mean INR value was lowered to 1.52.

If we take only the 43 patients who received the entire 10-mg-daily, three-day regimen (usually intravenous), the respective numbers are 1.90 to 1.57. Because we had only 10 patients classified as “compensated,” we felt that adequate power was lacking to make any meaningful comparisons with the 90 “decompensated” patients. However, it is notable that in those 10 patients, the respective means changed from 1.69 to 1.28, which was a trend toward a slightly more robust response.

Although these numbers were statistically significant (P < 0.0001), what is the clinical utility of a change in INR of 0.3 to 0.4 units? That is where larger studies looking at the true clinical outcomes of bleeding and clotting complications would be useful.

Hepatic cirrhosis leads to aberrations on both the bleeding and clotting side of the hemostatic cascade.1 We believe that simply attempting to normalize an INR, which measures only the effects upon Factors I, II, V, VII, and X, may not translate into a true clinical benefit in a decompensated patient with cirrhosis. Meanwhile, the impending risks, although unlikely to be severe, are largely unknown. That said, in actively bleeding patients with abnormal INRs, we have no compunctions about endorsing vitamin K administration at the time of presentation.

In summary, we agree with many of your assertions. Patients who have impaired cholestatic function but still maintain healthy hepatocytic reserve within the liver parenchyma, such as those with biliary atresia, will generally respond well to vitamin K in terms of both INR lowering and reducing bleeding risks. As we alluded to in our article, it also seems probable that patients with “early” cirrhosis might be more likely to have a more robust response to vitamin K, as they maintain adequate protein-synthetic capacity.

As a final caution to our readers, beware of the confusion between references to “liver disease” versus “cirrhosis.” The latter is a special subgroup of the former and, in a perfect world, the two terms should never be ambiguously lumped together in therapeutic discussions.

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REFERENCE


Article on Hospital Consolidation Misleads

A recent article in P&T (by Stephen Barlas, May 2019) misses the mark in its criticism of hospital mergers. Recycling studies that are old and otherwise unreliable,1 the article paints an erroneous picture of the impact of hospital mergers on quality, access, efficiency, and innovation, among other benefits, for the communities they serve. The fact is that hospital and health system mergers are creating coordinated systems of care for patients to lead the way on value-based care.

For example, a 2017 study2 from Charles River Associates confirmed that:

- Mergers decrease costs due to economies of scale, reduced capital costs, and clinical standardization, among other efficiencies. An empirical analysis showed a 2.5 percent reduction—equating to $5.8 million—in annual operating expenses at acquired hospitals. In a 2018 update3 to the study, Charles River Associates found that acquisitions of nearby hospitals resulted in larger cost decreases than acquisitions of more distant hospitals.
- Mergers have the potential to drive quality improvements through the standardization of clinical protocols, as well as investments to upgrade facilities and services at acquired hospitals.
- Mergers typically expand the scope of services available to patients, and build upon existing institutional strengths to provide more comprehensive and efficient care.

In the rapidly changing health care environment, building coordinated systems of care through organic growth and mergers is essential for providing value-based care to entire communities with diverse needs and expectations.

Melinda Hatton, American Hospital Association General Counsel

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Evaluation of Warfarin Patients with Low Time in Therapeutic Range (TTR) for Transition to Non–Vitamin-K Oral Anticoagulant (NOAC) Therapy

To the Editor:

Time in therapeutic range (TTR) is a widely accepted metric used to evaluate the safety and efficacy of warfarin therapy. Patients with low TTR (< 65%) are at higher risk of poor outcomes, and current antithrombotic guidelines recommend interventions to improve low TTR. One possible intervention includes switching therapy to a non–vitamin-K oral anticoagulant (NOAC), such as dabigatran, apixaban, edoxaban, betrixaban, or rivaroxaban, also referred to as direct-acting oral anticoagulants (DOACs). As a quality improvement initiative, we developed and applied a locally established systematic approach to determine which patients with low TTR (< 65%) met the criteria for transition to a NOAC.

Between May and July 2018, we conducted a retrospective chart review of an academic medical center’s anticoagulation clinic. The project was exempt from review by our Institutional Review Board. Each patient’s TTR was calculated over a three-month period, and patients with a low TTR were assessed for NOAC eligibility as described in Table 1.

We identified 140 adult patients taking warfarin with a target international normalized ratio (INR) of 2.0 to 3.0 and a recorded TTR. Seventy patients (50%) had a TTR < 65% and underwent further analysis. Most patients with low TTR were female (n = 39; 56%). The average age, weight, and body mass index (BMI) ± standard deviation were 62 ± 15 years, 93 ± 29 kg, and 32.5 ± 9.1 kg/m², respectively. The most common anticoagulation indications were venous thromboembolism (n = 27; 39%) and atrial fibrillation (n = 23; 33%). We found an identified cause for TTR < 65% in 61 patients (87%), with the most common reasons being poor adherence (n = 17; 28%) and diet fluctuations (n = 11; 18%).

Almost one-third (n = 22; 31%) of patients with TTR < 65% were candidates for NOAC therapy based on our pre-defined eligibility criteria (Table 1). Among the remaining 48 patients, the most common ineligibility criteria that were met included: valvular disease (n = 11; 23%); obesity (n = 9; 19%); adherence (n = 9; 19%); hypercoagulable condition (n = 9; 19%); severe renal or hepatic impairment (n = 6; 13%); and significant drug interaction (n = 4; 8%).

Data from our institution indicate that a sizeable percentage of warfarin-treated patients exhibit low TTR and would likely benefit from therapy intervention. Although NOAC therapy seems attractive for these patients, we believe a systematic review process is required to ensure that a NOAC is a safe and effective alternative. Our analysis showed that roughly one-third of patients with low TTR would be appropriate candidates for NOAC therapy based on the process employed. For the remaining patients, we were able to isolate other causes for low TTR, including suboptimal adherence and diet inconsistencies. Targeted interventions in these patients are likely warranted to improve clinical outcomes.

Overall, routine TTR monitoring combined with a structured assessment process can identify opportunities for improved anticoagulation care. For selected patients, this approach can help facilitate a safe and effective transition to NOAC therapy.

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REFERENCE