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Short Communication

The effectiveness of intravenous vitamin K in correcting cirrhosis-associated coagulopathy

Ryan M. Rivosecchi[a], Sandra L. Kane-Gill[b], Jeffrey Garavaglia[c], Adam MacLasco[d] and Heather Johnson[b]

[a]Department of Pharmacy, UPMC Presbyterian Hospital, [b]School of Pharmacy, University of Pittsburgh, Pittsburgh, PA, [c] West Virginia University Hospitals, Morgantown, WV, and [d]Virginia Commonwealth University Medical Center, Richmond, VA, USA

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Correspondence
Ryan M. Rivosecchi, UPMC Presbyterian Hospital, Room D527, 200 Lothrop Street, Pittsburgh, PA 15213, USA.
E-mail: rivosecchirm@upmc.edu

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Abstract

Objectives The goal of this study was to evaluate the effectiveness of intravenous (IV) vitamin K in cirrhosis.

Methods This was a retrospective study of cirrhotic patients, not on anticoagulation, with administration of IV vitamin K and a baseline INR > 1.5. The primary outcome was the effectiveness of therapy defined by a 30% decrease in INR or a reduction in INR to an absolute value of ≤1.5.

Key Findings A total of 96 patients were included in the cohort. There was an average decrease in INR of 0.31; however, 60 patients (62.3%) failed to achieve at least a 10% decrease. Sixteen patients (16.7%) met the primary effectiveness endpoint.

Conclusions The use of IV vitamin K to correct coagulopathy of cirrhosis may not be beneficial.

Introduction

In the United States, the prevalence of cirrhosis in adults totals over 600 000.[1] Up to 90% of patients with this diagnosis will develop oesophageal varices during their lifetime, with the prevalence increasing with severity of liver disease. Mortality associated with acute variceal bleeding remains as high as 20% within 6 weeks of bleeding event.[2]

The lack of bleeding control may be due to the vital role the liver plays in the synthesis of coagulation factors and inhibitors, including vitamin K-dependent clotting factors.[3] The progression of liver disease creates an expected decrease in the liver's synthetic ability to produce these factors.[4] Prothrombin time (PT) is used as a clinical surrogate and indirect marker of coagulopathy and is used in the calculation of international normalized ratio (INR). This value is limited by insensitivity as >30% decrease in coagulation factors is required prior to prolongation.[5]

Despite the lack of validation of INR in patients with cirrhosis, the correction of coagulopathy with vitamin K supplementation is common practice. Saja *et al.*[6] evaluated a small cohort of patients with cirrhosis, and the administration of subcutaneous (SQ) vitamin K resulted in a significant decrease in PT ($P = 0.047$). However, there are a few methodological questions that leave the use of vitamin K in cirrhosis patients unresolved.

Compared to intravenous (IV) administration, SQ is associated with delayed and unpredictable absorption.[7] Saja *et al.*[6] do not report INR values, a marker that is frequently used to determine whether coagulopathy reversal is necessary. The purpose of this study was to evaluate the effectiveness, as measured by INR response, of IV vitamin K in cirrhotic patients.

Methods

This study was approved by the Institutional Review Board of The University of Pittsburgh (PRO14030062). It was a retrospective review of the electronic health record (EHR) completed at the UPMC Presbyterian Hospital, a large, academic, urban, tertiary medical center.

A convenience sample of medication administration data from September 2013 to July 2014 was obtained. Cirrhotic patients were included if they received at least a single administration of IV vitamin K (phytonadione) and had baseline INR >1.5, and at least one repeat INR

within the 6–24 h post administration. Presence of cirrhosis was determined by a review of the physician notes. Exclusion criteria included concurrent use of therapeutic anticoagulation, acute liver failure and missing data. Additional data points were collected through a review of the EHR.

The primary outcome was the effectiveness of IV vitamin K as defined by a 30% decrease in INR or a decrease in INR to an absolute value of ≤1.5. A planned sensitivity analysis of the definition of effectiveness by altering the percentage of INR decrease was completed using a 10, 20, 40 and 50% reduction in INR. Additionally, predictors of an effective response were evaluated.

A descriptive statistical analysis was performed using IBM SPSS version 22 (Chicago, IL, USA). Normally distributed data are reported as mean ± standard deviation; non-normally distributed data are reported as median (interquartile range). A regression analysis to determine predictors of efficacy was completed with the following variables: baseline INR, use of fresh-frozen plasma (FFP), MELD and vitamin K dose. Significance was set at $P = 0.05$.

Results

A total of 96 patients were included in the cohort with an average MELD of 34.1. Greater than 75% of patients were not actively bleeding at the time of administration (Table 1). Vitamin K was administered an average of two times, with the most common dose being 10 mg (81%), while a dose of 5 mg was administered in 17%. The follow-up INR was drawn, on average, 10 h after administration. Of the 45% of patients receiving FFP, four units were administered on average.

Table 1 Patient characteristics

Male, *N* (%)	85 (61.2)
Ethnicity, Caucasian, *N* (%)	112 (80.6)
Age	54 ± 11
Weight, kg	86; 71.4–98
Height, cm	170 ± 10.1
ICU admission	72 (51.8)
Total bilirubin	12.6 ± 9.5
Albumin	2.9 ± 0.8
AST	66; 40–107
ALT	30; 18–47
MELD	34.1 ± 6.6
INR	3.0 ± 1.1
Childs–Pugh Class C, *N* (%)	85 (88.5)
Active bleeding, *N* (%)	21 (21.9)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICU, intensive care unit; INR, international normalized ratio; MELD, model for end-stage liver disease.
Normally distributed data reported as mean ± standard deviation, non-normally data reported as median; interquartile range.

Despite an average decrease in INR of 0.31, 60 patients (62.3%) failed to achieve at least a 10% reduction. Patients receiving <10 mg experienced no change from baseline INR. Sixteen patients (16.7%) met the primary effectiveness endpoint of either a 30% decrease in INR or a decrease to ≤1.5 (Table 2). The results of the regression analysis demonstrated that with each one unit increase in INR at baseline, the odds of achieving an effective response to vitamin K was doubled (OR: 2.0; 95% CI 1.1 to 3.8).

Discussion

The results of this study demonstrate that a small portion of cirrhotic patients, specifically those with higher INR elevations at baseline, are likely to benefit from the use of IV vitamin K. While retrospective in nature, this is an important finding as 20–40% of cirrhotic patients present to the hospital with coagulation abnormalities.[8] Approximately 20% were actively bleeding at the time of administration suggesting that the other 80% of use was to correct an elevated INR. The INR does not evaluate the multitude of additional factors that impact a patient's ability to achieve haemostasis.[9] Diagnostic tests such as thromboelastography provide additional information which is lacking in the INR.[10]

There is no accepted definition of effectiveness for the reduction of INR with vitamin K, so the use of a sensitivity analysis through altering the percentage decrease in INR that we deemed to constitute a clinically meaningful drop was completed. The results of this analysis demonstrate that even at the most lenient definition of effectiveness, 60 patients (62.5%) still did not achieve an effective response. Interestingly, 22 of 36 patients who met the criteria for effectiveness did so through achievement of a 10% reduction in INR, not an absolute decrease to ≤1.5.

The study has limitations that are primarily due to the retrospective nature including not having a standardized time to repeat INR after vitamin K administration. The cohort evaluated represents a severely ill cirrhotic

Table 2 International normalized ratio reductions and sensitivity analysis

	10% INR decrease	20% INR decrease	30% INR decrease	40% INR decrease	50% INR decrease
Reduction in INR					
N (%)	13 (13.5)	10 (10.4)	7 (7.3)	4 (4.2)	2 (2.1)
Effectiveness sensitivity analysis*					
N (%)	11 (11.5)	10 (10.4)	7 (7.3)	3 (3.2)	6 (6.3)

N = 96 patients.
INR, international normalized ratio.
*Effective defined as percentage reduction in INR or decrease in INR to absolute value of ≤1.5.

population, and these results may not be generalizable to all cirrhotic patients.

Conclusion

The results of this study demonstrate that the use of IV vitamin K to correct coagulopathy of cirrhosis may not be beneficial. Patients with higher degrees INR elevation are more likely to have an effective response. Further studies need to be conducted in this patient population, including a comparison of vitamin K use to a cohort of patients not receiving vitamin K therapy.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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Authors' contributions

RR was involved in all stages of manuscript preparation including study concept and design, data collection, data analysis and interpretation, and drafting of manuscript. SKG, HJ and JG were involved in study concept and design, interpretation of data and critical revision of manuscript. AM was involved in study concept and design, data collection and revision of manuscript.

Institutional Review Board statement

The study was reviewed and approved by the Institutional Review Board of the University of Pittsburgh.

Informed consent statement

Due to the observational and retrospective nature of the trial, informed consent was not obtained.

Data sharing statement

No additional data are available.

Core tip

This research aids in answering the question of 'Does vitamin K reversal in non-anticoagulated cirrhotic patients have a significant effect?' Often in the intensive care setting, cirrhotic patients present with elevated INRs without signs or symptoms of active haemorrhage. Surgical interventions are often delayed secondary to perceived elevated bleeding risk, and the ICU clinician attempting to correct the coagulopathy prior to intervention. The results of this study demonstrate that <15% of vitamin K administrations resulted in a clinically significant decrease in INR. The practicing clinicians will be able to use these results when determining whether administering IV vitamin K will be a useful tool in correcting coagulopathy.

References

1. Scaglione S *et al.* The epidemiology of cirrhosis in the United States: a population-based study. *J Clin Gastroenterol* 2015; 49: 690–696.
2. Kumar S, Asrani SK, Kamath PS. Epidemiology, diagnosis and early patient management of esophagogastric hemorrhage. *Gastroenterol Clin North Am* 2014; 43: 765–782.
3. Amitrano L *et al.* Coagulation disorders in liver disease. *Semin Liver Dis* 2002; 22: 83–96.
4. Strople J, Lovell G, Heubi J. Prevalence of subclinical vitamin K deficiency in cholestatic liver disease. *J Pediatr Gastroenterol Nutr* 2009; 49: 78–84.
5. Sokol RJ. Fat-soluble vitamins and their importance in patients with cholestatic liver diseases. *Gastroenterol Clin North Am* 1994; 23: 673–705.
6. Saja MF *et al.* The coagulopathy of liver disease: does vitamin K help? *Blood Coagul Fibrinolysis* 2013; 24: 10–17.
7. Nee R *et al.* Intravenous versus subcutaneous vitamin K1 in reversing excessive oral anticoagulation. *Am J Cardiol* 1999; 8: 286–288, A6–A7.
8. Shah NL, Northup PG, Caldwell SH. A clinical survey of bleeding, thrombosis and blood product use in decompensated cirrhosis patients. *Ann Hepatol* 2012; 11: 686–690.
9. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med* 2011; 365: 147–156.
10. Stravitz RT. Potential applications of thromboelastography in patients with acute and chronic liver disease. *Gastroenterol Hepatol* 2012; 8: 513–520.

