Possible Role of Vitamin K in Management of Gastrointestinal Bleeding

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Conflict of interest: None declared

Funding: No funding sources

Abstract

Cirrhosis leads to an imbalance within the coagulation cascade this imbalance increases the risk of both bleeding and clotting in patients with cirrhosis 8, there are six proposed mechanisms may contribute to hemostatic imbalance like decreased synthesis of procoagulant and anticoagulant proteins by the liver,impaired clearance of activated coagulation factors, platelet disorders, nutritional deficiency, fibrinolysis with dysfibrinogenemia, and disseminated intravascular coagulation (DIC). Vitamin K is a fat-soluble vitamin that allow the formation of coagulation factors and post-translational calcium binding to gamma-carboxylated proteins such as prothrombin, factors VII, IX, and X, protein C, and protein S, as well as those proteins found in bone and vascular smooth muscle by acting as a cofactor in the gamma-carboxylation of multiple glutamate residues. Vitamin K deficiency is common in certain types of liver disease, the decreased ability of the liver to complete the vitamin K cycle as a result of decreased function, despite evidence to the contrary, administration of vitamin K in a patient with cirrhosis to reverse an elevated INR has been a routine practice throughout the U.S. because patients with cirrhosis are categorically vitamin K-deficient also the administration of vitamin K is harmless but this repletion is not supported by clinical outcomes, and most research shows that replacement is not an effective treatment for the coagulopathy of liver disease, especially in cirrhosis. has been found that Vitamin K is significantly assosciated with decreasing in the PT and a PTT in cirrhotic Patients but does not affect any of the other measured parameters those decreases were not mirrored by other vitamin K-dependent proteins such as protein C, protein S, and factor VII, in contrast to the expected increase, protein C actually decreased after vitamin K administration and failure to show an increase in PIVKA-II levels at baseline in cirrhosis suggests that vitamin K deficiency does not play an integral role in the coagulopathy of these patients

Keywords: Vitamin K, Gastrointestinal Bleeding

Tob Regul Sci.™ 2023;9(1): 6330 - 6336

DOI: doi.org/10.18001/TRS.9.1.443

Introduction

Cirrhosis leads to an imbalance within the coagulation cascade this imbalance increases the risk of both bleeding and clotting in patients with cirrhosis 8, there are six proposed mechanisms may contribute to hemostatic imbalance like decreased synthesis of procoagulant and anticoagulant proteins by the liver,impaired clearance of activated coagulation factors, platelet disorders, nutritional deficiency, fibrinolysis with dysfibrinogenemia, and disseminated intravascular coagulation (DIC) **(1).**

Imbalances of the Coagulation Cascade in Cirrhosis

Increased Clotting Risk	Increased Bleeding Risk
Increased Procoagulants: Factor VIII von Willebrand Factor Decreased Anticoagulants: Antithrombin III Protein C Protein S	Decreased Procoagulants: Factors II, V, VII, IX, X, XI Thrombocytopenia

Nutritional Deficiency:

patients with liver cirrhosis may have coexisting biliary disease which leads to reduction in bile production and flow leads to decreased intraluminal concentrations of biliary salts and decrease in theabsorption of fat-soluble vitamins, including vitamin K which is responsible for the production of factors II, VII, IX, and X because of its role as a cofactor in the gammacarboxylation of glutamic acid residues. **(1).**

Platelet Disorders:

There are lower circulating levels of thrombopoietin in patients with liver cirrhosis which is a glycoprotein hormone produced in the liver that is responsible for the metamorphosis of megakaryocytes into mature platelets **(2)**

The progressive enlargement of the spleen leads to thrombocytopenia with platelet counts commonly below 100,000/mm3, but rarely lower than 30,000 to 40,000/mm due to hypersplenism ,Despite these relatively low platelet counts, spontaneous bleeding in cirrhosis is much less common 5 because there is an increase in von Willebrand factor at the same time which

increases the adhesive capabilities of platelets and leads to increasing the effectiveness of the remaining platelets. **(3)**

Decreased Synthesis and Impaired Clearance of Clotting Factors:

There are hemostatic abnormalities in cirrhosis that includes modifications in both the procoagulant and anticoagulant protein sides of the cascade, there is a reduction in the synthesis of pre activated factors II, V, VII, IX, X, and XI On the anticoagulant side but on the pro coagulant side and there is a decrease in antithrombin III and proteins C and S, with an increase in factor VIII and von Willebrand factor **(4).**

In liver cirrhosis there is a relative reduction in production of these pre-vitamin K activated coagulation factors also there is decrease in the level of circulating concentrations of all the inactivated coagulation factors, except factor VIII which also produced extrahepatically in endothelial cells , it is elevation together with von Willebrand factor in relation to the other coagulation factors because there is decrease in their clearance, also Proteins C and S are also synthesized in the liver and circulate in decreased concentrations in case of cirrhosis **(1).**

Fibrinolysis, Dysfibrinogenemia, and Disseminated Intravascular Coagulopathy:

About 31% of patients with compensated cirrhosis experience fibrinolysis compared to 93% of patients with ascites, Fibrinolysis results from the decreased hepatic clearance of tissue plasminogen activator, which subsequently leads to an increased thrombus breakdown so fibrinolysis and dysfibrinogenemia in chronic liver diseases leads to hemostatic imbalance, Patients often present with normal fibrinogen have mildly prolonged PT, mildly prolonged partial thromboplastin time (PTT), and markedly prolonged thrombin time (TT) **(1).**

DIC develop in 30% of patients with advanced liver disease with cirrhosis resulting in widespread intravascular fibrin deposition caused by the activation of the coagulation cascade and uncontrolled thrombin generation also usually occurs with a triggering clinical event such as sepsis, in DIC factor VIII levels are decreased along with all other coagulation factors, but in cirrhosis without DIC, factor VIII levels remain elevated. **(1)**

Coagulation Tests in Cirrhosis:

It has been found that the INR was found to be significantly higher in the group with cirrhosis than in the group without cirrhosis and that the increase mirrored the severity of the disease , Patients with Child-Pugh class C cirrhosis have the highest INRs also there is increase in PT and activated partial thromboplastin time (aPTT)

(5)

Risks of Venous Thromboembolism:

There is a higher risk for VTE in patients with compensated and decompensated cirrhosis up to the age of 45 years, an increase in INR in chronic liver disease does not protect against it 1,3 also it is associated with a higher mortality among patients with compensated and decompensated cirrhosis. (6)

Physiology of vitamin K

Vitamin K is a fat-soluble vitamin that allow the formation of coagulation factors and post-translational calcium binding to gamma-carboxylated proteins such as prothrombin, factors VII, IX, and X, protein C, and protein S, as well as those proteins found in bone and vascular smooth muscle by acting as a cofactor in the gamma-carboxylation of multiple glutamate residues. (7)

Vitamin K has two forms: phytonadione or phylloquinone (vitamin K1) and menaquinone (vitamin K2). Vitamin K2 is synthesized by bacterial flora and is found in our hepatic tissue, Vitamin K1 is found in our diet from both animal and vegetable sources, including green leafy vegetables, fruits, oils, and nuts, with the average daily intake being100 mcg/dL.12 and can be converted to vitamin K2 which then accumulates in extrahepatic tissues. (8)

Daily dietary intake and enterohepatic recirculation of menaquinones produced by the endogenous bacteria maintain Vitamin K stores and any decrease in it is absorption through small intestinal disease by surgical resection, or biliary obstruction or using antibiotics and diarrheal illness leads to Vitamin K deficiency by decrease in the level of endogenous menaquinone-producing gastrointestinal bacterial flora .14 also drugs that block vitamin K activation, such as warfarin, can decrease vitamin K stores.(7)

Vitamin K is absorbed in the small intestine in the presence of bile and metabolized by the liver before being excreted in either urine or feces ,the onset of action of oral vitamin K is six to 10 hours, with a peak effect around 24 to 48 hours and IV vitamin K has an onset of action of one to two hours with a peak effect occurring between 12 and 24 hours, it can be administered orally, intravenously, for patients with a deficiency or if the patient with active bleeding but subcutaneously or intramuscularly tend to be avoided due to the risk of hematoma , common doses range from 1 mg to 10 mg orally and from 0.5 mg to 10 mg intravenously. (9)

Assessment of Vitamin K Levels:

PT, vitamin K1 levels, and the proteins induced by vitamin K absence or antagonist-II (PIVKA-II) levels are three approaches used for measuring vitamin K level ,PT measures the amount of time it takes for blood to coagulate and which become prolonged in the absence of vitamin K because it measures changes in coagulation factors I, II, V, VII, and X, of which II, VII, and X are affected by the presence of vitamin K for gamma-carboxylation but PT tends to underestimate the deficiency of vitamin K because of its inability to detect a change until the coagulation factors are decreased by 30% to 40% also mn easurement of vitamin K1 levels in the blood does not reflect

total body vitamin K stores, so this idiosyncrasy in the test resulting in decreased in the efficacy in determining a true vitamin K deficiency **(10)**

Enzyme-linked immunosorbent assay kit is used to measure vitamin K by measuring the under-carboxylated precursors of the vitamin K cycle, known as proteins induced by PIVKA-II, they are the most sensitive marker of vitamin K status, since they are elevated only in the absence of vitamin K, normal PIVKA-II levels are considered to be below 3ng/mL, and vitamin K deficiencyis diagnosed with levels that are greater than 3ng/mL **(11).**

Vitamin K Deficiency in Cirrhosis:

Vitamin K deficiency is common in certain types of liver disease, the decreased ability of the liver to complete the vitamin K cycle as a result of decreased function, despite evidence to the contrary, administration of vitamin K in a patient with cirrhosis to reverse an elevated INR has been a routine practice throughout the U.S. because patients with cirrhosis are categorically vitamin K-deficient also the administration of vitamin K is harmless but this repletion is not supported by clinical outcomes, and most research shows that replacement is not an effective treatment for the coagulopathy of liver disease, especially in cirrhosis.**(12)**

The routine use of vitamin K to correct PT/INR in liver cirrhosis cases without significant and active bleeding should be avoided because it is unclear whether the administration of vitamin K is safe in these patients, as it could theoretically tip the balance toward thrombosis **(13).**

Use of Vitamin K in Upper GIT Bleeding:

It has been found that Vitamin K is significantly assosciated with decreasing in the PT and a PTT in cirrhotic Patients but does not affect any of the other measured parameters those decreases were not mirrored by other vitamin K-dependent proteins such as protein C, protein S, and factor VII, in contrast to the expected increase, protein C actually decreased after vitamin K administration and failure to show an increase in PIVKA-II levels at baseline in cirrhosis suggests that vitamin K deficiency does not play an integral role in the coagulopathy of these patients **(13)**

Because of the stable PT after vitamin K administration, it is possible that the mechanism resulting in decreased vitamin K-dependent, precursor proteins is not entirely owing to vitamin K deficiency **(14)**

It has been found that impaired synthesis of coagulation proteins was the primary reason for the coagulopathy of chronic liver disease, in a study by Feldshon et al, the authors concluded that impaired carboxylation was not an integral component of the coagulopathy of liver disease, and that vitamin K administration did not improve any of the coagulation parameters **(15)**

Vitamin K does not seem to add clinical benefit in the setting of cirrhotic induced coagulopathy also it is unclear whether the administration of vitamin K is safe, as it could theoretically tip the balance toward thrombosis. **(13)**

vitamin K is frequently administered in an attempt to correct the elevated PT/INR levels in cirrhotic patients, also it is unlikely appears that deficiency of vitamin K is significantly responsible for the coagulopathy of cirrhosis and even if it were a factor, because of the underlying impairment in synthesis of the coagulation precursor proteins, the administration of vitamin K has not been found to consistently lower the INR. **(16)**

No Conflict of interest.

References:

[1] Amitrano L, Guardascione MA, Brancaccio V, Balzano A. Coagulation disorders in liver disease. Semin Liver Dis 2002;22(1):83–96.

[2] Dabbagh O, Oza A, Prakash S, et al. Coagulopathy does not protect against venous thromboembolism in hospitalized patients with chronic liver disease [published online December 29, 2009]. Chest 2010;137(5):1145–1149.

[3] Lisman T, Bongers TN, Adelmeijer J, et al. Elevated levels of von Willebrand Factor in cirrhosis support platelet adhesion despite reduced functional capacity. Hepatology 2006;44(1):5–361.

[4] Ha NB, Regal RE. Anticoagulation in patients with cirrhosis: caught between a rock-liver and a hard place [published online February 9, 2016]. Ann Pharmacother 2016;50(5):402–409.

[5] Potze W, Arshad F, Adelmeijer J, et al. Routine coagulation assays underestimate levels of antithrombin-dependent drugs but not of direct anticoagulant drugs in plasma from patients with cirrhosis [published online October 8, 2013]. Br J Haematol 2013;163(5):666–673.

[6] Tripodi A, Anstee Q, Sogaard KK, et al. Hypercoagulability in cirrhosis: causes and consequences. J Thromb Haemost 2011; 9(9):1713–1723.

[7] Russell MR, Suter MP. Vitamin and trace mineral deficiency and excess. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine, 19th ed. New York, New York: McGraw-Hill Education; 2015. Available at: http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&sectionid=63653455. Accessed December 10, 2018.

[8] Okano T, Shimomura Y, Yamane M, et al. Conversion of phylloquinone (Vitamin K1) into menaquinone-4 (Vitamin K2) in mice: two possible routes for menaquinone-4 accumulation in cerebra of mice [published online December 14, 2007]. J Biol Chem 2008;283(17):11270–11279.

[9] Pazirandeh S, Burns DL. Overview of vitamin K. UpToDate. August 14, 2018. Available at: https://www.uptodate.com/ contents/overview-of-vitamin-k?search=Overview%20of%20 vitamin%20K&source=search_result&selectedTitle=1~150&us age_type=default&display_rank=1. Accessed February 7, 2019.

[10] Whalen KL, Borja-Hart N. Interpretation of clinical laboratory data. In: Nemire RE, Kier KL, Assa-Eley M, eds. Pharmacy Student Survival Guide, 3rd ed. New York, New York: McGraw-Hill; 2014:183–216. Available at: http://accesspharmacy.mhmedical.com/content.aspx?bookid=1593&sectionid=99824844. Accessed February 7, 2019

[11] Shearer MJ, Fu X, Booth SL. Vitamin K nutrition, metabolism and requirements: current concepts and future research. Adv Nutr 2012; 3(2):182–195.

[12] Shah NL, Intagliata NM, Northup PG, et al. Procoagulant therapeutics in liver disease: a critique and clinical rationale [published online July 15, 2014]. Nat Rev Gastroenterol Hepatol 2014;11(11):675–682.

[13] Saja MF, Abdo AA, Sanai FM, et al. The coagulopathy of liver disease: does vitamin K help? Blood Coagul Fibrinolysis 2013;24(1): 10–17.

[14] Blanchard RA, Furie BC, Jorgensen M, et al. Acquired vitamin K-dependent carboxylation deficiency in liver disease. N Engl J Med 1981;305(5):242–248.

[15] Feldshon SD, Earnest DL, Corrigan JJ. Impaired coagulant factor synthesis is more important than impaired carboxylation in the coagulopathy of liver disease. Hepatology 1983;3(5):858.

[16] Sarah M. Aldrich, PharmD, and Randolph E. Regal, PharmD. Routine Use of Vitamin K in the Treatment of CirrhosisRelated Coagulopathy: Is it A-O-K? Maybe Not, We Say .P&T® • March 2019 • Vol. 44 No. 3.