Appropriateness of using vitamin K for the correction of INR elevation secondary to hepatic disease in critically ill patients: An Observational Study

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Abstract

Background: Hepatic diseases have been associated with an increased risk of coagulopathy and increased odds of secondary thrombosis and bleeding. Using vitamin K for correction of coagulopathy in critically ill patients is controversial with limited evidence. This study aims to evaluate the efficacy and safety of vitamin K in the correction of international normalized ratio (INR) elevation secondary to liver disease in critically ill patients.

Method: A retrospective study of adult ICU patients with coagulopathy secondary to liver disease admitted to a tertiary teaching hospital in Saudi Arabia. The primary outcome was to evaluate the association between vitamin K administration and the incidence of new bleeding events in critically ill patients with INR elevation secondary to liver disease. Secondary outcomes were to evaluate the incidence of a new thrombotic event, and the degree of INR correction with vitamin K. Patients were divided into two groups based on vitamin K administration to correct INR elevation. The propensity score was generated based on disease severity scores and the use of pharmacological DVT prophylaxis.

Results: A total of 98 patients were included in the study. Forty-seven patients (48%) received vitamin K during the study period. The incidence of the new bleeding event was not statistically different between groups (OR 2.4, 95% CI 0.28-21.67, P=0.42). Delta of INR reduction was observed with a median of 0.63 when the first dose is given (p-value: <.0001). However, other subsequent doses of vitamin K were not statistically significant.

Conclusion: Using vitamin K for INR correction in critically ill patients with coagulopathy secondary to liver disease was not associated with a lower incidence of new bleeding events. Vitamin K was efficient in reducing INR level at the first dose, and other subsequent doses were not.

Introduction

Liver plays a major role in blood homeostasis via regulating the activation or inhibition of coagulation factors. Therefore, any failure in liver functionality to synthesize both antithrombotic and prothrombotic factors may lead to coagulopathy (1,2). The extent of coagulopathy depends on the functionality degree of liver parenchymal cells, responsible for producing most fibrinolytic and clotting factors (3-4).

Patients with end-stage liver disease (ESLD) have an imbalance coagulation profile and are at risk for excessive clotting and bleeding. Recently, it is recognized that hemostasis in patients with chronic liver disease is rebalanced, as the fall in anticoagulant proteins is accompanied by a parallel fall in clotting factor levels (5). However, compared to patients without liver disease, hemostasis balance is relatively unstable, and the risk for bleeding in cirrhosis seems to be particularly elevated in patients during decompensation, infections, or acute-on-chronic liver failure (ACLF) (6,7,8).

Critically ill patients with liver diseases, complications such as bleeding and thrombosis are prevalent, challenging, and may not be preventable (7,9). For example, the incidence of new-onset major bleeding in the intensive care unit (ICU) was found in 17–20% of cirrhotic patients (10). One of the reasons behind the hemostatic imbalance in patients with chronic liver disease is decreased synthesis of vitamin K-dependent and independent clotting factors (11). Vitamin- K plays a vital role in synthesizing active forms of coagulation and anticoagulation factors, including prothrombin, factor VII, XI, X, protein C, and S (12). Additionally, Vitamin- K has a strong correlation with international normalized ratio (INR) elevation in those patients (11). However, conventional coagulation tests in those patients do not fully reflect the actual derangement in hemostasis and demonstrated to be ineffective in either predicting and/or guiding the management of this impaired coagulation (5, 6, 10).

Patients with liver diseases usually experience hemostatic imbalanced risk for bleeding and thrombosis (8,13). Due to coagulopathy, these patients may have an elevated INR, and some clinicians still making important clinical decisions based on the INR interpretation as a general indication of a patient's overall bleeding risk due to auto-anticoagulation (14). Management of coagulopathy by correcting INR elevation is common, especially before major procedures, because some procedures progress to either hemorrhage or thrombosis depending on the patient's status and risk factors (15). Therefore, the management of coagulopathy secondary to liver diseases is controversial and not fully elucidated. This study aims to evaluate the efficacy and safety of using vitamin K in critically ill patients with INR elevation secondary to liver diseases

Methods

Study design

A retrospective case-control study of adult ICU patients with coagulopathy secondary to liver disease admitted between January 1st, 2018, and December 31st, 2018. All the patients who met the inclusion criteria during the study period were included. Patients were divided into two groups: patients who received any dose through any route of administration of phytonadione (vitamin K) compared to patients who did not receive vitamin K for INR correction secondary to liver disease. Patients were followed daily during ICU stay until ICU discharge after improving, or in-hospital death, whichever occurred first.

Participants

Patients were enrolled in the study if they were critically ill aged ≥18 years old with hepatic disease (s) and significant INR elevation (defined as INR≥ 1.5) within 24 hours of ICU admission. Exclusion criteria include receiving prolonged antibacterial therapy for ≥ 21 days, prior administration of any oral anticoagulant, or receiving prothrombin complex concentrate (PCC) or FFP simultaneously with vitamin K. Additionally, patients with comorbidity that cause coagulopathy other than hepatic diseases (i.e., systemic lupus erythematosus, lupus anticoagulant-hypoprothrombinemia syndrome, antiphospholipid antibody syndrome (APAS)), or comorbidity that increase bleeding/thrombosis risk (i.e., Hemophilia A,

Hemophilia B, von Willebrand disease, Protein C or S deficiency, Antithrombin III deficiency, APAS) were excluded based on the chart-review.

Setting

This study was conducted in the adult medical, surgical, trauma, and burn ICUs at KAMC, a tertiary-care academic referral hospital in Riyadh, Saudi Arabia. The ICU admits medical, surgical, trauma, burn patients and operates as closed units with 71 ICU beds capacity with 24/7 onsite coverage by critical care board-certified intensivists.

Data collection

Demographic and clinical data including age, gender, weight, body mass index (BMI), associated co-morbidities, laboratory baseline including but not limited to coagulation profile (e.g., INR, aPTT, d-dimer), liver function tests (LFTs), complete blood count within 24 hours of ICU admission. Additionally, Glasgow Coma Scale (GCS), Vasoactive Inotropic Score (VIS), Acute Physiology and Chronic Health Evaluation (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, Nutrition Risk in Critically ill (NUTRIC) score, and the use of pharmacological DVT prophylaxis were recorded for eligible patients on the first day. Moreover, mechanical ventilation**,** endoscopy, receiving proton pump inhibitor (PPI) treatment dose, transfusions during ICU stay (i.e., RBCs/platelets, fresh frozen plasma (FFP) transfusion, cryoprecipitate), radiology finding (i.e., CT scan, ultrasound, magnetic resonance imaging (MRI)), surgery during ICU stay, respiratory and blood cultures were reviewed and recorded.

Outcomes

This study aims to investigate the efficacy and safety of using Phytonadione (Vitamin K) to correct INR elevation secondary to liver disease in critically ill patients. The primary outcome was to evaluate the association between vitamin K administration and incidence of bleeding (i.e., major and minor bleeding) in critically ill patients with INR elevation secondary to liver disease. Secondary outcomes were to evaluate the degree of international normalized ratio (INR) correction with vitamin K, the incidence of thrombosis, RBCs/Platelets transfusion requirement, mechanical ventilation duration, ICU length of stay (LOS), and ICU mortality.

Definition (s)

- Thrombosis/infraction was defined using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD10-CM) code (i.e., ischemic stroke, pulmonary embolism, deep vein thrombosis) during ICU stay (16).
- Major bleeding was defined as clinically overt bleeding associated with a fall ≥Hgb 20g/L, transfusion of ≥2U PRBC or whole blood, retroperitoneal or intracranial bleeding, or requiring urgent medical intervention. While minor bleeding was defined as those not fulfilling the criteria of major or clinically significant bleeding.

- Acute kidney injury (AKI) was defined using Acute Kidney Injury Network (AKIN) definition.

Data management and Statistical analysis

Collected data was entered in Microsoft Excel after being coded. There were two arms considered in this study, patients who received Vitamin K versus non-Vitamin K. As expected in an observational study, differences in baseline characteristics between the two treatment groups may exist. To adjust for these differences, a propensity score for the use of Vitamin K was generated with APACHE II, SOFA scores and the use of pharmacological DVT prophylaxis. Multivariate logistic regression was used to find out the relationship between treatments and the different outcomes considered in this study, adjusting for the generated propensity score.

We summarized categorical variables as number (percentage) and numerical variables (continuous variables) as mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. The normality assumptions were assessed for all numerical variables using statistical test (i.e. Shapiro–Wilk test) and also using graphical representation (i.e. histograms and Q-Q plots). We compared categorical variables using the chi square or Fisher exact test, normally distributed numerical variables with the t test, and other quantitative variables with the Mann-Whitney U test. Baseline characteristics, baseline severity and outcome variables were compared between the two groups. The INR changes were compared using Wilcoxon signed-rank test in Vitamin K group alone.

We assessed model fit using the Hosmer-Lemeshow goodness-of-fit test. Generalized linear regression and Multiple linear regression were also used to find out the relationship between treatments and the different outcomes considered in this study, adjusting for the generated propensity score. The odds ratios (OR) and estimates with the 95% confidence intervals (CI) were reported for the associations. We considered a P value of < 0.05 statistically significant and used SAS version 9.4 for all statistical analysis.

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(OR) and estimates with the 95% confidence intervals (CI) were reported for the associations. We considered a P value of < 0.05 statistically significant and used SAS version 9.4 for all statistical analysis.

Results

Patient characteristics

A total of 1864 patients were screened. Ninety-eight patients were included; 47 (48%) had received vitamin K during the study period. Table 1 depicts baseline characteristics between vitamin K and non-vitamin K groups. Patients who received vitamin K were observed to be more diabetic, have a lower GCS baseline, higher rate of chronic kidney disease, ischemic heart disease, atrial fibrillation, heart failure. Additionally, eGFR, serum creatinine, ALT, AST, INR, aPTT, platelets, albumin, PaO2/FiO2 ratio, lactic acid, and fibrinogen baseline 24 hours of ICU admission was not significant between the two groups when adjusted for propensity score. On the other hand, patients who did not receive Vitamin K had a higher Vasoactive Inotropic Score (VIS) baseline, lower bilirubin, and D-dimer levels within 24 hours of ICU admission. When adjusted for propensity score using severity score within 24 hours of ICU admission (APACHE II, SOFA score, and the use of pharmacological DVT prophylaxis), all these differences became insignificant.

Outcomes

Vitamin K was given by IV route of administration in 93.6 % of the patients, with a median dose of 10 mg and for a median of three days. Using Vitamin K for correction of INR secondary to liver disease was observed at the first dose (p-value: <.0001); other subsequent doses of vitamin K were not statistically significant for correction. The changes were calculated as the difference between pre-measurements to post-measurements at each dose (Table 3). Patients who received vitamin K for INR correction have longer ICU LOS (Estimates (STD) 0.67, 95% CI 0.22-1.12, P=0.003), and mechanical ventilation duration (Estimates (STD) 0.93 , 95% CI 0.23 – 1.62, P=0.01 (Table 2).

The rate of venous thromboembolism (VTE) was 17 % (8/47) in the vitamin K group as compared to 3.9% (2/51) in the non-vitamin K group. Patients who received vitamin K were 2.4 times more likely to get VTE than patients who did not. However, this association was not statistically significant when adjusted for propensity score (OR 2.4, 95% CI 0.45- 13.12, P=0.30). Patients with any reported thrombosis cases were more likely to receive a cumulative dose of ≥ 35.3 mg of vitamin K. Neither all bleeding events (OR 2.4, 95% CI 0.28-21.67, P=0. 42) nor thrombosis (OR 1.2, 95% CI 0.32-4.85 P=0.76) were statistically significant between the two groups. Patients who received vitamin K had a lower requirement of RBCs transfusion; however, it was not statistically significant (Table 2).

Table 4 shows all bleeding events as well as all thrombosis events after stratification based on the level of severity using the Child-Pugh Score. Patients with a Child-Pugh score of C had a higher rate of all thrombosis cases (8.33 %) and all bleeding events (9.38%) than Child-Pugh B and A, respectively.

Discussion

Assessing the degree of coagulopathy in hepatic patients using PT and INR may not represent the best-practice or evidence-based approach to patient care (5). Moreover, administering Vitamin K is a common practice to manage patients with hepatic disease-associated coagulopathy with an effort to augment the synthetic function of clotting factors has been identified. (17) However, this approach may not be predictable, and the appropriateness of using vitamin K is not fully elucidated in critically ill patients in terms of safety and efficacy.

In the current study, we evaluated the efficacy and the safety of vitamin K administration to correct INR elevation secondary to liver diseases. APACHE II and SOFA were calculated within 24 hours of ICUs admission and adjusted between the two groups. In our study, the first dose of vitamin K administration was statistically significant in correcting INR with a median of 2.64 (1.52) pre-dosing to 2.01 (0.67) post vitamin K. However, our study shows that other subsequent doses of vitamin K were not having a significant reduction in INR. Also, using vitamin K to correct INR elevation did not decrease RBCs, platelets, or FFP transfusions requirements. In parallel to our finding, Rivosecchi et al. founds that the first dose of vitamin K was associated with INR reduction by 30 %; however, this result appeared only in 16% of patients who received vitamin K.(18) Rivosecchi R et al. concluded that the use of vitamin K is not efficient in correcting coagulopathy secondary to liver cirrhosis as about 62.3 % of this patients failed to reach these reductions. Saja et al. showed a similar conclusion when evaluating vitamin K administration efficiency in series of coagulation parameters in the four stages of liver diseases (12).

The liver is responsible for synthesizing nearly all procoagulants (e.g., factor I, II, III, X, Fibrinogen) and anticoagulant proteins (e.g., protein C, S, Z, Antithrombin) responsible for maintaining hemostasis. Hemostasis in cirrhotic patients is a dynamic balance. Therefore, patients with liver diseases usually experience an imbalanced hemostatic variable (8,13). Due to coagulopathy, these patients may have an elevated INR, and some clinicians still making important clinical decisions based on the INR interpretation as a general indication of a patient’s overall bleeding risk due to auto-anticoagulation (14). Our study shows that patients with Child-Pugh C having a high incidence of thrombosis (8.33%) comparing with Child-Pugh B and A (5.21 % and 2.08%, respectively). As patients with liver diseases have a defect in synthesized anticoagulation factors, including protein C, protein S, and antithrombin III, this may increase the VTE risk (8). A paradoxical phenomenon, increased bleeding risk does not rule out the development of a new thrombus. Therefore, it's important to note that elevation of INR secondary to liver diseases poses the risk of thrombosis and bleeding, suggesting using a different technique to assess this population's hemostasis (e.g., Viscoelastic tests).

A thromboelastogram can represent an alternate to bleeding time, PT measurement, and INR calculation in patients with hepatic dysfunction by assessing in vivo risk of hemorrhage to evaluate a true coagulation profile as thromboelastogram considers multiple factors that are associated with a true coagulopathy (e.g., coagulation cascade activation, clotting cascade inhibition, fibrinolytic activity, and platelet function) (8).

In general, cirrhotic patients who are truly vitamin-K deficient are roughly less than 15% (19). Administration of vitamin K only to correct an abnormal laboratory result should be minimized. Our study shows that patients who receive vitamin K were 2.4 times more likely to get VTE (whether DVT or PE) than the non-vitamin K group and more prone to thrombotic events; however, it was not statistically significant when adjusted using the propensity score. In addition, all bleeding events were not statistically significant between the two groups. Also, our finding shows that patients with any reported case of thrombosis were more likely to receive an increased cumulative dose of ≥ 35.3 mg of vitamin K, emphasizing the need to determine the appropriate indication (s), dosing, and duration when using vitamin K to correct and manage coagulopathy for patients with hepatic disease.

Similarly, several studies have provided data that suggested to assess the effectiveness and safety of vitamin K, and it should be avoided to correct an abnormal laboratory result only without significant bleeding in these patients. (8,13,20)

The study is distinctive and has a set of strengths in which nutritional risk and severity of illness between two groups were not significant (using NUTRIC and SOFA score, respectively). In addition, patients who received prolonged antibacterial therapy for ≥ 21 days or have at high risk of thrombosis and coagulopathy were excluded. However, some potential limitations have been noted, as the model's effect is based on a retrospective design and a small sample size. Besides, heterogeneity of ICU cases (e.g., Medical, Surgical patients) and secondary liver disease (e.g., acute on top of chronic disease) was not determined. Therefore, they are subjected to confounding that may influence our model findings. Further well-designed studies with a larger sample size are warranted to confirm our findings.

Conclusion

using vitamin K for INR correction in critically ill patients with coagulopathy secondary to liver disease was not associated with a lower incidence of new bleeding events. Vitamin K was efficient in reducing INR level at the first dose, other subsequent doses were not. Patients who received vitamin K were more likely to have longer ICU LOS and MV duration compared with patients who did not receive. The routine prescription of Vitamin K in critically ill patients with coagulopathy secondary to liver disease warrants further evaluation.

Declarations

Ethical consideration

The study was approved in August 2019 by King Abdullah International Medical Research Center Institutional Review Board, Riyadh, Saudi Arabia (IRB approval number: RC19/308/R). Participants' confidentiality was strictly observed throughout the study by using anonymous unique serial number for each subject and restricting data only to the investigators. Informed consent was not required due to the research's method as per policy of the governmental and local research center.

Author contributions

All authors contributed to data collections, analysis, drafted, revised and approved the final version of the manuscript.

Compliance with Ethical standards:

Funding: None

Disclosure: No author has a conflict of interest in this study.

Availability of data and material:

Data available on request due to privacy and ethical restrictions.

Consent for publication

Not applicable.

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Tables

Table 1: Baseline characteristics of the Vitamin K and Non-Vitamin K groups

	Vitamin K (N=47)	Non Vitamin K (N=51)	P value
Age (years), mean (SD)	63.5 (11.43)	58.2 (17.00)	0.0924^
BMI(kg/m2), mean (SD)	29.1 (8.06)	27.1 (7.75)	0.3110^
Gender, n(%)			
Male	26 (55.3)	28 (54.9)	0.9669^^
Female	21 (44.7)	23 (45.1)	
Weight (kgs) , mean (SD)	75.8 (23.56)	68.4 (18.22)	0.2129^
Hypertension (HTN), n (%)	22 (46.8)	19 (37.3)	<.0001^^
Asthma, n (%)	1 (2.1)	1 (2.0)	<.0001**
Chronic obstructive pulmonary disease (COPD), n (%)	0 (0.0)	1 (2.0)	<.0001**
DM , n (%)	28 (59.6)	16 (31.4)	<.0001^^
Chronic kidney disease (CKD), n (%)	11 (23.4)	5 (9.8)	<.0001^^
Ischemic heart disease (IHD), n (%)	4 (8.5)	2 (3.9)	<.0001**
Atrial fibrillation (AFib or AF), n (%)	3 (6.4)	1 (2.0)	<.0001**
Heart failure (HF), n (%)	3 (6.4)	1 (2.0)	<.0001**
Acute coronary syndrome (ACS), n (%)	1 (2.1)	1 (2.0)	<.0001**
Dyslipidemia (DLP), n (%)	5 (10.6)	8 (15.7)	<.0001^^
CVA (Stroke)			
Hypothyrodism , n (%)	4 (8.5)	2 (3.9)	<.0001**
Previous use of Abx. Within 3 months of ICU admission, n (%)	23 (48.9)	10 (19.6)	0.0021^^
Previous admission within 3 months, n (%)	26 (56.5)	11 (28.2)	0.0087^^
Baseline within 24 hours of ICU admission			
Acute Kidney Injury, n (%)	18 (38.3)	9 (17.6)	0.0223^^
Serum creatinine ±mg/dl) , mean (SD)	251.2 (205.65)	212.1 (220.23)	0.3268^
eGFR, mean (SD)	49.6 (50.04)	56.4 (39.52)	0.2396^
Blood urea nitrogen (BUN), mean (SD)	16.9 (10.65)	13.4 (8.69)	0.2225^
Total bilirubin , mean (SD)	202.1 (188.53)	63.5 (47.16)	0.0007^
INR, mean (SD)	2.3 (0.69)	2.0 (0.43)	0.0526^
Platelets count, mean (SD)	14.5 (21.69)	4.5 (7.75)	0.0164^
Activated partial thromboplastin time (aPTT) , mean (SD)	51.0 (23.33)	51.5 (22.25)	0.9410^
Gamma-glutamyl transferase (GGT), mean (SD)	116.1 (71.35)	217.8 (171.62)	0.2932^
Alanine aminotransferase (ALT), mean (SD)	235.7 (435.05)	232.1 (391.20)	0.6612^
Aspartate aminotransferase (AST), mean (SD)	475.4 (1005.58)	230.2 (359.88)	0.2897^
Albumin, mean (SD)	29.9 (8.13)	27.4 (5.36)	0.1294*
White blood cells (WBCs)), mean (SD)	14.7 (15.24)	10.9 (5.88)	0.3526^
Fraction of inspired oxygen (FiO2) requirement (%)	40.6 (20.37)	37.4 (14.68)	0.7372^
Glasgow Coma Scale (GCS), mean (SD)	10.2 (4.62)	13.5 (2.89)	0.0018^
Blood Glucose Level (mmol/l) , mean (SD)	14.4 (22.02)	15.5 (5.81)	0.0025^
Mean arterial pressure (MAP), mean (SD)	53.80 (14.33)	61.19 (14.56)	0.0130^
Lactic acid, mean (SD)	8.0 (7.66)	5.9 (6.66)	0.1885^
Hematocrit (Hct) , mean (SD)	0.3 (0.07)	0.3 (0.07)	0.0480*
Fibrigen, mean (SD)	2.0 (1.10)	2.6 (2.07)	0.6077^
D-dimer, mean (SD)	17.2 (13.04)	11.1 (7.08)	0.3039^
Vasoactive Inotropic Score (VIS) 24hrs, mean (SD)	58.4 (130.07)	71.3 (218.68)	0.0013^

APACHE II, Median (Q1,Q3)	22.00(14.00 , 29.00)	17.00(9.00 , 21.00)	0.0056^
SOFA, Median (Q1,Q3)	11.00(9.00 , 15.00)	7.00(5.00 , 9.00)	0.0001^
Pharmacological DVT prophylaxis	6 (12.5)	17 (33.3)	0.012

-Denominator of the percentage is the total number of patients

*T -Test / ^ Wilcoxon rank sum test is used to calculate the P-value.

^^Chi-square test is used to calculate the P-value.

$*propensity score adjusted Generalized linear model is used to calculate estimates and p-value.

$**propensity score adjusted multiple regression model is used to calculate estimates and p-value.

$ propensity score adjusted Logistic regression is used to calculate Odds ratio and p-value.

**Fisher Exact test is used to calculate the P-value.

Table 2: Outcomes of the Vitamin K and Non-Vitamin K groups

	Vitamin K (N=47)	Non-Vitamin K (N=51)	P value	Odds Ratio (OR) (95%CI)	P value
Major Bleeding, n (%)*&	3/27 (11.1)	1/51 (2.0)	0.12^^	2.4 (0.28, 21.67)	0.42
Minor bleeding, n (%)*&	0/27 (0)	0/51 (0.0)	NA	NA	NA
Bleeding (All cases), n (%)*&	3/27 (11.1)	1/51 (2.0)	0.12^^	2.4 (0.28, 21.67)	0.42
VTE (DVT / PE), n (%)	8 (17.0)	2 (3.9)	0.04**	2.4 (0.45, 13.12)	0.30
Thrombosis (All cases), n (%)	9 (19.2)	6 (11.8)	0.31^^	1.2 (0.32, 4.85)	0.76
30-day ICU mortality, n (%)	29 (61.7)	7 (13.7)	<.0001^^	2.7 (0.79, 9.01)	0.11
				beta coefficient (Estimates) (95%CI)	**P-value**
RBCs Transfusion (U) , mean (SD)	5.3 (4.62)	4.2 (9.41)	0.006^	-0.12 (-0.76, 0.51)	0.71
Platelets Transfusion (U) , mean (SD)	14.5 (21.69)	4.5 (7.75)	0.02^	0.36 (-0.71, 1.43)	0.51
ICU LOS, Median (Q1, Q3)	10.0(4.00 , 18.00)	4.0 (2.00 , 10.00)	0.0003^	0.67 (0.22, 1.12)	0.003
MV duration, Median (Q1, Q3)	3.0(1.00 , 8.00)	0.0(0.00 , 2.50)	0.002^	0.93 (0.23, 1.62)	0.01

*& Denominator of the percentage is non-bleeding at the time of vitamin K administration.

*T -Test / ^ Wilcoxon rank sum test is used to calculate the P-value.

**Fisher Exact /^^Chi-square test is used to calculate the P-value.

$*propensity score adjusted Generalized linear model is used to calculate estimates and p-

value.

$ Propensity score adjusted Logistic regression is used to calculate Odds ratio and p-value.

Table 3: Comparison of INR change between Vitamin K and Non-Vitamin K groups

	Vitamin K Group (N=47)		P value
	Pre	Post	
INR change at dose# 1, median (IQR)	2.64(1.52)	2.01(0.67)	<.0001
INR change at dose# 2, median (IQR)	2.09(0.63)	1.98(0.59)	0.2839
INR change at dose# 3, median (IQR)	2.19(1.39)	2.21(1.45)	0.5442
INR change at dose# 4, median (IQR)	2.83(1.80)	2.47(0.96)	0.6698

Wilcoxon rank sum test is used to calculate the P-value.

Table 4: All bleeding and thrombosis cases among different Child Pugh Score

	Child Pugh Score		
	Child Pugh A (N=29)	Child Pugh B (N=26)	Child Pugh C (N=41)
Bleeding (All case), n (%)	1(1.04%)	3 (3.13%)	9 (9.38%)
Thrombosis (All case), n (%)	2(2.08%)	5(5.21%)	8(8.33%)