Bull. Pharm. Sci., Assiut University, Vol. 45, Issue 2, 2022, pp.789-800.

Bulletin of Pharmaceutical Sciences
Assiut University
Website: http://bpsa.journals.ekb.eg/
e-mail: bullpharm@aun.edu.eg

THERAPEUTIC EFFICACY OF ORAL VERSUS INTRAVENOUS VITAMIN K IN PATIENTS WITH LIVER CIRRHOSIS

Tarek Refaat Mohameed[1], Haidi Karam-Allah Ramadan[2], Mohamed Mahmoud Abdel-Latif[3] and Sahar Badr Hassan[3*]

[1]*Clinical Pharmacy Unit, Al-Rajhy Liver Hospital, Assuit, Egypt.*
[2]*Department of Tropical Medicine and Gastroenterology, Faculty of Medicine, Assuit University.*
[3]*Department of Clinical Pharmacy, Faculty of Pharmacy, Assuit University.*

***Objective**: Patients with liver cirrhosis have different complications including bleeding disorders, due to vitamin K-dependent coagulation factors deficiency. Vitamin K is administered to correct bleeding complications, however the evidence for its efficacy either orally or intravenously is lacking. This study aimed to assess therapeutic role of vitamin K in cirrhotic patients.**Methods:** A prospective observational study was conducted on ninety liver cirrhotic patients at Al-Rajhy Liver Hospital. Patients received vitamin K orally (N= 45) or intravenously (N= 45) at doses of 10 mg/day for 3 successive days. Prothrombin time (PT), international normalization ratio (INR), serum vitamin K level, hemoglobin, liver and kidney function were assessed at baseline and after 3 days of vitamin K administration. Child-Pugh score and bleeding signs were reported. **Results:** After vitamin K administration, vitamin K serum level was significantly increased in the oral and the IV group. PT and INR were significantly decreased in the oral and the IV groups. Vitamin K serum level had negative significant correlation with PT (r= -0.42, P= 0.033) and INR (r= -0.40, P= 0.038). **Conclusion:** Oral and IV vitamin K administration showed similar efficacy in improving PT, INR and bleeding signs. Child B class patients more benefited from vitamin k administration than Child C class..*

***Keywords:** Intravenous, INR, Liver cirrhosis, Oral, PT, Vitamin K.*

INTRODUCTION

Liver cirrhosis is an advanced stage of chronic liver disease[1]. Liver cirrhosis is currently the 11th most common cause of death globally[2]. In Egypt, the major cause of liver cirrhosis is viral hepatitis, particularly HCV and HBV[3]. During the progression of liver cirrhosis, various complications occurred as ascites, hepatic encephalopathy and bleeding disorder[4&5]. Patients with liver cirrhosis have significant impaired liver synthetic function, including vitamin K-dependent clotting factors[6]. Reduction in the synthesis of these factors is correlated with the extent of cirrhosis and the loss of liver parenchymal cells[7]. Liver cirrhosis is considered a prototype of hemorrhagic disease[8]. Bleeding complications that appear in liver cirrhotic patients include bruising, purpura, epistaxis, gingival bleeding, hematemesis, bleeding per rectum, and bleeding associated with invasive procedures that may be related to defective hemostasis commonly seen in those patients[9]. The Child-Pugh score has been widely used to assess the extent and prognosis of liver cirrhosis[10].

Vitamin K deficiency was found in liver cirrhotic patients, and associated with bleeding complications[8&11]. In clinical settings, impaired synthesis of vitamin K dependent clotting factors was detected by prolonged PT and elevated INR[12&13]. It has been reported that vitamin K was administered empirically to exclude a contribution of vitamin K deficiency to the bleeding disorder[14].

Despite the lack of evidence supporting the efficacy of vitamin K in correcting the bleeding of liver cirrhosis, vitamin K administration remains a part of the common practice of treatment of many patients with liver cirrhosis who had abnormalities in their coagulation parameters[15]. Vitamin K can be

Received in 14/3/2022 & Accepted in 25/4/2022

*Corresponding author: Sahar Badr Hassan, E-mail: Sahar.badr@pharm.aun.edu.eg

administered orally or intravenously in patients with vitamin K deficiency or if the patient is actively bleeding[16]. The intravenous route is more accessible for the unconscious patient; but associated with the risk of hematoma, bleeding and pain[17]. On the other hand, the oral route of administration shows several benefits such as easy administration and maintenance of gastric function[17&18].

It has been reported that patients with severe acute liver damage had evidence of subclinical vitamin K deficiency at admission, which was corrected by a single dose of IV vitamin K[19]. On the other hand, Rivosecchi et al. had found that the use of IV vitamin K to correct coagulopathy of cirrhosis may not be beneficial[20]. Oral vitamin K administration to patients with liver cirrhosis may be beneficial in the correction of elevated INR and decrease prolonged PT[12]. Xiong et al. reported that the IV administration of vitamin K may improve the survival of patients with chronic liver failure[21]. The effectiveness of vitamin K administration has been controversial in the treatment of liver cirrhotic patients with bleeding complications[22].

The present study was aimed to investigate the therapeutic role of oral versus IV administration of vitamin K in liver cirrhotic patients.

PATIENTS AND METHODS

Study setting

Ninety patients with decompensated liver cirrhosis were recruited from Al-Rajhy Liver Hospital, Assiut, Egypt, between September 2018 and March 2020. The study was approved by the Medical Ethics Committee, Faculty of Medicine, Assiut University (IRB no:17100845). Informed consent was obtained from all patients.

The inclusion criteria involved all patients admitted to the hospital who had INR >1.5 and did not receive vitamin K therapy within the preceding 3 days with or without a history of bleeding. Exclusion criteria included patients with evidence of renal disease, thrombocytopenia, history of blood transfusion or blood products in the preceding 1-month, chronic cholestatic liver diseases, portal vein thrombosis and the use of either heparin or warfarin.

Study design

A prospective observational study was conducted on ninety patients received 10 mg/day vitamin K orally; konakion tablets - the oral group, (N= 45) or intravenously konakion ampoules - the IV group (N= 45) for 3 successive days. Konakion mixed-micellar (MM K1) formulations for oral and IV administration act to enhance oral absorption and lower risk of anaphylactic reactions after IV administration than other vitamin K formulas which contain the nonionic detergent Cremophor as solubilizer[19].

Collection of data

Demographic data and clinical characteristics were collected from all patients. Full clinical history included PT, INR, vitamin K serum level, hemoglobin level, liver and kidney function were obtained at baseline and after 3 days of vitamin K administration.

Serum vitamin K assay

Ten ml of venous blood samples were collected before and after 3 days of vitamin K administration. Blood samples were collected into plain tubes, protected from light and allowed to clot at -4° C. Serum was separated by centrifugation and stored at -70°C. Vitamin K serum level assay based on ELISA technique using a conformation-specific monoclonal antibody, this kit is an Enzyme-Linked Immunosorbent Assay (ELISA) was performed according to laboratory manufacturer. The plate has been pre-coated with a human vitamin K antibody. Vitamin K present in the sample is added and binds to antibodies coated in the wells, then biotinylated human vitamin K antibody is added and bound to vitamin K in the sample. Then Streptavidin -HPR is added and binds to the biotinylated vitamin K antibody. After incubation unbound streptavidin-HPR is washed away during a washing step. The substrate solution is then added and color develops in proportion to the amount of human vitamin K. The reaction is terminated by the addition

of acidic stop solution and absorbance is measured at 450 nm. (Vitamin K ELISA Kit is highly sensitive 2.5 ng/l, with standard curve range between 5 to 1500 ng/l).

Clinical outcomes

Assessments of PT, INR and serum vitamin K level at baseline and after 3 days vitamin K administration were performed. Clinical manifestations of bleeding (hematemesis, melena, epistaxis, gingival bleeding and bleeding per rectum) were monitored at baseline and after 3 days of vitamin K administration. Patients who required blood component transfusion were reported at discharge from the hospital.

Statistical analysis

Data were analyzed using Statistical Package for the Social Science (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). The Kolmogorov–Smirnov test was used to check the normality of data. The Wilcoxon rank-sum and Mann-Whitney U-test were used whenever appropriate. Spearman Rank was used to test the correlation between serum vitamin K level PT and INR. The Chi-square test and Fisher exact test were used to compare the difference in proportions in groups. Data were presented as mean ±SD or median (IQR). P value was considered significant if $P < 0.05$.

RESULTS AND DISCUSSION

Results

Demographics, clinical characteristics at baseline of the study patients

The present study included ninety eligible patients with 45 patients in the oral group and 45 patients in the IV group. The mean age of patients in the oral group was 49.98 ± 11.34 years and 25 (55.6%) of patients were male. For the IV group, the mean patients' age was 50.93 ± 9.33 years and 24 (53.3%) of patients were male. Hepatitis C viral infection was the major cause of liver cirrhosis, where 40 (88.9%) in the oral group and 38 (84.4%) in the IV group had liver cirrhosis secondary to hepatitis C virus infection. With regard to the severity of liver damage, the Child-Pugh score was recorded in each study group. In the oral group, 23 patients were of Child B class and 22 patients were of Child C class. On the other hand, the IV group included 22 patients of Child B class and 23 patients of Child C class. Bleeding signs such as hematemesis, melena, epistaxis, bleeding per rectum and gingival bleeding were statistically insignificant among both groups, Table 1. Laboratory investigations such as PT, INR, serum vitamin K, hemoglobin level, liver function and kidney function of the patients were statistically insignificant between the oral and the IV group at baseline, Table 2.

Table 1: Patients' demographics and clinical characteristics at baseline in the study patients.

Variable	Oral group (N = 45)	IV group (N = 45)	P value
Age	49.98±11.34	50.93±9.33	0.66
Sex			
Male	25 (55.6%)	24 (53.3%)	0.5
Female	20 (44.4%)	21 (46.7%)	
Cause of cirrhosis			
Hepatitis C virus	40 (88.9%)	38 (84.4%)	0.39
Hepatitis B virus	5 (11%)	7 (15.6%)	0.69
Child class			
Child B	23 (51.1%)	22 (48.9%)	0.5
Child C	22 (48.9%)	23 (51.1%)	
Comorbidities			
Diabetes	14 (31.1%)	15 (33.3%)	0.82
Hypertension	10 (22%)	7 (15.5%)	0.39
Bleeding signs			
Hematemesis	22 (48.8%)	25 (55.5%)	0.66
Melena	7 (15.5%)	6 (13.3%)	0.89
Epistaxis	6 (13.3%)	0	0.06
Bleeding per rectum	5 (11.1%)	0	0.08
Gingival bleeding	3 (6%)	6 (13.3%)	0.36
Liver cirrhosis signs			
HE	14 (31.1%)	17 (37.7%)	0.33
SBP	8 (17.7%)	11 (24.4%)	0.45
Asities	16 (35.5%)	12 (26.6%)	0.56

P value (Chi-square test), HE: hepatic encephalopathy, SBP: spontaneous bacterial peritonitis.

Table 2: Laboratory investigations of liver cirrhotic patients at baseline in the study patients.

Variable	Oral group (N = 45)	IV group (N = 45)	P value
Direct bilirubin (mmol/l) Reference range (0-5)	25.40 (15.50)	30.67 (19.61)	0.16
Albumin (mg/dl) Reference range (30-50)	27.81 (6.27)	27.11 (6.50)	0.71
AST (U/L) Reference range <50	164.76 (77.96)	137.76 (62.51)	0.07
ALT (U/L) Reference range <50	181.96 (89.09)	134.04 (67.62)	0.11
ALP (U/L) Reference range (50-136)	180.28 (72.01)	152.91 (64.29)	0.06
Creatinine (mmol/l) Reference range (62-106)	101.84 (20.83)	109.44 (13.47)	0.43
Urea (mmol/l) Reference range (2.5-10.7)	9.30 (2.32)	12.05 (5.06)	0.23
Hemoglobin (g/dl) Reference range (11.5-17.5)	9.91 (0.89)	9.63 (0.76)	0.12
PT (sec) Reference range (10-12)	17.8 (1.4)	18.2 (1.1)	0.76
INR Reference range <1.2	1.58 (0.15)	1.59 (0.14)	0.87
Serum vitamin K level (ng/l) Reference range (392- 475)	318.5 (22.6)	305.42(27.9)	0.67

Median (IQR), P value (Mann Whitney U test).

Serum vitamin K level, PT and INR after 3 days of vitamin K administration.

There was a significant increase in vitamin K serum level after vitamin K administration either orally or intravenously. In the oral group, vitamin K serum was increased from 318.5 (22.6) ng/l to 413.06 (19.8) ng/l, (P= 0.01). Similarly, there was a significant increase from 305.42 (27.9) ng/l to 416 (29.94) ng/l, (P= 0.009) in the IV group. Prothrombin time was significantly decreased after vitamin K administration from 17.8 (1.4) sec to 14.5 (0.75) sec, (P= 0.02) and from 18.2 (1.1) sec to 14.8 (0.66) sec, (P= 0.023) in the oral and the IV group respectively. A significant decrease in INR in the oral group from 1.58 (0.15) to 1.41 (0.14), (P= 0.035) and from 1.59 (0.14) to 1.39 (0.15), (P= 0.031) in the IV group, Table 3.

Table 3: PT, INR and serum vitamin K at baseline and after vitamin K administration**.**

Variable	Oral group (N = 45)	IV group (N = 45)	P value
PT (sec)			
Baseline	17.8 (1.4)	18.2 (1.1)	0.76
After vitamin K administration	14.5 (075) (P*=0.02)	14.8 (0.66) (P*=0.023)	0.81
INR			
Baseline	1.58 (0.15)	1.59 (0.14)	0.87
After vitamin K administration	1.41 (0.14) (P*=0.035)	1.39 (0.15) (P*=0.031)	0.66
Serum vitamin K level (ng/l)			
Baseline	318.5 (22.6)	305.42 (27.9)	0.67
After vitamin K administration	413.06 (19.8) (P*=0.01)	416 (29.94) (P*=0.009)	0.73

Median (IQR), P value (Mann Whitney U test)

Serum vitamin K level, PT and INR according to Child-Pugh score.

Vitamin K serum level in Child B class patients was significantly increased from 323.43 (25.10) ng/l to 415.09 (18.31) ng/l, (P= 0.009) and from 317.78 (24.44) ng/l to 423.32 (22.94) ng/l, (P= 0.009) in the oral and IV group respectively. Child C class patients showed a significant increase in vitamin K serum level from 314.82 (25.26) ng/l to 410.18 (23.73) ng/l, (P= 0.01) and from 280.91 (50.01) ng/l to 405.73 (23.65) ng/l, (P= 0.01) in the oral and IV group, respectively. The prothrombin time in Child B class patients was significantly decreased from 16.56 (1.38) sec to 12.14 (0.14) sec, (P= 0.02) and from 17.12 (1.07) sec to 12.1 (0.13) sec, (P= 0.021) after the oral and the IV vitamin K administration, respectively. Child C class patients' PT was statistically insignificant after the oral and the IV vitamin K administration compared to baseline (P= 0.94) and (P= 0.21), respectively. There was a significant difference in PT after oral or IV vitamin K administration between Child B class, (P= 0.02) and Child C class (P= 0.01). INR was significantly decreased from 1.35 (011) to 1.28 (0.16), (P= 0.021) after oral administration of vitamin K and significantly decreased from 1.39 (0.12) decreased to 1.21 (0.13), (P= 0.03) after IV administration. Whilst, in Child C class patients; INR was insignificantly changed after oral and IV vitamin K administration, (P= 0.31) and (P= 0.045), respectively. There was a significant difference in INR after oral or IV vitamin K administration between Child B class, (P= 0.04) and Child C class, (P= 0.029), Table 4.

Table 4: PT, INR and vitamin K serum level at baseline and after vitamin K administration according to patients with Child-Pugh score.

Variable	Oral group (N=45)			IV group (N=45)		
	Child B (N=23)	Child C (N=22)	P value	Child B (N=22)	Child C (N=23)	P value
PT (second)						
Baseline	16.56 (1.38)	19.07 (1.60)	0.23	17.12 (1.07)	19.33 (1.02)	0.21
After vitamin K administration	12.14 (0.14) (P*=0.02)	16.99 (1.93) (P*=0.94)	0.02	12.1 (0.13) (P*=0.021)	17.58 (1.71) (P*=0.21)	0.01
INR						
Baseline	1.35 (0.11)	1.61 (0.19)	0.09	1.39 (0.12)	1.60 (0.21)	0.20
After vitamin K administration	1.28 (0.14) (P*=0.021)	1.54 (0.17) (P*=0.31)	0.04	1.21 (0.13) (P*=0.03)	1.58 (0.20) (P*=0.45)	0.029
Vitamin K (ng/l)						
Baseline	323.43 (25.10)	314.82 (25.26)	0.16	317.78	280.91	0.26
After vitamin K administration	415.09 (18.31) (P*=0.009)	410.18 (23.73) (P*=0.01)	0.28	(24.44) 423.32 (22.94) (P*=0.009)	(50.01) 405.73 (23.65) (P*=0.01)	0.24

Median (IQR), P value (Mann Whitney U test), P*value (Wilcoxon test).

Clinical signs of bleeding after 3 days of vitamin K administration.

Signs of hematemesis, melena, epistaxis, gingival bleeding and bleeding per rectum were observed in the study patients of both groups. There was insignificant difference between the oral and the IV group, Table 5.

Patients suffering from bleeding complications in the oral group were 23 patients compared to 25 patients in the IV group. Patients who clinically improved (no bleeding signs) after 3 days of vitamin k administered were 7 patients (7/23, 30%) in the oral group and 8 patients (8/25.33%) in the IV group. No thrombosis events had recorded among the study patients after vitamin K administration. Patients who required blood transfusion after 3 days of vitamin K administration were 30 in the oral group and 32 in the IV group, Table 6.

The number of patients who died was 4 patients in the oral group and 3 patients in the IV group. Three patients in the oral group and two patients in the IV group suffered from acute hemorrhage as the cause of death. The recorded cause of death for one patient in the oral group was cardiac arrest and for one patient in the IV group was respiratory failure and lactic acidosis. At discharge of patients, PT and INR in Child B class were insignificantly changed. Whilst, in Child C patients, PT was significantly decreased from 16.99 (1.93) sec to 13.9 (0.77), (p= 0.04) in the oral group and from 17.58 (1.71) sec to 12.5 (0.35) sec (p= 0.035) in the IV group. In Child C class patients INR was significantly decreased from 1.54 (0.17) to 1.22 (0.02), (P= 0.031) in the oral group and from 1.58 (0.20) to 1.3 (0.5), (P= 0.038), Table 7.

Table 5: Clinical signs of bleeding at baseline and after 3 days of vitamin K administration in the study patients.

Variable	Oral group (N=45)			IV group (N=45)		
	Child B (N=23)	Child C (N=22)	P value	Child B (N=22)	Child C (N=23)	P value
	No. (%)	No. (%)		No. (%)	No. (%)	
Hematemesis:						
Baseline	9 (39.1%)	13 (69.6%)	0.115	9 (40.9%)	16 (39.6%)	0.562
After vitamin K administration	6 (26.1%)	9 (40%)	0.235	5 (23%)	12 (52.2%)	0.041
	(P=0.523)	(P=0.91)		(P=0.421)	(P=0.890)	
Melena:						
Baseline	5 (21.7%)	2 (9.1%)	0.643	5 (22.7%)	1 (4.3%)	0.
After vitamin K administration	4 (17.4%)	1 (4.5%)	0.725	2 (9.1%)	1 (4.3%)	0.675
	(P=0.843)	(P*=0.675)		(P*=0.643)	(P*=1)	
Epistaxis:						
Baseline	4 (17.4%)	2 (9.1%)	0.824	0	0	0
After vitamin K administration	2 (8.7%)	1 (4.5%)	0.675	0	0	0
	(P*=0.824)	(P*=0.675)				
Bleeding per rectum:	3 (13.0%)	2 (9.1%)	0.586	0	0	0
Baseline	2 (8.7%)	1 (4.5%)	0.675	0	0	0
After vitamin K administration	(P*=0.324)	(P*=0.675)				
Gingival bleeding:						
Baseline	1 (4.3%)	2 (9.1%)	0.675	4 (18.2%)	2 (8.7%)	0.824
After vitamin K administration	0 (0%)	1 (4.5%)	0.921	2 (9.1%)	2 (8.7%)	1
	(P*=0.921)	(P*=0.675)		(P*=0.824)	(P*=1)	

P value (Chi-square test), P*value (Fisher exact test).

Table 6: Bleeding signs and blood transfusion of the study patients.

Variable	Oral group (N= 45)	IV group (N=45)	P value
	No. (%)	No. (%)	
Patients suffered from bleeding	23 (51%)	25 (55.5%)	0.678
Patients with improved bleeding after 3 days of vitamin K administration	7/23 (30%)	8/25 (33%)	0.672
Patients still bleeding after 3 days of vitamin K administration	16 (35.5%)	17 (37.7%)	0.581
Blood transfusion after 3 days of vitamin K administration	30 (66.7%)	32 (71.1%)	0.648
Hospital stays (days) Mean ± SD	**6.44 ± 1.80**	**7.91 ± 3.15**	**0.008**[#]

P value (Chi-square test). ([#]P value independent samples t-test).

Table 7: Assessment of PT and INR at the time of discharge.

Variable	Oral group (N=41)			IV group (N=42)		
	Child B (N=21)	Child C (N=20)	P value	Child B (N=20)	Child C (N=22)	P value
PT (second)						
After vitamin K administration	12.14 (0.14)	16.99 (1.93)	0.02	12.1 (0.13)	17.58 (1.71)	0.021
At discharge	12.5 (0.18) (P*=0.88)	13.9(0.77) (P*=0.04)	0.79	12 (0.27) (P*=0.89)	12.5(0.35) (P*=0.035)	0.81
INR						
After vitamin K administration	1.28 (0.14)	1.54 (0.17)	0.04	1.21 (0.13)	1.58 (0.20)	0.02
At discharge	1.26 (0.09) (P*=0.73)	1.22 (0.02) (P*=0.031)	0.81	1.29 (0.08) (P*=0.76)	1.3 (0.5) (P*=0.038)	0.79

Median (IQR), P value (Mann Whitney U test), P* value (Wilcoxon test).

Discussion

Liver cirrhosis is a health burden and was associated with coagulopathy disorders[23]. There are many risk factors affecting the causation and prognosis of liver cirrhosis such as viral hepatitis HCV, HBV, chronic alcoholism and autoimmune hepatitis[5&24]. Our findings showed that viral hepatitis HCV was the most common cause of liver cirrhosis. it has been previously demonstrated that HCV was the common factor in the causation of liver cirrhosis in Egypt[24&25]. In general, the Child-Pugh classification was used to detect the severity of liver damage in liver cirrhotic patients[26], and have shown that the majority of the patients were nearly equally distributed regarding Child-Pugh score in the oral and the IV groups. There was no significant difference regarding age and gender between the study patients in the oral and the IV groups.

It is known that patients with liver cirrhosis usually had vitamin K deficiency[27]. Our study has shown that all patients had decreased vitamin K levels. The deficiency in Vitamin K may be related to many reasons as poor oral intake, loss of vitamin K synthetizing intestinal flora after broad-spectrum antibiotic therapy and impaired absorption of fat-soluble vitamins K due to impaired bile synthesis in liver cirrhotic patients[8&15]. In a previous study, over a quarter of the study patients had subclinical vitamin K deficiency at admission, if untreated, may progress to overt vitamin K deficiency with a raised INR and bleeding tendency[20]. Clinically vitamin K deficiency was detected by prolonged PT and elevated INR value in a wide spectrum of liver diseases[16].

The present study showed that all patients had abnormal values of PT and INR at baseline. Generally, liver cirrhotic patients were associated with prolonged PT and elevated INR[9&28]. Patel et al. reported that prolonged PT and elevated INR indicate decreased synthesis, reduced in plasma level of vitamin K dependent coagulation factors and increased bleeding tendency in chronic liver disease[9&29].

The current study showed that vitamin K administration either oral or IV was associated with an increased vitamin K serum level. It has been demonstrated that 10 mg of vitamin K injection for 3 days was adequate to correct the vitamin K deficiency and should be given to patients with decompensated liver cirrhosis[8]. Shearer et al. reported that 40–70% of an oral dose of vitamin K was absorbed from the jejunum and ileum of the upper intestine[30]. Furthermore, it has been reported that oral or IV vitamin K therapy at a dose of 10 mg was sufficient to maintain supraphysiological vitamin K blood levels for at least a week[20].

Regarding the severity of liver cirrhosis, patients with Child B class have shown a significant improvement in PT and INR after 3 days of vitamin K administration either orally or intravenously than Child C class liver cirrhotic patients. Tsoris et al. have reported that Child B class hepatocytes still partially maintain their functions utilizing vitamin K and synthesis of vitamin K dependent coagulation factors, consequently, this was associated with a reduction in PT and INR compared with Child C class which did not respond to vitamin K administration[11&26].

Mehta et al. found that oral or parenteral vitamin K administration did not correct coagulopathy in advanced stage liver cirrhotic patients[15]. Another study included 96 liver cirrhotic patients, not on anticoagulation and a baseline INR > 1.5; demonstrated that IV administration of vitamin K resulted in a 30% reduction in INR in only 16.6% of patients, and recommend that the use of IV vitamin K to correct coagulopathy of cirrhosis may not be beneficial[20]. Meyer et al. found that vitamin K administration did not have a positive impact on INR changes or bleeding in patients with liver cirrhosis[31]. In a case report study for oral vitamin K administration to Child C class liver cirrhotic patient with INR of 2.1 on admission, who received three daily doses of oral vitamin K 10 mg INR was decreased to 1.7 at the last day of vitamin K administration[12]. A previous study assessing the pharmacokinetics of oral versus IV administration of mixed micellar vitamin K in severe acute liver disease found that patients had subclinical vitamin K deficiency at admission and corrected by IV vitamin K administration, but the intestinal absorption of oral vitamin K was unreliable[19].

Furthermore, there was insignificant difference in bleeding signs at baseline and 3 days of vitamin K administration. Tripodi et al. reported that PT and INR were not considered as a bleeding predictor, with significant reduction in PT and INR of administration of vitamin K in Child B liver cirrhosis[32&33].

After 3 vitamin K administration, the signs of bleeding were improved in 30% of patients in the oral and the IV group. About three-quarters of patients' required blood transfusion to correct bleeding complications. It has been suggested that a “watchful waiting” approach to the transfusion of PRBCs, platelets and fresh-frozen plasma with a bedside assessment of the patient’s actual hemorrhagic risk[23].

Child C class liver cirrhotic patients showed significant decrease in PT and INR to nearly normal values after blood transfusion; while PT and INR in Child B class patients have not been affected after blood transfusion. Meyer et al. reported that vitamin K administration to child C class liver cirrhotic patients did not affect INR; however, Child C patients during the first 7 days of admission who received fresh frozen plasma and initial INR greater than 1.6 was associated with a decrease in INR at 72 hrs[31].

Clearly, there has been a contradiction in the administration of vitamin K either oral or IV in the treatment of liver cirrhotic patients bleeding disorder; since no evidence was found to recommend or refute this practice[22]. The present study demonstrated a beneficial role for vitamin K therapy in liver cirrhotic patients. Both oral and IV vitamin K administration had similar efficacy in correcting PT, INR and bleeding complications in Child B class than Child C class liver cirrhotic patients. Further studies are warranted to assess the beneficial role of vitamin K in the treatment of liver cirrhotic patients.

REFERENCES

1. H. Yoshiji, S. Nagoshi, T. Akahane, Y. Asaoka, Y. Ueno, K. Ogawa, T.

Kawaguchi, M. Kurosaki, I. Sakaida, and M. Shimizu, "Evidence-based clinical practice guidelines for Liver Cirrhosis", ***J Gastroenterol,*** 56(7), 593-619 (2021).
2. S.K. Asrani, H. Devarbhavi, J. Eaton, and P.S. Kamath, "Burden of liver diseases in the world", ***J Hepatol,*** 70(1), 151-171 (2019).
3. WHO, Global hepatitis report 2017, ***World Health Organization,*** (2017).
4. E. Scarpellini, C. Luigiano, G. Svegliati-Baroni, D. Dumitrascu, T. Larussa, V. Santori, and L. Abenavoli, " Liver Cirrhosis Complications Management at the Emergency Department", ***Rev Recent Clin Trials***, 15(4), 331-338 (2020).
5. P. Ginès, A. Krag, G.J. Abraldes, E. Solà, N. Fabrellas, and S.P. Kamath, " Liver cirrhosis" **Lancet,** 398(10308), 1359-1376 (2021).
6. B, Long, and A. Koyfman, "The emergency medicine evaluation and management of the patient with cirrhosis", ***Am J Emerg Med,*** 36(4), 689-698 (2018).
7. P.R. Garg, A. Agrawal, S.A. Bhake, and S,Vagha, "Correlation Study of Coagulation Profile in Spectrum of Liver Diseases", ***J Evol Med Dent Sci,*** 9(8), 549-554 (2020).
8. P.D. Amarapurkar, and D.N. Amarapurkar," Management of coagulopathy in patients with decompensated liver cirrhosis", ***Int J Hepatol,*** 2011, 596792 (2011).
9. B. Erwin, "Gastrointestinal bleeding in cirrhotic patients with portal hypertension", ***Int Sch Res Notices,*** 2013, 1-20 (2013).
10. B. Kok, and J.G. Abraldes, "Child-Pugh Classification: Time to Abandon?", ***Semin Liver Dis,*** 39(1), 96-103 (2019).
11. A. Craxi, C. Camma, and M. Giunta, "Clinical aspects of bleeding complications in cirrhotic patients", ***Blood Coagul Fibrinolysis***, 11, S75-S79 (2000).
12. S.M. Aldrich, and R.E. Regal, "Routine use of vitamin K in the treatment of cirrhosis-related coagulopathy: is it A-O-K? Maybe not, we say", ***J Pharm &Ther***, 44(3), 131-136 (2019).
13. N. Zakeri, and E.A. Tsochatzis, "Bleeding risk with invasive procedures in patients with cirrhosis and coagulopathy",***Curr Gastroenterol Rep***, 19(9), 45 (2017).
14. S.P. Pereira, P.G. Langley, and R. Williams, "The management of abnormalities of hemostasis in acute liver failure", INC semin, ***Thieme Medical Publishers***, 16(4), 403-414 (1996).
15. M.F. Saja, A.A. Ayman, F.M. Sanai, S.A. Shaikh, and A.M. AbdelGader, "The coagulopathy of liver disease: does vitamin K help?", ***Blood Coagul Fibrinolysis***, 24(1), 10-17 (2013).
16. S. Caldwell, M. Hoffman, T. Lisman, B. Macik, P. Northup, K. Reddy, A. Tripodi, and A. Sanyal, " Coagulation disorders and hemostasis in liver disease: pathophysiology and critical assessment of current management", ***Hepatology***, 44(4), 1039-1046 (2006).
17. P. Verma, A.S. Thakur, K. Deshmukh, A.K. Jha, and S. Verma, "Routes of drug administration"***, Int J Pharm Sci Res,*** 1, 54-59 (2010).
18. S.M. Alqahtani, "Advances in oral drug delivery", ***Front Pharmacol***, 12, 618411, (2021).
19. P.P. Stephen, D. Rowbotham, S. Fitt, M.J. Shearer, J. Wendon, and R. Williams, "Pharmacokinetics and efficacy of oral versus intravenous mixed-micellar phylloquinone (vitamin K1) in severe acute liver disease", ***J Hepatol***, 42(3), 365-370 (2005).
20. R.M. Rivosecchi, S.L. Kane-Gill, J. Garavaglia, A.M. Lasco, and H. Johnson,"The effectiveness of intravenous vitamin K in correcting cirrhosis-associated coagulopathy", ***Int J Pharm Pract***, 25(6), 463-465 (2017).
21. Z. Xiong, Y. Liu, T. Chang, X. Xu, S. Huo, H. Deng, T. Liu, and Y. Leng, " Effect of vitamin K1 on survival of patients with chronic liver failure: A retrospective cohort study", ***Medicine (Baltimore)***, 99(13), e19619 (2020).
22. A.J. Martí-Carvajal, and I. Sola, "Vitamin K for upper gastrointestinal bleeding in people with acute or chronic liver diseases", ***Cochrane Database Syst Rev***, 2015(6), CD004792 (2015).

23. M.F. Harrison, "The misunderstood coagulopathy of liver disease: a review for the acute setting", ***West J Emerg Med***, 19(5), 863-871 (2018).
24. W. Zhou, Q. Zhang, and L. Qiao, " Pathogenesis of liver cirrhosis", ***World J Gastroenterol***, 20(23), 7312-7324 (2014).
25. G. Esmat, M.H El-Sayed, M. Hassany, W. Doss, and I. Waked, "One step closer to elimination of hepatitis C in Egypt", ***Lancet Gastroenterol Hepatol***, 3(10), 665(2018).
26. A. Tsoris, and C.A. Marlar. "Use of the Child-Pugh score in liver disease", ***StatPearls Publishing***, PMID: 31194448, (2019) p. 18.
27. E.T. Tsiaousi, A.I. Hatzitolios, S.K. Trygonis, and C.G. Savopoulos," Malnutrition in end stage liver disease: recommendations and nutritional support", ***J Gastroenterol Hepatol***, 23(4), 527-533 (2008).
28. A. Grant, and J. Neuberger, "Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology", ***Gut***, 43, 1–11 Suppl 4(Suppl 4), IV1-IV11(1999).
29. A. Tripodi, "Tests of coagulation in liver disease", ***Clin Liver Dis***, 13(1), 55-61 (2009).
30. M.J. Shearer, A. Mc. Burney, and P. Barkhan, "Studies on the absorption and metabolism of phylloquinone (vitamin K1) in man", ***Vitam Horm***, 32, 513-542(1975).
31. A.V. Meyer, M. Green, H.M. Pautler K. Korenblat, E.N. Deal, and M.S. Thoelke, "Impact of vitamin K administration on INR changes and bleeding events among patients with cirrhosis", ***Ann Pharmacother***, 50(2), 113-117, (2016).
32. A. Tripodi, and P.M. Mannucci, "The coagulopathy of chronic liver disease", ***N Engl J Med***, 365(2), 147-156, (2011).
33. A. Tripodi, S.H. Caldwell, M. Hoffman, J.F. Trotter, and A.J. Sanyal, "The prothrombin time test as a measure of bleeding risk and prognosis in liver disease", ***Aliment Pharmacol Ther***, 26(2), 141-148 (2007).
34. A. Kratz, M. Ferraro, M.P. Sluss, and B.K. Lewandrowski, "Normal reference laboratory values", ***N Engl J Med***, 351, 1548-1563, (2004).
35. A.J. Sadowski, S.J. Hood, E.G. Dallal, and J.P. Garry, "Phylloquinone in plasma from elderly and young adults: factors influencing its concentration", ***Am J Clin Nutr***, 50(1), 100-108, (1989).

Bull. Pharm. Sci., Assiut University, Vol. 45, Issue 2, 2022, pp.789-800.

نشرة العلوم الصيدلية
جامعة أسيوط

BULL. PHARM. SCI. Assiut Univ.

الدور العلاجي لفيتامين ك المعطي عن طريق الفم مقابل الوريد في مرضى تليف الكبد

طارق رفعت محمد[١] – هايدي كرم الله رمضان[٢] – محمد محمود عبداللطيف[٣] – سحر بدر حسن[٣]*

[١]وحدة الصيدلة الإكلينيكية ، مستشفى الراجحي للكبد ، جامعه أسيوط ، أسيوط ، مصر

[٢]قسم أمراض الجهاز الهضمي وطب المناطق الحارة ، كلية الطب ، جامعة أسيوط ، أسيوط ، مصر

[٣]قسم الصيدلة الإكلينيكية ،كلية الصيدلة ، جامعة أسيوط ، أسيوط ، مصر

تليف الكبد مشكلة صحية كبرى في جميع أنحاء العالم. يعاني مرضى تليف الكبد من مضاعفات مختلفة بما في ذلك إضطرابات النزيف ، بسبب نقص عوامل التخثر المعتمدة على فيتامين ك. يتم إعطاء فيتامين ك لتصحيح مضاعفات النزيف ، ولكن لا يوجد دليل على فعاليته سواء عن طريق الفم أو الوريد. كان الهدف من هذه الدراسة هو تقييم الدور العلاجي لإعطاء فيتامين ك عن طريق الفم مقابل الحقن في الوريد في مرضى تليف الكبد. أجريت الدراسة الحاليه على تسعين مريضاً من مرضى تليف الكبد بمستشفى الراجحي للكبد. مجموعه من المرضي تتلقى فيتامين ك عن طريق الفم (ن = ٤٥) ومجموعه أخري عن طريق الوريد (ن = ٤٥) بجرعات ١٠ ملغ / يوم لمدة ٣ أيام متتالية. تم تقييم زمن البروثرومبين ((INR ،PT))، ومستوى فيتامين ك في الدم ، ومستوى الهيموجلوبين ، وإختبارات وظائف الكبد والكلى قبل وبعد ٣ أيام من إعطاء فيتامين ك. تم الإبلاغ أيضًا عن تقييم درجة Child-Pugh وعلامات النزيف. وضحت النتائج أن متوسط عمر المرضى في المجموعة الفموية ٤٩.٩٨ ± ١١.٣٤عام و ٥٠.٩٣ ± ٩.٣٣ عام في المجموعة الوريديه. عند إختيار المرضي في بدايه الدراسه لم يكن هناك اختلافات بين مجموعتي الدراسة فيما يتعلق التركيبة السكانية للمرضى والخصائص السريرية والنتائج المختبرية. وأكدت النتائج ان بعد تناول فيتامين ك ، زاد مستوى فيتامين ك في الدم بشكل ملحوظ في المجموعة الفموية من ٣١٨ (٢٢.٦) نانوغرام / لتر إلى ٤١٣.٠٦ (١٩.٨) نانوغرام / لتر ؛ (P = 0.01) ، ومن ٣٠٥.٤٢ (٢٧.٩) نانوغرام / لتر إلى ٤١٦ (٢٩.٩٤) نانوغرام / لتر ، (P = 0.009) ، في المجموعة الوريديه. انخفض PT بشكل ملحوظ من ١٧.٨ (١.٤) ثانية إلى ١٤.٥ (٠.٧٥) ثانية ، (P = 0.02) ، ومن ١٨.٢ (١.١) ثانية إلى ١٤.٨ (٠.٦٦) ثانية ؛ (P = 0.023) في المجموعتين الفمويه والوريديه على التوالي. انخفض INR أيضًا بشكل كبير من ١.٥٨ (٠.١٥) إلى ١.٤١ (٠.١٤) ؛ (P = 0.035) ، في المجموعة الفمويه، ومن ١.٥٩ (٠.١٤) إلى ١.٣٩ (٠.١٥) في المجموعة الوريديه ؛ (P = 0.031). كان لمستوى فيتامين ك في الدم علاقة معنوية سالبة مع (PT (P = 0.033 ،r = -0.42) ومع (r INR (P = 0.038 ،= -0.40). أظهر تناول فيتامين ك عن طريق الفم والوريد تحسنًا مماثلاً في النزيف. (٧ / ٢٣،٣٠٪) مرضى في المجموعة الفموية و (٨ / ٢٥،٣٣٪) مرضى في المجموعة الوريديه. أظهر

مرضى تليف الكبد ذوي تقييم شيلد B انخفاضًا معنويًا في (PT (P = 0.02) ، و (INR (P = 0.029 مقارنة ذوي تقييم شيلدC .

الخلاصة: تناول فيتامين ك عن طريق الفم و الوريد فعالية مماثلة في تصحيح النزيف في مرضى تليف الكبد. استفاد مرضى تقييم شيلد B من إعطاء فيتامين ك أكثر من مرضى تقييم شيلد .C