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Clinical Usage of Vitamin K and FFP in Reduction of Hospitalization in Patients with Warfarin Overactivity

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ABSTRACT

In clinical practice, warfarin toxicity can cause recurrent patient hospitalization and even may lead to morbidity and mortality. The anticoagulant effect of warfarin could be reversed by a variety of methods such as simple dose administration of vitamin K and fresh frozen plasma. We designed a retrospective study to analyze of patients with upon admission diagnosis of warfarin overactivity. Sixty seven out patients admitted for overdose of warfarin from 2006 to 2010 in Alborz Hospital, Karaj, Iran: A significant decrease in mean length of hospitalization in patients received FFP and vitamin K (4.1±1.9 and 4.6±0.9 days, respectively) in comparison to patients who did not receive FFP and/or vitamin K (6.1±1.2 days) were observed. The presented study showed that usage of vitamin K and FFP can lead to reduction in hospitalization and reduce their economic burden in patients with warfarin toxicity.

Key words: Warfarin toxicity, adverse drug reactions, vitamin K, fresh frozen plasma, duration of hospitalization

INTRODUCTION

Adverse Drug Reactions (ADRs) are the most causes of hospital admission with 6.5% of all admissions in western countries (Davies *et al*., 2007, 2009). ADRs directly increased duration of hospitalization and a significant cause of morbidity therefore can be corresponding to a significant economic burden (Davies *et al*., 2009; Oshikoya and Njokanma, 2007). Warfarin is an oral anticoagulant most frequently used for patients with proximal Deep-Vein Thrombosis (DVT) of the lower limbs, prevention in atrial fibrillation, recurrent venous thrombosis, maintaining mechanical prosthetic heart valves, pulmonary embolism, anti-phospholipid syndrome, preventing acute myocardial infarction and stroke (Hirsh *et al*., 2003; Schulman *et al*., 2008; Tadros and Shakib, 2010). Due to narrow therapeutic index and long-term warfarin therapy, in patients annually receiving warfarin, risks of fatal bleeding, major and minor hemorrhage are 0.6, 3.0 and 9.6%, respectively (Landefeld and Beyth, 1993). In addition, major bleeding can ultimately lead to death or hospitalization in 1.2-8.1% of patients during each year (Wiedermann and

Stockner, 2008; Cruickshank *et al.*, 2001; Beyth *et al.*, 1998; Ouirke *et al.*, 2007). The risk of bleeding complication depends on two major factors; the intensity of anticoagulant therapy and the amount of time at a high International Normalized Ratio (INR) (Hanley, 2004).

Several approaches to achieve reversal warfarin-induced excessive anticoagulation have been employed. INR can be decreased slowly by administering of vitamin K in patients with prolonged INRs without active bleeding but with an estimated high risk for bleeding (Hanley, 2004; Ansell *et al.*, 2001). The patients with a high risk for bleeding, rapid replacement of vitamin K-dependent coagulation proteins requires to reversal of active bleeding. Conventionally, this replacement has been achieved by transfusion fresh-frozen plasma (FFP) or prothrombin complex concentrates (Hanley, 2004; Ansell *et al.*, 2001; Garcia, 2010).

Our goals, in this study, were to determine reason of admission, duration of hospitalization and usage of vitamin K and FFP in patients who had been admitted with diagnosis of warfarin toxicity.

MATERIALS AND METHODS

Study population: The study design was a retrospective survey using hospital records at Alborz hospital, Karaj, Iran between November 2006 and October 2010. We gauged patients who were admitted with diagnosis of warfarin toxicity. All patients were admitted through emergency department. Patients that INR elevation was not related to warfarin were excluded. A special protocol for retrospective evaluation was designed and information on the following was extracted from the patient recorder: ages, genders, time of hospitalizations, initial symptoms, appearance time of initial symptoms, clinical and laboratory findings, management dispositions (discharge or admission to the clinical decision unit or the hospital), hospitalization periods and outcomes. Two trained abstractors collected data using standardized abstract forms. All aspects of the study were approved by the research Committee of Social Security Organization Alborz Hospital, Karaj, Iran.

Statistical analysis: Data are presented here as Mean±SD or percentage. The differences between the two groups were calculated with student's paired t-test and $p<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS software version 15.

RESULTS

A total of sixty-seven out patients were identified for overdose of warfarin and 79% of them stay in hospital. The main clinical characteristics of patients admitted with diagnosis of warfarin toxicity are shown in Table 1. The two most common clinical reasons of warfarin therapy were Congestive Heart Failure (CHF) and deep venous thrombosis that accounted for 64 and 21% of the hospital admittance, respectively. Mean INR at the time of admission and discharge were 7.8±2.0 and 1.9±0.4, respectively. Mean weekly dose of warfarin was 30.9±2.2 mg. Results showed that 34% of patients did not receive vitamin K and/or FFP, 41% of patients received vitamin K (1-2.5 mg orally) and 25% of patients received FFP (15 mL kg^{-1}), each FFP unit was 150-300 mL. The majority of bleedings were due to hematuria with 40.5%. Rectal bleeding, epistaxis and Gastro Intestinal (GI) bleeding accounted for 27, 15 and 11%, respectively.

A patient's risk of bleeding is greatest in the first three months after starting therapy. The risk factors for bleeding complication were age, gastrointestinal, medications, renal and cardiac with 21, 17, 15, 11 and 11%, respectively (Table 2).

Table 1: The main characterizes of patients who admitted with diagnosis of warfarin toxicity

Patients status	Value
Age	58±8
Gender	
Female	62%
Male	38%
Clinical reasons of warfarin therapy	
Congestive heart failure (CHF)	64%
Deep venous thrombosis (DVT)	21%
Others	15%
Mean weekly dose of warfarin	30.9±2.2 mg
International normalized ratio (INR) at	
Admission	7.8±2.0
Discharge	1.9±0.4
Reasons of admission	
Hematuria	40.50%
Rectal bleeding	27%
Epistaxis	15%
GI bleeding	11%
Haemoptysis	2%
Others	4.50%Admissions for
Warfarin overdose	79% (53 of 67)

Table 2: Risk factors for bleeding complication in patients who admitted with diagnosis of warfarin toxicity

Patients status	No. of patient
Age	21% (21 of 53)
> 65 year	
Cardiac	
Uncontrolled hypertension	11% (6 of 53)
Gastrointestinal	
History of gastrointestinal hemorrhage	17% (9 of 53)
active peptic ulcer	
hepatic insufficiency	
Hematologic	2% (1 of 53)
Thrombocytopenia	
Neurologic	4% (2 of 53)
History of stroke	
Renal	11% (6 of 53)
Renal insufficiency	
Medications	15% (8 of 53)
Aspirin	
Non-steroidal anti-inflammatory drugs	
Unknown	19% (10 of 53)

A significant decrease in mean length of hospitalization in patients received both FFP and vitamin K (4.1±1.9 and 4.6±0.9 days, respectively) in comparison to mean length of hospitalization in patients who did not receive FFP and vitamin K (6.1±1.2 days) were conspicuous ($p<0.01$ and $p<0.001$, respectively) (Table 3).

Table 3: Percentage of patients admitted to hospital with diagnosis of warfarin toxicity and time of stay in hospital

Medical status	No. of patients (%)
Percentage of patients received vitamin K	41% (22 of 53)
Percentage of patients received FFP	25% (13 of 53)
Percentage of patients did not receive vitamin K and /or FFP	34% (18 of 53)
Mean length of hospitalization in patients who did not receive FFP and vitamin K	6.1±1.2 days
Mean length of hospitalization in patients who received vitamin K	4.6±0.9 days***
Mean length of hospitalization in patients who received FFP	4.1±1.9 days**

All data are presented as Mean±SD, A p value of 0.05 denotes the presence of a statistically significant difference, **Significant difference between mean length of hospitalization in patients who received FFP and patients who did not receive FFP and vitamin K, $p<0.01$. ***Significant difference between mean length of hospitalization in patients who received vitamin K and patients who did not receive FFP and vitamin K, $p<0.001$

DISCUSSION

Most common complication of warfarin usage is adverse bleeding (Hanley, 2004; Ansell *et al*., 2001; Garcia, 2010). Despite of this, warfarin and other coumarin anticoagulants is used in the worldwide (Sadrai *et al*., 2008; Makris and Watson, 2001). Warfarin effective dose is influenced by many factors including, age, hepatic impairment, concurrent medications, variability of vitamin K intake, diet and ethanol ingestion (Makris *et al*., 2010; Atreja *et al*., 2005; Baker *et al*., 2004). Based on our study, more than 50% of risk factors for bleeding were age, GI bleeding and renal failure and as well as medications (Table 2). In contrast, Ouirke *et al*. (2007) showed the most frequent reason for over anticoagulation was drug interaction. Age was the most important of risk factors and over 20% of the patients with bleeding complications were older than 65 years, which corroborates this postulation. Previous studies indicated that risk of bleeding increases especially in patients 50 years and older (Schulman *et al*., 2008; Beyth *et al*., 1998; Ansell *et al*., 2001; Levine *et al*., 2004). On the other hand, Fihn SD *et al*. have demonstrated that age did not appear to be a significant reason and patients with 80 years or older may be need to conscious (Fihn *et al*., 1996). These controversial finding may be related to functional variants of genes affecting warfarin metabolism and activity (Ghadam *et al*., 2009; Kianmehr *et al*., 2010). Consequently, due to elderly patients have increased sensitivity to warfarin and require a lower mean daily dose than younger patients these group should be made aware of this risk factor. In addition, significant risk factors for bleeding were found to be a clinical history of associated disease in 28% of cases. Schulman *et al*. (2008) have speculated that a history of concomitant disease states such as GI bleeding and renal failure can appear as an important determinant of bleeding risk in patients receiving warfarin. Furthermore, other risk factor is cross reactivity with medication such as aspirin and non-steroidal anti-inflammatory drugs in 15% of patients. This could be critical and even life threatening, therefore to minimize the bleeding risk, combination of warfarin and antiplatelet drugs should be avoided (Tadros and Shakib, 2010; Beyth *et al*., 1998).

The anticoagulant effect of warfarin may be reversed by a variety of methods. Options include simple dose omission or administration of vitamin K (Hanley, 2004). For serious bleeding, the replacement of coagulation factors is required. The administration of Fresh Frozen Plasma (FFP) has been the most widely used method for coagulation factor replacement (Wiedermann and Stockner, 2008; Hanley, 2004; Ansell *et al*., 2001; Baker *et al*., 2004). Present study showed that

in 34% of cases, medication has been reduced or utterly discontinued and 41 and 25% of patients have received vitamin K and FFP, respectively. Moreover, the mean length of hospitalization in patients received vitamin K and FFP in the present study were significantly lower than that for patients who did not receive vitamin K and FFP ($p<0.01$ and $p<0.001$, respectively). A recent comprehensive review by Makris and Watson (2001) demonstrates that warfarin and insulin products together can be accounted for 16% of all adverse drug events and in patients 50 years and older, they accounted for 69 percent of unintentional overdoses and 33% of all adverse drug event hospitalizations (Makris *et al*., 2010).

In spite of the disadvantages of using FFP and vitamin K (Lankiewicz *et al*., 2006), our results have shown that simultaneous use of vitamin K and FFP in case of patients admitted for warfarin overdose and increased INR levels could be beneficial to reduction or obviate the need for hospitalization and results in significant cost saving.

CONCLUSION

This study demonstrates that usage of vitamin K and FFP can lead to significant reduction in hospitalization and might reduce their economic burden in patients with warfarin toxicity. Consequently, these patients are more likely to visit lower levels of care such as stay at home or clinics.

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