Analysis of patients admitted to the emergency service for warfarin complication and determination of their levels of knowledge and requirements of knowledge about warfarin use

Ali Duman*, Ayhan Akoz, Bekir Dagli, Mucahit Kapci, Mucahit Avcil, Ferdi Ozdemir

Department of Emergency Medicine, Faculty of Medicine, Adnan Menderes University, Aydın, Turkey

ARTICLE INFO

* Correspondance to:

Ali Duman
Department of Emergency Medicine,
Faculty of Medicine,
Adnan Menderes University,
Aydın, Turkey
e-mail: aliduman3489@hotmail.com

ABSTRACT

Warfarin is a cumarol derivative anticoagulant. It shows its effect by antagonizing the effects of Vitamin K. Warfarin is metabolized in the liver. International normalized ratio has been developed in the monitorization of warfarin. It is a drug which has a limited therapeutic index. The difference in sensitivity for therapy dose among individuals depends on the genetic polymorphism of the two enzymes in the liver. The objective of our study was to assess the information about the demographic characteristics, complications, treatments and the related factors of the patients who were admitted to our emergency service for high INR in routine controls and of the cases who had bleeding due to warfarin overdose. Of the 18-year-old and older patients who were admitted to our emergency service with a complaint related to warfarin use and who had been using warfarin on admission and patients who had an INR value of over 3.0 although the patient had no complaints, those who accepted to participate in the study were included in the study. The results of the demographic characteristics, complications and treatments of the 59 patients included in the study were in parallel with the literature. The rate of patients' being informed was found as 61%. Although difference was found when the demographic data of the informed and non-informed groups and their answers to the questions asked for warfarin information level were compared, no statistically significant difference was found (p>0.005). This brings to mind that the information given to patients at the time of first prescription is not sufficient and it does not turn into a regular training.

1. Introduction

Warfarin is the most used oral anticoagulant. It blocks the Vitamin K dependent clotting factors and coagulation inhibitors. Warfarin is metabolized in the liver (Alay et al., 2011). Warfarin is a widely used coumarin anticoagulant prescribed for patients with venous thrombosis and pulmonary embolism, chronic atrial fibrillation and prosthetic heart valves (Guven et al., 2012).

Initially, prothrombin time (PT) was used in warfarin monitorization. In time, international normalized ratio (INR) was developed to eliminate the heterogeneity which occurred due to the use of different tissue thromplastins in this measurement. The difference in sensitivity for therapy dose among individuals depends on the genetic polymorphism of the two enzymes in the liver. These enzymes are hepatic cytochrome P-450 2Cp (CYP2C9) and Vitamin K

epoxide reductase complex 1 (VKORC1). In addition, warfarin is known to interact with a great number of drugs since its metabolism occurs through CYP2C9. At the same time, substances such as red pepper, fish oil and daisy can increase INR and cause bleeding. Warfarin's most important and most frequent side effect is bleeding. Recently, the increase in the number of patients who are admitted to the emergency service due to warfarin related complications is remarkable. One of the most important reasons of this is the prevention of stroke in atrial fibrillation patients and the increase in the frequency of use due to the increase in valve operations (Altuntas et al., 2013). Besides the absence of special anticoagulant clinics in our country, there are also no standard patient education approaches among clinics that prescribe and follow warfarin use and pharmacology polyclinics (Yaka et al., 2011). The objective of our study was to assess the information about the demographic characteristics, complications, treatments and the related factors of the patients who were admitted to our emergency service for high INR in routine controls and of the cases who had bleeding due to warfarin overdose.

2. Material and methods

Our study was conducted at Adnan Menderes University, Faculty of Medicine, Emergency Service between July-December 2015 after local ethical board approval (2015/614) was taken. Of the 18-year-old and older patients who were admitted to our emergency service with a complaint related to warfarin use and who had been using warfarin on admission and patients who had an INR value of over 3,0 although the patient had no complaints, those who accepted to participate in the study were included in the study (Dentali et al., 2006; Eroğlu et al., 2011). Demographic data of the patients included in the study such as age and gender and their PT/INR levels, treatments and results were recorded in the study form. Questions were asked to patients who agreed to participate in the study or to their relatives in order to assess their information about warfarin treatment and the answers were recorded in the study form.

Statistical evaluation

Statistical analysis of the data was performed by using Kruskal-Wallis and Chi-square tests. The level of significance was considered as $p < 0.05$. When significant differences were found among groups, pairwise comparisons were performed between groups in order to detect the groups from which the differences originated.

3. Results

The average age of the 59 patients included in the study was 68.1 ± 11.3 years. 27 (45.8%) of the patients were men, while 32 (54.2%) were women (Table 1). 26 (44%) of the patients used warfarin due to coronary artery diseases and arrthymia, 15 (25.4%) used warfarin due to valve replacement, 6 (10.2%) used warfarin due to cerebrovascular disease, 4 (6,8%) used warfarin due to deep vein thrombosis, 3 (5.1%) used warfarin due to pulmonary thromboembolism and 5 (8.5%) used warfarin due to other reasons.

Table 1. Demographic data and laboratory results of patients and groups.			
	Total Patients n=59 (%100)	**Group 1** n=36 (%61)	**Group 2** n=23 (%39)	**p**
Age (years)	68.1 ± 11.3	69.56 ± 10.25	65.83 ± 12.70	0.249
Female	32 (%54.2)	21 (%58.3)	11 (%47.8)	0.433
Male	27 (%45.8)	15 (%41.7)	12 (%52.2)	
INR	9.7 ± 1.8	4.7 ± 11.60	4.66 ± 2.08	0.860
Hemoglobin (gr/dl)	10.8 ± 2.5	10.91 ± 2.56	10.86 ± 2.47	0.901

Nineteen patients (32.2%) were admitted to the emergency service for high INR, 4 (6.8%) were admitted due to ecchymosses on the skin, 4 (6.8%) were admitted due to gingival bleeding, 3 (5.1%) were admitted due to intracerebral bleeding, 4 (6.8%) were admitted due to stomach ache, 3 (5.1%) were admitted due to hematuria and 3 (5.1%) were admitted due to internal joint bleeding.

While the average INR of the patients on admission to the emergency service was 9.7 ± 1.8, INR of 10 patients were too high to be measured and the average hemoglobin was $10,8 \pm 2,5$ gr/dl (range between 4.2-10.8 gr/dl) (Table 1). The average warfarin use time of the patients was 5.1 ± 5.5 months (range between 0.1-20 months). 32 patients (54.2%) were given fresh frozen plasma (FFP) treatment, 4 patients (6.8%) were given erythrocyte suspension (ES), 6 patients (10.2%) were given ES+FFP, 2 patients (3.2%) were given prothrombin complex, 1 patient (1.7%) was given Vitamin K, 1 patient (1.7%) was given total blood, while 13 patients (22%) were not given any treatment. 39 (66.1%) patients were hospitalized in the services while 4 (6.1%) were hospitalized in the intensive care and 16 (16.1%) were discharged from the emergency service. While 84.7% of the patients had a chronic comorbid disease, 93.2% used comorbid drugs regularly.

The patients were grouped in 2 in terms of being informed about warfarin. While Group 1 consisted of 36 (61%) patients who were informed about warfarin, Group 2 consisted of 23 (39%) patients who were not informed. When the groups were compared in terms of their demographic data, laboratory results, ways of using warfarin and their answers for questions of level of drug information, no significant difference was found (P>0.005) (Table 2).

Table 2. Answers of patients and groups to the questions about their ways of warfarin use and their drug information levels

	Total Patients n=59 (%100)	Group 1 n=36 (%61)	Group 2 n=23 (%39)	p
State of education (none)	24 (%40.7)	15 (%41.7)	9 (%9.1)	0.665
Does the patient take the drug himself/herself? (No)	22 (%46.3)	9 (%25)	12 (%52.2)	0.035
Does the patient know the reason for Warfarin use? (No)	15 (%25.4)	6 (%16.7)	9 (%39.1)	0.055
Does the patient know the Warfarin dose? (No)	17 (%28.8)	6 (%16.7)	11 (%47.8)	0.011
Does the patient know Warfarin complications? (No)	36 (%61)	17 (%47.2)	19 (%82.6)	0.007
Does the patient have regular INR follows? (No)	16 (%27.1)	6 (%16.7)	10 (%43.5)	0.0 25
Does the patient mention warfarin use on admission to hospital? (No)	7 (%11.9)	2 (%5.6)	5 (%21.7)	0.063
Has the patient been informed about Warfarin use? (No)	23 (%39)	0	23 (%39)	

4. Discussion

Warfarin is a cumarol derivative oral anticoagulant. At least 48-72 hours are needed for it to show its full effect. Its bioavailability is close to 100%. Bile juice is required for its absorption from the gastrointestinal system. Since it is dependent on albumin on the plasma with a rate of 99%, its renal elimination is slow. Plasma half-life time is 36 hours (Eroglu et al., 2012). The gene of the major protein component of VKOR is found in the complex subunit 1, known as VKORC1. Mutations in this gene have been associated with a deficiency in vitamin-K-dependent clotting factors, resulting in increased sensitivity to warfarin or warfarin resistance or insensitivity (Turkdogan et al., 2013).

In Acar et al.'s study (2012) study, 64% of the patients were women, while 36% were men and the average age was 67.5 years. In Yaka et al. (2011)'s study, 62.3% of the patients were women, while 37.7% were men and the average age was 64±14 years. Our results were in parallel with the literature.

In Eroğlu et al. (2011)'s study, warfarin therapy was started on 50% of the patients due to atrial fibrillation, on 10% due to deep vein thrombosis, on 10% due to pulmonary embolism and on 30% due to valvular heart disease. In Alay et al. (2011)'s study, warfarin was used due to cardiac valve replacement in 30 patients, vascular thrombosis in 13 patients, cardiac thrombosis in 3 patients, atrial fibrillation in 13 patients and pulmonary embolism in 1 patient.

The results of our study were similar to the results in literature. In Eroğlu et al. (2011)'s study, hematuria was found in 26% of the patients, rectal bleeding or darkening in stools color was found in 36%, brusing on the skin was found in 13%, nasal bleeding was found in

10% and high INR was found in the controls of 6.6% and hemarthrosis was found in 6.6%. In Alay et al.'s study (2011), the most frequent was gastrointestinal bleeding (33.3%), followed by mucosal bleeding (21.7%), urinary system bleeding (13.3%), intraabdominal bleeding (10%), vaginal bleeding (10%), intracranial bleeding (5%), lower gastrointestinal bleeding (3.3%), pericardial bleeding (1.7%) and intramuscular hematoma (1.7%). The results of our study were in line with the literature.

In three study the average INR level was measured as 9.46, 13.42 and 7.2 respectively (Alay et al., 2011; Eroğlu et al., 2011; Eroglu et al., 2012). In our study, the average INR level was measured as 9.7 ± 1.8, which was in line with the literature.

The current approach to warfarin-related bleeding is primarily warfarin discontinuation of use, risk status of the patient and K vitamins according to the presence of the bleeding, fresh frozen plasma transfusion and protombin complex concentrates should be given (Acar et al., 2011). In Eroğlu et al. (2011)'s study, intravenous Vitamin K treatment was given to 83% of the patients, FFP treatment was given to 76% and erythrocyte suspension treatment was given to 43%. In Acar et al. (2011)'s study, erythrocyte and fresh frozen plasma transfusion was given to 11 (30%) patients, only frozen plasma transfusion was given to 19 (53%) patients, while 6 (17%) patients did not need any kind of transfusion. The treatments given in our study were similar to those in literature.

In Mercan and Enç (2011)'s study, it was found that 51.8% of the patients had a comorbid disease that required regular drug use other than warfarin, while 73.7% were found to have a drug or drug group they used all the time. In our study, comorbid disease and additional drug use rates were high, which was in line with the literature.

In our study, 40.7% of the patients were illiterate. Similar to the results of our study, 33.3% and 33.6% of the patients were found to be illiterate in literature (Beyan et al., 2010; Yaka et al., 2011). In Yaka et al. (2011)'s study, 64.8% of the patients stated that they had been informed about warfarin. In our study, the ratio of being informed was 61%. Although difference was found when the demographic data of the informed and non-informed groups and their answers to the questions asked for warfarin information level were compared, no statistically significant difference was found (p>0.05). This brings to mind that the information given to patients at the time of first prescription is not sufficient and it does not turn into a regular training. Warfarin-induced complications may not be decreased with only through education or the factors that influence it since the warfarin metabolism has genetic, drug and different food interactions. As well as the information given to patients during prescription, complications

can be solved through a compact approach which includes regular monitorization, genetic predisposition and repetitive education. This compact approach can be built through pharmacology polyclinics formed by primary care physicians and hospitals.

REFERENCES

Acar, A., Hasbahçeci, M., Başak, F., Canbak, T., Çalışkan, M., Alimoğlu, O., 2012. Bleedings caused by warfarin overdose. Dicle Med. J. 39, 223-226.

Alay, M., Demir, C., Atmaca, M., Esen, R., Dilek, İ., 2011. Oral antikoagulan tedavi seyrinde kanama komplikasyonu ile gelen hastaların değerlendirilmesi. Van Tıp Derg. 18, 9-14.

Altunbaş, G., Ercan, S., Davutoğlu, V., Al, B., 2013. Overview of warfarin treatment and answers to questions. JAEM. 12, 38-42.

Beyan, E., Beyan, C., Vaizoğlu, S.A., 2010. Predisposing prevent-able factors in patients with bleeding due to warfarin us-age: Evaluation of 114 patients. Clin. Appl. Thromb. Hemost. 16, 684-687.

Dentali, F., Ageno, W., Crowther, M., 2006. Treatment of coumarinaqssociated coagulopathy: A systematic review and proposed treatment algorithms. J. Thromb. Haemost. 4, 1853-1863.

Eroğlu, M., Çınar, O., Çevik, E., Yamanel, L., Durusu, M., İnal, V., Cömer, B., 2011. The analysis of cases admitted to ıntensive care units from emergency department due to complications related to warfarin treatment. Turk. J. Emerg. Med. 11, 9-12.

Eroğlu, S.E., Denizbaşı, A.A., Özpolat, Ç., Akoğlu, H., Onur, Ö.E., Ünal, E.A., 2012. The ınvestigation of the relation between ınr levels and risk of complication in patients with a history of warfarin use. Marmara Med. J. 25, 138-142.

Güven, F.M.K., Yavuz, C., Turkdogan, K.A., Karahan, O., Demirtas, S., Caliskan, A., Celik, M., 2012. Investigation of VKORC1 gene polymorphism in patients with bleeding complaints due to warfarin. Int. J. Basic and Clin. Studies. 1, 27-40.

Mercan, S., Enç, N., 2011. Educational needs of patients with warfarin. Turk. J. Cardio. Nursing. 1, 12-17.

Turkdogan, K.A., Karabacak, M., Akpinar, O., Karahan, O., Güven, F.M.K., Engin, A., Turkdogan, F.T., 2013. The VKORC1 gene homozygous polymorphism is markedly higher in Crimean Congo Hemorrhagic Fever patients. Biomed. Res. 24, 415-420.

Yaka, E., Pekdemir, M., Yılmaz, S., Akalın, E., 2011. Acil servis hastalarında oral antikoagülan tedavi bilgi düzeylerinin araştırılması. Tr. J. Emerg. Med. 11,155-160.