

Original Research Article

In-hospital and post discharge mortality in patients hospitalized for warfarin overdose

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ABSTRACT

Background: This study aimed to examine the in-hospital and post-discharge mortality rates in patients followed up for warfarin overdose in the cardiology clinic and the factors affecting the mortality.

Methods: This study included patients receiving warfarin treatment for atrial fibrillation (AF) and prosthetic heart valve and those hospitalized when warfarin overdose. Furthermore, 48 patients with and without hemorrhagic complications were detected. The causes and rates of mortality of the patients during hospitalization and post discharge were monitored during a mean follow-up of three years.

Results: The mean age of 48 patients (32 [66.17%] women) hospitalized for warfarin overdose was 77 ± 10 years. The mean hospitalization period of the patients was 5 ± 4 days, 2 ± 1 day in 11 patients without hemorrhage (22.9%), and 6 ± 3 days in 37 patients with hemorrhage (77.1%). Moreover, 38 patients were receiving warfarin for AF (79.2%) and 10 patients for prosthetic heart valve (20.8%). The mean INR value before hospitalization in patients hospitalized for warfarin was 6.67 ± 2.4 , hemoglobin was 10.6 ± 2.3 , hematocrit was 33.1 ± 7.5 , platelet count was 225 ± 64 , and creatinine was 0.9 ± 0.3 . In the statistical analysis of 11 patients (22.9%) without hemorrhage and 37 patients (77.1%) hospitalized because of hemorrhage who were being followed up for warfarin overdose, hemoglobin, hematocrit, and platelet count and INR level were considerably low and high in patients with hemorrhage, respectively (Table 2). Figure 1 shows the causes of hemorrhage detected in the patients. On mortality examination, five patients (10.4%) were found to be dead.

Conclusions: Being unable to obtain the target INR level or warfarin overdose may lead to serious problem in patients using oral anticoagulants. Whether hemorrhage is observed in patients hospitalized because of warfarin overdose, close monitoring of the patient's clinical and laboratory parameters is absolutely necessary.

Keywords: Hospitalize patient, Mortality, Overdose, Warfarin

INTRODUCTION

Warfarin, an oral anticoagulant, is a vitamin K antagonist, which is a widely used treatment and prophylaxis of thromboembolic events. Due to the narrow

therapeutic index, it is a complex treatment and requires close monitoring because of thrombotic and hemorrhagic complications. International normalized ratio (INR) is used for the safe and effective use of warfarin.¹⁻³ Target INR value recommended is 2.5 to 3.5 in patients with

mechanical prosthetic mitral valve, 2.0 to 3.0 in patients with mechanical prosthetic aortic valve, and 2.0 to 3.0 in patients with atrial fibrillation (AF), pulmonary embolism, and deep vein thrombosis.¹

Earlier studies emphasize the importance of training for warfarin use. In a study evaluating the knowledge level of warfarin treatment, it was observed to be 4.7 ± 2.8 before training and 8.1 ± 1.2 after training. With this result, we emphasized that training the patients more would decrease warfarin-associated complications, thus reducing the costs.⁴

The incidence of bleeding complications associated with anticoagulation is reported to be between 15-20% and fatal bleeding between 1-3%.⁵ This study aimed to assess the demographic characteristics, hospitalization periods, hemorrhage sites, and morbidity and mortality rates during hospitalization and post discharge in patients who are being treated and followed up for warfarin overdose.⁵

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METHODS

Study was conducted during follow-up between January 1, 2015 and December 31, 2016. Warfarin overdose was defined as an INR of more than 3 for AF and prosthetic aortic valve and more than 3.5 for prosthetic mitral valve. Patients were grouped as those with and without hemorrhagic complications. Patients' demographic characteristics, hospitalization periods, hemorrhage sites, the amount of transfusion, comorbidities, and causes and rates of mortality during hospitalization and a mean follow-up of 3 years after discharge were assessed.

Inclusion criteria

Patients with complete data who were hospitalized for warfarin overdose were included in the study.

Exclusion criteria

Patients with incomplete data were excluded from the study. This study included 48 patients receiving warfarin treatment for AF and prosthetic heart valve and who were hospitalized because of detected warfarin overdose.

Statistical analysis

The statistical analysis of the patients' data was performed using SPSS 24.0 software. Categorical variables were expressed as numbers or percentage and continuous variables as mean \pm standard deviation. Chi-square test was used for comparing categorical variables. For comparing continuous variables, first the distribution normality of the parameters was tested using the Shapiro-Wilk test. Mann-Whitney U test was used for comparing non-normally distributed data. A p-value below 0.05 was considered statistically significant.

RESULTS

The mean age of 48 patients (32 women [66.7%] and 16 men [33.3%]) hospitalized for warfarin overdose was 77 ± 10 years. The mean hospitalization period of the patients was 5 ± 4 days, 2 ± 1 days in 11 patients without hemorrhage (22.9%) and 6 ± 3 days in 37 patients with hemorrhage (77.1%). Furthermore, 38 patients were receiving warfarin for AF (79.2%) and 10 for prosthetic heart valve (20.8%). In addition, 11 patients (22.9%) had diabetes mellitus, 40 (83.3%) had essential hypertension, 24 (50%) had hyperlipidemia, 25 (52.1%) had coronary arterial disease, and 23 (47.9%) had heart failure. No statistical difference was observed between sexes regarding laboratory parameters and chronic illnesses (Table 1).

Table 1: The assessment of the difference between sexes.

	Female (n=32)	Male (n=16)	p- value
Mean age (years)	78 ± 8	74 ± 13	$P > 0.05$
Hemoglobin (g/dL)	10.8 ± 2	10.2 ± 2.8	$P > 0.05$
Hematocrit (%)	33.1 ± 6.9	33.2 ± 8.8	$P > 0.05$
Platelet (counts/ μ L)	232 ± 70	218 ± 60	$P > 0.05$
Creatinine (mg/dL)	0.9 ± 0.2	1.0 ± 0.2	$P > 0.05$
INR Value	6.62 ± 2.4	6.70 ± 2.6	$P > 0.05$
Atrial fibrillation	27 (84.4%)	11 (68.8%)	$P > 0.05$
Prosthetic valve disease	8 (25%)	4 (25%)	$P > 0.05$
Diabetes mellitus	8 (25%)	3 (18.8%)	$P > 0.05$
Hypertension	29 (90.6%)	11 (68.8%)	$P = 0.55$
Coronary arterial disease	16 (50%)	9 (56.3%)	$P > 0.05$
Hyperlipidemia	18 (56.3%)	6 (37.3%)	$P > 0.05$
Heart failure	14 (43.8%)	9 (56.3%)	$P > 0.05$

The mean INR value before hospitalization in patients hospitalized for warfarin overdose was 6.67 ± 2.4 , hemoglobin was 10.6 ± 2.3 , hematocrit was 33.1 ± 7.5 , platelet count was 225 ± 64 , and creatinine was 0.9 ± 0.3 . In the statistical analysis of 11 patients (22.9%) without

hemorrhage and 37 patients (77.1%) hospitalized because of hemorrhage who were being followed up for warfarin overdose, hemoglobin, hematocrit, and platelet count and INR level were considerably low or high in patients with hemorrhage (Table 2).

Table 2: The assessment of the difference between the groups with and without hemorrhage.

	Non-hemorrhagic (n=32)	Hemorrhagic (n=16)	p- value
Mean age (years)	79 ± 8	76 ± 11	$p > 0.05$
Hemoglobin (g/dL)	12.3 ± 2	9 ± 2.8	$p < 0.01$
Hematocrit (%)	36.1 ± 7	30 ± 8.8	$p < 0.01$
Platelet (counts/ μ L)	242 ± 70	198 ± 80	$p < 0.01$
Creatinine (mg/dL)	1.0 ± 0.1	0.9 ± 0.2	$p > 0.05$
INR Value	6.1 ± 2.1	8.2 ± 2.8	$p < 0.01$
Atrial fibrillation	9 (81.8%)	29 (78.4%)	$p > 0.05$
Prosthetic valve disease	3 (27.3%)	9 (24.3%)	$p > 0.05$

Among patients with AF who were hospitalized for warfarin overdose, 33(68.7%) received vitamin K, 18(37.5%) received 16 units of erythrocyte suspension, and 19(18.8%) received 8 units of fresh frozen plasma. Figure 1 shows the causes of hemorrhage detected in the patients.

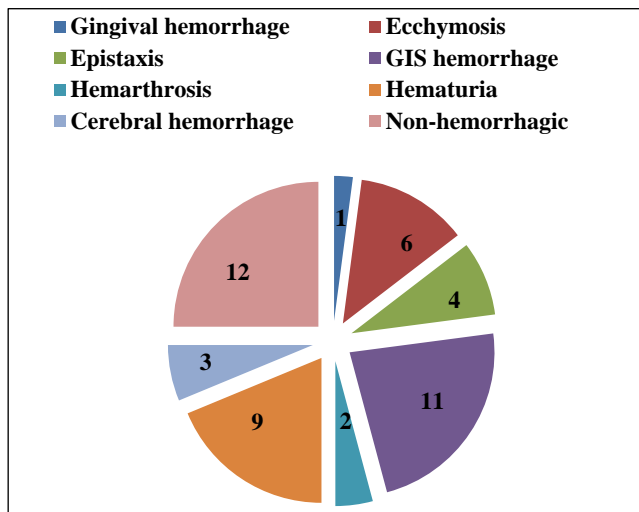


Figure 1: The number of hemorrhages seen in patients.

On mortality examination, five patients (10.4%) were found to be dead. One patient died because of massive pulmonary embolism on the 13th day of hospitalization due to hemarthrosis, one because of warfarin overdose-induced subdural hematoma eight months after their hospitalization for epistaxis, one because of pneumonia three months after discharge from hospitalization without hemorrhage, one because of cerebrovascular embolism six months after discharge from hospitalization for hematuria, and one because of ventricular fibrillation eight months after discharge from hospitalization for

gastrointestinal hemorrhage. None of the other patients died during the follow-up.

During the 3-year follow-up period of the patients, one patient hospitalized without hemorrhage (9.1%) and four for hemorrhage (10.8%) died without a statistically significant difference.

DISCUSSION

As AF is a frequently seen arrhythmia and valve operations became more frequent, the need for anticoagulant treatments increases day by day. Warfarin is the most widely used anticoagulant agent for the treatment and prevention of thromboembolic events.^{6,7} The dose should be adjusted carefully because of its narrow therapeutic index. Regular monitoring is necessary because of thromboembolic and hemorrhagic complications. A mortality rate of 6.6% in the study examining warfarin-associated complications and 5.5% in the study examining warfarin overdose-associated hemorrhages show its importance.^{8,9}

The rate of effective INR level was determined in 50% of the patients using warfarin in a Chinese study.¹⁰ Furthermore, it was determined in 47.6% of patients in a study in our country.¹¹ Although the lowest rate of effective INR level was found in patients who underwent mitral valve replacement, the highest rate of effective INR level was found in patients who underwent aortic valve replacement. At the end of the study, the determined rate of effective INR level was emphasized to be low.⁵ The rate of effective INR level was 52.6% similar to literature findings. The rate of effective INR level was 100% in pulmonary embolism, 54% in AF, 50% in operated valve disease, and 28.5% in deep vein thrombosis. The low number of patients suggests that these rates may not be reflective of the true values.

The most common reason for warfarin use in AF is the prevention of stroke in the overall and patient population. With the influence of the recent studies in the European and American Guidelines, novel oral anticoagulants that might be alternative to warfarin, particularly for the prevention of stroke in non-valvular AF, were approved by the US Food and Drug Administration (FDA). These include a direct thrombin inhibitor, dabigatran, and factor Xa inhibitors, rivaroxaban and apixaban. At first appearance, these treatments may be considered to be more favorable than warfarin, as they do not require INR monitoring; however, their biggest disadvantages include the lack of current FDA-approved antidote in case of possible hemorrhagic complications and the lack of indication, except for the prevention of stroke in non-valvular fibrillation. Studies sponsored by pharmaceutical companies evaluated the cost-effectivity of the novel oral anticoagulant treatment and found that they may reduce the total cost by reducing hospitalizations and major hemorrhagic complications. However, these medications are highly expensive, and the studies did not clearly emphasize the sustaining period and status of the target INR level.¹¹

Although the rate of obtaining effective INR level was found to be 52.6% in this study, which is comparable with the literature, these rates can be increased to much higher levels after adequate training and awareness. Currently, the more rational approach for our country seems to increase the rate of obtaining and sustaining effective INR level and reducing major hemorrhagic stroke complications by training our patients better about warfarin instead of using novel oral anticoagulants, particularly in non-valvular AF patients, which may greatly burden the national economy.¹²

Studies underline the importance of training for warfarin use. In a study in our country, the knowledge level on warfarin was found to be 4.7 ± 2.8 before training and 8.1 ± 1.2 after training. With this result, we emphasized that training the patients more would decrease warfarin-associated complications, thereby reducing the costs.⁴ The importance of training in patients using warfarin can be seen from the facts that in this study, 45.7% of the patients did not know the target INR level, 38.6% were illiterate, 28.1% did not know complications, 17.6% do not return for regular INR test, 17.5% had minor hemorrhage, 8.8% stated that they were not informed about the medication, 8.7% had major hemorrhage, 7.1% did not use their medication regularly, and 1.7% did not know for what the medication was used for. The low effective INR level in this study may be associated with these factors. We did not find a statistically significant difference between the patient group obtaining effective INR level and the group that did not obtain effective INR level for the assessed parameters. Authors think that this may be because of the low number of patients.

The limitations of this study include the following: a small number of patients, an observational study, and

lack of evaluation of concurrent therapies and dietary habits.

CONCLUSION

Warfarin should be used with caution as it is widely used and has a narrow therapeutic index. Necessary information about the medication must be given when the medication is initiated, and the training should be provided again in follow-up examinations. The low rate of obtaining effective INR level in patients using warfarin also draws attention to this study. Therefore, we believe that the knowledge level of the patients who started using warfarin should be increased. In addition, novel anticoagulant medications can be used instead of warfarin as anticoagulant therapy in patients who did not obtain their target INR level and could not reach it despite adequate training.

Being unable to obtain the target INR level or warfarin overdose may lead to serious problem in patients using oral anticoagulants. Whether hemorrhage is observed during hospitalizations because of warfarin overdose, close monitoring of the patient's clinical and laboratory parameters is absolutely necessary.

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REFERENCES

1. <https://reference.medscape.com/drug/coumadin-jantoven-warfarin-342182>. Accessed 24 January 2019.
2. Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C, et al. British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin - fourth edition. *Br J Haematol.* 2011 Aug;154(3):311-24.
3. Altunbaş G, Ercan S, Davutoğlu V, Al B. Warfarin Tedavisine Genel Bakış ve Sorulara Cevaplar. *JAEM* 2013 Mar 1;12(1):38.
4. Özcan T, Altiok M, Babalikli F. Warfarin kullanan hastalara ilaca ilişkin verilen grup eğitiminin bilgi düzeylerine etkisi/The effect of group education about drug usage in the patient's on warfarin therapy. *Anadolu Kardiyoloji Dergisi: AKD.* 2013 May 1;13(3):292.
5. Zareh M, Davis A, Henderson S. Reversal of warfarin-induced hemorrhage in the emergency department. *Western Journal of Emergency Medicine.* 2011 Nov;12(4):386-92.
6. Alisir MF, Kecebas M, Fesli F, Caliskan S, Gungoren F, Yildirim A, et al. Effective INR levels and its relationship with etiology in warfarin patients. *Clin J Med Scie Turk.* 2013;33(3):868-73.
7. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the

- vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(3):204-33.
8. Eroglu M, Cinar O, Cevik E, Yamanel L, Durusu M, Inal V, et al. Analysis of the cases admitted to the intensive care unit from the emergency department due to the complications related to warfarin treatment. *Turk J Emerg Med*. 2011; 11: 9-12.
 9. Acar A, Hasbahçeci M, Başak F, ve ark, Canbak T, Çalışkan M, Alimoğlu O. Warfarin doz aşımına bağlı oluşan kanamalar. *Dicle Tıp Dergisi* 2012;39(2):223-6.
 10. You JH, Chan FW, Wong RS, Cheng G. Is INR between 2.0 and 3.0 the optimal level for Chinese patients on warfarin therapy for moderate-intensity anticoagulation? *Br J Clin Pharmacol* 2005;59(5):582-7.
 11. Yaylacı S, Ösken A, Aydın E, Genç AB, Şahinkuş S, Can Y, et al. İç hastalıkları polikliniğine başvuran varfarin kullanan hastalar ve etkin INR'ye ulaşma oranları. *Kocaeli Med J*. 2014;3(3):18-21.
 12. Amin A, Stokes M, Makenbaeva D, Wiederkehr D, Wu N, Lawrence JH. Estimated medical cost reductions associated with use of novel oral anticoagulants vs warfarin in a real-world on-valvular atrial fibrillation patient population. *J Med Econ*. 2014 Nov 1;17(11):771-81.

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