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Original Article

Comparison of seasonal pattern in patients with warfarin overdose

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Abstract

Objectives: The most common anticoagulant drug in the world is warfarin. Overdoses of warfarin may follow seasonal patterns, but the information is scarce. This study investigated possible seasonal variations in warfarin overdose among various age groups living in cold climates.

Methods: This retrospective study was carried out on 235 patients between 2014 and 2019 at Shahid Madani Hospital, Tabriz, Iran. The analysis was performed on the patients who had overdosed on warfarin and had INR (International Normalized Ratio) levels higher than four. After reviewing our database, we found seasonal patterns in admissions for overdoses caused by warfarin. The seasonality of access of patients older and younger than 65 years of age was compared between the two groups. The independent t-test was used to compare the quantitative data, and the Chi-square test was used to compare categorical variables using SPSS V. 20.0 software.

Results: Seasonal patterns were observed in warfarin overdoses. Warfarin overdoses were more common among the patients under 65 years old during winter (P-value = 0.03), whereas almost identical findings were found among the patients 65 and older, although numerically more cases were seen during the summer season (P-value = 0.8).

Conclusions: The results of the current study showed that warfarin overdoses in the patients younger than 65 years showed a seasonal pattern peaking in the winter months. However, these findings did not have any relation with older patients. To confirm the results of the present study, larger prospective multicenter studies in a variety of climate settings are needed.

Keywords: Comparison; Warfarin; Drug overdose; Season Age

Introduction

The most common anticoagulant medication worldwide is warfarin. The drug is used in the treatment of venous thromboembolism and to prevent thrombosis in atrial fibrillation and valvular heart disease. In addition to inhibiting the intrinsic pathway, warfarin also lowers vitamin K levels, which are necessary for gamma-carboxylation of coagulation factors such as factors 2, 7, 9, 12, and 33 (1). Due to its high value as a preventative for thromboembolic diseases and its low cost, warfarin is very popular

with doctors. The risks associated with warfarin bleeding have led many physicians to prescribe newer medications with fewer bleeding side effects, such as direct oral anticoagulants (DOACs) (2). The International Normalized Ratio (INR) values are monitored regularly in patients taking warfarin to ensure therapeutic levels are met and toxic levels are avoided. In most cases, INR levels of 2-3 are optimal. A high INR level may also result in bleeding in addition to supratherapeutic measures (1). Warfarin is metabolized in the liver by cytochrome P 450. Besides drugs and foods, these enzymes also metabolize other substances. The metabolic process of warfarin and the blood level is affected by many factors, including liver disease and alcohol usage (3). Furthermore, seasonal variations in the incidence and consequences of various cardiovascular diseases (CVD) such as myocardial infarction have long been recognized (3). This phenomenon, also called the "winter cardiovascular phenomenon," develops in cold seasons. Incidence and mortality of different CVD like myocardial infarction, pulmonary edema, and atrial fibrillation increase significantly in winter compared to warmer seasons (4-6).

There is a paucity of information regarding the seasonality of warfarin overdose and the resulting mortality among different age groups. In this study, we aimed to shed light on the seasonal pattern of warfarin overdose.

Materials and Methods

All the 325 patients diagnosed with warfarin overdose in Madani Heart Center-Tabriz- Iran were enrolled between April 2014 and February 2019 (as a referral, research and training center in northwestern Iran). The inclusion criteria were higher INRs when taking warfarin. Patients with incomplete data as well as elevated INR levels without warfarin use were excluded. The databases compiled demographic and clinical details such as the INR level during hospitalization, warfarin directions, the season of the hospitalization, and mortality from medical records.

The patients were divided into two groups, older and younger than 65, the mean age of the patients was 65.9 year (7), and their seasonal patterns and prognoses in the hospital were compared. This study was conducted in Tabriz, a semi humid and four-season city in northwest of Iran. The seasons are defined as follows: summer from June 22 to September 22, autumn from September 23 to December 21, winter from December 22 to March 19, and finally spring from March 20 to June 21.

Qualitative variables were expressed as percentages and continuous variables as mean±standard deviation. A one-way ANOVA test was used to compare INR levels in four seasons using independent t-test and Chi-square test. We conducted chi-square test (a linear by linear association) to assess the relationship between seasons and warfarin overdose. SPSS 20 software was used for the statistical analysis. Statistically significant P-values were considered less than 0.05.

The ethics approval and written consent from patients were obtained. According to the Ethical Committee of Tabriz University, this study was approved under the code of 63071. We received consent from the Deputy of Research at Tabriz University of Medical Sciences and from the Director of Madani Heart Hospital - Tabriz- Iran to collect patient data in context.

Results

A total of 235 patients have died of warfarin overdose in the past five years, and 54.9 % of them were female. In the group younger than 65 years and those older than 65 years, the mean age was 51.26±11.93 and 76.9±7.0 years, respectively. Table 1 presents demographic and presentation information at a baseline.

The most common presenting signs were ecchymosis (18.51%) and hematuria (14.93%). Overall, warfarin was most commonly prescribed for atrial fibrillation and mechanical valve replacement in patients over 65. There were 14 deaths during hospitalization, primarily in patients over 65 years of age (p=0.2). On average, the prevalence of warfarin toxicity differed significantly over the year (p-value=0.3). Winter was the most common time for poisoning.

The overdose rate of warfarin was higher in people over 65 than in younger people (p-value 0.006).

Warfarin overdose patients' demographics, clinical status, and preclinical condition are affected by several factors (Table 1). In addition, the table shows the seasonality of INR levels.In comparison with two groups of patients with overdoses (under 65 and over 65 years old), we analyzed the INR values of these patients across different seasons (Table 2). Warfarin toxicity in different seasons of the year can be found in Table 3. Winter is the season when poisoning is most common.

Table 1. Baseline characteristics of the study participants

	Variables	<65 years N=100 (42.5)	>65 years N=135 (57.5	Total N=235	*P-value*
Demographics	Age (Mean±SD, years)	51.26 ± 11.93	76.9 ± 7.01	65.9	
	Gender (Female), F (%)	53 (53%)	76 (56.3%)	129(54.9%)	0.06
	Warfarin (Mean±SD, mg)	4.62 ± 1.72	4.32 ± 1.83	4.45 ± 1.79	0.2
	Digoxin use F (%)	40 (40%)	67 (51.1%)	109 (46.4 %)	0.06
	INR (Mean±SD)	9.82 ± 12.99	8.23 ± 7.48	7.31 ± 2.70	0.2
	Death, F (%)	3(3%)	11(8.1%)	14(6%)	0.2
	CHF, F (%)	8(8%)	19(14.07%)	27(11.79%)	0.5
	HLP,F(%)	19(1%)	1(0.74%)	2(0.85%)	0.5
	IHD, F (%)	6(6%)	15(11.11%)	21(8.94%)	0.5
	COPD, F (%)	1(1%)	9(6.67%)	10(4.26%)	0.5
	HTN, F (%)	27(27%)	51(37.78%)	78(33.19%)	0.5
	DM, F (%)	7(7%)	24(17.77%)	31(13.19%)	0.5
Clinical presentations	Asymptomatic	15(15%)	31 (22.96%)	46 (19.57%)	NS
	Ecchymosis	24 (24%)	23 (17.04%)	47 (20%)	NS
	Cardiac tamponade	1(1%)	0(0%)	1 (0.43%)	NS
	Palpitation	2(2%)	11 (8.15%)	13 (5.53%)	NS
	Dyspnea	5(5%)	16 (11.85%)	21 (8.94%)	NS
	Epistaxis	5(15%)	10 (7.41%)	25 (10.64%)	NS
	Gastrointestinal bleeding	6(6%)	3 (2.22%)	9 (3.83%)	NS
	Otorrhea	2(2%)	2 (1.48)	4 (1.70%)	NS
	Cerebellar bleeding	1(1%)	1 (.74%)	2 (.85%)	NS
	Conjuctival bleeding	1 (1%)	1 (.74%)	2 (.85%)	NS
	General weakness	2 (2%)	8 (5.93%)	10 (4.26%)	NS
	Altered mental state	1 (1%)	5 (3.7%)	6 (2.55%)	NS
	Hematuria	23 (23%)	15 (11.11%)	38 (16.17%)	NS
	Hemoptysis	2 (2%)	9 (6.67%)	11 (4.68%)	NS
	Atrial fibrillation	33 (33%)	88 (65.19%)	120((51.06%)	NS
Treatment indications	Valve replacement	44 (44%)	15 (11.11%)	59 (25.11%)	NS
	Not mentioned	3 (3%)	9 (6.67%)	12 (5.11%)	NS
	Cerebrovascular accident	4 (4%)	5 (3.70%)	9 (3.83%)	NS
	Venous thromboembolism	16 (16%)	18 (13.33%)	34 (14.47%)	NS

F(%): Frequency (Percentage); SD: Standard Deviation; NS: Not significant; INR: International normalized ratio; CVD: Cardiovascular diseases; TTR: Time in therapeutic range; DOAC: Direct oral anti-coagulants; CAD: Coronary artery disease; CHF: Cardiac heart failure; HLP: Heper lipedmia; IHD: Ischemic heart disease; COPD: Chronic obstructive pulmonary disease; HTN: Hypertension

Table 2. INR levels comparison among different seasons in two groups of patients with warfarin overdose (<65 and >65)

	INR (Mean±SD)			
Seasons	<65 years	>65 years	Total	*P-value*
Spring	6.62 ± 1.65	7.88 ± 2.73	7.37±2.41	0.07
Summer	6.95 ± 1.96	8.38 ± 3.34	7. 0±3.01	0.1
Autumn	6.71 ± 2.12	6.93 ± 2.70	6.83±2.43	0.7
Winter	7.30 ± 2.84	7.30 ± 2.84	7.26±2.87	
	0.4	0.2	0.2	0.8

Table 3. Warfarin toxicity in seasons of the year

Season	< 65 years	>65 years	Total	*P-value*
Spring	20(20%)	57(24.26%)	77(22.99%)	.230
Summer	17(17%)	64(27.23%)	81(24.18%)	.006
Autumn	27(27%)	59(25.11%)	86(25.67%)	.439
Winter	36(36%)	55(23.40%)	91(27.16%)	.460

Discussion

Overdoses of warfarin are relatively rare, but they can be deadly. It is difficult to find information on how warfarin overdoses and their associated mortality occur according to the season by focusing on various age groups.

The result of a study showed that heart disease prevalence increases in cold seasons, such as coronary heart disease and heart failure (8).

This study suggests that the causal factors of these diseases are: (I) environmental factors including temperature and ultraviolet radiation (UV) and (ii) lifestyle factors including diet and physical activity (iii) other factors including blood pressure, cholesterol levels, coagulation factors and blood glucose levels; and (iv) acute and chronic infections, which can cause acute-phase reactions and thus increase fibrinogen levels during the winter (2, 3).

The findings of the present study showed that the fluctuations in the prevalence of warfarin overdose over the course of the year was statistically significant. According to this study, warfarin overdose rates were significantly higher during cold seasons. In our study, warfarin overdose occurred more frequently in summer in the older adults compared to younger adults (p=0.06), and we analyzed the prevalence of disease [b1] and seasonality rather than INR level variations (explained at the end of the paper).

Some herbal teas have been linked to warfarin overdoses in China, and the reason is that some tea compounds have inhibitory properties against CYP2C9, which is the enzyme responsible for warfarin metabolism. In Iran, and particularly Tabriz, being a relatively traditional society, we would conclude that the study's results are similar to those of China. Herbal tea is widely used drinking during the cold seasons of the year because it prevents colds and treats many other ailments. During winter, consumers may consume excessive amounts of warfarin due to these herbal teas that contain unknown substances with unknown effects (9, 10). In older patients, warnings are shared about possible liver and kidney damage. Still, the message is not as strong for younger patients, who are more likely to consume these herbal products and possibly overdose on warfarin.

In some studies, elevated temperatures are associated with increased admissions for cardiovascular diseases such as heart disease and arrhythmias, and these hospitalizations are usually related to aging. To be more effective, these patients require anticoagulant therapy, and warfarin is the first common choice. As a result of concomitantly, using warfarin and heparin and possibly using a loading dose, these treatments suppress Factor VIII more severely. Those older than 65 may be more prone to warfarin overdose due to this factor (11, 12). The main reason may be related to ethnicity, dietary habits, and weather conditions. There are a few possible explanations for the difference in seasonal patterns between older and younger patients. First, previous studies have shown the increased levels of fibrinogen in older patients (13). In the cold season, older adults produce more of this hormone than younger adults do. Therefore, this enhanced fibrinogen production may result in hypercoagulable states in the elderly in the winter, which may decrease INR levels and reduce warfarin overdose in cold seasons compared to summer.

1) During the cold season, older adults produce more of this hormone than young adults. Due to this enhanced fibrinogen production, the elderly may be hypercoagulable in the winter, which leads to a lower INR and a reduced warfarin overdose in the cold seasons compared to the summer (3-5, 14, 15). Winter may also be when young patients experience increased warfarin overdose due to reduced intake of foods containing vitamin K, including green leafy vegetables (6, 16-19). A study by Fares showed that plasma fibrinogen levels are associated with the season in the elderly: plasma fibrinogen was 21% higher in cold months than in warmer months. According to the authors, these fluctuations may be contributing to the increased frequency of cardiovascular disease in winter (19, 20). Our study lacks a detailed history of diet and antibiotic use as confounding factors - factors are largely hypothesis-generating. They need further evaluations of fibrinogen levels in the patients and dietary habits. It is well known that anticoagulant

effect of warfarin can be affected by several confounding factors, such as allergies, concomitant diseases, drug interactions, and dietary habits. (4, 21). There are some limitations in this study: 1) This was a retrospective study performed in a small hospital and has no long-term follow-up; 2) No serum levels of various coagulation factors were measured, such as fibrinogen and factor VII; 3) Dietary habits were not recorded; 4) TTR (time in the treatment range) was not analyzed because recent studies indicate that it is predictive of warfarin toxicity. 5) This study was conducted in semi-cold climates, so the generalizability of the results does not make sense, 6) A prospective multicenter study in different climatic environments should be conducted to confirm the present study's results considering the limitations of this study. Therefore, this study should be closely monitored and redesigned with dose adjustments made.

Generally, the cause of warfarin poisoning is not currently known, since the medication is over-prescribed because of a potential risk of heart disease because of diet changes and infection risk.

Conclusion

In conclusion, the findings of this study show that the prevalence of warfarin overdose differs during the year and that this difference is statistically significant. As a whole, warfarin overdose prevalence was higher during cold seasons—the older group presented with warfarin overdose more often than the younger group in summer.

Conflicts of Interest

It is not necessary to declare anything.

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