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The Frequency of Use of Warfarin-Interfering Drugs in Patients Suffering from Warfarin Toxicity Referred to the Emergency Department of Imam Reza Hospital, Mashhad

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: With the progress made in the treatment of cardiovascular patients, the use of anticoagulants such as warfarin, aspirin, ticlopidine ,etc. have increased. This study aimed to investigate the frequency of use of warfarin-interfering drugs in warfarin toxicity patients admitted to the emergency ward of Imam Reza Hospital, Mashhad, Iran, from March to August 2016.
Materials and Methods: In this original cross-sectional study after obtaining the approval of the university's ethics committee, 133 patients with warfarin toxicity admitted from March to August 2016 were included in the study. The hospital records of the patients were reviewed, and based on the detailed history taken from the patients the information related to the simultaneous use of different drugs, the duration of warfarin use, the reasons for warfarin use, and the symptoms of warfarin toxicity were extracted. SPSS version 24 software was used for data analysis ($p<0.05$).
Results: Artificial heart valve was the most common indication for warfarin use (48%). Potentially fatal bleeding occurred in 85% of patients, and gastrointestinal bleeding was the most common symptom of warfarin toxicity (37.6%). The most common drugs used were aspirin (62.4%), metoprolol (33.1%), and statins (28.8%).
Conclusion: In this study, a high frequency of drug interactions with warfarin was observed, which seems to play a significant role in the occurrence of warfarin toxicity. The most common drug interactions were observed in the simultaneous use of aspirin, metoprolol, and statins. Careful monitoring of the type of drugs used by patients is extremely important in providing safe and effective treatment and reducing side effects.

Keywords: Warfarin toxicity; drug interaction; aspirin; cardiovascular disease.

1. INTRODUCTION

Nowadays, with the advances made in the treatment of cardiovascular patients, such as the use of intravascular stents, heart valves and intracavitary patches, and heart transplantation, many cardiovascular patients have to use anticoagulants and antiplatelet drugs, Such as Warfarin, Aspirin, Ticlopidine, and other drugs [1,2]. Warfarin is one of the most important oral anticoagulant drugs prescribed for cardiovascular disorders. It was first used as a rodenticide in 1948 and as a human anticoagulant in the early 1950s [3,4]. It was one of the most effective oral coumarin anticoagulants for more than 50 years. Unfortunately, warfarin has a narrow therapeutic window, and the clinical response to this drug is not very predictable, and it is difficult to reach a safe dose to achieve clinical goals and prevent complications related to it. Sensitivity to warfarin is a multifactorial and multigenetic phenomenon, age, weight, gender, and ethnicity. use of other drugs and oral supplements, and individual clinical conditions such as various liver diseases also affect sensitivity to warfarin [5-9]. In addition, it interferes with many drugs and food, this interference occurs through various mechanisms such as reduction of metabolism, increasing the effect of anticoagulants, reduction of vitamin K production, etc. resulting in irreversible complications [10,11]. Warfarin toxicity can range from an elevated INR (international normalized ratio) without clinical symptoms to life-threatening bleeding [12,13]. The primary side effect of warfarin toxicity is bleeding, which depends on the dosage, treatment length, the patient's basic clinical condition, and the simultaneous use of other warfarin-interfering drugs [13,14]. Studying the causes of this disease, according to the genetic, individual, environmental, food characteristics, and co-morbidities drugs that can be used in any region [15-17]. Due to the severe and irreparable complications observed following warfarin toxicity, several studies have been conducted in the field of warfarin toxicity management in different countries [18-24].

However, to the best of the author's knowledge, no study has been conducted to investigate the causes of warfarin toxicity and frequency of drug interaction in Iran. For this purpose, the frequency of use of warfarin-interfering drugs in 133 patients suffering from warfarin toxicity admitted to the Edalatian Emergency Center of Imam Reza Hospital in Mashhad was investigated from March to August.

2. MATERIALS AND METHODS

This original cross-sectional study was conducted in the emergency department of Imam Reza Hospital of Mashhad University of Medical Sciences. After obtaining the approval of the University Ethics Committee (IR.MUMS.REC.

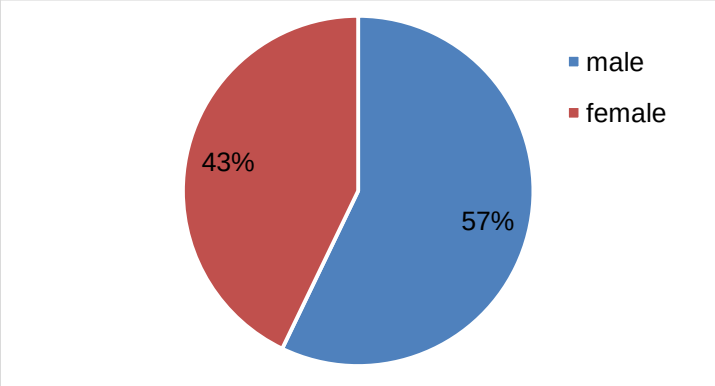
1396.108), 133 adult patients (27 years or older) with warfarin toxicity, were considered to the emergency ward were admitted to this study. For each patient, the available hospital records including clinical notes, laboratory results, and prescription data were reviewed. Information related to the dose of warfarin consumption, the duration of warfarin use, the reasons for warfarin consumption, the symptoms of warfarin toxicity, as well as all the drugs that were taken by the patient, were extracted from the detailed patient's history. Additional data regarding demographic information, admission and discharge date, INR (international normalized ratio), PT (Prothrombin Time), PTT (Partial thromboplastin time) measurements, platelet count, presence or absence of bleeding, bleeding site, bleeding complications, management, and possible cause of warfarin toxicity as recorded in the clinical notes were also collected. Patients with an INR of 4 or more were included in the study. Patients with high INR for reasons other than warfarin toxicity (such as snakebite, severe bleeding, and ingestion of rat poison) were excluded from the study. However, no agreement was reached regarding the number of drugs taken by patients to determine the multidrug interaction. But in this study, polypharmacy was considered if 5 or more drugs were used simultaneously for each patient [25].

2.1 Statistical Analysis

All hospitalized patients diagnosed with warfarin toxicity were included in this study. The data were analyzed using SPSS software for Windows (IBM Corp. 2016, Version 24.0. Armonk, NY: IBM Corp). The normality of the data was evaluated using the Shapiro-Wilk test. Normally distributed data were evaluated using mean and standard deviation (SD). While non-normally distributed data were analyzed using median and interquartile range (IQR). The p-value threshold for significance was considered less than 0.05.

3. RESULTS

During the study period, 133 patients with warfarin toxicity with INR ≥ 4 presented to the emergency department, the average age was 62.27 years (range 27 to 82 years), 57 women and 76 men, (Graph 1). there was no statistical difference in gender distribution (*P = 0.53*). There was no statistically significant difference in INR, PTT, PT, and platelet levels between men and women, but the average dose of warfarin was higher in women *(P=0.07)* (Table 1). An INR between 4 and 10 was observed in 106 patients (80%) and more than 10 were observed in 27 patients (20%).



Graph 1. Frequency distribution of gender (n=133)

Table 1. Gender distribution of anticoagulation outcomes among the study population (n=133)

Particulars	Female (n=57) (mean±SD)	Male (n=76) (mean±SD)	P Value
Time to use warfarin (month)	16.46±21.85	12.84±14.16	.25
Dosage (mg/kg)	2.10±0.27	1.45±0.16	.07
INR	7.61±2.85	7.48±2.64	.78
PTT	88.87±46.28	81.77±48.57	.39
PT	50.72±13.70	50.37±14.76	.89
Platelet	237.24±91.68	222.60±85.26	.34

INR: International Normalized Ratio; PTT: Partial Thromboplastin Time; PT: Prothrombin Time

3.1 Indications for Warfarin Use in Patients

A prosthetic heart valve was the most common indication of warfarin use among the study population. About 36% of patients were using Warfarin due to the use of artificial heart valves. Other indications for warfarin use in the study population included pulmonary embolism (21%), dysrhythmias (20%), prevention of arterial embolism (6%), and stroke (3%) (Table 2).

Table 2. Indication for warfarin use in patients (n=133)

Clinical indication	No. patients (%)
Prosthetic heart valve	48 (36)
DVT	28 (21)
dysrhythmia	26 (20)
Pulmonary embolism	17 (14)
Prophylaxis for arterial embolism	10 (6)
Stroke	4 (3)

**DVT: Deep Vein Thrombosis*

3.2 Clinical Manifestations of Patients with Warfarin Toxicity

Potentially fatal bleeding occurred in 85% of patients. Gastrointestinal bleeding was the most common comorbidity among the study population (37.6%). Other common complications include intracerebral bleeding (24.1%), urinary (12.8%), and respiratory (11.3%). Also, 14% of the patients did not bleed during the presentation (Table 3).

3.3 Simultaneous Use of Warfarin with Other Drugs with Potential Warfarin Interactions

126 (95%) of 133 patients were on concomitant medications with at least one potential drug interaction with warfarin (Table 4). The most used drug with potential drug interactions were aspirin (62.4%), metoprolol (33.1%), and statins (28.8%). Other potentially interacting drugs concurrently used concurrently with warfarin included: ranitidine (19.5%), losartan (10.5%), furosemide (9%), carvedilol (8.3%), antibiotics (7.5%), heparin (6.8%) and clopidogrel. (3.8 percent). One of the patients taking amiodarone also reported a bleeding complication.

4. DISCUSSION

This study allowed investigation of the frequency and characteristics of drug interactions with some drugs that are commonly used with warfarin. The results showed that the most common reason for taking warfarin was cardiovascular problems, which was consistent with similar studies conducted in Africa, Europe, and America [26-29]. In addition, the results showed that a high percentage of patients with warfarin toxicity used drugs with a potential risk of interaction with warfarin. The most important clinical symptoms of hospitalized patients included gastrointestinal (50%), cerebral (32%), respiratory (15%), and urinary (17%) bleeding. No specific bleeding was observed in 19% of patients. Despite the higher dose of warfarin in women, there was no significant difference in the symptoms of warfarin toxicity between the two sexes, this is probably due to gender differences in warfarin metabolism [30]. Examining the drugs that were used together with warfarin in these patients showed that most of the prescribed drugs were cardiovascular drugs. Acetylsalicylic acid (62%), statins (37%), ranitidine (26%), and antibiotics. 11%, clopidogrel (10%) and heparin (9%). Antihypertension drugs such as metoprolol, losartan, and furosemide were also used in 68% of patients. 10% of patients had also used antibiotics, and the most common antibiotic used in patients was metronidazole. Metronidazole increases the effect of warfarin by inhibiting the metabolism [31]. Many cases of metronidazole and warfarin interaction have been reported, in a case study in 2008, concomitant use of metronidazole and warfarin caused intracranial bleeding in a 78-year-old patient [32]. In 2014, Lin reviewed interactions between warfarin and antibiotics. The most important antibiotics associated with an increased risk of bleeding in these patients were azithromycin, cotrimoxazole, ciprofloxacin, levofloxacin, and clarithromycin [33]. In this study, regular and safe use of specific herbal products or food item was not observed. Based on the findings of this study and similar literature, it is understood the drugs used together with warfarin can increase the effect of warfarin through different mechanisms, therefore, the simultaneous use of these drugs with warfarin should be done more cautiously. Considering the increasing use of warfarin by patients and the lack of recognition of many dangerous and life-threatening drug interactions, it is of immense importance to educate patients as well as doctors to use warfarin with other drugs.

Table 3. Clinical presentation of patients with warfarin toxicity (n=133)

Clinical presentation	No. patients (%)	Symptoms
Gastrointestinal	50 (37.6)	Red or black stools, pain
Intracerebral	32 (24.1)	Nausea, Dizziness, Headache
Respiratory	15 (11.3)	Coughing up blood
Urinary	17 (12.8)	Pink or brown urine, Pain
Asymptomatic	19 (14.3)	Undefine

Table 4. Concurrent warfarin uses with other medications with potential drug-drug interactions (pDDIs)* (n=133)

Concurrent drug use	Number of patients on the drug (%)	Interaction risk	Probable mechanism	Probable clinical effect
Aspirin	83 (62.4)	D	Additive effects	Increased risk of bleeding
Metoprolol	44 (33.1)	B	Additive effects	Increased risk of bleeding
Statins	37 (28.8)	C	Competition for cytochrome P450. 3A4 mediated metabolism	Increased risk of bleeding
Ranitidine	26 (19.5)	C	Decreased warfarin metabolism	Increased risk of bleeding
Losartan	14 (10.5)	B	Additive effects	Increased risk of bleeding
Furosemide	12 (9)	B	Additive effects	Increased risk of bleeding
Clopidogrel	11 (8.3)	D	Additive effects	Increased risk of bleeding
Antibiotics	10 (7.5)	C	Disruption of vitamin K synthesis	Increased risk of bleeding
Heparin	9 (6.8)	C	Additive effects	Increased risk of bleeding
Carvedilol	5 (3.8)	B	Additive effects	Increased risk of bleeding

**According to the Lexi-InteractTM Online database*

5. CONCLUSION

It seems that the simultaneous use of warfarin with other drugs play a significant role in the occurrence of warfarin toxicity. In this study, a high frequency of drug interactions with warfarin was observed, which seems to play a significant role in the occurrence of warfarin toxicity. Careful monitoring of the type of drugs used by patients is extremely important in providing safe and effective treatment and reducing side effects. If necessary, it is suggested to prescribe drugs that have less interaction with warfarin.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

DISCLAIMER

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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