Predisposing Factors Leading to Warfarin Toxicity

ABSTRACT

Introduction: Warfarin is a commonly utilized anticoagulant in the management of thrombosis, either prevention or treatment, with bleeding problems as one of the major adverse effect because of its narrow therapeutic index.

Objective: To determine the frequency of various factors leading to warfarin toxicity which was defined as patients presented with International Normalized Ratio (INR) greater than five.

Setting: Department of Adult Cardiology at National Institute of Cardiovascular Diseases (NICVD), Karachi, Pakistan.

Methodology: The study type is descriptive, cross sectional. All patients who fulfilled the inclusion criteria and visited Department of Adult Cardiology at NICVD, Karachi, Pakistan were included. After ethical approval and informed and written consent. The collected data was entered using IBM SPSS - 21, for variables that were continuous mean Standard Deviation was calculated and for variables that were categorical frequency percentage were calculated.

Result: Total of 87 patients with warfarin toxicity were included. 52 patients (60%) were males & 35 (40%) were females with the mean age of 48.5287 ± 13.1386 years. The factors leading to warfarin toxicity were dietary non-compliance 19 patients (21.83%), drug non-compliance in 18 (20.68%), drug-drug interactions in 12 (13.79%), irregular follow up in 23 (26.39%) and deranged liver functions in 26 (29.88%) patients.

Conclusion: Warfarin toxicity has multifactorial causes. Deranged liver functions and irregular follow up of patients accounted for the most prominent factors leading to warfarin toxicity.

Key words: warfarin, toxicity, drug noncompliance, drug interaction, liver function tests

INTRODUCTION:

Among the anticoagulants, Warfarin is most commonly utilised drug in the world for the management of thromboembolic disorders. The prophylaxis and treatment of conditions like valvular heart diseases, pulmonary embolism, DVT etc. uses the drug Warfarin. 1-7 though thoroughly in use, the drug's narrow therapeutic range, interactions with other drugs and it's variability in doses between different individuals make establishment of optimal warfarin dose for anticoagulation is difficult. 8,9

Despite these common uses of warfarin, the associated risk of bleeding and other possible adverse outcomes cannot be overlooked. Therefore, regular follow up and strict monitoring of international normalized ratio (INR) is required to minimize its toxicity. High international normalized ratio (INR) levels predispose patients to significant haemorrhage and consequent increase in associated morbidity and mortality. 5,6 10-13 Bleeding complications categorised as major include gastrointestinal haemorrhage, retroperitoneal bleed, and intracranial haemorrhage and minor include haemorrhages of the sub-conjunctiva, epistaxis, haematuria and ecchymosis. A systemic review illustrates the mean annual rates of Warfarin related bleeding complications

as 4.9% for major and as high as 15% for minor bleeding events in individuals using it for anticoagulation. 6

Pharmacokinetics include the concentration of a drug require the body for proper working, pharmacodynamics involve the impact of certain drug on our body system. Genetic variations dealing with drug metabolisms, impaired liver activity, drug to drug interactions, vitamin K rich diet, Congestive Heart Failure etc. have been accounted for increasing the risk of over-anticoagulation in people using Warfarin. Sahay RN et al. reported the frequency of potential causes among the patients with INR greater than four as, female gender (60%), drug-drug interactions (40%), and acute liver disease (17.5%). 6 Moreover, dietary non-compliance (lack of daily intake of dietary vitamin K) was reported to be 33% among the patients with International normalised ratio (INR) greater than four. 14 Other than these factors irregular follow up (19%) and drug non-compliance (19%) were reported to be potential factors leading to warfarin toxicity. 15

Warfarin is one of the most commonly prescribed but trickiest drug in use. In spite of detailed studies and measures taken to attain a tight control of the INR, Warfarin is still the most common pharmacological cause of emergency room visits excluding Insulin. Very limited local data are available on factors leading to warfarin toxicity; therefore, we expect to see variations in results of our population. This study is designed with the aim to study the factors leading to toxicity of warfarin in our population and highlighting the major ones, so that the complications can be prevented.

MATERIALS AND METHODS:

The design for this study is cross-sectional, conducted from 21st Oct 2020 to 20th Apr 2021 for 6 months at the National Institute of Cardiovascular Disease (NICVD), Department of Adult Cardiology, Karachi, Pakistan. Cross-sectional research are independent studies looking at statistics from a group of people at one particular moment in time. They are frequently used to assess the prevalence of health outcomes, comprehend health factors, and describe demographic characteristics.

WHO sample size calculator version 2.0 was utilized to accurately calculate the sample size? 95% was the confidence interval; eight percent margin of error and 17.5% of expected prevalence (p) with a total of n = 87 patients. The technique used was consecutive sampling with non probability. The patients included consisted of age group between 18-75, both male and female and those who presented with warfarin toxicity. Contrarily; intentional, accidental ingestion or people with incomplete or ambiguous history were excluded

Demographic profile of the patients like gender, age (years), residence, monthly income (PKR), and educational status was recorded as per the operational definitions. Patient's clinical history was obtained regarding hypertension, diabetic mellitus, and smoking as per the operational definitions. International normalized ratio test was performed for all patients by experts with more than five years of INR clinic experience. All data was recorded by a principal investigator on a predesigned proforma. The criteria of both exclusion and inclusion along with stratification

were used to assure control over confounding variables and general bias. Patient information was safeguarded and only made available to persons authorized.

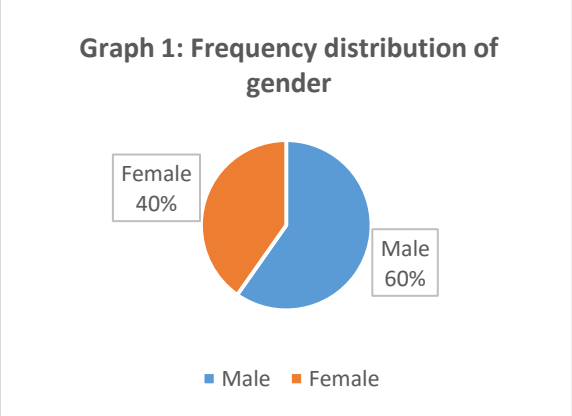
STATISTICAL ANALYSIS:

SPSS version-21 (IBM SPSS) was used to analyze the data. Then, to check the hypothesis of normality for quantitative variables such as age (years), and monthly income (PKR) Shapiro-Wilk test was applied. Descriptive statistics for example mean ± SD, median, skewness, maximum and minimum were also calculated appropriately via the same test. For categorical variables percentages and frequency were calculated. Effect modifiers were controlled through stratification. Chi-square test or fisher exact test was applied after stratification appropriately. The criteria of statistical importance were two-sided p-value of ≤ 0.05.

RESULT:

A total of 87 patients with warfarin toxicity were selected to conduct this study. The mean age was 48.5287±13.1386 years. 52 patients (60%) were males & 35 patients (40%) were females. (as shown in graph 1).

The residence of 52 patients (60%) were rural & 35 patients (40%) were urban. The mean



monthly income from all sources was 39655.1724±21791.73493 rupees. The descriptive analysis of income alongside age is shown in Table-1

Table 1: Descriptive statistics of age, monthly income of all sources

Statistics	Age (years)	Monthly income of all sources (rupees)
Minimum	30	10000
Maximum	75	100000
Mean	48.5287	39655.1724

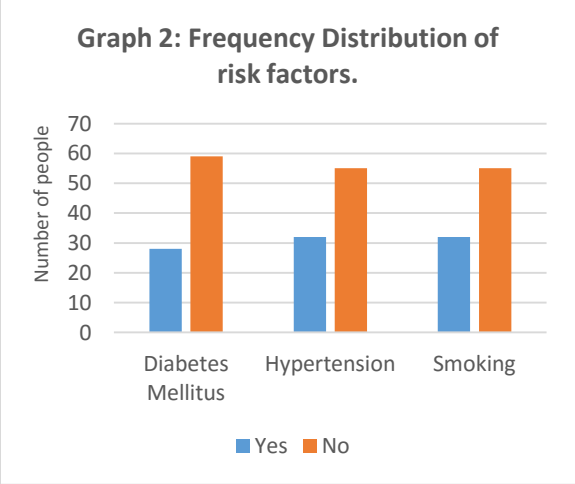
Std. Deviation	13.13865	21791.73493

31 patients (35.63) had no formal education (at school) 23 patients (26.43%) had up to secondary level and 23 (37.93%) had education and higher than secondary level education, (as shown in Table-2)

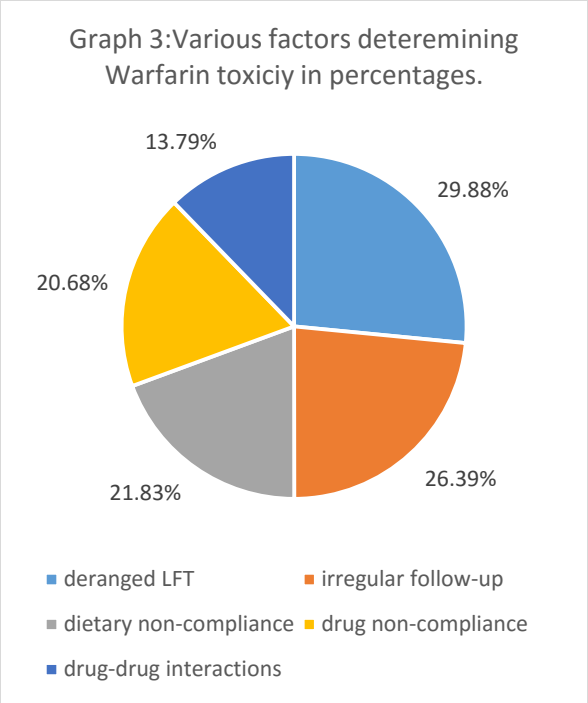
Table 2: Frequency distribution of Educational Status (n=87)

Educational Status	Frequency	Percentage
No formal education	31	35.63%
Up to secondary level education	23	26.43%
Higher than secondary level education	33	37.93%
Total	87	100%

In our study the diabetic mellitus was noted in 28 patients (32.18%), hypertension was noted in 32 patients (36.78%) and smoking was noted in 17(19.54%), as shown in Graph 2.



The factors leading to warfarin toxicity were dietary noncompliance (defined as reported by the patient to be taking vitamin K containing food substances at least once per day over the past one month) 19 patients (21.83%), drug noncompliance (defined as a score of <8 on Morisky Medication Adherence Scale -MMAS-8) in 18 (20.68%), drug interaction in 12(13.79%), irregular follow up in 23 (26.39%) and deranged liver functions in 26 (29.88%) as shown in Graph 3 in percentages.



In our study the factors leading to warfarin toxicity (dietary noncompliance, drug noncompliance, drug interaction, irregular follow up, deranged liver functions) were common in age group of 41-75 years, predominant in male gender, were more common in rural patients, more common in patients with monthly income 10000-50000 rupees, were slightly more common in patients with no formal education, and significant association was noted between DM, hypertension, smoking and the factors leading to warfarin toxicity.

DISCUSSION:

As known after the introduction of Direct Oral Anticoagulant (DOAC) medications usage of warfarin has decreased, but it still remains a common part of prescriptions in our region. It is a big challenge for health care workers to employ the drug Warfarin in management, as the considerable individual variations in the appropriate dosage predispose patients towards the possibility of being over-anticoagulated very commonly. Moreover, the narrow therapeutic window of the drug causes it to result in bleeding complications, which can sometimes be life-threatening. It is exemplified by the gastrointestinal, urinary tracts or other major bleeds occurring in 6.5% of the total annual anticoagulated patients. One of the major variables consistently increasing the risk of anticoagulation is the intensity of dosing, which is depicted in the elevation of the standard prothrombin time, the INR ratio

In our study the common age group affected was between 41 to 75 years. Age was labelled as one of the major factors influencing bleeding risks in patients taking Warfarin. In multiple studies assessing this relationship between ages and bleeding episodes, the bleeding was

significantly higher in older patients, especially those with unstable INRs. Thus, younger individuals with stable INRs were at a lower risk of bleeding, as a result, the authors suggested to extend the INR checks duration from three to four weeks to eight to twelve weeks in young people. In another study, it was highlighted that INR levels were higher in older patients than younger ones taking the same Warfarin dose. Fang et al. in their study of over 13000 atrial fibrillation patients, of age above 80, found increased bleeding rates, though interestingly similar in those taking or not taking warfarin. 20

In our study, the age was 48.5287+13.1386 years as compare to Sahay et al [5] study the mean age of patients was 42.9 years with majority of individuals were of age bracket between 30 to 39 years (22.5%) with second most common being 40 to 49 years and elderly patients more than 60 years. The risk of bleeding is higher in elderly population with higher warfarin dose used. In this study, 14 out of 26 patients in the age group of >50 years had bleeding complications. Therefore, for the elderly population the dose of warfarin should be kept below five mg/d with vigilant monitoring of the INR. The reasons that with increasing age, individuals become more prone to Warfarin toxicity are due to decreased body weight, impairment of kidney functions, impairment of liver functions, low intake of Vitamin K in diet, etc. Gurwitz JH, et al in Annals of Internal Medicine concludes Coumadin as the most common medication bringing elderly patients in in the emergency in America, with 17.3% of all drug related complications. 21

Secondly considering the education of patients who visit ED with bleeding complications, it was concluded that 83% of our patients had either primary school level education or even less. This high percentage must strike the clinicians to prioritize the drug education and effective counselling of the patient while prescribing the drug as issues like irregular follow-up, and noncompliance accounted as major risk factors of warfarin toxicity according to the study.

In our study deranged liver function was factor of warfarin toxicity in 30% cases as compare to Sahay et al study, in which 17.5% patients were documented to have acute liver disease; however, there was no statistical significance between poor liver functions and bleeding complications in patients presenting with warfarin toxicity, with a p-value of 0.826. Only one patient had deranged renal functions with increased creatinine (2.6). The reduction in clotting factor synthesis in patients with liver diseases is the root cause of coagulopathy with deranged hepatic functions. Such patients are perceived to have “auto-anticoagulation” with deranged INRs. Moreover, compromised hepatic function also diminishes the breakdown and clearance of warfarin. In the context of renal functions, the moderate to severe impairment of kidney activity resulted in much higher INR levels, and thus consequently have more bleeding complications.

In our study the factors other than deranged LFTs, leading to warfarin toxicity were dietary noncompliance noted in 21.83% cases, drug noncompliance 20.68% subjects, drug interaction in in 13.79% and irregular follow up in 26.39% cases.

Drug-drug interactions also had a fair share in bleeding problems with warfarin. There are many agents which either increase or decrease the metabolism of the drug and its overall activity. One of the most problematic drugs, interacting with Warfarin is Acetylsalicylic acid, as it is regularly being used and its mechanism of action on inhibiting the plate let functions act synergistically

with the drug warfarin, and thus increases the risk of bleeding. It has been studied that acetylsalicylic acid increases the risk of major and minor bleed with 1.5-2 % overall.

Gando et al. also found out that severe infections trigger the coagulation pathways thus increases the bleeding risk in patients. One must expect substantial chances of bleeding complications in individuals who have severe infections.

Even though significant conclusions were reached during this study, more investigations with a larger sample size and variable efficacy of commonly available warfarin in local market should be taken in consideration.

CONCLUSION:

Warfarin toxicity has multifactorial cause. Deranged liver functions and irregular follow up of patients were the most common factors influencing warfarin toxicity, according to our study. Apart from that, drug noncompliance, dietary noncompliance and drug-drug interactions also made an imminent share in causing bleeding complications in patients using Warfarin.

Ethical Approval And Consent

Ethical review committee of NICVD approved the study before collecting the data. Before enrolling the aim and benefits of the study were explained to all participants and written informed consent was acquired by the principal investigator from all patients.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

REFRENCES:

1. Ma C, Zhang Y, Xu Q, Yang J, Zhang Y, Gao L et al. Influence of warfarin dose-associated genotypes on the risk of hemorrhagic complications in Chinese patients on warfarin. Int J Hematol. 2012 Dec;96(6):719-28. doi: 10.1007/s12185-012-1205-8. Epub 2012 Oct 27. PMID: 23104259.

2. Jaakkola S, Nuotio I, Kiviniemi TO, Virtanen R, Issakoff M, Airaksinen KEJ. Incidence and predictors of excessive warfarin anticoagulation in patients with atrial fibrillation-The EWA

study. PLoS One. 2017 Apr 20;12(4):e0175975. doi: 10.1371/journal.pone.0175975. PMID: 28426737; PMCID: PMC5398615.

3. Fischer HD, Juurlink DN, Mamdani MM, Kopp A, Laupacis A. Hemorrhage during warfarin therapy associated with cotrimoxazole and other urinary tract anti-infective agents: a population-based study. Arch Intern Med. 2010 Apr 12;170(7):617-21. doi: 10.1001/archinternmed.2010.37. PMID: 20386005.

4. Qayyum, Aisha. (2014). EFFECT OF AGE ON WARFARIN DOSE REQUIREMENT IN PAKISTANI POPULATION. Pakistan Heart Journal. 47. 61-66.

5. Wittkowsky AK, Devine EB. Frequency and causes of overanticoagulation and underanticoagulation in patients treated with warfarin. Pharmacotherapy. 2004 Oct;24(10):1311-6. doi: 10.1592/phco.24.14.1311.43144. PMID: 15628828.

6. Sahay, Ravindra & Salagre, Kaustubh & Dedhia, Khushali. (2017). Study of environmental and genetic factors determining warfarin toxicity. International Journal of Research in Medical Sciences. 5. 463. 10.18203/2320-6012.ijrms20170133.

7. Piatkov I, Rochester C, Jones T, Boyages S. Warfarin toxicity and individual variability-clinical case. Toxins (Basel). 2010 Nov;2(11):2584-92. doi: 10.3390/toxins2112584. Epub 2010 Oct 28. PMID: 22069565; PMCID: PMC3153177.

8. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. JAMA. 2006 Oct 18;296(15):1858-66. doi: 10.1001/jama.296.15.1858. PMID: 17047216.

9. Lindh JD, Holm L, Dahl ML, Alfredsson L, Rane A. Incidence and predictors of severe bleeding during warfarin treatment. J Thromb Thrombolysis. 2008 Apr;25(2):151-9. doi: 10.1007/s11239-007-0048-2. Epub 2007 May 20. PMID: 17514429.

10. Dodson JA, Petrone A, Gagnon DR, Tinetti ME, Krumholz HM, Gaziano JM. Incidence and Determinants of Traumatic Intracranial Bleeding Among Older Veterans Receiving Warfarin for Atrial Fibrillation. JAMA Cardiol. 2016 Apr 1;1(1):65-72. doi: 10.1001/jamacardio.2015.0345. PMID: 27437657; PMCID: PMC5600874.

11. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation. 2007 May 29;115(21):2689-96. doi: 10.1161/CIRCULATIONAHA.106.653048. Epub 2007 May 21. PMID: 17515465.

12. Dowlatshahi D, Butcher KS, Asdaghi N, Nahirniak S, Bernbaum ML, Giulivi A et al. Canadian PCC Registry (CanPro) Investigators. Poor prognosis in warfarin-associated intracranial hemorrhage despite anticoagulation reversal. Stroke. 2012 Jul;43(7):1812-7. doi: 10.1161/STROKEAHA.112.652065. Epub 2012 May 3. PMID: 22556194.

13. Koo S, Kucher N, Nguyen PL, Fanikos J, Marks PW, Goldhaber SZ. The Effect of Excessive Anticoagulation on Mortality and Morbidity in Hospitalized Patients With Anticoagulant-Related Major Hemorrhage. Arch Intern Med. 2004;164(14):1557–1560. doi:10.1001/archinte.164.14.1557

14. Verstuyft C, Robert A, Morin S, Loriot MA, Flahault A, Beaune P et al. Genetic and environmental risk factors for oral anticoagulant overdose. Eur J Clin Pharmacol. 2003 Mar;58(11):739-45. doi: 10.1007/s00228-002-0538-2. Epub 2003 Feb 18. PMID: 12634980.

15. Cruickshank J, Ragg M, Eddey D. Warfarin toxicity in the emergency department: recommendations for management. Emerg Med (Fremantle). 2001 Mar;13(1):91-7. doi: 10.1046/j.1442-2026.2001.00185.x. PMID: 11476421.

16. Holford NH. Clinical pharmacokinetics and pharmacodynamics of warfarin. Understanding the dose-effect relationship. Clin Pharmacokinet. 1986 Nov-Dec;11(6):483-504. doi: 10.2165/00003088-198611060-00005. PMID: 3542339.

17. "Warfarin Sodium". The American Society of Health-System Pharmacists. Archived from .the original on 8 June 2018. Retrieved 8 January 2017.

19. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e44S-e88S. doi: 10.1378/chest.11-2292. PMID: 22315269; PMCID: PMC3278051.

20. Fang MC, Chang Y, Hylek EM, Rosand J, Greenberg SM, Go AS et al. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. Ann Intern Med. 2004 Nov 16;141(10):745-52. doi: 10.7326/0003-4819-141-10-200411160-00005. PMID: 15545674.

21. JH Gurwitz, Terry SF, Jerry A, Danny M, Shailavi J, Marie E et al. Incidence and preventability of adverse drug events in nursing homes. The American Journal of Med, 2000 Aug, 2:87-94. doi.org/10.1016/S0002-9343(00)00451-4.