Warfarin Induced Abnormal Uterine Bleeding: A Case Report

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ABSTRACT

Background: The objective of this clinical case report is to highlight the importance of early identification of patients who are at a higher risk of developing bleeding complications after receiving Warfarin. **Case Presentation:** A 40 year old female patient visited the tertiary care hospital's Gynecology OPD on 1st April 2021 with the complaints of heavy menstrual cycle for last eight months along with increased frequency of cycles. She had undergone Tubectomy 18years back during which she was diagnosed with Cardiac disease. Two years back she was diagnosed with Hypothyroidism and is on medication. One year back she had complaints of bilateral upper and lower limb weakness for which she visited a local hospital and found abnormalities in her ECG report. She underwent Aortic Valve Replacement surgery in July 2020 and was given Warfarin 5mg and a Beta- Blocker. After a month of surgery the patient noticed increased menstrual flow along with increased frequency of menses, lasting for 10-12 days. The patient was admitted and underwent hysterectomy. Post-surgery Warfarin dose was increased to 7.5mg once daily. **Discussion:** The risk of bleeding while taking Warfarin increases with certain factors like: - advanced age, drug-drug interactions, genetic polymorphism and gender- usually females require a lower dose of anticoagulants. In this case two possible drug-drug interactions were identified. As she is also a known case of hypothyroidism her risk for developing bleeding complications increases further. **Conclusion:** The case highlights the need for anticoagulation clinics in the hospitals, use of software's in monitoring and dosage adjustments in such patients, use of risk stratification tools to identify high risk patients and also the need for self-monitoring by the patients.

Key words: Anticoagulants, Warfarin, Drug Interactions, Hypothyroidism, Menstrual cycle.

INTRODUCTION

Abnormal Uterine Bleeding (AUB) or Heavy Menstrual Bleeding (HMB) can be defined as menstrual bleeding of abnormal quantity, durations or intervals. It includes heavy bleeding more frequently, irregularly and also intermenstrual bleeding. It affects a woman's physical, emotional, social, and material well-being, and can occur on its own or in conjunction with other symptoms. When checking for AUB and/or HMB specifically, the rates are as high as 67% among people taking Vitamin K antagonists like warfarin.[1] It's a common but usually underreported side effect that affects 70% of menstrual women who take blood thinners especially the anticoagulants. Abnormal uterine bleeding can lead to anemia and iron deficiency, as well as greater risk for hospitalizations, need for medical interventions, and a lower quality of life.[2]

Warfarin was not discovered until 1920s when an outbreak of an unusual disease characterized by fatal bleeding in cattle in Northern USA and Canada. In 1939 Campbell and Link identified that the cattle feed Mouldy Silage made from spoiled sweet clover contained a hemorrhagic factor Bishydroxycoumarin (Dicoumarol) that decreased the activity of Prothrombin and was responsible for the bleeding complications. Further in 1948 synthesis

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of a more potent synthetic congener took place, it was initially approved as a rat poison and in 1954 warfarin was approved for use in human. It was named after the patent holder, Wisconsin Alumni Research Foundation (WARF) and 'arin' from coumarin.[3]

The case presented here is of a female patient with the complaint of heavy blood loss during menses for eight months, after taking warfarin.

CASE DESCRIPTION

A 40 year old female patient with an obstetric score P3L3 (para 3 and live 3) visited the tertiary care hospital's Gynecology OPD on 1st April 2021 with the complaints of heavy menstrual cycle for eight months along with increased frequency of cycles. She had undergone Tubectomy 18years back during which she was diagnosed with Cardiac disease and was administered Inj. Penicillin. From then on the patient had been taking the Fixed Dose Combination Torsemide 5mg-Spironolactone 50mg and Tab. Aspirin 75mg. Two years back she was also diagnosed with Hypothyroidism and is on medication Tab. Thyroxine Sodium 75mg once daily in the morning. One year back she had complaints of bilateral lower and upper limb weakness for which she visited a local hospital and found abnormalities in her ECG. She underwent Aortic Valve Replacement surgery in July 2020 and was given anticoagulant (WARFARIN 5mg) and Beta-Blocker (METOPROLOL 25mg). After a month of the surgery, patient noticed an increase in her menstrual flow along with increased frequency of menses, which lasted for 10-12 days or 15-20 days along with clots. The laboratory investigation reports showed a slight decline in Hemoglobin level (Table 1).

Table 1: Laboratory investigation data.

Parameters	Reference range	Observed value
Hemoglobin	12.1-15.1g/dL	11.7
Total count	4000-11000cells/cumm	11000
PCV	35.5-44.9%	37.6
N	40-80%	71
L	20-40%	22
E	0-2%	01
Platelets	1.5-4.5lakhs/cumm	388
PTT (T/C/R)	10-13sec	17.3/14.5/1.19
aPTT (T/C/R)	25-36sec	41.0/28/1.46
UREA	16.6-48.5mg/dL	14
Creatinine	0.7-1.2mg/dL	0.7
Na	136-145mEq/L	139
K	3.5-5.4mEq/L	4
Uric Acid	3.4-7mg/dL	6.1
HCO3	22-26mmol/L	23.2
T-Bilirubin	0-1.4mg/dL	0.2
Direct Bilirubin	0-0.3mg/dL	0.1
T-Protein	6.3-8.4g/dL	7.5
Albumin	3.5-5.2g/dL	4.1

PCV-Packed Cell Volume, RCC- Recticulocyte Count, N-Neutrophils, L- Lymphocytes, E-Eosinophils, PTT (T/C/R)- Partial Thromboplastin Time(Test/Control/Ratio), aPTT (T/C/R)- Activated Partial Thromboplastin Time(Time/Control/Ratio), Na- Sodium, K- Potassium, HCO_3- Bicarbonate, T-Bilirubin- Total-Bilirubin, T-Protein-Total Protein.

DISCUSSION

Here the patient had no other complaints of bleeding other than heavy blood loss during menses. Since AUB is not usually life-threatening and are chronic in nature, it is not usually a separate prespecified end point in clinical trials of anticoagulant therapy. The Naranjo Causality Assessment Scale resulted in a score 5 (Table 2). Any score between 5 and 8 shows that the drug has PROBABLY caused the ADR. According to the Hartwig *et al.* ADR Severity Assessment, it is a MODERATELY SEVERE ADR (Level 4a) as the reason for the patient's hospital admission was the ADR itself.

The risk of bleeding while taking warfarin increases with certain factors like:

- Advanced age
- History of bleeding
- Anemia
- Liver diseases
- Hypertension
- Genetic polymorphism of VKORC1 and CYP2C9 could predispose to a higher risk of bleeding which calls for the need for personalized dosage regimens based on the individuals genetic susceptibility.
- Concomitant medications like other blood thinning agents, NSAIDs, thyroid hormones.
- Gender- usually females require a lower dose of anticoagulants.

Gender is also a factor that increases the bleeding risk. This was supported by a systematic review and meta-analysis of 8 DOAC RCTs involving 9400 patients with VTE on Dabigatran, Apixaban, or Rivaroxaban against Warfarin revealed that women experiences higher bleeding problems than males receiving DOACs.[4]

Table 2: Naranjo Causality Assessment Scale.

Sr.No	Questionnaire	Yes	No	Do not know	Score
1	Are there previous conclusive reports on this reaction?	1	0	0	1
2	Did the adverse event occur after the suspected drug was administered?	2	-1	0	2
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	1	0	0	0
4	Did the adverse reaction reappear when the drug was readministered?	2	-1	0	0
5	Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	2	0	0
6	Did the reaction reappear when a placebo was given?	-1	1	0	0
7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	1	0	0	0
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	1	0	0	0
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0	1
10	Was the adverse event confirmed by any objective evidence?	1	0	0	1
Total					5

NOTE: Referred from Naranjo CA *et.al*. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-245.

Thyroid hormone has an effect on the coagulation system; however it is less well documented. Thyroid hormone deficiency causes the haemostatic system to become more hypocoagulable and hyperfibrinolytic, according to several studies. Thyroid hormone deficiency thus appears to increase the risk of bleeding. Although it is widely acknowledged among clinicians that hypothyroidism increases the risk of irregular vaginal bleeding, research on the subject is limited. Menorrhagia or heavy menstrual bleeding was shown to be more common in 171 women with hypothyroidism than in 214 healthy controls in one study (7 % vs. 1%).[5] In this case, the patient is a known case of hypothyroidism and is on medication for 2 years.

Warfarin is known for its variable dose–response relationship, Narrow Therapeutic Index, potential bleeding risk and numerous drug and dietary interactions. In this case, 2 possible Drug-Drug interactions were identified using the IBM Micromedex® Drug Interaction Checker. A major interaction between the antiplatelet ASPIRIN 75mg and WARFARIN 5mg, a Minor interaction by concomitantly taking THYROXINE SODIUM 75mcg and WARFARIN 5mg once in the morning.

As patients on anticoagulants, especially warfarin requires close monitoring. Various risk stratification tools have been developed that can be followed in day to day clinical set ups for identifying low and high risk group of patients and also to reassure the low risk group patients that they are unlikely to have significant bleeding complications.[6]

Management of AUB includes Hormonal therapy using Levonorgesterol releasing IU systems, Non-Hormonal therapies like NSAIDs at their pharmacological doses will reduce prostaglandin production hence reducing menstrual bleed, use of Tranexamic acid an antifibrinolytic agent and surgery which is a definitive treatment option for those who no longer wish to conceive; but have many side effects like increased number of adverse events, longer recovery period and high initial health care cost. In this case the patient had to undergo Hysterectomy in which patient's uterus was removed surgically and warfarin dose was increased up to 7.5mg post-surgery.

CONCLUSION

This case shows the importance of close monitoring of patients with higher risk of developing bleeding complications while on warfarin therapy. It highlights the need for anticoagulation clinics in the hospitals, use of softwares in monitoring and dosage adjustments in such patients, use of risk stratification tools to identify high risk patients and also the need for self-monitoring by the patients and early reporting of side effects.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

HMB: Heavy Menstrual Bleeding; **OPD:** Out Patient Department; **ECG:** Electrocardiography, **ADR:** Adverse Drug Reaction; **VKORC1:** Vitamin K Epoxide Reductase Complex Subunit 1; **CYP2C9:** Cytochrome P2C9; **IU:** Intra Uterine; **NSAIDs:** Nonsteroidal Anti-Inflammatory Drugs; **VTE:** Venous Thromboembolism; **DOACs:** Direct Oral anticoagulants; **RCTs:** Randomized Controlled Trial; **OACs:** Oral Anticoagulants; **AVR:** Aortic Valve Replacement.

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