



## Clinical Cases Anticoagulation Overdose with Concomitant Assumption of Vitamin K Antagonists and Asteraceae Family Green: A Review of the World's Medicine

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### KEYWORDS

Anticoagulation overdose, vitamin K antagonist anticoagulants, bleeding, Asteraceae.

### ABSTRACT:

**Introduction:** The world has had some studies on the effects of cruciferous vegetables on coagulation disorders as well as bleeding complications, but there are still many angles that need further research, especially the effects of green vegetables close to cruciferous vegetables such as Asteraceae family. The Asteraceae family is also a rarely mentioned food group.

**Case series Description:** Study on 3 cases of atrial fibrillation (AF), heart failure with dilated heart chambers, and artificial heart valve surgery who were using vitamin K antagonist anticoagulants (VKAs) drugs with green vegetables of the Asteraceae family that can cause anticoagulation overdose and was discovered when they were medical examination. Clinical cases found to have hemorrhagic bleeding in the background were acutely managed with timely resuscitation and returned the coagulation index to normal.

**Conclusion:** The case series of coagulation disorders who patients receiving anticoagulant therapy with vitamin K antagonists when using green vegetables of the Asteraceae family may be considered a risk factor for coagulation disorders and an increased risk of hemorrhagic complications.

### INTRODUCTION

Coagulation disorders in patients taking vitamin K antagonist anticoagulants (VKAs) when treating patients with cardiovascular diseases that cause cardiovascular disease, embolization to prevent thromboembolic complications caused by atrial fibrillation, artificial heart valves surgery, heart failure with severely dilated heart chambers, severe left atrial enlargement, etc., complications may occur [1], [2], [3], [4], [5]. When complications occur, it is a medical emergency accounting for about 11% of cases [6] or more [2], [3]. Many cases of late arrival or late detection can lead to severe blood loss, hemodynamic

instability, hemorrhagic shock, and even hemorrhagic stroke [7], [8] requiring both resuscitation and intervention and/or emergency surgery [1], [2], [6]. The world has had some studies on the effects of cruciferous vegetables, but there are still many angles that need further research, especially the effects of green vegetables close to cruciferous vegetables such as the Asteraceae family. The Asteraceae family is also a rarely mentioned food group [9], [10]. Due to the influence of the region having a lot of green vegetables, many patients were found to have coagulation disorders as well as bleeding complications while being treated with vitamin K anticoagulant drugs and using foods from this green vegetables of the cruciferous or



Asteraceae family, especially vegetables close to the cruciferous family such as Asteraceae family vegetables are rarely mentioned; Therefore, we proceed to report typical case series using vitamin K anticoagulants drugs with Asteraceae family greens in a long time and these are only 3 cases out of many detected cases.

#### CASE DESCRIPTION

Study on 3 patients receiving anticoagulant therapy with vitamin K antagonists when using green vegetables of the Asteraceae family [9], [10], [11] who were

discovered when visiting for medical examination and treatment at Haiphong - Vinhbao International General Hospital at Vietnam in 2022. In terms of general characteristics, all 3 cases with two Females and a Man belong to the elderly group (64-year-old, 74-year-old, and 64-year-old). The age characteristics of these patients are also quite consistent with the study of other authors, most of which fall into the elderly group [1], [2]. The reason for admission in all 3 cases was due to severe bleeding. The main diseases for the use of vitamin K antagonist anticoagulants in the three cases above are atrial fibrillation, heart failure, and artificial valve disease.

**Table 1: Basic characteristics of the subject study**

Basic characteristic	Case 1	Case 2	Case 3
Gender	Female	Female	Male
Age (year)	64	74	64
Body Mass Index (BMI)	26.0	22.6	19.5
Reason for hospitalization	Black stools	Extensive bleeding and bruising under the skin	Subcutaneous hemorrhage with extensive subcutaneous bruising
Main disease	Atrial Fibrillation	Heart Failure and atrial fibrillation	Mitral valve surgery and atrial fibrillation, heart failure improves function
Heart Beat (Heart rate)	102	88	82
Blood pressure (mmHg)	120/70	112/68	122/70
Asteraceae geen	Crown daisy (Chrysanthemum green) vegetables of the Asteraceae family	Artemisia Vulgaris vegetables of the Asteraceae family	Chrysanthemum green vegetables of the Asteraceae family
International normalized ratio (INR) index	6.59	10.91	7.63

These patients are examined and followed up at many centers for about 6 months - 1 year at many different centers before coming to our hospital and often have results of coagulation disorders. These patients have had the habit of regularly using chrysanthemum vegetables in the past few months and irregular used this green vegetable in about one month recently.

**The first case is a 64-year-old, female patient** who was admitted to the hospital because of black stools with atrial fibrillation and heart failure improved function (EF: 64%) on the background of mitral regurgitation grade's 3/4, aortic regurgitation grade's 3/4, overweight and obesity with a Body Mass Index (BMI) of 26.0, heart rate of 102 heart beats/min, blood pressure's 120/70 mmHg, Platelet's 328 G/L. The patient with an anticoagulation overdose has an INR of 6.59 and the patient had a habit of often Crown daisy (Chrysanthemum green) vegetables of the Asteraceae

family for a long time (some months). The patients with atrial fibrillation and heart failure, there is an indication for vitamin K anticoagulation drugs and it is necessary for the INR target range from 2-3 levels. The patient has an anticoagulation overdose with bleeding by a status of high INR index, so in addition to the emergency management of anticoagulation overdose by injecting a single dose intravenously 10 mg of vitamin K1 and 12 hours later repeat a dose of 10 mg of vitamin K after 12 hours to reverse the blood clotting; besides that, also have to the emergency management of high gastrointestinal bleeding due to gastric ulcer – duodenal ulcer with PPI regimen intravenous bolus 80 mg, after followed by a continuous intravenous infusion of 8 mg/hour for 72 hours, the patient is soon stabilized [2], [3].

**Commented [NB1]:** Table 1 must be cited within the main text of the manuscript, and it currently is not. Please include a citation of Table 1 within the main text of the manuscript prior to resubmission.



**The second case is a 74-year-old, female patient**, who was admitted to the hospital because of extensive bleeding and bruising under the skin of the arms, forearms, knee joints, ankles, and lower legs, in the knee and leg joints, and the neck on both sides. The result of the INR test showed an high INR index (INR = 10.91) and the patient using many *Artemisia vulgaris* vegetables of the Asteraceae family for a long time [9], [10]. Clinical Examination showed a heartbeat of 88 beats/min, blood pressure of 112/68 mmHg, Platelet's 355, and BMI of 22.6. The main disease is atrial fibrillation and heart failure with EF of 50% on the background of diabetes, and mild renal failure, so the INR target ranges of the patient should be from 2.0-3.0 levels, the patient was treated urgently in resuscitation, deal with the factors that cause severe coagulation disorders by injecting a dose of 10 mg of vitamin K1 intravenously immediately and 12 hours after repeating a dose of 10 mg of vitamin K after 12 hours to reverse the blood clotting, the disease is soon stabilized [2], [3].

**The third case is a 64-year-old, male patient** with mitral heart valve surgery, atrial fibrillation, heart failure improves function (EF: 73%) on the background of multiple dilated heart chambers, mitral regurgitation grade's 1/4, aortic regurgitation grade's 2/4, BMI: 19.5, Platelet's 240 G/L, heart rate of 82 beats/min, blood pressure's 122/70 mmHg. The patient with an anticoagulation overdose has an INR of 7.63 and the patient had a habit of often *Chrysanthemum* green vegetables of the Asteraceae family [9], [10]. The patients with mitral heart valve surgery, atrial fibrillation and dilated heart chambers, there is an indication for vitamin K anticoagulation drugs and it is necessary to the INR target ranges from 2.5-3.5 levels. The patient subcutaneous hemorrhage with extensive subcutaneous bruising of the shoulder, arm, and forearm, detected anticoagulation overdose (INR = 7.63). The patient was also treated with emergency resuscitation and intravenous vitamin K to treat anticoagulation overdose, after treatment, the patient's coagulation disorder was stabilized [2].

## DISCUSSION

The results showed that the INR test index of all 3 patients of coagulation disorder with bleeding complications above Who had INR index's anticoagulation overdose in the group with high bleeding risk's INR > 5 (INR index are 6.59, 10.91, and 7.63, respectively) [1], [2], [6]. All three cases of patients above used foods containing nutritious green vegetables belonging to the Asteraceae family in the

past period, which is similar to cruciferous vegetables with vitamin K-rich properties [5], [6], [9], [10].

The pathophysiological causes of the increased risk of bleeding events are multifactorial [3]. They may be a direct consequence of urea-associated platelet dysfunction or impaired platelet adhesion and aggregation; impaired platelet glycoprotein IIb or IIIa receptor activation and subsequent glycoprotein binding [6]. Vitamin K is a group of fat-soluble vitamins that are structurally similar and play an important role in the regulation of blood clotting, which is necessary for the assistance of blood clotting. The function of vitamin K as a coenzyme for carboxylase is dependent on vitamin K, an enzyme required for the synthesis of proteins involved in hemostasis (blood clotting) and bone metabolism, and diverse physiological functions. is different. Prothrombin (clotting factor II) is a plasma vitamin K-dependent protein directly involved in blood clotting. Therefore, patients taking these anticoagulants need to maintain a consistent intake of vitamin K to avoid coagulopathy [2], [6]. The study by Eichinger S (2016) in Austria reported that the complication of anticoagulant overdose had a bleeding rate of about 11% [6], in addition, to the study of Karen EG. (2004) statistics show that the rate of bleeding can be up to 10% but up to 25% of patients are likely to bleed at least once a year [4]. Statistics by Connolly SJ. (2009) showed a dangerous complication rate with a hemorrhagic stroke rate of 3.36% and a mortality rate of 4.13% per year in the warfarin group [1].

Patients are using vitamin K anticoagulants with green vegetables containing a lot of vitamin K should moderate and stabilize their diet, because green leafy vegetables such as Asteraceae family containing a lot of vitamin K will reduce the effect of vitamin K anticoagulants drugs [9], [10], [11], this invisibly leads to the need to increase the dose of anti-vitamin K antagonists to achieve the dose or adjust the increase or decrease erratically depending on the INR test index, which is more difficult to control in the adjustment of anticoagulants, When there is an imbalance in the nutritional source of green vegetables rich in vitamin K, it is easy to cause coagulation disorders, including bleeding complications with high INR index.

In principle, in the case of over-dosage with vitamin K antagonists, if there is any sign of bleeding with an increase in INR of any value, the vitamin K anticoagulant should be stopped immediately with 10 mg of vitamin K1 intravenously, can re-inject vitamin



K1 after 12 hours. Blood transfusion, fresh frozen plasma transfusion depending on clinical condition. For cases with coagulation disorders but no signs of bleeding, depending on the level of INR, we treat differently: In cases with  $INR < 5$ , the dose of warfarin can be reduced or stopped 1 warfarin dose and dose adjustment; With an index of  $5 < INR < 9$  usually stop 2 doses of warfarin and then retest and adjust the dose again (or stop 1 dose of Warfarin and take 1-2,5 mg of Vitamin K1); With an  $INR > 9$  but no bleeding, warfarin is usually discontinued with a 10 mg dose of vitamin K1 followed by reevaluation and dose adjustment [2]. All cases of coagulopathy, especially hemorrhagic events, are treated quickly and promptly stabilized by anticoagulation to bring INR back to normal, depending on the patient's condition. As well as the degree of bleeding to choose the time to re-use Vitamin K antagonists or other anticoagulants to ensure safety and stable treatment. When the INR is stable, continue to be monitored periodically every 4 weeks. We can completely handle the situation in time and control the situation [2].

New generation coagulants act directly on blood clotting factors (such as Rivaroxaban inhibits factor Xa, Dabigatran inhibits factor II - Thrombin) thereby preventing the formation of blood clots. Because of their direct impact on blood clotting factors, NOACs are less affected by diet. The effects of new generation oral anticoagulants (Apixaban, dabigatran, edoxaban, rivaroxaban) are not affected by foods high in vitamin K, we suggest that new oral anticoagulants (NOAC) are not expected to interact Asteraceae family green (echinacea); Therefore, we can consider prescribing the NOAC as an alternative to vitamin K antagonists for patients who have difficulty quitting the habit of consuming green vegetables that interact with vitamin K antagonists, but costs will have to be considered due to long-term therapy [2].

## CONCLUSION

The case series of coagulation disorders patients receiving anticoagulant therapy with vitamin K antagonists when using green vegetables of the Asteraceae family may be considered a risk factor for coagulation disorders and an increased risk of hemorrhagic complications, so further research is needed into risk factors in coagulation disorders such as Asteraceae family as well as other green vegetables group with a larger sample to confirm that these side effects for patients when they using vitamin K anticoagulants drugs.

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**Ethical Statement:** Informed consent was obtained from each participant, the confirmation that informed consent for publication of their data and images from each participant. The study approval of an appropriate ethics committee by Haiphong - Vinhbao International General Hospital, the Ethical approval number's 45a/QD-DKQTVB on 19/2/2022.

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