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Research Article

Management of the Bleeding Complications in Patients on Warfarin Therapy

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Journal of Liver and Clinical Research

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Submitted: 26 September 2018

Accepted: 24 October 2018

Published: 26 October 2018

ISSN: 2379-0830

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Keywords

• Bleeding complication; INR; Deep venous thrombosis; Warfarin

Abstract

Background: With the discovery of vitamin K antagonists more than 50 years ago as an oral anticoagulant drug for the treatment and prevention of venous thromboembolism (VTE), the need for coagulation testing emerged. Vitamin K antagonists, such as warfarin sodium, are efficient in reducing venous and arterial thromboembolism. However, these drugs have a narrow therapeutic window. The efficacy of them is assessed by international normalized ratio (INR). The INR values should be kept between 2 and 3 throughout the course of warfarin treatment in patients with VTE. Therefore, warfarin therapy is like a sharp sword with two edges due to its narrow therapeutic window. While INR values below the targeted levels do not prevent thrombosis propagation, elevated INR values increase the risk of bleeding complications.

Patients and methods: We retrospectively present 30 patients with deep vein thrombosis (DVT) and warfarin-induced bleeding. Patients were excluded if they used new direct oral anticoagulant drugs. The type of bleeding complications was classified as major and minor bleeding groups.

Results: There were 14 female and 16 male patients ranging in age from 18 to 72 years. The time interval between the onset of anticoagulant treatment and the bleeding complication ranged from 4 months to 18 months. There were gastrointestinal bleeding in 2 patients, hematuria in 6 patients, epistaxis in 7 patients, and subcutaneous hematoma in 15 patients. We interrupted warfarin therapy in all patients due to bleeding complication. Vitamin K combined with fresh frozen plasma (FFP) was administered in 2 patients with gastrointestinal bleeding. Twenty eight patients with minor bleeding were treated by warfarin withdrawal alone.

Conclusion: During warfarin treatment, INR values should be regularly measured and kept within targeted values to prevent possible bleeding complications and to maintain treatment with effective drug doses. Thus, patients with an INR greater than the targeted values should be closely monitored to avoid bleeding complications. In patients with minor bleeding, it is usually sufficient to stop the treatment of warfarin.

INTRODUCTION

With the discovery of vitamin K antagonists more than 50 years ago as an oral anticoagulant drug for the treatment and prevention of venous thromboembolism (VTE), the need for coagulation testing emerged [1]. Vitamin K antagonists, such as warfarin sodium, are efficient in reducing venous and arterial thromboembolism. These drugs are prescribed in more than 1% of adult people in developed countries [2]. Vitamin K is required for the synthesis of clotting factors II, VII, IX, and X [3]. Vitamin K antagonists have anticoagulant effects by inhibiting these factors.

Although vitamin K antagonists have been found highly efficacious anticoagulant agents in the prevention and treatment of VTE [4], they have a narrow therapeutic window and their anticoagulant effect is unpredictable [2]. The efficacy of vitamin K antagonists is assessed by prothrombin time or international normalized ratio (INR) value. In patients with deep venous thrombosis (DVT), the INR values should be kept between 2 and 3 throughout the course of warfarin treatment. INR values above the target values may cause bleeding complications. Therefore,

warfarin therapy is like a sharp sword with two edges due to its narrow therapeutic window. While INR values below the targeted levels do not prevent thrombosis propagation, elevated INR values increase the risk of bleeding complications.

Bleeding is the most important adverse effect related with warfarin use and is directly related to the level of INR [5]. The bleeding risk increases significantly with an INR value of above 5.0 [6]. Patients with an INR level greater than 10 have a significant risk of hemorrhagic complications [7]. The annual incidence of major bleeding has been found to be between 1.1% and 2.3% in patients using warfarin to maintain the INR levels between 2.0 and 3.0 [8]. In addition to high INR levels, advanced age, hypertension, creatinine level, duration of warfarin treatment, concomitant aspirin use, and genetic mutations (vitamin K epoxide reductase complex (VKORC) 1 and Cytochrome P450 2C9 (CYP2C9)) are also the patient-related risk factors for hemorrhagic complications while using warfarin [9]. Recently, new direct oral anticoagulant agents have been used instead of warfarin. However, in some cases, a switch to warfarin treatment from these new drugs has been required due to bleeding, re-

Cite this article: Ekim M, Ekim H (2018) Management of the Bleeding Complications in Patients on Warfarin Therapy. J Liver Clin Res 5(2): 1050.

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thrombosis and renal deterioration [10]. In addition, any drug that will replace warfarin therapy in mechanical heart valves has not been suggested to date. Because of all these and being cheap, warfarin remains its importance as an anticoagulant agent.

The aim of our study was to evaluate the warfarin-induced complications in patients with deep vein thrombosis (DVT) and to review the relevant literature.

PATIENTS AND METHODS

Thirty patients with DVT and warfarin-induced bleeding treated at Dursun Odabaşı Medical Center and Bozok University Hospital between May 2005 and March 2017 were included in the study. Patients were excluded if they used new direct oral anticoagulant drugs. In addition, patients with diabetes mellitus and patients with liver disease were not included in the study. Routine laboratory tests and radiological examinations (chest radiography and abdominal ultrasonography) were performed in all patients. Of the patients, 12 had hypertension and 6 had chronic venous insufficiency.

The type of bleeding complications was classified as major and minor bleeding groups. The minor bleeding group included patients with skin bleeding, epistaxis and hematuria who were treated with warfarin withholding alone. The major bleeding group included patients with gastrointestinal bleeding requiring blood transfusion. The hemoglobin and coagulation profile were measured and evaluated daily in all patients.

RESULTS

There were 14 female and 16 male patients ranging in age from 18 to 72 years, with a mean age of 33.2 years. All patients were using herbal products. Twelve patients were using garlic extract and 28 were using herbal tea. The time interval between the onset of anticoagulant treatment and the bleeding complication ranged from 4 months to 18 months and the mean was 9 months. There were only 2 patients with gastrointestinal bleeding in the major bleeding group. In the minor bleeding group, there were hematuria in 6 patients, epistaxis in 7 patients, and subcutaneous hematoma in 15 patients.

In patients with major bleeding, the INR values were 18 and 22. Both patients were using aspirin. The remaining 28 patients with minor bleeding had an INR levels between 5-9.

We interrupted warfarin therapy in all patients due to bleeding complication. Vitamin K combined with fresh frozen plasma (FFP) was administered in 2 patients with gastrointestinal bleeding. Twenty eight patients with minor bleeding were managed by warfarin withdrawal alone.

We found previously unrecognized malignancy in two patients with DVT. These patients were referred to the thoracic surgery department for endoscopic examination. Histological examination of biopsy specimens obtained by bronchoscopy revealed squamous cancer in both cases. They were referred to oncology department.

DISCUSSION

A higher risk of VTE has been reported in patients with malignancy [11]. In addition, these patients have an increased risk

of VTE recurrence and bleeding complications [11]. Therefore, routine radiological examinations including chest radiograph and abdominal ultrasonography should be performed in these patients.

Although warfarin overdose may cause bleeding complications at any age, it is more after fifth decades [12]. In patients with more than eighty years old who have an INR level more than 4.0 and who had been taking warfarin for more than three months, bleeding complications significantly increase [13]. Furthermore, warfarin treatment has been reported to be associated with an increased risk of bleeding complications, even in normal-range INR in elderly patients [14]. Therefore, elderly patients should be monitored more frequently.

In this series, the most common form of bleeding was subcutaneous hematoma as previously reported [12]. In patients with minor bleeding, interruption of warfarin therapy with or without the administration of vitamin K is sufficient to ensure the control of bleeding [8]. In contrast, withholding warfarin alone has no significant role in the emergency situation, because of the very slow resolution of the anticoagulant effect of the warfarin [15]. Therefore, in patients with major bleeding, immediate reversal of anticoagulation should be required to avoid life-threatening complications [8]. FFP and prothrombin complex concentrates (PCC) are two suitable products for increasing the levels of vitamin K dependent coagulation factors. Both products contain procoagulant factors II, VII, IX, and X, which are down-regulated due to warfarin treatment [8].

The main adverse effects of FFP are volume overload, transmitted viral infections, allergic reactions and lung injury due to transfusion [6]. The main concerns about PCCs are the potential to induce thrombosis and disseminated intravascular coagulation (DIC), and the risk of virus transmission [15]. Preexisting DIC and uncompensated liver disease are significant contraindications to the use of PCC [15].

The risk of major bleeding was found 0.96% in patients with an INR level of 5-9 but was found increased (9.5%) in patients with INR more than 9.0. Therefore, in patients with INR more than 9.0, cessation warfarin treatment alone may not be enough [6]. Thus, patients with an INR value of more than 9 should be closely monitored to avoid bleeding complications.

Although vitamin K can be given to lower an elevated INR value, its use may lower the INR too much and thus cause a thrombotic tendency or that resistance to warfarin will develop when it is restarted [6]. Furthermore, parenterally injected vitamin K may cause anaphylactic reactions and should therefore be administered carefully with slow intravenous infusion [16]. Additionally, intravenously injected vitamin K may fail to reverse warfarin coagulopathy up to 40% of cases [16]. Therefore, vitamin K should be administered in combination with PCCs or FFP in patients with life-threatening warfarin-induced bleeding.

Standard anticoagulant therapy is initiated with heparin or low molecular weight heparin (LMWH) and oral warfarin (coumadin), and is continued for at least five days until targeted INR values (between 2.0 and 3.0) are obtained for at least two consecutive measurements. Then, heparin or LMWH treatment is discontinued and oral warfarin treatment is continued for at

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least six months. Although the optimal duration of anticoagulant therapy after unprovoked VTE is unclear [17], we believe that the duration of warfarin therapy should be adjusted by considering hereditary and environmental risk factors and warfarin-related bleeding complications.

Warfarin has a narrow therapeutic window and requires frequent laboratory monitoring due to interacting with multiple food and drugs [18]. Therefore, new oral anticoagulant drugs such as dabigatran, rivaroxaban, apixaban and edoxaban have been marketed. These agents have been approved for the treatment and prophylaxis of VTE, and prevention of thromboembolic complications associated with atrial fibrillation. Although these new anticoagulant agents have low drug and food interactions and wide therapeutic indices, they are not exempt from bleeding complications. Their mainly reported bleeding complications are ecchymosis, gastrointestinal bleeding and intracranial hemorrhage [19]. Furthermore, they have no fully effective antidotes against the risk of bleeding. However, after the introduction of these agents, some new molecules have been developed to antagonize their anticoagulant activity [20]. These are synthetic, selective and reversible inhibitors of factor Xa (rivaroxaban, apixaban and edoxaban) or thrombin (dabigatran) [17]. They have the potential to ensure that VTE is treated without hospitalization [17]. Some side effects of these new drugs may be appeared incidentally over time due to genetic differences between patients. Therefore, we believe that hepatic and renal function tests should be carefully monitored for the duration of treatment with these drugs.

In patients using warfarin, the quality of anticoagulant therapy may be measured in practice by means of the time-intherapeutic range (TTR) [21]. Patients who are rarely in the therapeutic range during warfarin therapy may have little or no benefit from treatment with this drug. In these patients, treatment with new direct oral anticoagulant drugs has been recommended. However, patients with good anticoagulation control on warfarin therapy (TTR \geq 70%) do not need to switch to new anticoagulant drugs [21]. In patients using new direct oral anticoagulant drugs, the INR value cannot be used to assess the efficacy of these drugs [20]. Factor Xa inhibitory activity may be more accurately assessed using anti-FXa chromogenic assays. However, anti-FXa chromogenic assays, such as ecarine clotting time (ECT) levels, are still not available in most medical centers [20].

A number of drugs and chemical products may affect the response to warfarin by changing its pharmacokinetic profile [22]. Some herbal products including garlic and some herbal teas potentiate the effect of warfarin and, consequently, the associated risk of bleeding [23]. Therefore, physicians should avoid prescribing herbal products in patients using warfarin. Furthermore, there is no available information about the potential pharmacodynamic interactions of new direct oral anticoagulant agents with foods and herbal products yet [18].

CONCLUSION

During warfarin treatment, INR values should be regularly measured and kept within targeted values to prevent possible bleeding complications and to maintain treatment with effective drug doses. Thus, patients with an INR greater than the targeted values should be closely monitored to avoid bleeding complications. In patients with minor bleeding, it is usually sufficient to stop the treatment of warfarin.

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Cite this article

Ekim M, Ekim H (2018) Management of the Bleeding Complications in Patients on Warfarin Therapy. J Liver Clin Res 5(2): 1050.