
Low Predictive Value of an Elevated Prothrombin Time for Bleeding on Oral Anticoagulation

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This study is a retrospective analysis of 39 consecutive patients who had a prothrombin time of over 25 seconds with respect to the bleeding complications. This study finds that the overall risk of bleeding is low, 2/39 (5.1%), that there is no statistical difference in the values of the patients who bled when compared to those who did not, and that patients who bled tended to have a clearly identifiable precipitating event.

Introduction

The prothrombin time (PT) has long been the standard measurement of the degree of anticoagulation achieved in patients on oral anticoagulants, notably warfarin (Coumadin). This has been used as a predictor of the risk of bleeding. A PT within the range is regarded as safe, and a PT above the range as dangerous. Many patients are put through unrealistic regimens and frequent venous punctures just to manipulate the PT up or down 1 or 2 seconds. The use of the international normalized ratio (INR) allows for elimination of interlaboratory variations, but the same premise is unchanged. This study analyzes the incidence of bleeding in a group of patients who had a PT of over 25 seconds as recorded by a local hospital hematology laboratory over a randomly chosen period of 3 months. This study attempts to evaluate just how risky it is to have an elevated PT, the nature of the bleeding events and whether the risk increases linearly with the magnitude of the PT.

Materials and Methods

A request was made to the director of the hematology laboratory of Straub Clinic and Hospital to randomly choose a 3 month period and identify all patients in this period who had a PT of over 25 seconds. A retrospective analysis was made of the patients' clinic and hospital charts to obtain the incidence and nature of any bleeding events. The period empirically chosen was January 1 to March 31, 1992 and the analysis was made in July 1992.

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Results

A total of 39 patients were identified as having a PT of over 25 seconds. They all were on warfarin. The laboratory had not adopted INR at that time and the values are, therefore, unavailable. The patient characteristics, the PT values, and the nature of the bleeding events are shown in Table 1.

The mean age of the patients was 63 years \pm 13 years. The most common indication for anticoagulation was deep vein thrombophlebitis, occurring in 15 out of 39 patients (38%), 5 of whom had concurrent pulmonary embolism. Two patients were anticoagulated for pulmonary embolism alone. The next most frequent indication was atrial fibrillation, with 7/39 (18%), followed by transient ischemic attack (10%), stroke (10%), valve replacement or repair (7.7%), and vascular graft thrombosis (5.1%). Less common indications include cardiomyopathy, arterial embolism, post thrombotic syndrome, and hypercoagulable state, each with 1/39 (2.6%).

In 20 of these patients, the PT values were obtained during chronic warfarin therapy; in the rest, the PT values were recorded sometime during initiation of warfarin. In 4 of these patients (No 1, 24, 29, 39), the elevated PT values were obtained within 1 week of initiation of therapy. Patients No 1 and 39 also were on heparin.

Two patients (No 19 and 38, Table 1) had a bleeding event.

The first patient was a 58-year-old woman with blue-toe syndrome, aortoiliac embolization requiring warfarin. The PT was recorded to be 26.2 seconds and 26.9 seconds on 2 separate days. She developed a thigh hematoma secondary to trauma, which resolved without specific therapy.

The second patient was a 78-year-old woman who suffered a right hip fracture during a fall, and she underwent hip replacement on the same day. Five days postoperatively, she exhibited hypoxemia with pulmonary embolism and left leg deep vein thrombophlebitis, necessitating the use of warfarin and an inferior vena caval filter. Her PT was documented to be as high as 34.9 seconds. She had bleeding into her right hip requiring transfusion and Vitamin K. She did well on conservative management.

Discussion

The incidence of bleeding in this group of 39 patients with a PT \geq 25 seconds was 5.1%. This is at the lower limit of the incidence of bleeding of all patients on warfarin in the literature (1.2% to

42.4%).¹ The PT for the entire group was 32.3 ± 8.5 seconds (mean ± 1 standard deviation). It is notable that the mean PT of the 2 patients who bled was actually higher than the mean PT of the remaining 37 who did not (30.9 ± 5.7 versus 32.4 ± 8.7 seconds, respectively). The lack of a linear relationship between the magnitude of the PT and the actual bleeding risk is further highlighted by the fact that there was no bleeding at all in the patients with the highest PTs (3 over 40 seconds, 1 over 50 seconds, and 1 over 60 seconds). Despite the advanced age in this high risk group, with its attendant predisposition to ischemic cerebrovascular disease,^{1,2} there was no intracranial hemorrhage. Demonstrating the PT in INR values rather than seconds may smooth out some fluctuations in individual values, but these findings should not be significantly affected. In the majority of these patients, the PT values were obtained at least 1 week after initiation of therapy and should not reflect spuriously high values related to the early depletion of the clotting factors with shorter half-lives (for example, factor VII with a half-life of 6 hours). Only 2 patients were on heparin concurrently, and neither of these patients bled.

The 2 patients who bled had a clearly identifiable precipitating cause: Prior hip surgery or physical trauma to the thigh. It may be inferred that bleeding from anticoagulants is relatively uncommon without a precedent cause or precipitating factor.

Frequently in medicine, there is a near religious or fanatical faith in numbers, as in drug levels or therapeutic ranges. The presence of a therapeutic range virtually binds the physician to doing everything humanly possible to keep the patient in range, frequently without prior knowledge or interest of how such values are determined in the first place, and without appreciation that no 2 patients are alike. The notion of something that can be defined in seconds implies precision, and the availability of a fixed range promises effectiveness and safety. In the case of PT and warfarin, it has been shown that in patients with higher INR, the risk of bleeding is increased.^{1,3} This is, however, far from being an all-or-none phenomenon, as this study demonstrates. The value of a high PT in predicting bleeding is in reality very poor. In a major study comparing 2 levels of anticoagulant intensities in patients with prosthetic heart valves, it was actually the minor bleeding that was increased with the higher INR, with no statistical difference in major bleeding (bleeding requiring transfusion) among the 2 groups.³ It might be more important to be cognizant of the established risk factors of bleeding with warfarin therapy (age ≥ 65 years, female, history of gastrointestinal bleeding, stroke, atrial fibrillation, recent myocardial infarction, congestive heart failure, renal insufficiency, alcoholism, cancer or severe anemia).⁴ It is perhaps wiser to lessen the dosage in these patients, with tighter control of the PT rather than to accept a blanket therapeutic range for all patients—high or low risk. It is quite probable that a high-risk patient would bleed despite strict control, and a low-risk patient easily tolerates a PT of, for example, 35 seconds or an INR of 9.

Even though less intense warfarin therapy could reduce the risk of bleeding, the current system of PT measurement (be it by seconds or by INR) as an index of bleeding risk is far less

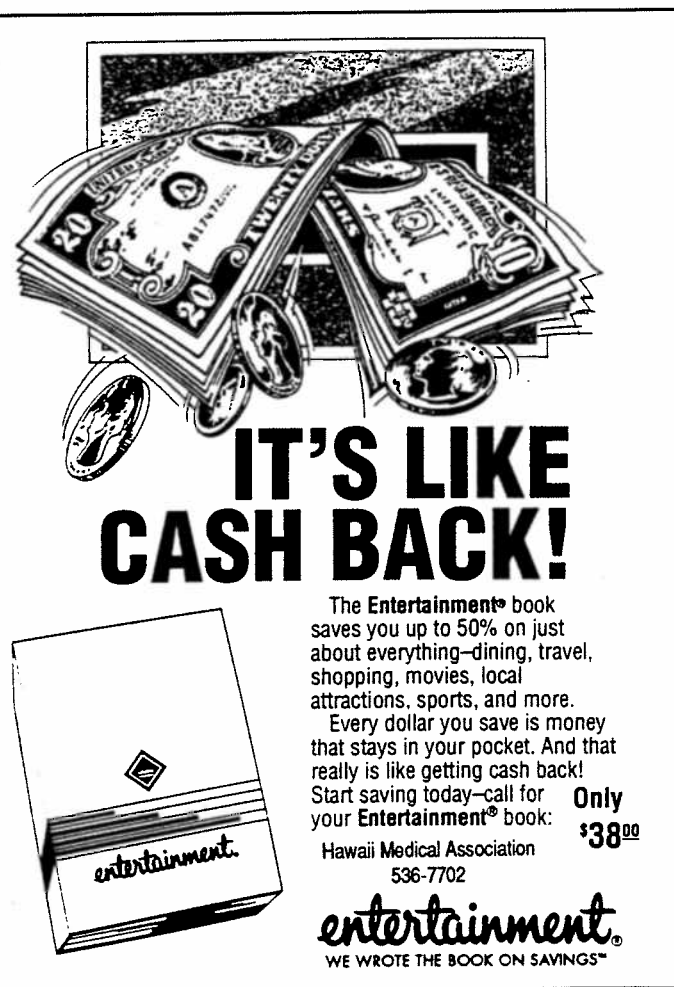
precise than the term “therapeutic range” implies. Alternate parameters should be sought, for example, monitoring the native prothrombin antigen.⁵ These, together with an astute awareness of risk factors and potential precipitating causes, can serve to ultimately diminish the bleeding risk of patients on warfarin.

Conclusion

Prothrombin time has long been the standard by which anticoagulant activity and bleeding risk with warfarin have been measured. This study demonstrates that the magnitude of the PT itself had a very low predictive value for bleeding events, that most patients with high PT did not bleed, and that bleeding was generally related to a clear predisposing factor. This also suggests the need for a more sensitive risk index than that afforded by PT and an awareness of high risk subgroups rather than blind adherence to a therapeutic range.

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