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Regular Article

A 10 mg warfarin initiation nomogram is safe and effective in outpatients starting oral anticoagulant therapy for venous thromboembolism

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ABSTRACT

The optimal means of initiating warfarin therapy for acute venous thromboembolism in the outpatient setting remains controversial. We have previously demonstrated the efficacy of a 10 mg initiation nomogram in a randomized controlled trial; however, some clinicians remain reluctant to use this nomogram due to a fear of potential increased bleeding. To review the safety and efficacy of a 10 mg warfarin nomogram we conducted a retrospective cohort study of patients prospectively treated for venous thromboembolism according to a 10 mg nomogram in an outpatient thrombosis clinic. All patients received standard treatment with low molecular weight heparin for 5 to 7 days and warfarin for at least 3 months. Four-hundred and fourteen patients were included in the analysis, of whom 295 (71%) fully adhered to the nomogram. In the whole cohort, 8 patients (1.9%) experienced recurrent thrombosis, 4 (0.97%) suffered a major bleeding event, and 3 (0.72%) suffered a minor bleeding event. There were no deaths related to thrombosis or bleeding. Four patients (0.97%) died from unrelated causes. Twenty-two (5.3%) patients experienced an INR ≥5.0 in the first 8 days of therapy, and none of these patients experienced a bleeding event. Eighty-four percent of patients achieved a therapeutic INR by day 5. In outpatients, a 10 mg nomogram results in timely achievement of a therapeutic INR with an acceptable incidence of bleeding and recurrent thromboembolism.

Introduction

Venous thromboembolism is a common medical problem in Western countries [1,2]. Historically, anticoagulation therapy was initiated with intravenous unfractionated heparin, which required hospitalization and frequent laboratory testing. In recent years, the use of low-molecular-weight heparin (LMWH) as a bridge to warfarin therapy has allowed a significant percentage of patients with venous thromboembolism to be treated on an outpatient basis [3–5]. Standard outpatient treatment for venous thromboembolism consists of LMWH for a minimum of 5-7 days and oral anticoagulation with warfarin for a minimum of 3 months [5]. Treatment with LMWH is continued until a therapeutic INR (>1.9) is reached. Consequently, the timely achievement of a therapeutic INR is desirable, as it minimizes the inconvenience and expense associated with prolonged parenteral treatment.

The use of fixed dose nomograms has been shown to decrease the number of INR tests required and provides a standardized way to initiate warfarin therapy; however, the optimal nomogram remains a subject of much debate. In 1999, Crowther *et al.* published the results of a randomized controlled trial comparing 5 mg and 10 mg initiation nomograms in a group of 53 patients, and concluded that a 10 mg loading dose did not hasten the achievement of a therapeutic INR [6]. In contrast, in 2003 our group reported the results of a trial comparing the Crowther 5 mg nomogram with our 10 mg nomogram in a group of 201 outpatients, which found that patients in the 10 mg treatment group achieved a therapeutic INR 1.4 days earlier than those in the 5 mg group [7]. Despite there being no increased incidence of recurrence or bleeding in the 10 mg arm, critics of our nomogram cite two major concerns: First, that a 10 mg initiation nomogram potentially exposes patients to an unnecessarily high risk of bleeding [8–11], and second, that a 10 mg loading dose may produce a transient hypercoagulable state by rapidly depleting the vitamin K-dependent natural coagulation inhibitors [9,12–15]. In addition, randomized controlled trials might not reflect the reality of daily practice, raising concerns about the generalizability of the findings outside the usually stringent study setting. Aiming to evaluate the 'real world' performance of our 10 mg warfarin initiation nomogram in the routine outpatient management of venous thromboembolism, we conducted a retrospective cohort study in order to review its safety and efficacy by examining the rates of bleeding complications and recurrent thrombosis.

Methods

Patients and data

We performed a retrospective chart review of patients treated consecutively in the outpatient thromboembolism clinic of a tertiary care hospital between January 2004 and April 2007. All patients were

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treated for objectively confirmed venous thromboembolism diagnosed according to previously published criteria [7]. In all patients, treatment consisted of standard subcutaneous LMWH for 5-7 days and warfarin for a minimum of 3 months. Warfarin therapy was initiated according to our 10 mg nomogram (Fig. 1). Exclusion criteria for use of the nomogram were a baseline INR greater than 1.4, a platelet count less than 50×10^9 /L, age under 18 years old, and treatment with oral anticoagulants within the previous 2 weeks. Patients not using the 10 mg nomogram for the aforementioned reasons or treated with LMWH monotherapy were excluded from the study. In our centre, the majority of patients with known active malignancy receive LMWH monotherapy for venous thromboembolism based on the results of the CLOT study [16] unless thrombosis occurred in the setting of a central venous catheter [17]. Patients were further categorized as adherent (i.e. those who fully adhered to the nomogram) or non adherent (i.e. those who did not). Due to the inability of obtaining INR testing on Sundays or holidays, physicians in our centre will frequently order INR testing on day 7 instead of day 8, as specified by the nomogram. Consequently, patients who had an INR measured on days 3, 5 and 7 instead of days 3, 5 and 8 were included in the adherent subgroup. Supratherapeutic INRs (INR>5.0) were managed by holding warfarin.

Data on safety and efficacy were collected for 90 days following the initiation of anticoagulation. Demographic data were collected on age, weight, sex, and presence of active malignancy, which was defined as malignancy diagnosed or requiring treatment within the past year, or diagnosed within 90 days after the initiation of anticoagulation.

Study endpoints

The study's primary endpoints were the 90-day cumulative incidence of: recurrent venous thromboembolism, major and minor bleeding, and all-cause mortality. Recurrent venous thromboembolism and major bleeding were defined as per previously published criteria [7,18]. Minor bleeding was defined as bleeding that was overt but did not meet the criteria for major bleeding. Secondary endpoints included the proportion of patients achieving a therapeutic INR (>1.9) by day 5, the proportion of patients with an INR≥5.0 in the first 8 days, and the number of INR measurements in the first 28 days. Mean INR values for the first 8 days of treatment were calculated for patients who fully adhered to the nomogram.

Statistical analysis

Given that the retrospective nature of our study limited the number of patients that might have been included, we performed a sample size analysis in order to determine its appropriateness. Assuming that the true maximum frequency for any of the outcomes was 7%(±5%) [3] and a design effect of 4, a sample size of 401 would provide a 95% confidence level to detect such proportion. Primary analysis was done on an intention-to-treat basis and additional subgroup analyses (adherent vs. non-adherent and <75 years-old vs. ≥75 years-old) were also conducted. Continuous variables were analyzed using central tendency measures. For dichotomous variables the 95% confidence intervals (CI) for the proportions were estimated by the normal approximation method. Comparisons between subgroups were done by using either unpaired Student's t-tests, χ^2 tests with Yates correction, or Fisher's exact tests, as appropriate. Two-sided *P*-values <0.05 were considered statistically significant. All analyses were performed using Microsoft Excel XP Version (Microsoft Corp., Redmond WA, USA) and SPSS release 13.0 (SPSS, Chicago IL, USA).

Results

Patient population

Between January 2004 and April 2007 479 patients (age 18 to 99 years) were treated for acute venous thromboembolism with

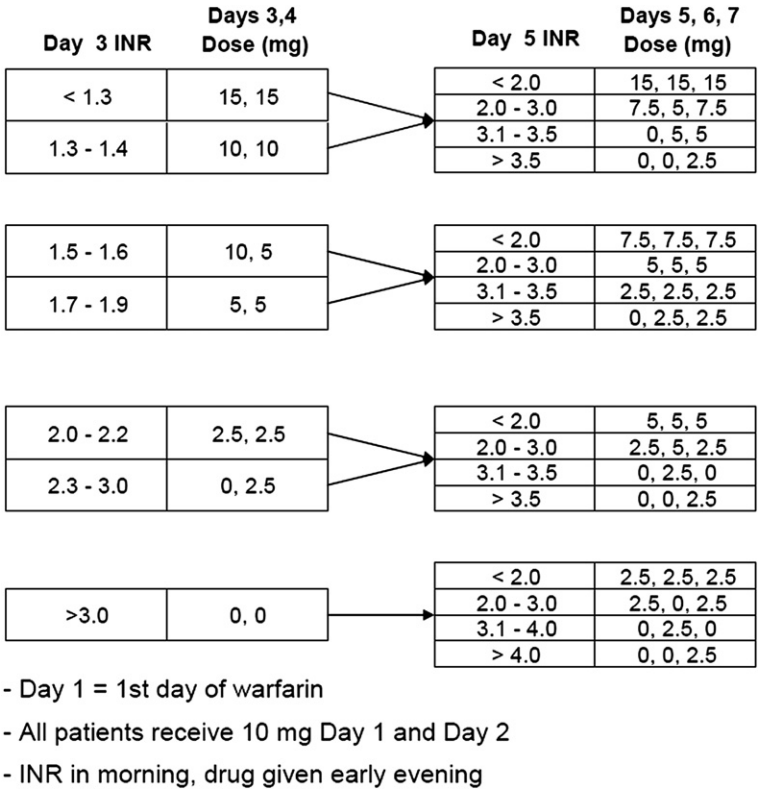

Fig. 1. 10 mg warfarin initiation nomogram (Reproduced with permission from the American College of Physicians).