Thrombosis Research 176 (2019) 33–35

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Letter to the Editors-in-Chief

Comparison of 10-mg and 5-mg warfarin initiation nomograms in a South Indian population - An open label trial

ARTICLE INFO

Keywords:
Warfarin
Initiation nomogram
5 mg nomogram
10 mg nomogram
South Indian population

ABSTRACT

Introduction: Early achievement of therapeutic INR leads to shorter hospital stay and lesser cost. Two warfarin initiation nomograms (10 mg nomogram and 5 mg nomogram) are widely used but it is not yet clear which one is better. They have been validated in the West but there are no studies from India. We undertook this study to compare the efficacy and safety of the 10 mg and 5 mg nomograms in the Indian population.

Methods: 169 patients were enrolled between august 2014 to July 2016. Patients with venous thromboembolism or atrial fibrillation secondary to valvular heart disease were included. Patients were allocated to 10 mg or 5 mg nomogram as per the policy of the treating unit.

Results: 52% of patients in the 10 mg nomogram achieved therapeutic INR by day 5 as compared to only 17% in the 5 mg nomogram (P = 0.022). The median time to achieve therapeutic INR was much shorter in the 10 mg nomogram (5 days vs 14 days, p = 0.018). Two patients in the 10 mg group (2.3%) and none in the 5 mg group had INR > 4 but they did not have any bleeding.

Conclusion: The 10 mg nomogram achieved therapeutic INR significantly earlier with less INR measurements and appears safe. Indian patients require higher a dose of warfarin at initiation and maintenance as compared to other ethnic groups.

1. Introduction

Despite the emergence of non-vitamin K oral anticoagulants (NOACs) as the choice for many indications, warfarin is still widely used particularly in resource poor countries. Early achievement of therapeutic INR is important in patients with venous thromboembolism. It permits shorter hospital stay, shorter heparin course and lower cost. The need to quickly achieve a therapeutic INR should be balanced against the risk of over anticoagulation. The dose of warfarin depends on several factors including age, gender, body weight, vitamin K content of the diet, concurrent medications and genetic factors. For initiation of warfarin, two nomograms have been published [1,2]. Guidelines do not agree on which one is preferred [3–5]. These two nomograms have been extensively used in the Western population [1,6–10], but there are no studies from India. We undertook this study to compare the 5 mg and 10 mg warfarin initiation nomograms in the Indian population.

2. Materials and methods

The study was conducted in the Department of Medicine at Jawaharlal Institute of Postgraduate Medical Education Research (JIPMER), a tertiary care hospital in Pondicherry, South India between August 2014 and July 2016. Patients with deep venous thrombosis and/or pulmonary embolism or valvular atrial fibrillation were enrolled. Age < 13 years or > 70 years, body weight < 40 kg, pregnancy, allergy or intolerance to warfarin, concurrent antiplatelet therapy, baseline INR > 1.4, platelet count < 50,000/μL, creatinine ≥ 1.5 mg/dL, significant liver disease, bleeding diathesis, history of major bleeding in the past, cerebral venous thrombosis, haemorrhagic stroke any time in the past, ischaemic stroke within the last 3 months, cardiac failure, concurrent amiodarone therapy were the exclusion criteria. Significant liver disease was defined as elevated bilirubin, ALT or AST elevated more than twice the upper limit of normal, ascites or prolonged INR.

Consecutive patients who met the inclusion and exclusion criteria were enrolled after written informed consent. The patients received warfarin as per the 5 mg nomogram or the 10 mg nomogram, depending on the policy of the admitting unit. The Department of Medicine has 6 units. Each unit admits on a particular weekday and the case-mix of these units is identical. Some units followed the 5 mg nomogram, and other units followed the 10 mg nomogram (Electronic supplement A1 and A2). There was no blinding or allocation concealment. Patients with DVT also received unfractionated heparin or low molecular weight heparin till discharge or till therapeutic INR was achieved. Warfarin was given early evening and INR was drawn in the AM in both the groups. Patients were followed upto1 month.

The primary outcomes were the **proportion of patients who achieve therapeutic INR by day 5** (INR between 2 and 3 was considered therapeutic) and the **proportion of patients who achieve therapeutic INR by day 8**. The secondary outcomes were time taken in days to achieve first INR in the therapeutic range, major or minor bleeding and rate of recurrence of thrombosis. Bleeding and recurrent DVT or PE have been previously defined [11]. Sample size was calculated to be 80 in each group, to detect a difference of at least 20% in the proportion of patients achieving therapeutic INR on day 5 (two-way alpha error of 0.05; 80% power; 10% attrition). Comparison of means was done with Mann Whitney *U* test or Student's *t*-test and comparison of proportions was done with Chi-square test. Data were analysed using IBM SPSS software version 21. The time to achievement of therapeutic

https://doi.org/10.1016/j.thromres.2018.12.026
Received 4 September 2018; Received in revised form 28 November 2018; Accepted 31 December 2018
Available online 19 January 2019
0049-3848/

Table 1
Baseline characteristics.

Variable	Total N = 169 (%)	10 mg nomogram group (N = 87)	5 mg nomogram group (N = 82)	P value
Mean age ± SD	40.8 ± 13.6	42 ± 13.9	40 ± 13.4	0.318
Gender: male n (%)	73 (43.2)	41 (47)	32 (39)	0.288
Mean body weight ± SD	51.1 ± 7.6	51.5 ± 7.3	50.8 ± 7.8	0.548
Smoking n (%)	63 (37.3)	36 (41.4)	27 (33)	0.256
Alcohol use n (%)	49 (29)	32 (36.8)	17 (21)	**0.022**
Hypertension n (%)	27 (16)	15 (17.2)	12 (14.6)	0.644
Diabetes n (%)	17 (10.1)	7 (8)	10 (12.2)	0.370
Indication for anticoagulation				0.095
Provoked DVT n (%)	47 (27.8)	21 (24.1)	26 (31.7)	
Unprovoked DVT n (%)	102 (60.3)	59 (67.8)	43 (52.4)	
AF n (%)	20 (11.8)	7 (8)	13 (15.9)	
Mean Hb ± SD g/dL	10.5 ± 1.5	10.7 ± 1.6	10.4 ± 1.5	0.231
Mean TLC ± SD	8831 ± 2150.2	9210 ± 2291	8430 ± 1923	**0.018**
Mean platelets ± SD cells/μL	3.96 ± 4.2	3.5 ± 0.8	4.3 ± 0.60	0.238
Mean urea ± SD mg/dL	22 ± 4.17	22 ± 4.3	21.07 ± 3.92	0.081
Mean creatinine ± SD mg/dL	0.91 ± 0.2	0.8 ± 0.05	0.94 ± 0.20	0.050

The items shown in bold have a p value less than 0.05.

INR was compared using Kaplan-Meier survival analysis. The study was approved by the Institute Ethics Committee (human studies), JIPMER and was done in accordance with the 1964 Declaration of Helsinki and its later amendments.

3. Results

176 patients were enrolled. 90 patients followed the 10 mg nomogram and 86 patients followed the 5 mg nomogram. 3 patients in the 10 mg group and 4 patients in the 5 mg group did not complete even 5 days of the protocol and they were excluded from analysis (one patient in each group left against medical advice; 2 patients in the 10 mg group and 3 patients in the 5 mg group did not have INR done on appropriate days, but their INR values did not exceed therapeutic range). The remaining169 patients completed at least 5 days of the protocol and were included in the analysis (87 in the 10 mg group and 82 in the 5 mg group).

3.1. Baseline characteristics (Table 1)

Both the groups were comparable with respect to baseline characteristics but the proportion of alcohol users and total leucocyte count were higher in the 10 mg nomogram. In those with provoked DVT, the underlying causes were similar in both the groups.

3.2. Outcomes

3.2.1. Primary outcomes (Fig. 1)

By day 5, therapeutic INR was achieved in 47 patients (52%) in the 10 mg nomogram group but only in 14 patients (17%) in the 5 mg nomogram group (P < 0.001). By day 8, therapeutic INR was achieved in 68 patients (78%) in the 10 mg nomogram group but only in 30 patients (37%) in the 5 mg nomogram group (P < 0.001).

3.2.2. Secondary outcomes

Only 2 patients (2.2%) in the 10 mg group but 17 patients (21%) in the 5 mg group failed to achieve therapeutic INR even by day 30 of follow up. Among those who achieved therapeutic INR, the median time taken was much shorter in the 10 mg group: 5 days [IQR 5–8] vs 14 days [7–21], P < 0.001. The mean number of INRs done between day 9 and day 30 was only 1.2 and 1.1 in the two groups reflecting poor follow up after discharge. There were no major bleeding or recurrent DVT/PE episodes during the study period of 30 days in either of the groups. Two patients in the 10 mg group but none in the 5 mg group had INR value > 4. None of them had bleeding manifestations. The median maintenance dose was similar. It was and 7.5 mg [7.5 to 10] in the 10 mg group and 7.5 mg [7.5 to 8.9] in the 5 mg group. The range was 5 to 10 and 5.2 to 10 in the two groups.

4. Discussion

The present study compared two widely used warfarin initiation nomograms for efficacy, and safety. The proportion of patients who achieved therapeutic INR on day 5 was much higher in the 10 mg group as compared to the 5 mg group. This was true on day 8 as well. In addition, the median time to achieve therapeutic INR was very much shorter in the 10 mg group. The proportion failing to achieve therapeutic INR even at the end of one month is much lower in the 10 mg

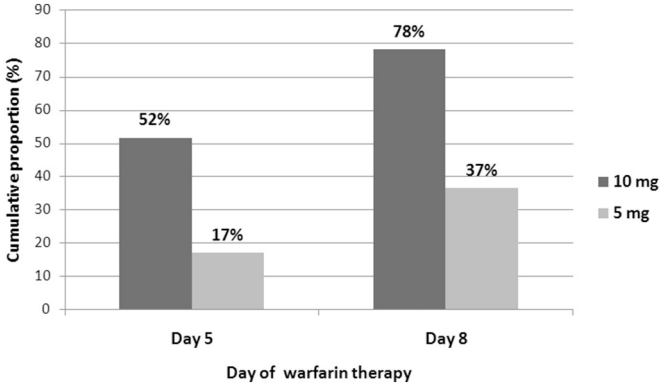

Fig. 1. Proportion of patients achieving therapeutic INR by day 5 and day 8 in 10 mg and 5 mg warfarin initiation nomograms.

group. Inadequate follow up after discharge has led to a high proportion failing to achieve therapeutic INR even at the end of one month and the long median time to achieve therapeutic INR in the 5 mg group. A nomogram which achieves therapeutic INR quickly is *even more important in the developing countries*, given the inadequate follow up.

The proportion achieving therapeutic INR by day 5 in the 10 mg nomogram varied from 56% to 90% in the different studies reported from the West as compared to only 52% in our study. In the 5 mg nomogram, the proportion achieving therapeutic INR by day 5 varied from 46% to 88% as compared to 17% in the present study (see table, Electronic supplement A3) [1,6–10]. That is, significantly lower proportion of Indian patients achieve therapeutic INR by day 5 in the 5 mg as well as the 10 mg nomograms as compared to patients in the Western studies. The 5 mg nomogram particularly is inefficient. This is so, despite the fact that Indian patients are of significantly lower weight. The mean weight was only 51.2 kg in the present study compared to about 80 kg in the Western studies. This perhaps is due to genetic differences in warfarin metabolism or to differences in the vitamin K content of the food, leading to higher warfarin requirements in the Indian patients. However this needs to be confirmed by further studies. This is the only study from India on warfarin initiation nomograms.

Our study was not powered to make out any differences in recurrent thrombosis or bleeding between the two groups. However, the safety and efficacy of the 10 mg nomogram outside of clinical trials have been evaluated by two studies [9,10].

In our study, the median maintenance dose in both the nomogram groups was 7.5. Since the number of INRs done after discharge is limited, it is difficult to draw definite conclusions regarding maintenance dose. In a study from Malaysia, ethnic Indians required a maintenance dose of 6.9 mg; patients of Chinese and Malay ethnicity required a significantly lower dose [12]. The average warfarin maintenance dose in Caucasians, Chinese and Afro-Carribeans were approximately 4 mg, 3 mg and 6.7 mg respectively, as per previous studies [13,14].

This is the first study on warfarin initiation from India. A very high proportion of enrolled patients (169 patients out of 176, 96%) completely followed the nomograms. These are the strengths. Patients were allocated to the 5 mg and 10 mg nomograms as per the policy of the admitting medical unit. This is a major limitation. However, the baseline characteristics were similar in both the groups except for minor differences. Another limitation of the study is inadequate follow up after discharge. However, the primary end points i.e., the proportion achieving therapeutic INR by day 5 and day 8, are assessed before discharge and are not affected by inadequate follow up. The secondary end points such as median time to therapeutic INR depend on proper follow up. Only 2 patients (2.3%) had INR above 4 in the first 30 days but both did not have clinical bleeding. The study excluded patients at high risk of bleeding. So the findings of the study cannot be generalized to all patients.

The 10 mg nomogram may be adopted in Indian patients provided the exclusion criteria applied in this study are respected, but ensuring proper follow up is important. Additional randomized trials or at least registry based studies are warranted to further establish the safety.

Conflict of interest

The authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2018.12.026.

References

[1] M.J. Kovacs, M. Rodger, D.R. Anderson, B. Morrow, G. Kells, J. Kovacs, et al., Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism. A randomized, double-blind, controlled trial, Ann. Intern. Med. 138 (2003) 714–719.
[2] M.A. Crowther, Reply: warfarin: less may be better, Ann. Intern. Med. 127 (1997) 333.
[3] P. Garcia, W. Ruiz, Munarriz C. Loza, Warfarin initiation nomograms for venous thromboembolism, Cochrane Database Syst. Rev. 10 (7) (2013) CD007699.
[4] P. Garcia, W. Ruiz, Munárriz C. Loza, Warfarin initiation nomograms for venous thromboembolism, Cochrane Database Syst. Rev. 29 (1) (2016) CD007699.
[5] C. Kearon, E.A. Akl, A.J. Comerota, P. Prandoni, H. Bounameaux, S.Z. Goldhaber, et al., Antithrombotic therapy for vte disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines, Chest 141 (2012) e419S–e494S.
[6] L. Harrison, M. Johnston, M.P. Massicotte, M. Crowther, K. Moffat, J. Hirsh, Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy, Ann. Intern. Med. 126 (1997) 133–136.
[7] M.A. Crowther, J.B. Ginsberg, C. Kearon, L. Harrison, J. Johnson, M.P. Massicotte, et al., A randomized trial comparing 5-mg and 10-mg warfarin loading doses, Arch. Intern. Med. 159 (1999) 46–48.
[8] R. Quiroz, M. Gerhard-Herman, J.M. Kosowsky, S.M. DeSantis, N. Kucher, S.C. McKean, et al., Comparison of a single end point to determine optimal initial warfarin dosing (5 mg versus 10 mg) for venous thromboembolism, Am. J. Cardiol. 98 (2006) 535–537.
[9] P.S. Wells, G. Le Gal, S. Tierney, M. Carrier, Practical application of the 10-mg warfarin initiation nomogram, Blood Coagul. Fibrinolysis 20 (2009) 403–408.
[10] K. Monkman, A. Lazo-Langner, M.J. Kovacs, A 10 mg warfarin initiation nomogram is safe and effective in outpatients starting oral anticoagulant therapy for venous thromboembolism, Thromb. Res. 124 (2009) 275–280.
[11] M. Levine, M. Gent, J. Hirsh, J. Leclerc, D. Anderson, J. Weitz, et al., A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis, N. Engl. J. Med. 334 (1996) 677–681.
[12] G.G. Gan, A. Teh, K.Y. Goh, H.T. Chong, K.W. Pang, Racial background is a determinant factor in the maintenance dosage of warfarin, Int. J. Hematol. 78 (2003) 84–86.
[13] H.C.M. Yu, T.Y.K. Chan, J. Critchley, K.S. Woo, Factors determining the maintenance dose of warfarin in Chinese patients, QJM 89 (1996) 127–136.
[14] A. Blann, J. Hewitt, F. Siddiqui, D. Bareford, Racial background is a determinant of average warfarin dose required to maintain the INR between 2.0 and 3.0, Br. J. Haematol. 107 (1999) 207–209.

Sivaramakrishna Naik D[a], Vivekanandan Muthu Pillai[a,*], Prashant S. Adole[b]

[a] *Department of Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006, India*

[b] *Department of Biochemistry, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006, India*

E-mail address: drvivekvivek@gmail.com (V.M. Pillai).

* Corresponding author.