IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
September 2020 Vol.:19, Issue:2

Assessment of Adequacy in Estimating Time in Therapeutic Range (TTR) for Patients Receiving Oral Anticoagulation Therapy

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
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ISSN 2349-7203
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Submission: 25 August 2020
Accepted: 31 August 2020
Published: 30 September 2020

Keywords: Oral anticoagulation therapy, Rosendaal method, Time in Therapeutic Range, Vitamin K antagonists

ABSTRACT

Anticoagulation control is conventionally assessed by INR monitoring. Time in Therapeutic Range (TTR) is a novel approach for achieving better quality of oral anticoagulation. TTR is defined as the duration of time in which the patient's INR values are within a desired range, in terms of percentage (%). This study evaluates the adequacy of TTR in clinical practice for patient management which remains hypothetical. This is an observational study over a period of 6 months from March 2018 to August 2018 in the department of Cardiology in a tertiary care teaching hospital. Patients above 18 years of age receiving Oral Anticoagulation therapy (Vitamin K Antagonists) were enrolled. Patients with irregular follow up, Prosthetic heart valve replacement and hepatic dysfunction were excluded. Calculation of TTR was done by Rosendaal method. As per TTR calculation, 86.67% of patients were poorly controlled (TTR <65%) and 13.33% were in good control (TTR ≥65%). The mean TTR was 33.12% for the treatment period. The INR of the population ranges from 1.26 to 5.14 with a mean INR of 2.5 ± 0.81. As per INR 54% of patients maintained normal INR. Even though TTR and INR are well maintained, 20% of the population developed complications. TTR calculation as an additional tool along with regular INR monitoring could give beneficial outcome in the tailoring of dose and forecasting complications in clinical practice.

INTRODUCTION:

Oral Anticoagulation Therapy (OAC) reduces the coagulability of blood by maintaining International Normalised Ratio (INR) in optimal therapeutic range[1]. Dose adjustments for OAC such as Vitamin K Antagonists (VKA) have been done based on INR. Abnormal INR values can predict complications such as Bleeding and thromboembolic events. Time in Therapeutic Range (TTR) is a value that estimates the percentage number of days a patient's INR is within the desired treatment range[2,3]. Many studies reported TTR as a tool to comprehend anticoagulation control. The results of various studies conducted worldwide shows poor control of anticoagulation[4-6]. TTR helps in prediction of complications. Poorer TTR contributes to increased incidence of complications[7]. However, its use has not been well established clinically. On that account, we indent to evaluate to what extent TTR is an adequate tool to use in clinical practice for OAC therapy. The aim of the study was to assess the adequacy of oral anticoagulation therapy by estimating TTR.

MATERIALS AND METHODS:

The observational study was carried out in the department of Cardiology in a tertiary care teaching hospital, Coimbatore, India for a period of 6 months (March 2018 to August 2018). The study protocol has been approved by Institutional Human Ethical Committee (approval number 18/026). All participants have signed informed consents for inclusion in the study.

Patients above 18 years of age receiving VKA like Acenocoumarol and Warfarin as OAC for Atrial fibrillation (AF) and Venous thromboembolism were included in the study. Patients with irregular follow up, Prosthetic Heart Valve Replacement and hepatic dysfunction were excluded as it affects the calculation of TTR.

The data were collected from patient medical record and hospital information system. All the patients were followed for three months and three consecutive INR values were collected. Calculation of TTR was done by Rosendaal method[8] which was performed with the assistance of a template produced and made freely available by INR Pro. The template was validated by IHEC. This method calculates TTR by incorporating the frequency of INR measurements and their actual values. The patients were categorized as good control (≥ 65% TTR) and poor control (< 65% TTR) based on percentage of TTR.

Independent student T-test was used to find the association of TTR with clinical events. One way ANOVA was applied to analyze the difference between various INR ranges and occurrence of complications. Statistical package for social sciences version 16 was used for the interpretation of results. P value less than 0.05 was considered statistically significant.

RESULTS:

A total of 150 patients receiving VKAs such as Warfarin (8 patients) and Acenocoumarol (142 patients) were included in the study. Dose adjustment of OAC therapy for all the patients in this study has been done based on the INR values.

TTR values for the OAC therapy were calculated for all the patients. The Mean TTR for the population was 33.12% which is the percentage of days the patients INR is within therapeutic range for the treatment period. This portrays a poor control of anticoagulation in the population. Among the population, 87% were in poor control of anticoagulation therapy and 13% were in good anticoagulation control. Overall, 20% of patients developed complications such as Bleeding (17%) and Thromboembolic event (3%).

Regardless of being in good control of anticoagulation therapy (13%), 15% of population developed complications such as bleeding (2 patients) and thromboembolic event (1 patient). In poorly controlled population (87%), 21% of patient developed complications such as bleeding (23 patients) and thromboembolic event (4 patients). There was no significant difference in the clinical events between good and poorly controlled oral anticoagulation therapy (p=0.609) [Table 1].

Table No. 1: Association of TTR with clinical events

TTR	CLINICAL EVENTS		P VALUE
	YES	NO	
Poor control (n = 130)	27 (20.77%)	103 (79.23%)	0.609
Good control (n = 20)	3 (15.00%)	17 (85.00%)	

All the patients' VKA dose was adjusted based on the INR values at the time of each visit. It ranges from 1.26 to 5.14 which are out of the desired range. Target INR range of 2-3 was maintained by 54% of the population, 18% and 28% of the population were above and below the target INR range respectively. However, dose adjusted to attain the normal range also led

to 20% of clinical events. The development of clinical complications was significantly high in patients maintaining an INR of 4-5 (45%), followed by INR of 2-3 (20%) (p=0.02) [Table 2].

Table No. 2: Association of INR ranges with clinical events

INR	POPULATION	CLINICAL EVENTS	P VALUE
1 – 2	42	6 (14%)	0.02*
2 – 3	81	17 (20%)	
3 – 4	16	2 (12%)	
4 - 5	11	5 (45%)	

*significant p value (<0.05)

TTR calculation was poor in 79% of the patients maintaining normal INR range. INR was out of desired range in 4.3% of the patients maintaining good TTR. Even though TTR and INR are well maintained, 20% of the population developed complications. INR conveys the maintenance of anticoagulation therapy at a specific point of time whereas TTR depicts the anticoagulation control over a period of time [Table 3].

Table No. 3: INR vs. TTR

INR	TTR	COMPLICATIONS
Normal (54%)	Poor (79%)	21%
Abnormal (46%)	Good (4.3%)	19%

Patients with normal INR at the time of a visit were calculated to have poor TTR because TTR calculates the percentage number of days the patients were in range from the previous visit. Interpretation of INR helps in the prediction of complications and TTR aids in forecasting treatment outcome.

Even though TTR depends on INR values, TTR takes into account the INR values and the number of days from the previous visit. This helps in understanding how many days the patient's INR values were in range and out of range. Hence considering TTR along with INR for dose adjustment would give beneficial results.

DISCUSSION:

Vitamin K antagonists (VKA) have been the conventional therapy for management of thromboembolic events in spite of potential drug interactions and narrow therapeutic window[9]. Percentage of TTR is being considered as the quality measure for determining the efficacy and safety of oral VKA such as warfarin and acenocoumarol. Poor control of TTR (<65%) increases the risk of bleeding and thromboembolic event. The maintenance of INR in definite target range is reflected in TTR, which is the measure of the period in which patient was in optimal INR range. TTR can be calculated using three general approaches such as Rosendaal method, cross-sectional method and traditional method. Among this, Rosendaal method is considered as golden standard in which INR-specific person-time is calculated by incorporating the frequency of INR measurements and their actual values.

In NICE guidelines TTR percentage of < 65% was considered as poor control[10]. In our study 86.67% of patients had < 65% TTR and categorised as poor control. The mean TTR in our study was 33.12%. ROCKET AF, a double-blind trial assessed the anticoagulation control for 6983 patients taking warfarin showed a mean TTR of 36% in India[11]. Thus we could infer the mean TTR ranges from 30 – 40% in India, which is comparatively less than other studies worldwide[4-6].

In our study, 86.67% of patients were poorly controlled during OAC therapy out of which 20% of patients had complications. Prabhat Singh *et al* evaluated the quality of OAC in 77 patients from Neurology patients unveiled that 28.6% of patients developed complications[7]. So the incidence of complication in patients receiving OAC is greater than or equal to 20%.

Increase in mean TTR was significantly associated with decreased rate of both major bleeding and systemic embolism[12]. In spite of maintaining good control of anticoagulation therapy, 15% of the population developed complications such as bleeding in 2 patients and thromboembolism in 1 patient. In poorly controlled population, 23 patients had bleeding and 4 patients had thromboembolism which contributes to 21% of the population. We could not project a statistical significance between poor TTR and clinical events. But the percentage difference between patients who got a clinical event in poor control population and good control population supports the results produced by other articles.

Another aspect of critical importance in patients receiving OAC therapy is regarding dose adjustment. Dose was adjusted for all the patients to maintain a target INR range of 2-3. Even

though, 54% of the patients maintained normal INR range, 20% of them developed clinical events. TTR calculation was poor in 79% of the patients maintaining normal INR range.

For a patient, dose adjustment would not be statutory according to INR but TTR would unveil poor control of anticoagulation. This reveals that the patient requires dose alteration. But TTR doesn't apprise whether to escalate or deescalate the dose.

INR monitoring is inevitable in view of the fact that TTR rely on INR. Alteration of dose solely based on INR or TTR values is not appropriate according to our study. Therefore, monitoring TTR along with INR helps in understanding how many days the patient were in range and out of range which aids in better management of anticoagulation for patient with normal INR.

The adequacy of TTR can be more clearly elucidated with increased sample size and a control group of INR monitoring compared with a test group of TTR calculation for dose adjustment and prediction of clinical events.

CONCLUSION:

TTR calculation as an additional tool along with regular INR monitoring could give beneficial outcome in the tailoring of dose and forecasting complications in clinical practice. A study portraying test group of TTR calculation with increased sample size would clearly elucidate the magnitude of adequacy of TTR.

ACKNOWLEDGEMENT:

We express our heartfelt gratitude to Ethics committee of PSG Hospitals. We are grateful to the clinical pharmacist of cardiology department, Dr. Mintu George for her kind support throughout the course of study.

CONFLICT OF INTEREST:

The authors declare no other conflict of interest.

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