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Research Article

Evaluation of Efficacy and Determining Various Factors Associated with the Effective Use of Vitamin-K Antagonist Therapy in the Indian Population

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Abstract

Aim: To assess the efficacy of Vitamin K antagonist to maintain stable INR in a tertiary care hospital.

Methodology: All the patients who are on Vitamin K antagonists therapy for more than 6 months before the initiation of the study were included. Data, which include demographics, Personal history, medical history, medication history, Dietary habits, laboratory data (INR), and other relevant data, are collected. The laboratory results are further evaluated using the Rosendaal method and Time in Therapeutic Range, which was obtained which is evaluated, for assessing the use of medication, and other correlations were further made.

Results and Discussion: The study showed a mean TTR of 25.638%, the mean TTR above and below the therapeutic range is 19.23% (±17.14), 55.11% (±29.64) respectively, this represents that the patients in the sample population are at higher risk of developing a new clot during the therapy with VKA, various chronic conditions such as Diabetes mellitus, the use of NSAIDs, PPI also showed a statistically significant difference on the patients TTR.

Conclusion: Despite patients being therapeutically anticoagulated, based on the available data, many patients in the study population are at high risk of developing complications of anticoagulants and also the development of new clots even during the treatment, there are not many reports of TTR measurement in INDIAN population, The use of Vitamin K Antagonist comes with many limitations, many Newer Oral Anticoagulants (NOAC) can be used in patients as they are proven to be providing better control of TTR.

Keywords: Vitamin K Antagonist; Warfarin; Acitrom; Time in Therapeutic Range; Rosendaal method; Vitamin K Diet; Anticoagulation; Bleeding; Atrial Fibrillation

Abbreviations

VKA: Vitamin K Antagonist; TTR: Time in Therapeutic Range; AF: Atrial Fibrillation; HTN: Hypertension; CKD: Chronic Kidney Disease; DM-II: Diabetes Mellitus; NSAIDs: Non-Steroidal Anti Inflammatory Drugs; PPI's: Proton Pump Inhibitors

Introduction

Vitamin K is a fat-soluble vitamin, the most naturally occurring K Vitamins are phylloquinone, which is called Vitamin k1, this Vitamin K1 is mostly available from green leafy vegetables, and Phylloquinone in plants is helpful for photosynthesis. Menaquinone is Vitamin K2; this Vitamin K2 differs from that of K1 with variation in the length of the side chain, which is formed from intestinal bacteria. There is another form of Vitamin K, which is Menadione which is not a naturally occurring substrate, but it can be manufactured synthetically [1,2].

Vitamin-K cycle

Vitamin K is itself is an inactive form (quinine) when reduced into quinol form with the help of vitamin k1 quinone reductase. This helps in forming the active form of Vitamin k1 and this active form is used as a substrate in posttranslational modification of the amino-terminal of glutamic acid. Which residues to 4-carboxyglutamic acid (GLA) in the vitamin K-dependent clotting factors II, VII, IX, X, protein S, C, Z [3] with help of carboxylate epoxidase to its active forms. Thereafter, carboxylation Vitamin k1 (active form i.e. quinol) is converted into an inactive form which is Vitamin k1 2,3 epoxide, and with the help of vitamin k1 2,3 epoxide reductase that results in the formation of the Quinone form of Vitamin K which is again the parent compound [4-6].

Coagulation pathway

The mechanism of formation of a blood clot (Hemostasis) involves different pathways, which include the intrinsic pathway and the extrinsic pathway. The intrinsic pathway consists of coagulation factors I, II, IX, X, XI, and XII, and the extrinsic pathway includes factors I, II, VII, and X. Factor II is prothrombin which when activated in turn increases the activity of Factor XI, VIII, V, XIII which leads to the formation of a stable clot. The extrinsic pathway is activated by the tissue factors, which are released from the endothelial cells after external damage; the intrinsic pathway is activated when exposed

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through endothelial collagen [7].

Oral anticoagulants

These drugs act through different mechanisms for preventing clot formation, which can be chiefly classified as [10]:

- Direct thrombin Inhibitors: Argatroban, Bivalirudin, Dabigatran, Desirudin [11,12].
- Direct factor Xa inhibitors: Rivaroxaban, Apixaban, Edoxaban [13,14].
- Vitamin k antagonist: Warfarin, Acenocoumarol [15].

Time in therapeutic Range (TTR)

When patients are being treated with Vitamin K antagonists, the effect of these drugs should be monitored closely as there is an increased risk of bleeding in these patients.

The effectiveness of these drugs can be monitored by checking PT, INR of the patients at regular intervals for most of the indications such as Prophylaxis for DVT, Treatment for DVT, Post CABG patients, Heart failure, Peripheral vascular diseases, Atrial Fibrillation. The required therapeutic INR is 2-3 [16,17], but for some indications such as Myocardial Infarction, the Therapeutic INR requires to be 3.0 to 4.0 for the optimal effectiveness of drug therapy [18,19].

Measurement of TTR

Linear interpolation methods (Rosendaal method): This method involves the calculation of TTR by incorporating the frequency of INR measurements and their actual values and assuming that changes between consecutive INR measurements are linear over time [20].

Factors affecting TTR

Many factors influence the TTR such as age, body weight, nutrition status, acute and chronic disease, Polypharmacy [21], high vitamin k diet, vitamin k supplements [22], adherence to the therapy [23,24], awareness about the therapy [25], which can result in therapeutic failure [26,27].

Methodology

All the patients who were prescribed Vitamin K antagonists and who were on the therapy for more than 6 months before the initiation of the study were included. Data includes demographics, personal history, medical history, medication history, dietary habits, laboratory data (INR), and other relevant data were collected. The laboratory results were further evaluated using the Rosendaal method and Time in Therapeutic Range, which were obtained which was evaluated, for assessing the use of medication, and other correlations were further made.

Statistical analysis

Data were analyzed using Minitab software, 2 sample t-test, a p-value of <0.05 is considered to be statistically significant, the data obtained in the study was analyzed by 2 sample t-test

Results

The patients were classified into 3 groups based on the TTR; TTR of >70% is considered to be good Control, TTR of 50%-70% is considered to be intermediate control, TTR of <50% is considered to be poor control, the mean (±SD) TTR of the patients involved in the study was 25.64% (±20.82),

Fifty patients were enrolled over 6 months, the mean TTR among the sample population was 25.46%, a total of 23 males, 27 female patients were enrolled.

The good control group had 1 patient with a mean TTR of 88.9%, the intermediate control group had 7 patients with a mean TTR of 56.74%, 42 patients were having poor control of TTR with a mean TTR of 18.94%.

The demographics of the patients involved in the study are described in (Table 1) as seen in the below table there is no statistically significant difference between the patients based on age and gender (P= 0.664, 0.456 respectively).

The effect of various medical conditions, medications on a patient's TTR are discussed in Table 2, The patients with MVR, Diabetes mellitus, on NSAIDs, PPIs had a significant difference in the mean TTR (P= 0.001, 0.021, 0.004, 0.017 respectively) (Table 2).

The mean TTR values of patients on various no. of concomitant medication is shown in Figure 2; it shows patients with 3 concomitant medications had a mean TTR of 29.8% followed by patients with 4 concomitant medications with a mean TTR of 29.26., the lowest being patients using only 1 concurrent medication with a mean TTR of 3.8% followed by 15.45% in patients using 5 medications (Figure 2).

The deviation of INR above 3 and below 2 defines the supratherapeutic and sub-therapeutic values, the mean TTR of the sample population below the Therapeutic level was 55.11% (±29.64), the mean Time above the therapeutic range is 19.23% (±17.14) (Figure 3).

Discussion

Time in therapeutic range is widely used in the measurement of quality of treatment with Vitamin k Antagonist, According to

Table 1: Demographic parameters and personal history of the studied patients.

		Good Control N (TTR%)	Intermediate Control N (TTR%)	Poor Control N (TTR%)	P-Value
Age	>60 Years	1 (88.9)	2 (52.4)	21 (21.4)	0.664
	<60 Years	0	5 (58.48)	21 (16.48)	
Sex	Male	0	4 (54.97%)	19 (16.96%)	0.456
	Female	1 (88.9)	3 (59.1%)	23 (20.91%)	
Smoking	Yes	0	1 (57.3%)	3 (4.4%)	0.570
	No	1 (88.9)	6 (56.65%)	39 (20.26%	

Table 2: TTR of the studied population based on various parameters.

		Good Control	Intermediate Control	Poor Control	Mean TTR (%)	P-Value
AF	Yes	1 (88.9)	2 (52.4)	21 (21.4)	21.8	0.709
	No	0	5 (58.48)	21 (16.48)	20.2	
MVR	Yes	0 (0)	1 (50.9)	4 (41.7)	43.54	0.001
	No	1 (88.9)	6 (57.71)	38 (16.55)	23.6	
DM-II	Yes	0	0	20 (17.99)	18	0.021
	No	1 (88.9)	5 (57.6)	24 (23.1)	30.7	
HTN	Yes	1 (88.9)	2 (59.1)	18 (16.73)	24.2	0.694
	No	0	5 (55.8)	24 (20.91)	26.7	
CKD	Yes	0	0	8 (15.46)	15.5	0.098
	No	1 (88.9)	7 (56.74)	34 (19.95)	27.6	
HYPOTHYROIDISM	Yes	1 (88.9)	0	3 (24.7)	37.9	0.526
	No	0	7 (56.74)	39 (18.79)	24.6	
NSAIDS	Yes	0	0	2 (6.35)	6.35	0.004
	No	1 (88.9)	7 (56.74)	40 (19.57)	26.4	
PPI's	Yes	0	0	9 (13.93)	13.9	0.017
	No	1 (88.9)	7 (26.74)	33 (20.31)	28.2	

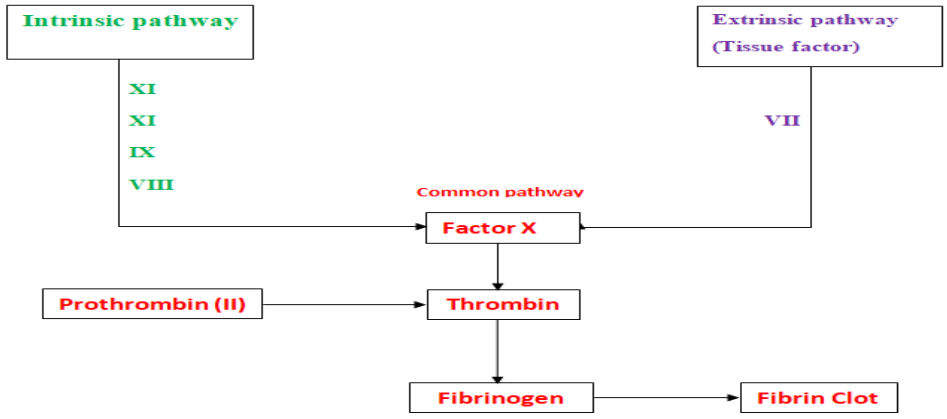

Figure 1: Coagulation Cascade [8,9].

many studies conducted on patients receiving VKA, patients with a mean TTR of >70% had a decrease in risk of thromboembolic and hemorrhagic events, in comparison to the patients with a mean TTR of <70% [28].

The mean TTR of the patients involved in the study is 25.63%, 83% of the study population are having poor control of INR with a mean TTR of 19.08%, indicating that the patients were poorly managed and are at increased risk of developing complications.

The mean TTR of the patients involved in the study is 25.63%, 83% of the study population are having poor control of INR with a mean TTR of 19.08%, indicating that the patients were poorly managed and are more prone to the adverse effects.

Various risk factors associated with TTR

Influence of patient's comorbid conditions on the efficacy of VKA therapy: The lower levels of mean TTR may also be the result of various comorbid conditions, based on a study done by Meegan EV et al. [29] the patients who had chronic conditions such as liver disease and CHF had a higher incidence of increased INR levels. Similarly, in this study, the patients who had DM-II had lower TTR values when comparison to non-diabetic patients a mean difference of 12.7% (P=0.021) was observed.

Effect of polypharmacy on the patients TTR: According to studies done by Farsad BF, a decrease in TTR was observed in patients who are receiving 5 or more than five medications, in patients who received less than 4 medications the rate of TTR was above 85%. In the present study of 50 sample population 22 patients received more than 5 medication with a mean TTR of 26.3%, 8 patients received 4 medications with a mean TTR of 29.26%, 4 patients had 3 concomitant medication showed a mean TTR of 29.8% this shows that patients who received 3 medication had a higher percentage of TTR when compared to patient received 4, 5 and more than five medications, Patients TTR was also dependent on the class of the drugs they have been using in the study the patients who are on NSAIDs and Proton

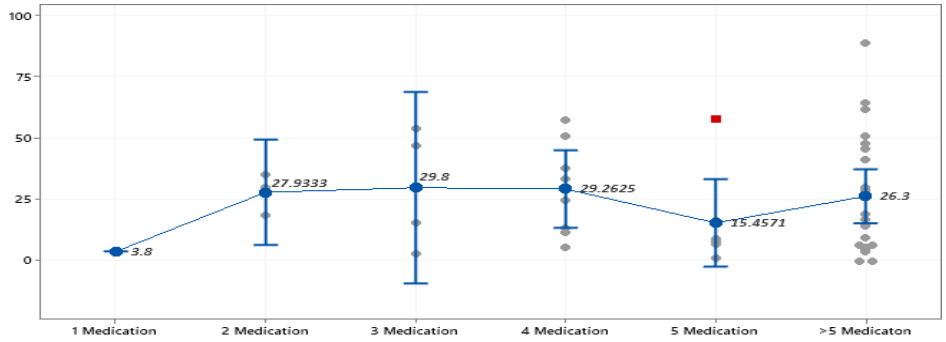

Figure 2: Effect of polypharmacy on patients TTR.

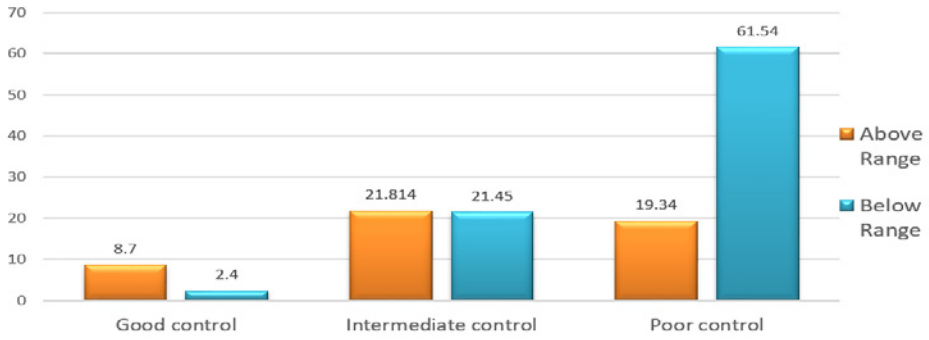

Figure 3: TTR above and below Therapeutic range.

pump inhibitors had a lower TTR value (P=0.004; 0.017 respectively).

Impact of smoking on anticoagulation therapy: The prevalence of low levels of TTR was also found to be associated with smoking according to a study done by Mwita JC [30] and Gatemen D [16] similarly, in this study a difference in mean TTR of 8.72% among smokers and non-smokers in this study (P=0.570).

Conclusion

Despite patients being therapeutically anticoagulated, many patients in the study population are at high risk of developing complications of anticoagulants and also the development of new clots even during the treatment, there are not many reports of TTR measurement in the INDIAN population, only a small group of the population studied as a subset in ROCKET AF which showed mean TTR of 36% [33,34], in this study the mean TTR was found to be 25.638%, 21.65 as a median. The use of Vitamin K Antagonist comes with many limitations, which include many dietary restrictions, regular monitoring of INR and dose adjustment, and the use of these drugs in patients who are on multiple medications, which can cause many Drug-Drug interactions, unpredictable dose-response owing to its genetic association, and many more. Many Newer Oral Anticoagulants (NOAC) can be used in patients with the above limitations and can help in achieving desired anticoagulation effects.

Limitations

All studies have their limiting factors, being a retrospective study; this too has some limitations, which have been noted during the study.

One confounding factor that had been observed during the study was the variations in the interval between measurements of INR; this can lead to variation in the overall TTR of the patient.

Further Directions

A study on, comparing the risk factor analysis such as ATRIA score for assessment of bleeding; CHA2DS2-VASC score for assessing the risk factor for stroke with the patients TTR, helps in better validating the procedure.

Comparison of the different classes of oral anticoagulants can provide better insights on understanding the difference in the effectiveness of various drugs.

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