Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

Evaluation of clinical pharmacist initiated interventions on anticoagulation management in a selected tertiary care hospital in south India

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ARTICLE HISTORY

Received: 23.06.2019

Accepted: 29.08.2019

Available online: 30.09.2019

Keywords:

INR, Anticoagulation, Adverse drug reactions, Clinical pharmacist

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ABSTRACT

Anticoagulation management is a challenge for the healthcare providers including clinicians due to its narrow safety margin with either bleeding or clot formation beyond its therapeutic range. Periodic monitoring of INR levels and identification of risk factors have a major role in oral anticoagulation therapy and hence close monitoring of patients is a must. The purpose of this study was to analyse the impact of clinical pharmacist initiated interventions in anticoagulation management in a selected tertiary care hospital. Prospective interventional study was conducted using retrospective data of the patients as control. Patients in intervention group received care from the clinical pharmacists in addition to the routine care by clinicians and other healthcare providers. Out of 51 patients enrolled in the study, 41 patients were same in retrospective and prospective arm. There was a statistically significant improvement in knowledge score of patients in the intervention group when compared with control group ($p<0.01$). A significant improvement in medication adherence of patients between control group and interventional group ($p <0.01$) was also observed. Knowledge about the anticoagulation therapy and medication adherence to treatment has a significant role in anticoagulation management as there was improvement in time on target INR range in the intervention arm compared to control arm. The therapeutic outcome of treatment improved in this study as the percentage of patients on target INR range increased from baseline. Qualified clinical pharmacist can thereby play an important role in anticoagulation management by imparting knowledge to the patients on the same.

INTRODUCTION

Vitamin K antagonists like Warfarin and Acenocoumarol have been used since decades as a standard therapy for prevention and treatment of thrombotic events [1]. Warfarin is a highly efficacious oral anticoagulant agent, but its use is associated with the well fear of bleeding [2]. Anticoagulants are used in patients with a history of atrial fibrillation, recent major surgery or immobility, heart valve replacement, ischemic stroke or other thrombotic event. Warfarin is a drug with narrow therapeutic window and has significant variability in dose response across individuals. Patients receiving warfarin therapy should have regular blood tests to measure how long blood takes to clot, called International Normalised Ratio (INR). The INR value must remain within the therapeutic range. Frequent monitoring of INR lab values and dose adjustments, therefore, are necessary for safe and efficacious use of warfarin[1] .Vegetables like broccoli, Brussels sprouts, kale, parsley, spinach etc contain high sources of vitamin K and eating large quantities or making sudden changes in the consumption of these vegetables, may interfere in the effectiveness and safety of warfarin therapy. Changes in the use of concomitant medications, diet, alcohol consumption, acute illness, liver disease, and unknown factors can also interfere with warfarin therapy. So regular monitoring of INR and dose adjustments of warfarin are frequently required during anticoagulation therapy with warfarin. There are various factors that could lead to fluctuation in the INR and also affect patient response to warfarin therapy. These factors vary from poor compliance, lack of patient knowledge, dosage error, concomitant illness, and concomitant use of other medications, dietary interactions, laboratory error and ageing [2].

Mutations in genes encoding for cytochrome P450 2C9 enzymes are responsible for reduced warfarin requirements in some individuals; altering pharmacokinetics of the drug. The most common and best documented alleles, designated CYP2C9*2 or CYP2C9*3 to differentiate it from, the wild type CYP2C9*1 are associated with an impaired ability to metabolize S- Warfarin resulting in an increased elimination half- life of the same. Also, mutations in the VKORC1 gene have been identified, leading to varying sensitivities to inhibition by Warfarin which thereby affects the pharmacodynamics of it. These mutations are likely to be the cause of hereditary warfarin resistance in some individuals. Another genetic mutation which alters the pharmacodynamics of warfarin is the factor IX propeptide. It can cause selective reduction in factor IX during treatment with coumarin drugs without excessive prolongation of the prothrombin time[3,4]. A major cause of acquired warfarin resistance is drug interaction; also, consumption of large amounts of vitamin K rich food may also be an etiologic factor[5]. Heterozygous protein C deficiency is associated with an increased risk for thrombosis. Activated protein C (APC) resistance, which is associated with a mutation in the W gene (W Leiden), is a common and strong risk factor for thrombosis [6].

Many medications, foods and herbal supplements can alter the pharmacokinetics and pharmacodynamics of warfarin. Since warfarin is highly bound to plasma proteins, other substances or medications that compete for protein-binding sites (e.g., ibuprofen, quinidine, fenofibrate, losartan, valsartan, amlodipine, felodipine, sulfinpyrazone, phenylbutazone and the principal metabolite of chloral hydrate. i.e. trichloracetic acid) displaces warfarin, thereby potentiating the anticoagulant action of VKAs. This effect, leads to increased PT-INR. Most of the drug interactions affecting warfarin metabolism occurs due to inhibition of the expression and/or activity of CYP450 enzymes involved in warfarin metabolism (CYP2C9 for the S-enantiomer and CYPs 1A2, 2C19, 3A4 for R-enantiomer of warfarin). The concomitant use of medications that induce CYP2C9 (e.g., rifampin and phenobarbital) leads to increased clearance of warfarin and thus anticoagulation effect is reduced [7].

The goals of the study were to assess the level of patient knowledge, their medication adherence, to assess adverse effects of the drug in the study population and thereby ensure safer and effective use of oral anticoagulants by the impact of clinical pharmacist initiated interventions. Since periodic monitoring of INR levels and identification of risk factors have a major role in oral anticoagulant therapy, close monitoring of patients is a must. Continuous patient education with aid of patient information leaflet which contain all the relevant details regarding the use of anticoagulants and for noting down their subsequent INR values make sure that their anticoagulants are safe and effective.

MATERIALS AND METHODS

STUDY DESIGN AND SETTINGS

A prospective interventional study was conducted using retrospective data of the patients as control. The study was carried out in various departments of tertiary care referral hospital, Kochi India which is a 500 bedded multispecialty tertiary care referral teaching hospital with wide range of amenities. A six months study was designed and retrospective data of previous six months were collected. A total of 51 patients who satisfied the inclusion and exclusion criteria and agreed to participate in the study were enrolled. Patients of either gender with age ≥18 years on anticoagulants and willing to participate in the study were included in the study. Pregnant or lactating women, Patients with Psychiatric illness or chronic renal or hepatic failure were excluded from the study.

A specially designed data collection form was prepared and pertinent data including demographic details, medical and medication history, social history, current medications, INR values during visits and the dose of their anticoagulant, etc were obtained by direct interview of patient and /or their care givers.

Initial baseline knowledge of the patients on various aspects of anticoagulation therapy was obtained using a standardized questionnaire and scored separately. Scoring of the questionnaire included a positive score for each question answered correct and 0 score to that not answered or answered wrong. Among 19 questions prepared six of them were scored a +2 if answered correct as these questions were more important aspects of knowledge about anticoagulation. The knowledge assessment score had a minimum of 0 marks and maximum of 25 marks. Their medication adherence was also assessed using Morisky medication adherence questionnaire which can have a maximum score of 8.

The severity of drug interactions was analysed using Lexicomp drug interaction checker. Each interaction indicates a risk rating of A,B,C,D or X. Adverse drug reactions to the anticoagulation therapy were identified during patient interview or from patient medication chart. The causality assessment was done using NARANJO SCALE

All the patients included in the study received a standard care of treatment from the physicians and other healthcare providers in corresponding departments. In addition to this Clinical pharmacist counselling which included awareness about importance of proper anticoagulation therapy, common ADRs and its management, importance of regular follow-up and compliance, time of anticoagulation administration, influence of dietary changes, etc were given to these patients during baseline data collection. On follow-up, the patients' knowledge was re-assessed using the previous questionnaire, score was recalculated and also adherence was re-assessed. The comparison between previous and recent scores in knowledge and adherence of patients after clinical pharmacist initiated counselling was carried out.

Anticoagulation control was assessed by TTR (Time in Therapeutic Range.) TTR was determined for patients who had both retrospective and prospective data using the fraction of INR's in range. The fraction of INR's in range was calculated by taking the number of times INR' values within target range for all patients divided by total number of INR' tests conducted during the selected time interval.

STATISTICAL TEST

Difference between interventional group and control group were analysed using paired t test and considered statistically significant when p value was less than 0.05.

RESULTS

The study involved 51 patients who satisfied the inclusion and exclusion criteria. Out of 51 patients, retrospective data of 46(90.19%) patients were collected. 50(98.27%) patients successfully completed their follow up. There were no drop outs in the study. Out of 51 patients, 41 patients had both their prospective and retrospective data. Five patients were newly started on anticoagulation therapy. Remaining 5 patients had no

Table 1 : Oral anticoagulants and percentage of patients in therapeutic target in range.

	WARFARIN		ACENOCOUMAROL	
	PRE TEST	POST TEST	PRE TEST	POST TEST
TOTAL NUMBER OF PATIENTS	21	21	20	20
PERCENTAGE OF PATIENTS IN TTR	24.5	29.94	33.8	40.08

regular follow up. There was a male preponderance in our study population with 27 male patients. More number of patients was above 59 years of age; 25.49% each in age class of 59-68years and 69-78 years followed by 21.56% in the age class of 49-58 years.

COMORBIDITIES OF STUDY POPULATION

The most common comorbidity among the study population was a combination of Coronary artery disease and Hypertension (17.64%) followed by rheumatic heart disease (15.68%). Among all comorbidities observed, hypertension was the most common one although patients with Hypertension alone were nil.

INDICATIONS FOR OAC.

Atrial fibrillation was the most common indication for oral anticoagulation (OAC) among the study population. A total of 22 (43.13%) patients were on OAC for atrial fibrillation. Five (9.80%) patients had double valve replacement, 2 (3.92%) for aortic valve replacement and 3 (5.88%) for mitral valve replacement. Triple vessel disease, acute limbic ischemia, acute on chronic limbic ischemia, ASD (Atrial septal defect) closure with pericardial patch, atrial flutter with 2:1 AV block, ectatic coronary artery disease (CAD) and venous thrombus in central nervous system (CNS), all had one patient each (1.96%). 6 (11.76%) patients had recurrent stroke and 4 (7.84%) patients had deep vein thrombosis. 2 (3.92%) patients had Cerebral venous thrombosis (CVT) for which they were on oral anticoagulation.

Table No.1 narrates the percentage of patients in therapeutic target INR range in both retrospective and prospective arm either with Warfarin or Acenocoumarol. TTR comparison of 41 patients was carried out. Out of this there were 21 Warfarin patients and 20 Acenocoumarol patients. The difference in TTR from retrospective data was compared to that in prospective data. There was an elevation of TTR value of Warfarin patients from 24.5% to 29.94% and that of Acenocoumarol patients from 33.8% to 40.08%.

DRUG INTERACTIONS WITH OAC

Drug interactions of oral anticoagulants with co-prescribed drugs were observed in the study population. The most common CATGORY D interacting drugs were antiplatelets involving aspirin and clopidogrel which showed an increased risk of bleeding followed by other cardiovascular agents.

ADVERSE DRUG REACTIONS OBSERVED IN STUDY POPULATION

One out of 3 patients on oral anticoagulants suffered from adverse drug reactions among which gum bleeding was the most prominent reactions in both warfarin and acenocoumarol groups. Hematuria was the second common adverse reaction with 2 warfarin patients and 1 acenocoumarol. Increased menstrual bleeding was next common adverse effect with one case each in warfarin and acenocoumarol patients. One case each of gum bleeding with epistaxis, ecchymosis, gum bleeding with ecchymosis, intracranial bleed was observed in warfarin patients. While acenocoumarol patients had one case each of internal hematoma, hemoptysis and increased bleeding from site of puncture. Among 18 adverse drug reactions occurred 17 (33.33%) patients had non- major bleed including gum bleed, hematuria, increased menstrual bleed epistaxis and ecchymosis. But 1 major case of intracranial bleed was observed. Out of 18 ADRs observed 13 were probable and remaining 5 were possible ADRs as per Naranjo causality assessment scale.

The improvement in knowledge about anticoagulants and medication adherence were statistically significant using paired t-test.

3.7. Pre and Post test TTR values with respect to knowledge and adherence to the prescribed anticoagulants.

Table No.4 narrates the comparison of baseline and follow up knowledge, medication adherence and TTR of 41 patients with

Table 2 : Mean S.D. and t value to compare the pre-test & post-test levels of patient knowledge assessment questionnaire in anticoagulation therapy.

Test	Mean	S.D.	n	Difference between mean	t	df	Significance (p-value)
Pre-test	14.92	5.972 18	50	4.82	7.09	49	$p<0.01$*
Post-test	19.74	3.821 58					

Table 3 : Mean S.D. and t value to compare the pre-test & post-test levels of medication adherence.

Test	Mean	S.D.	n	Difference between mean	t	df	Significance (*p*-value)
Pre-test	6.13	1.900 75	50	1.06	4.66	49	$p<0.01$*
Post-test	7.19	0.847 51					

Table 4 :

Pre and post test TTR with respect to knowledge on anticoagulation management.						
	PRETEST			**POST TEST**		
	NUMBER	**PERCENTAGE%**	**TTR %**	**NUMBER**	**PERCENTAGE%**	**TTR%**
LOW (=8)	3	7.31	30.7	0	--	--
MEDIUM (9-18)	26	63.4	28.57	11	26.82	38.63
HIGH (19-25)	12	29.26	35.82	30	73.17	39.58
Pre and post test TTR with respect to Medication adherence on anticoagulation management.						
LOW (<6)	12	29.26	47.22	4	9.75	61.53
MEDIUM (6-7)	15	36.58	30.15	19	46.34	39.65
HIGH (=8)	14	34.1	35	18	43.90	40.47

both retrospective and prospective data. There was a significant difference in the pre-test and post-test in patient knowledge on anticoagulation therapy. There is a rise in TTR between the baseline data and follow up data in both cases.

DISCUSSION

The most common indication for OAC in our study population was for Atrial fibrillation. In a study conducted by Adelina-Mihaela Sorescu and Tudor Enache, most of the patients (63.8%) in the study population were on oral anticoagulant for Atrial Fibrillation as an indication similar to ours; so our study is in accordance with this study[8].A study conducted by Anila.K.N and J.Emmanuel, in India, the percentage of INRs within therapeutic range was 43.2% for control group and 62% for interventional group which indicates an improvement in anticoagulation management[9]. But in our study there was a limited elevation in TTR percentage which might be due to the fact that it was for the first time that such a study conducted in our study site by clinical pharmacists. In addition dosage adjustment was also carried out in the above mentioned study but in our study we could intervene to educate the patients about anticoagulants and importance of medication adherence only. The rise in TTR along with an improvement in knowledge about anticoagulants and medication adherence of these patients strengthens the fact that the knowledge about the medications and the adherence to prescribed medications has a significant impact on achieving target INR range.

Various drug interactions were observed with both Warfarin and Acenocoumarol in our study. A prospective observational study conducted by Gebrehiwot, Nuredin et al concluded that Warfarin had several drug interactions [10]The most frequent interacting drugs were antibiotics, followed by antiplatelet, cardiovascular agents and NSAIDs which is in contrary to our study where, most common interacting drugs were antiplatelets involving aspirin and clopidogrel followed by other cardiovascular agents like Amiodarone [11].

A total of 18 adverse drug reactions were observed in our study population. In a study by Babatunde O. Sonuga1 and Derek A. Hellenberg reported 14% adverse drug reactions as bleeding but in our study we identified 33.33% adverse drug reactions among which one was a major bleeding and the remaining were non major bleed including gum bleed, hematuria etc.

Our study results show that there was a statistical significant rise (5% level of significance) in knowledge of patients about anticoagulation management after counselling by clinical pharmacist. A study conducted by Anila K.N and J Emmanuel[9] patients in the interventional group showed improvement in knowledge showing that there is a statistically significant

difference in pre and post test results; which supports our findings.

Also, there was a statistical significant improvement in adherence of study population to their medication after counselling by clinical pharmacist. Also a rise in TTR was observed between the baseline data and follow up data. This rise in TTR along with an increment in adherence of these patients strengthens the fact that understanding importance of proper medication adherence and proper patient education can play a major role in achieving target INR range.

CONCLUSION

The percentage of patients on target INR range a surrogate marker of anticoagulation therapy,- increased from baseline due to the additional knowledge regarding the anticoagulation management as well as the importance of medication adherence imparted to the patients by the clinical pharmacists in addition to the routine clinical care received from other healthcare providers. A significant number of patients on anticoagulation suffered from adverse drug reactions like bleeding. So close monitoring of these patients is mandatory to prevent such negative outcomes.

AUTHOR CONTRIBUTIONS

Conducted the research work: Christy Maria Babu, Minnu Mariya Joy, Shija Kuruvila

Wrote or contributed to writing of the manuscript: Christy Maria Babu, Minnu Mariya Joy, Shija Kuruvila, Siby Joseph

Supervised the work: Siby Joseph, Sujith Kumar S, Shintu Shaji

Analysed the data: Christy Maria Babu, Minnu Mariya Joy, Shija Kuruvila, Siby Joseph, Shintu Shaji.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENT

We extend our sincere gratefulness to our faculty and all physicians for their timely guidance and support that helped in completion of this research work.

FUNDING

This research did not receive any funding from any sources.

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