

Impact of pharmacist intervention on prescribing pattern of anticoagulation in patients admitted to intensive care unit in a Tertiary Care Hospital, India

Impacto de la intervención del farmacéutico en el patrón de prescripción de anticoagulación en pacientes ingresados en la unidad de cuidados intensivos en un Hospital de Atención Terciaria, India

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Abstract

Objectives: To assess and compare the International Normalized Ratio (INR) results between a physician (Retrospective) and clinical pharmacist dosing (Prospective) of Oral Anticoagulation drugs and to analyze the control of INR and incidence of complications during clinical pharmacist managed therapy.

Methodology: A prospective hospital-based observational study was carried out for 6 months at Tertiary Care Hospital, Bangalore. The research student attended ward rounds on daily basis and collected the cases which were mentioned under inclusion criteria. The pattern of prescribing was checked from the medication chart and the case sheet was analyzed for any drug-related problems.

Results: During our study period, 86 patients were forwarded by the physicians to the clinical pharmacist managing the oral anticoagulation clinic. Only 70 patients could complete the study, where 4 patients did not visit the clinic, other 12 patients did not meet the inclusion criteria and hence they are excluded. The data were collected using the data collection form for the study sample. After the interventional study, there was a significant improvement in patients maintaining % of INRs which were in target therapeutic range, % of transthyretin (TTR) along with decreased adverse effects. It was also found that patient's awareness of the target INR values is correlated with the improved accuracy of anticoagulation control.

Conclusion: Hence, our study results reflect the need for a clinical pharmacist in oral anticoagulation management and the necessity of implementing anticoagulation services in various hospital settings. The clinical pharmacist managing anticoagulation service was able to achieve the INRs of the patient in to target therapeutic range by proper and timely dose adjustments based on the INR value, to identify adverse drug reactions/ adverse events, drug-drug interactions, and drug-food interactions and bring about proper interventions by working in association with physicians.

Key words: Anticoagulant, clinical pharmacist intervention, INR results, physician intervention.

Resumen

Objetivos: Evaluar y comparar los resultados del índice internacional normalizado (INR) entre un médico (Retrospectivo) y la dosificación del fármaco clínico (Prospectivo) de los fármacos de Anticoagulación Oral y analizar el control del INR y la incidencia de complicaciones durante la terapia gestionada por el farmacéutico clínico.

Metodología: Se llevó a cabo un estudio observacional prospectivo basado en el hospital durante 6 meses en el Tertiary Care Hospital, Bangalore. El estudiante de investigación asistió a las rondas diarias y recogió los casos mencionados en los criterios de inclusión. Se comprobó el patrón de prescripción a partir del cuadro de medicación y se analizó la hoja de casos para detectar cualquier problema relacionado con los medicamentos.

Resultados: Durante el período de estudio, los médicos remitieron 86 pacientes al farmacéutico clínico que gestionaba la clínica de anticoagulación oral. Sólo 70 pacientes pudieron completar el estudio, donde 4 pacientes no acudieron a la consulta, otros 12 pacientes no cumplían los criterios de inclusión y por tanto están excluidos. Los datos se recogieron mediante el formulario de recogida de datos de la muestra del estudio. Tras el estudio de intervención, hubo una mejora significativa en los pacientes que mantuvieron el % de INRs que estaban en el rango terapéutico objetivo, el % de transtiretina (TTR) junto con la disminución de los efectos adversos. También se descubrió que el conocimiento de los pacientes de los valores INR objetivo se correlaciona con la mejora de la precisión del control de la anticoagulación.

Conclusión: Por lo tanto, los resultados de nuestro estudio reflejan la necesidad de un farmacéutico clínico en la gestión de la anticoagulación oral y la necesidad de implementar servicios de anticoagulación en varios entornos hospitalarios. El farmacéutico clínico que gestiona el servicio de anticoagulación fue capaz de conseguir que los INR de los pacientes estuvieran dentro del rango terapéutico objetivo mediante ajustes de dosis adecuados y oportunos basados en el valor del INR, para identificar reacciones adversas a los fármacos/eventos adversos, interacciones entre fármacos y alimentos y llevar a cabo intervenciones adecuadas trabajando en asociación con los médicos.

Palabras clave: Anticoagulante, intervención del farmacéutico clínico, resultados del INR, intervención del médico.

Introduction

The primary intent of the drug utilization pattern is to smooth the process & rational use of drugs in the population. Drug Utilization Evaluation (DUE) is a study to identify variability in drug use & to support interventions that will improve patient's therapeutic outcomes. Drug use indicators are intended to measure specific aspects of health providers & drug use in a hospital or health center. Indicators will provide information to health care managers concerning drug use, prescribing habits & important views of patient care¹.

Anticoagulants are the drugs which are usually referred to as blood thinners² and these are prescribed in clinical settings to treat hospitalized patients like acute and deep venous thromboembolism (VTE), unstable angina, atrial fibrillation³ and to prevent coronary arteries from blockage and in cardiac invasive procedures. Anticoagulants are highly prescribed in cardiology and neurology departments. For more than 40 years the only anticoagulants available to clinicians are Coumarins and unfractionated Heparin (UFH)⁴. With the simplicity of subcutaneous administration treatment and prevention of thromboembolism by Unfractionated Heparins and Coumarins are potentially now replaced during the past decade by Enoxaparin and Dalteparin which are low molecular weight heparins². Anticoagulation management is a challenging task for health care professionals especially for clinical pharmacists, because of the individual variability in response to the anticoagulants, alterations in a patient's consumption of vitamin K- rich foods and alcohol, change in medications, or change in health status all of which can alter the INR values. It is important to manage anticoagulation therapy of patients in a department like cardiology as many drug-related problems and patient non-compliance are common and hence there is a need for better pharmaceutical care and effective care that can be provided by a clinical pharmacist⁵. Pharmacists can also bring expertise in managing oral and parenteral anticoagulation therapy of both inpatients and outpatients by providing important information regarding therapy through effective counseling and about potential interactions⁶. Therefore, we aimed to study the drug utilization pattern of anticoagulants among inpatients of Tertiary Care Hospital, Bangalore, India.

Materials and methods

The study was conducted in the cardiology ward at Tertiary Care Hospital. Tertiary Care Hospital is a 1200 bedded hospital providing secondary health care to people. A Bidirectional (prospective and retrospective) observational and interventional study will be conducted to include patients receiving oral anticoagulation drugs (Warfarin, Acitrom) among adult patients.

Data was collected using a well-structured data collection form which includes patient's demographics, clinical information which includes (indication for anticoagulation therapy, desired INR range, expected duration of therapy, anticoagulation therapy received), social habits, past medical history, current medications and the prescribed oral anticoagulant (Warfarin/Acitrom).

The International Normalized Ratio (INR) values of the study sample were collected from the hospital medical record database for 3 consecutive reviews for the physician dosing retrospectively, the PT (prothrombin time) and INR values were recorded prospectively in the clinical pharmacist managed oral anticoagulation clinic during the study period for the same selected patients on 3 regular follow-ups with the relevant source of information. INR values were monitored for the patients included in the study and dosage adjustment was done according to the standard protocol based on the INR value. The patients were also provided with effective counseling regarding the therapy and dietary modifications. All the patients were monitored for any adverse drug events/effects or any possible drug and food interactions during the study period. In case of any reported adverse events/drug interactions in the anticoagulation clinic, the proper intervention was done by the clinical pharmacist in association with a physician to achieve rational drug therapy.

Result

A total number of 70 patients who met inclusion criteria from the Inpatient ward of Tertiary Care Hospital were recruited. Out of which 34 (48%) were male and 36 (52%) were female. My result was found to be similar to the study carried by RC Anakwul et al⁷ and differs from the study conducted by Hossien khalili et al⁸ and Singh V et al⁹.

Among 70 patients included, 34 (48.19%) patients were found to be in the age group of 51-60 years which covered the majority of patients in the study, followed by 20 patients (28.91%) between the age group of 41-50 years, 46 (25%) patients between the age group of 31-40, 10 (15.66%) patients were lesser than 30 years and only one patient (7.23%) and the results are found to be similar with the study carried out by Singh V et al⁹. **Table I.**

Table I: Age distribution in the study sample.

Age Group	No. of Patients	% of Patients
18 - 30	6	7.23
31 - 40	10	15.66
41-50	20	28.91
51-60	34	48.19
Total	70	100

Out of 216, INRs checked for 70 patients (total of 3 follow-ups), the target therapeutic range was found to be 100 (45.78%) and 140 (64.25%) respectively for physician and clinical pharmacist dosing. **Figure 1**, Our study results showed a significant increase in target INR values during the period of clinical pharmacist managing oral anticoagulation therapy. **Table II**, Similar results were found in the study carried out by Nadia a Amruso¹⁰.

Figure 1: Physician Vs Clinical Pharmacist Dosing in the study sample.

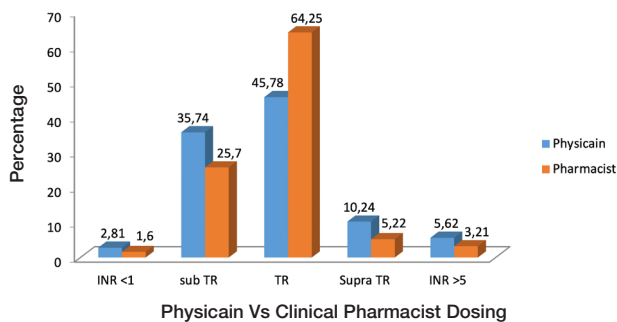


Table II: Indications for Oral Anticoagulation in the study sample.

Indications	No. of patients	% of patients
Mitral Valve Replacement (MVR)	32	38.55
Atrial Fibrillation (AF)	12	16.86
Deep Vein Thrombosis (DVT)	10	13.25
Aortic Valve Replacement (AVR)	8	12.04
Pulmonary Embolism (PE)	6	9.63
Mitral Valve Replacement MVR + Atrial Fibrillation AF	2	6.02
Total	70	100%

Table III: Management of patients with Oral Anticoagulation drugs.

Management	No. of Patients	% of Patients
Warfarin	30	45.12
Acitrom	40	54.87
Total	70	100

Table IV: Paired sample t-test for comparison of INR results in Physician and Clinical Pharmacist intervention:

INR results	Differences of the Mean	Paired t-value	Degree of Freedom	P-value
INRs in target value	-0.6642	4.803	82	< 0.0001
INRs > target value	0.1646	2.541	82	0.0088
INRs < target range	0.3002	2.608	82	0.0044
INRs > 5	0.07229	1.228	82	0.1114
INRs < 1	0.03814	1.398	82	0.1813

p value < 0.01 is significant

Tables V and **VI** show the evaluation of the frequency and cause of oral anticoagulant-related adverse effects/ events are mainly due to lack of knowledge regarding anticoagulation therapy, irregular follow-up, and unavailability of 0.5mg of Acitrom and concurrent administration of other drugs. Some of the occurred events were taken to the knowledge of the physician for further management whereas in remaining patients dose adjustment was done according to the standard protocol of oral anticoagulation therapy along with effective

counseling. Our study results are also supported by the Gregory Piazza *et al.*, who conducted a similar study in anticoagulation-associated adverse events¹¹. Apart from the above, drug and food interactions were also observed in few patients receiving oral anticoagulation therapy which was depicted in **table VII**.

Most of the patients received useful information from an anticoagulation service and the convenience, accessibility, and services provided by the clinical pharmacist were better. This was assessed by questioning patients/caretakers answering a set of satisfaction assessment questionnaires and about satisfaction was reported in the present study. Similar studies Lakshmi R *et al.*¹², also support the fact of patient satisfaction by the anticoagulation service offered by the clinical pharmacist.

Table V: Fraction of INRs in the therapeutic range for the study sample.

INR results	Physician	Clinical Pharmacist
Total INR's checked	216	216
INR's within TR	86	130
Fraction of INR within TR	0.457	0.642

After the interventional study, there was a significant improvement in patients maintaining % of INRs which were in target therapeutic range, % of transthyretin (TTR) along with decreased adverse effects. It was also found that patient's awareness of the target INR values is correlated with the improved accuracy of anticoagulation control. Hence, our study results reflect the need for a clinical pharmacist in oral anticoagulation management and the necessity of implementing anticoagulation services in various hospital settings.

My study suggests that there is a strong relationship between the safety of anticoagulants and BMI. According to my study, adverse drug reactions were observed mostly in patients with normal BMI compared to overweight and obese patients with a P-value of 0.058, which is statistically significant. The result was found to be similar to the study carried out by Avgil *et al.*¹³.

The fate of the ADR is decided based upon the severity of the reactions and also by the need for the drug. Out of 15 ADRs, 11 (73.33%) drugs withdrawn, 3 (20%) dose was tapered and one drug was continued.

In all drug interactions identified, it was observed that Enoxaparin was involved in interactions with other drugs like Aspirin, Acenocoumarin, and Fondaparinux, and the results were found to be similar to the study carried out by Sing V *et al.*⁹. **Table IX**.

The safety and effectiveness of any medical therapy depend on taking their medication as prescribed and the extent of this is defined as medication adherence.

Table VI: Adverse Drug Event Occurred in Anticoagulation Clinic:

Enrolling anti-coagulation clinic	Drug	Adverse event	Hospitalized	Cause	Clinical Pharmacist Intervention	Outcome
Subtherapeutic INR (< 2)						
Yes	Acitrom	Chest tightness, Upper body discomfort	No	Missed follow-up	Dose adjustment done	Recovered
Yes	Acitrom	Tenderness in shoulder Joints	No	Took Hopace (Ramipril) Thinking as Acitrom	Counseled the patient about the drug	Recovered
Yes	Acitrom	Chest tightness	No	Took 2MG Instead of 2.5Mg (due to unavailability of (0.5mg) at Hospital Pharmacy)	Dose adjusted	Recovered
Yes	Acitrom	Chest tightness	No	Patient Stopped Drug By Tapering the Dose And Tried to Manage by yoga (not took drug)	Counseled the patient about the Disease And Therapy	Recovered
Supra therapeutic INR (> 5)						
Yes	Acitrom	Haematuria	Yes	Took 8mg instead of 4mg	Informed to Physician	Recovered
Yes	Warfarin	Tongue Bleeding	Yes	Took NSAID's	Informed to Physician	Recovered
Yes	Warfarin	Bleeding Stools	Yes	Missed Follow up with anticoagulation clinic	Informed to Physician Hb-6gm/dl	Transfused, Recovered
Yes	Warfarin	Black color stool	Yes	Irregular follow-up	Informed to physician	Recovered
Yes	Acitrom	Haematuria	Yes	Unknown cause	Informed to physician	Recovered

Table VII: Drug and Food Interactions observed in the study sample.

	Interacting agents	Drug	Interactions	N° of occurrence	Clinical Pharmacist intervention
Drug Interaction	Tegritol (Carbamazepine)	Warfarin	Increased anticoagulation effect	1	Informed to physician and regimen was changed to Epilive (Levetiracetam)
	Tragic-MF (Tranexamic Acid)	Warfarin	Increased anticoagulation effect	1	Patient Counseled not to take OTC medications and to consult physician on any disability and inform the physician about the anticoagulant drug
Food Interactions	Green Tea	Warfarin (3) /Acitrom (2)	Decreased INR	3	Patient Information given on interaction of green tea with the drug

Table VIII: Distribution of ADRs Based on BMI.

BMI	SAFETY		TOTAL	P-Value*
	ADR	NO ADR		
UNDERWEIGHT	1(8.3%)	5(4.1%)	6(4.4%)	0.058
NORMAL	9(75%)	50(40.7%)	59(43.7%)	
OVERWEIGHT	2(16.7%)	44(35.8%)	46(34.1%)	
OBESE	0(0%)	24(19.5%)	24(17.8%)	
TOTAL	12(100%)	123(100%)	135(100%)	

Table IX: Details on Individual Drug-Drug Interactions.

DRUG-DRUG COMBINATION	INTERACTING DRUG	PHARMACOLOGICAL RESPONSE	FREQUENCY
Enoxaparin	Aspirin	Hemoptysis	1
Enoxaparin	Aspirin	Epistaxis	1
Enoxaparin	Acenocoumarin	Increase INR	2
Enoxaparin	Fondaparinux	Hypokalemia	1
TOTAL			5

Poor adherence is an important factor to consider when explaining the instability of anticoagulation control and the impact of under-dosing on the outcomes of patients receiving anticoagulants. In my study, poor adherence was observed in conditions such

as cancer, deep venous thrombosis, and embolic encephalopathy. Fever, forgetfulness, and cost were the most common reasons for non-adherence. Our results were found to be similar to a study carried by RA Rodriguez *et al*³. **Table X.**

Table X: Medication Adherence Level of Patients.

DRUG	FREQUENCY	PATIENT CONDITION	MMAS- 8 SCORE	LEVEL OF ADHERENCE	REASON FOR NON-ADHERENCE
Inj.Enoxaparin 40mg	OD	Cancer	4	Poor	Fever
Tab.Dabigatran (110mg)	BD	DVT	3	Poor	Costly
Tab.Acenocoumarol (2/3mg)	OD	Embolic Encephalopathy	4	Poor	Forgetness
Inj.Enoxaparin 60mg	BD	Sub Clavian Thrombosis	8	High	–
Tab.Acenocoumarol (10mg)	OD	Respiratory Disorders	6	Moderate	–
Inj.Enoxaparin 40mg	OD	Pulmonary Embolism	8	High	–
Inj.Enoxaparin 40mg	BD	Cortical venous Thrombosis	6	Moderate	–
Tab.Acenocoumarol (1mg)	OD	LRTI	7	Moderate	–
Tab.Acenocoumarol (3mg)	OD	Shock	7	Moderate	–

Conclusion

Anticoagulants are medicines that help prevent blood clots. They're given to people at a high risk of getting clots, to reduce their chances of developing serious conditions such as strokes and heart attacks. A blood clot is a seal created by the blood to stop bleeding from wounds. While they're useful in stopping bleeding, they can block blood vessels and stop blood from flowing to organs such as the brain, heart, or lungs if they form in the wrong place. Anticoagulants work by interrupting the process involved in the formation of blood clots. They're sometimes called "blood-thinning" medicines, although they don't make the blood thinner. Although they're used for similar purposes, anticoagulants are different from antiplatelet medicines, such as low-dose aspirin and clopidogrel.

Due to the increased number of patients receiving OAT it is quite difficult for the physician to educate all the patients due to lack of time. From our study, we concluded that the clinical pharmacist managing anticoagulation service was able to achieve the INRs of the patient in to target therapeutic range by proper and timely dose adjustments based on the INR value, to identify adverse drug reactions/ adverse events, drug-drug interactions and drug-food interactions and bring about proper interventions by working in association with physicians. Poor doctor-patient communication can also

be overcome by the involvement of clinical pharmacists in anticoagulation management through effective counseling regarding the medication, the importance of monitoring INR values, lifestyle, and dietary modifications. Moreover, clinical pharmacists can also act as good communicators between physicians and patients.

In my study, 15 adverse drug reactions were observed in 13 patients and out of 15 ADRs, statistical analyzing, gender and BMI and the result was found to be statistically insignificant for age and gender with P-value of 0.462 and 0.217 respectively, whereas the result was found to be statistically significant for BMI with P-value of 0.058 is was done concerning. Thus, there is a strong association between BMI and ADRs related to anticoagulants. Drug interactions related to anticoagulants were observed in only 5 patients and the most common anticoagulant prone to interact with other drugs was found to be enoxaparin. Adherence to therapy is the most important factor in the success of the treatment. In my study, poor medication adherence was observed in cases of DVT, cancer, and embolic encephalopathy.

Conflict of Interest

The authors report no conflicts of interest.

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