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Clinical impact of pharmacist led anticoagulation services in a tertiary care hospital

Akhila Muralidharan[1], Arjun Ghosh A[1], Anees M.K[1], Justin S George[1], Siby Joseph[1] , Sujith Kumar.S [2]

1 Department of Pharmacy Practice, St. Joseph's College of Pharmacy, Cherthala, Kerala, India - 688524.
2 Department of Cardiology, Lourdes Institute of Medical Science and Research, Pachalam, Kochi, Kerala, India - 682012.

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*Corresponding author:

Phone : + 91 -
Email : sibymadappallil@gmail.com

ABSTRACT

Background. Anticoagulants known as blood thinners, prevent or reduce blood coagulation. Anticoagulation management is a challenge as slight change in drug concentration can result in either bleed or blood clot formation. Aim of the study. The aim was to analyse the clinical impact of pharmacist-led anticoagulation services with objectives to analyse the impact of patient counselling on knowledge, attitude, practice and medication adherence of oral anticoagulation, to identify adverse drug reactions and to assess dosage initiation and dosage adjustment of anticoagulants. Method. A prospective interventional study was conducted in clinical departments of Lourdes Hospital Kochi. Medication adherence assessed using 8 item MMAS and initial baseline knowledge about oral anticoagulants collected using a validated KAP questionnaire. Patients counselled by clinical pharmacist and followed up. Dosing of parenteral anticoagulants were monitored, ADRs identified, assessed using Naranjo scale. Results. One hundred and forty-two patients (84 parenteral and 58 oral) were enrolled in the study. Major adverse reactions were hematuria and gum bleeding. Dosing related problems were identified and intervened. Statistically significant improvement in medication adherence, knowledge, attitude and practice of patients on oral anticoagulants in addition to significant improvement in time in therapeutic range were observed. The correlation coefficient was positive ($p<0.01$) which interpreted that as the practice increases time in therapeutic range also increases. Conclusion. Additional Care given to the intervention group by clinical pharmacist resulted in a statistically significant improvement in knowledge, attitude, practice and medication adherence supported by improvement of time in therapeutic range, which highlights the importance of clinical pharmacist in anticoagulation management.

INTRODUCTION

Blood clot formation is the conversion of liquid state of blood to a gel -like/semisolid state. Coagulation factors are proteins which play a specific role in proper blood clot formation. Any injury to blood vessel that result in damage to endothelium lining the blood vessel, results in initiation of coagulation [1]. Disorders of coagulation is considered as a disease state which may lead to hemorrhage, bruising, thrombosis etc. Thrombus when mobile becomes an emboli that occlude blood vessels and cause ischemia.

Anticoagulant medicines are classified as high-risk medications and if errors are made in dosing, monitoring or inappropriate administration, there is a real risk of bleeding events or failure of therapy [2]. Options for anticoagulation have been expanding steadily for past few decades providing a greater number of agents for prevention and management of thromboembolic diseases [3]. Appropriate use of these agents requires knowledge of their individual characteristics, risk and benefits.

Anticoagulation therapy is used for multiple indications such

as Atrial fibrillation (AF), Acute coronary syndrome (ACS), Myocardial Infarction (MI), Deep vein Thrombosis (DVT), Stroke, Pulmonary embolism (PE) etc [4]. Drug adherence appears to be relatively similar in large population although these may differ in some individual or clinical setting. Adherence to medication is one of the problems affecting anticoagulation. Adherence may be affected by economic, survivor, medication and condition related factors [5]. Factors that must be considered while selecting an anticoagulant are: availability of antidotes, cost of drug, safety and efficacy, route of administration etc.

Parenteral anticoagulants include heparin, low molecular weight heparin (LMWH)- enoxaparin, dalteparin and fondaparinux. The impetus for the development of LMWH as potential antithrombotic agents came from two observations in the mid 1970s. LMWH fractions prepared from standard commercial grade heparin progressively lost their ability to prolong the activated partial thromboplastin time (aPTT) while retaining the ability to inhibit activated factor X. Second observation was LMWH cause less bleeding [6]. LMWH are excreted via kidney resulting in a potential for accumulation of the drug in patients with renal impairment [7]. In such cases LMWH may increase the risk of bleeding. Enoxaparin and fondaparinux require dosage adjustment [8]. If creatinine clearance (CrCl) less than 15ml/min; Fondaparinux cannot be used and enoxaparin's dose should be reduced. In such conditions it can be switched to unfractionated heparin or dalteparin.

As with all anticoagulants, bleeding is the major side effect because these drugs increase the time for blood clots to form [9]. Risk of bleeding depends on comorbidities of patient. Lower incidence of bleeding, thrombocytopenia, longer half life, better subcutaneous bioavailability and fewer injection site hematoma made LMWH the most recommended parenteral anticoagulant than heparin in the recent times [10].

Oral anticoagulants include warfarin, acenocoumarol and novel oral anticoagulants (dabigatran, rivaroxaban, edoxaban, apixaban). Inter individual variations in warfarin dosage requirements is the result of a complex interaction between environmental and genetic factors. Dosage adjustments of warfarin based on international normalised ratio (INR) values should always lie between 5-20%, whether escalation or de-escalation, ie, the new dose should differ from old dose in a range of 5-20%.

$$\% \text{ Difference in dose} = \frac{\text{Difference in weekly dose}}{\text{Past weekly dose}} \times 100$$

INR level must be checked regularly for patients taking oral anticoagulants. Close monitoring is necessary to avoid adverse reaction of anticoagulants [11]. After initiating warfarin therapy INR should be monitored every 2-3 days during first week of therapy. Once the condition is stable INR should be monitored once a week for the first 1-2 weeks then every 2 weeks and eventually monthly thereafter.

Bridging anticoagulation aims to reduce patient risk for developing blood clots, but may also increase the risk for developing serious bleeding complications after surgery. Bridging means use of short acting anticoagulants for a period of time during interruption of warfarin therapy when the INR is not within a therapeutic range. Bridging is also used during the initiation of an oral anticoagulant therapy. On initiation, there is always a risk of hypercoagulability induced by depletion in levels of protein C and S. Therefore, heparin or low molecular weight heparin is used for bridging so as to avoid this presumable risk [12].

Time in therapeutic range, (TTR) is a commonly used quality measure for anticoagulation therapy [13]. INR is always a measure of stability of anticoagulation whereas TTR represents the percentage of appropriate anticoagulation intensity. Quality of oral anti coagulant (OAC) is maintained with a good time therapeutic range (TTR), indeed a TTR > 70% is associated with low rate of cardiovascular events and bleeding complications. Non adherence to medication is one of the problems that affect anticoagulation therapy. Patients with limited health literacy may have decreased medication adherence and increased risk of adverse events such as bleeding. Quality of care for patients on anticoagulation can be provided by increasing adherence to anticoagulation guidelines and also by improving patient compliance through education and established protocols. The education can be provided directly to patient, to caretakers by using patient information leaflets, education materials etc [14].

The lack of awareness about the importance of anticoagulants and the decreased medication adherence can lead to failure of achieving the expected result out of anticoagulation therapy. Studies have shown that clinical pharmacists in association with the clinicians can impart knowledge regarding anticoagulation and the importance of medication adherence and assess outcomes of anticoagulation therapy.

Our aim was to analyse the clinical impact of pharmacist-led anticoagulation services in a tertiary care hospital. The objectives were to analyse the impact of patient counselling on knowledge and medication adherence of oral anticoagulation therapy, identify adverse drug reactions (ADRs) of anticoagulants, and assess the dosage initiation and dosage adjustment of anticoagulants.

MATERIALS AND METHOD

Study design

A prospective interventional study was conducted and the retrospective data of patients on oral anticoagulants for the previous six months was taken as control group.

Setting

The study was conducted in Lourdes Hospital, Kochi, a tertiary care hospital.

Sample size and study duration

The study was carried out for six months (November 2019-April 2020) with a minimum sample size requirement of 98 patients.

Inclusion and exclusion criteria

Patients of either gender, aged ≥ 18years on anticoagulants and willing to participate in the study were included. Pregnant and lactating woman, psychiatric patients and patients on hemodialysis were excluded from the study.

Data collection tools

Lourdes mediware system, specially designed data collection form, Knowledge assessment questionnaire, Morisky medication adherence scale, Naranjo ADR causality assessment scale.

Patients were recruited based on inclusion and exclusion criteria. Knowledge about oral anticoagulants and the medication adherence was assessed using a specially designed knowledge assessment questionnaire and Morisky medication adherence questionnaire (MMAS). Knowledge, attitude and practice (KAP) questionnaire was validated by 10 competent experts in anticoagulation management. Patients on oral anticoagulants in the prospective populace was given specific counselling regarding the anticoagulants, importance of periodic INR monitoring and dietary consideration with the help of a specially prepared patient information leaflet. The dosing of parenteral anticoagulants administered to in-patients was monitored. The ADR identified due to anticoagulants during the study period was assessed using Naranjo ADR causality assessment scale.The collected data were compiled using Microsoft Excel and analysed using paired t test in Statistical Package for the Social Sciences (SPSS). Difference between interventional group and control group were considered statistically significant when p value was less than 0.05.

RESULTS

From the total of 142 patients enrolled in the study, 84 patients were on parenteral and 58 patients were on oral anticoagulants. Among the 58 patients on oral anticoagulants, retrospective data were available for 47 patients. Eleven patients were newly started with oral anticoagulants and 5 patients were deceased during the study period. The number of patients who completed the follow up was 53.There was a male preponderance with 94 patients in the study and more number of patients came under the age class of 58-77 years (50.70%). Majority patients among study population were from cardiology (65%), followed by internal medicine, neurology, vascular surgery and oncology departments. Most commonly prescribed parenteral anticoagulant was low molecular weight heparin and was specifically indicated for acute coronary syndromes (ST segment elevation myocardial infarction -STEMI, Non-ST segment elevation myocardial infarction- NSTEMI, unstable angina). Likewise, most commonly prescribed oral anticoagulant was warfarin and was indicated for AF. Oral anticoagulants were also prescribed for mitral valve replacement, cardioembolic stroke, venous thromboembolism (VTE), cerebral venous thrombosis, basilar artery aneurysm and Left Ventricular apical clot.

A total of 33 (23%) ADRs were observed during the study period. Among 84 patients on parenteral anticoagulants 19 (22.6%) patients were identified with ADR. In case of oral anticoagulants out of 58 cases 14 (24%) patients were identified with ADR. The most predominant ADR due to parenteral anticoagulant was hematuria which accounted for 63.15% of the ADR identified. Gum bleeding was the frequently reported ADR due to oral anticoagulant; of which 4(11.76%) patients were on warfarin and 2(8.69%) on acenocoumarol. The adverse drug reactions reported were assessed using Naranjo ADR causality assessment scale. This transpired that, out of the 33 ADRs 20 were possible and 13 were probable.

The pre-test and post-test knowledge-attitude-practice assessment of 53 patients on oral anticoagulants who completed the study was carried out. The pre-test assessment showed that 30 (56.60%) patients had low KAP score, 22 (41.20%) patients had medium KAP score and only 1 (1.88%) patient had high knowledge. The post test scores taken after providing patient education showed that the results have improved to 6 (11.32%) patients with high KAP score,47 (88.67%) patients with medium KAP score and zero patients with low KAP score. A statistically significant improvement was seen in all the three domains in paired t test. (Table II).

The pre and post medication adherence of 42 patients on oral anticoagulants with retrospective data was assessed using Morisky medication adherence scale. During pre test there were 9 (21.42%) patients with low adherence (score less than 6), 11(26.19%) patients with medium adherence (score 6-8) and 22(52.38%) patients with high adherence (score 8 and above) to

Table 1 : Adverse drug reactions of anticoagulants

ADVERSE DRUG REACTIONS	NO: OF CASES	
	PARENTERAL	ORAL
Hematuria	12	3
Gum bleed	1	6
Hyperkalemia	2	0
Hematoma	2	1
Easy bruising of skin	1	1
Nasal bleed	1	1
Heavy menstrual bleed	0	1
Gastric irritation	0	1

Table 2 : Pre-test, Post-test Mean, Standard Deviation (SD) and t value of knowledge, attitude and practice

Test		Mean	S.D	N	Mean improvement	T	df	p-value
Pair 1	Pre-test knowledge	10.6981	4.41613	53	6.81132	11.229	52	P<0.001
	Post-test knowledge	17.5094						
Pair 2	Pre-test attitude	7.6415	1.92097		2.66038	10.082		
	Post-test attitude	10.3019						
Pair 3	Pre-test practice	7.7547	4.07789		4.79245	8.556		
	Post-test practice	12.5472						

*n= 53; include patients already on anticoagulants and newly started.

Table 3 : Pre test Post test Mean, S.D, and t value of medication adherence

Test	Mean	S.D	N	Mean improvement	T	Df	p value
Pre-test	7.74	2.48	42	1.38	4.78	41	P<0.001
Post-test	9.12	1.25					

*n= 42; patients whose retrospective data was available and followed up

Table 4 : Pre test, Post test Mean, SD, and t value of TTR

Test	Mean	SD	N	Mean improvement	T	Df	Significance
Pre-test TTR	0.3061	0.21097	28	0.14464	3.628	27	P<0.01
Post-test TTR	0.4507						

their medication. The post test result shown that there were 0% patients with low adherence, 6(14.28%) patients with medium adherence and 36(85.71%) patients with high adherence. A statistically significant improvement in medication adherence of study population was found in paired t test. (Table III)

Out of 58 patients on oral anticoagulants, the pre and post TTR comparison was carried out only for 28 patients as most of them were not maintaining a proper record of their laboratory investigation reports in the pre-test. (Table IV)

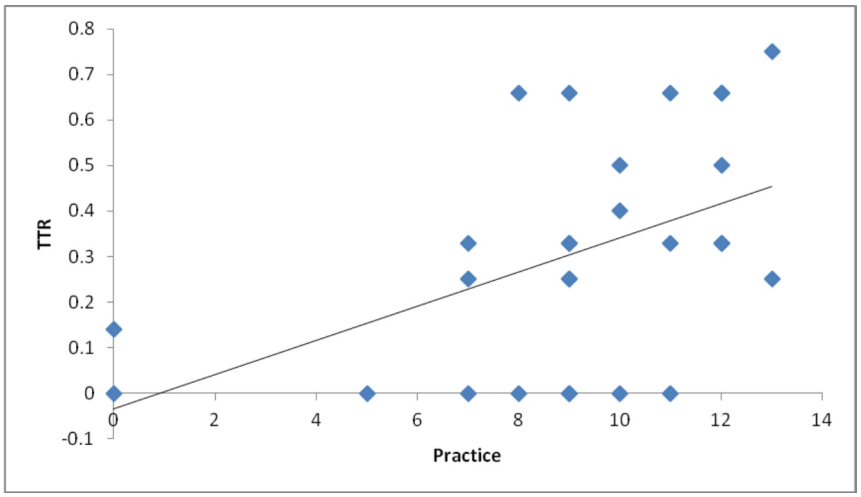

Fig 1 : Scatter diagram for correlation between KAP and TTR

On scrutinizing the correlation between KAP and TTR, a positive correlation which was statistically significant at the 0.01 level was observed. (Figure.1). But on analysing the correlation between medication adherence and TTR, a positive correlation was seen which highlights that, as the adherence increases TTR also increase but the result was not statistically significant.

Dosage initiation and dosage adjustments of anticoagulants were monitored during the study period. Oral anticoagulants were newly started for 11 patients with proper bridge therapy using low molecular weight heparin or heparin. The total number of dosing related problems identified were 48; out of which 36(75%) were due to parenteral anticoagulants and 12 (25%) were of oral anticoagulants. The problems identified were mainly dosage adjustments of parenteral anticoagulants based on creatinine clearance, inappropriate monitoring of lab parameters, improper escalation or de escalation (between 5 to 20%) of dose of oral anticoagulants (warfarin, acenocoumarol).

DISCUSSION

Considering the age and gender wise distribution of study population, there was a predominance of male patients and majority of patients came under the age category of 58-77 years. In a study conducted by Vijay Singh, Krishnappa Gopinath et al [15] on anticoagulant utilisation evaluation shown similar results with 69% male patients and most patients belong to the age group of 51-70 years. A total of 27 patients with unstable angina, 24 patients each with STEMI and NSTEMI were given parenteral anticoagulants. In a study conducted by Rassaele De Catarina, Steen Husted et al [16], most common indication for parenteral anticoagulants was ACS prophylaxis. Among 31 patients indicated with AF, 17 patients were given warfarin which accounted for 50% of the warfarin population, 13 patients were on acenocoumarol which accounted for 56.52 % of acenocoumarol population, and 1 patient was on dabigatran. A study conducted by Jeffrey I Weitz [17] showed that the greatest unmet need regarding long term anticoagulant therapy is in AF which was also relatable to our study.

In a study conducted by Sugandha Kassere, Juhi Kalra et al [18] on adverse drug reaction monitoring of anticoagulants, the most common ADR was hematuria, in our study also hematuria was the major ADR. In a study conducted by Chatree Chai Adisaksopha, Crowther M et al [19] bleeding complications were more for oral anticoagulants, which was in correspondence with our study.The difference in the post and pre counselling assessment results marked a significant increase in knowledge-attitude and practice of study population on oral anticoagulation therapy. Fiona C Taylor, Ramsay M E et al [5] conducted a study on evaluation on patient's knowledge about anticoagulation which stated that effective counselling is required for patients on anticoagulation. The improvement in medication adherence resulted an increase in TTR of patients who completed their follow up. So, educating patients about their medication and improvement in adherence to medication plays a major role to achieve the target INR range. In a study conducted by Leiliane Rodrigues Marcatto, Sacilotto et al [13] shown that an improvement in TTR value was seen after pharmacist managed warfarin therapy.

In our study we found that there was an improvement in KAP related to anticoagulation, medication adherence and TTR with positive correlation between them. As the study was conducted in a single centre with additional care given to the intervention group by the clinical pharmacist, a statistically significant improvement in KAP, medication adherence and TTR in the intervention group highlights the importance of clinical pharmacist in anticoagulation management.

This study was confined to one single centre with limited sample size and only few patients were periodically checking their INR in the retrospective group were the limitations of our study.

CONCLUSION

The outcomes of our study on anticoagulation therapy revealed that proper education of patient about the disease and the drug used plays a vital role in providing the maximum benefit for the patient. Proper counselling about the various aspects of drug therapy helps to improve the patient knowledge as well as improve their attitude and practice towards following their therapeutic regimen . A significant number of study population suffered from different adverse reactions due to anticoagulants. Regular laboratory investigations of required parameters, adequate dosage adjustment through individualisation and close monitoring of patients helps to minimize these ADRs.

Anticoagulation therapy can be properly managed with help of professionally qualified clinical pharmacists who can educate patients regarding anticoagulation therapy, its beneficial outcomes as well as bleeding risks. This would additionally support the clinical care delivered by clinical practitioners and other health care providers.

Conflict of interest

The authors declare no conflict of interests.

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