International Journal of Medical Science and Clinical Inventions 4(10): 3234-3252, 2017
DOI:10.18535/ijmsci/v4i10.05 **ICV 2015: 52.82**
e-ISSN:2348-991X, p-ISSN: 2454-9576

Research Article

Clinical and Laboratory Profile of Patients Presenting With Warfarin Coagulation Abnormality Following Heart Valve Replacement- A Descriptive Study

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INTRODUCTION

Despite revolutionary changes in the field of medicine and eradication or prevention of many diseases worldwide in the past few decades, rheumatic heart disease (RHD) still remains as one of the largest preventable disease burdens in the world and is seen to be more prevalent in the developing countries[1]. Majority of RHD patients develop valvular heart disease with mitral valve incompetence as the most common valvular lesion seen in these patients[2]. In symptomatic patients or those in whom evidence of impaired LV function at rest is seen, surgical intervention is the definitive treatment [3].

Patients who undergo surgical intervention may have either a bio prosthetic valve replacement or a mechanical valve replacement. Those in the latter group requires to be initiated on vitamin K receptor antagonist drugs like warfarin in order to prevent thrombus formation of the mechanical valves.

Since its discovery in 1940 [4], warfarin has withstood the test of time despite many newer oral anticoagulants in the current medical scenario.

In our Indian scenario, warfarin continues to be the mainstay oral anticoagulant of choice among majority of physicians [5]. The main disadvantage is the narrow therapeutic index with patients on warfarin 'walking a tight rope between bleeding and clotting' [5]. Warfarin does not require any loading doses and can be begun along with unfractionated heparin or low molecular heparin (LMH) with an overlap of 4 to 5 days to prevent rebound thrombosis from fall in protein C levels [5]. Current recommendations indicate that patient can be started on warfarin at a dose of 4mg to 5mg daily [5] . Initial check INR can be performed at least four times a week until the desired INR value is attained. Current recommendations state that once a stable therapeutic INR is achieved , follow up can be done at 1 month intervals [5].

Certain issues exist with warfarin which are peculiar to the Indian population which results in coagulation abnormality.

Therefore this study was done in heart valve replacement patients who require lifelong warfarin treatment with an aim to understand issues related to warfarin interaction and how to minimize them.

AIM

To evaluate the determinants of bleeding in post heart valve replacement patients on warfarin therapy

OBJECTIVES

1. To identify contributing factors for bleeding Manifestations or INR >4.5 in patients already on warfarin therapy following heart valve replacement.

2. To identify factors, which are likely to increase patient compliance.

RESEARCH QUESTION

1. What factors contribute to excessive anticoagulation abnormality in post heart valve replacement patients on warfarin therapy?

REVIEW OF LITERATURE

Heart is a hollow muscular organ situated obliquely in the middle mediastinum and is most rightly described as the "pump" house of the body [6]. The importance of heart dates back to 400-200 BC when the pumping action of the heart and the connection between heart and lungs were studied and described by eminent scholars and physicians such as Hippocrates and Aristotle [7]. Heart has also been cited in various parts of the Bible in context of purity and desires [8].

The evolution of heart valve replacement can be traced back through history as long as 1902 when British cardiologist, Lauder Brunton [9] suggested surgical methods to open up valves in severe mitral stenosis and thus help in improvement of the output of the heart.

The safety and reproducibility of closed mitral valvuloplasty for mitral stenosis was described by Dwight Emery Harken in the year 1948[10] which paved a way in the field of cardiothoracic surgery

At present, mechanical valve, donor implantation valve and bio prosthetic heart valves are being employed in heart valve replacement surgeries. Among these three, patients on mechanical heart valve prostheses are more prone to develop valve thrombosis and systemic embolism and therefore require long term oral anticoagulants mainly on coumarin derivatives.

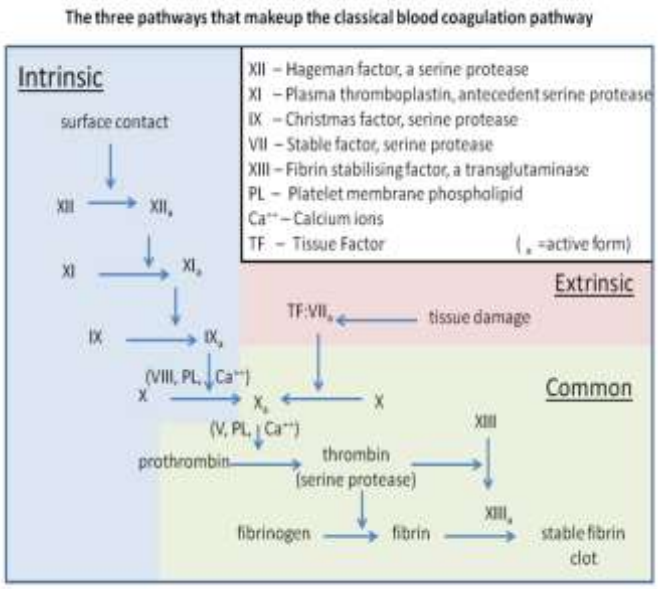
Mechanical heart valves can be advised according to patient preference, and can be prescribed for patients who wish to avoid a second surgery which is indicated in bioprosthetic valves. On the other hand, bio prosthetic valves decrease the need for long term treatment with warfarin, but have limited durability and may require a second surgery in case of failure.

However the outcomes are similar with implantation of either a mechanical valve or bio prosthetic valve between 60 and 70 years of surgery [11]. One of the main complications of mechanical prosthetic valve is thrombosis. It is seen that the prevalence of thrombosis of mechanical heart valve is only 0.3-1.3% per patient-year in developed countries, as compared to 6.1% per patient –years seen in developing countries[11]. Therefore mechanical heart valve replacements requires proper understanding about the coagulation cascade, mechanism of action of warfarin and factor influencing its metabolism.

BLOOD COAGULATION

Hemostasis is the process of blood clot formation at the site of vessel injury. Haemostasis and blood coagulation involve complex interactions between injured vessel wall, coagulation factors and platelets . The process of clot formation requires a well regulated relationship between the pathways of thrombin stimulated fibrin clot formation and plasmin induced clot lysis which when works effectively leads to clot formation initially and later by lysis of clot and tissue remodeling. The factors for abnormal bleeding may be due to diminished thrombin generation (e.g. due to factor VIII deficiency) or increased clot lysis (e.g. due to alpha 2 antiplasmin deficiency). The coagulation process that generates thrombin consists of two interrelated pathways- extrinsic and intrinsic systems.

The extrinsic system is initiated by the activation of the clotting Factor VII. The intrinsic system is initiated by activation of clotting Factor XII, following its contact in vitro by glass. Both intrinsic and extrinsic systems involve a cascade of enzymatic reactions which leads to transformation of various plasma factors (proenzymes) to their active (enzymatic) enzymes leading to thrombin production. This coagulation cascade forms the basis of oral anticoagulants



NEWER ANTICOAGULANTS IN THE HORIZON:-

Direct thrombin inhibitors :- As the name suggests, these group of anticoagulants act directly with the thrombin and inhibit the activity of thrombin bound to fibrin as well as well as soluble thrombin which leads to limitation of thrombus progression [12]. Dabigatran etexilate belongs to this group and has been approved for prevention of stroke in atrial fibrillation. It is currently marketed in India. Dabigatran has a low bioavailability of 6% and its activation is not mediated by cytochrome P450 enzymes. It has a half life of 12- 24 hrs and is excreted mainly by renal. Many serious side effects have been reported with the use of dabigatran. It also has drug – drug interactions. When used with drugs like rifampicin, the therapeutic effect is decreased whereas co administration with NSAIDs, clopidogrel leads to increased risk of bleeding [13].

Factor Xa inhibitors

Rivaroxabane is a direct competitive inhibitor of factor Xa . The metabolism is by CYP3A4, CYP2J2 and other mechanisms which lead to variety of drug interactions. It is therefore contraindicated with anti- HIV protease inhibitors and azole group of drugs and in renal failure patients. Rivaroxabane is bound extensively to plasma proteins and with a half life of 7-11 hrs and a high bioavailability (80%). The main side effects are bleeding and anemia and other associated side effects are tachycardia , pruritis, elevated liver enzymes , hypotension and nausea.

Another direct selective inhibitor of factor Xa is apixaban. It has > 30,000 fold selectivity over other coagulation proteases. Currently Apixaban is undergoing various clinical trials for thrombo-prophylaxis in knee and hip replacement and prevention of stroke in atrial fibrillation. It has a half life of 8-15 hours when given orally and can be given once or twice daily. Its metabolism is through O-demethylation. It reacts with drugs that induce or inhibits CYP3A4.

Edoxaban, betrixaban , TAK442 and YM150 are other factor Xa inhibitors currently undergoing development.

Despite these newer drugs and availability of dabigatran in the Indian market, warfarin still continues to be the leading oral anticoagulant used in our Indian population due to physician comfort and prohibitive cost of dabigatran.

'Advantages and Disadvantages of Newer Anticoagulants [5,14]

Advantages

• Rapid onset of action, so no need for bridging therapy

• Short half-life, so easy control of anticoagulant effect

• Little or no food interaction, so no dietary restrictions like warfarin

• Limited drug interactions unlike warfarin

• Predictability of anticoagulation effect without a need for routine coagulation monitoring.

Disadvantages

• Prohibitively high cost resulting in poor compliance

• No monitoring is possible if needed

• No specific antidote

• Serious bleeding in renal impaired patients and elderly more than 80 years. If glomerular filtration rate (GFR) is 15–30 mL/min, warfarin should be preferred.'

WARFARIN

Warfarin traces its history back to the year 1940 , when it was discovered by Professor Karl Paul Link and his student Harold Campbell in Wisconin from sweet clover after several reports of outbreaks of bizarre bleeding disorder of cattles in that region [15]. The name warfarin is derived from WARF (Wisconin Alumini Research Foundation) and – arin from coumarin in honour of the Wisconsin alumini research foundation to which professor Link signed over his patent rights as gratitude for their financial support and funding in the discovery of dicumarol and warfarin. Further work done by them led to the approval of warfarin as rodenticide in USA in 1952. Historically the use of warfarin soared after it was used to successfully treat United States President Eisenhower when he suffered heart attack in 1955 [16]. Recent evidences have shown that warfarin may have been used to poison Soviet leader Joseph Stalin in 1953 [17].

WARFARIN MECHANISIM OF ACTION

Warfarin is a coumarin derivative which produces anticoagulant effect by interfering with cyclic inter conversion of Vitamin K and its 2, 3 epoxide. Vitamin K plays an important role as a cofactor in the carboxylation of glutamate residue to carboxyglutamates on the N-terminal regions of vitamin K dependent proteins. Vitamin K is required for the γ-carboxylation of coagulation factors II,VII,IX and X. Warfarin by inhibiting vitamin K conversion cycle, induces hepatic production of partially decarboxylated proteins with reduced coagulant activity [18] . The binding of vitamin K dependent coagulation factor to phospholipid surfaces is regulated by carboxylation which leads to acceleration of blood coagulation. γ -Carboxylation essentially requires the reduced form of vitamin K (vitamin KH2) [19]. By blocking vitamin KH2 formation , coumarins inhibit the enzyme vitamin K epoxide reductase which in turn leads to limiting of the γ - carboxylation of vitamin K dependent coagulant proteins.

Vitamin K anatagonists also inhibits carboxylation of the regulatory anticoagulant protein C and S and therefore exert procoagulant response. Low doses of vitamin K 1 (phytonadione) helps to overcome the effect of coumarins by bypassing vitamin K epoxide reductase. Warfarin also interferes with the carboxylation of Gla proteins synthesized in bone [20] [21] [22] . Due to these reasons, warfarin is thought to contribute to fetal bone abnormalities especially when mothers are treated with warfarin at the time of pregnancy. However there is no clear cut evidence suggesting direct relationship of warfarin and bone metabolism when administered to children or adults.

WARFARIN PHARMACOKINETIC AND PHARMACODYNAMICS

Warfarin is a racemic mixture of 2 optically active isomers, the R and S forms [23]. In which potency of S-warfarin is approximately 5 times more than that of R-warfarin. Cytochrome P450 (CYP) 2C9 enzyme is responsible for the metabolism of S-warfarin while metabolism of R- warfarin occurs through CYP3A4 & CYP1A2 [24]. It has a high bioavailability owing to the fact of rapid absorption from the gastrointestinal tract and is found to reach maximum blood concentration within 90 minutes after oral administration. The half life of warfarin is 36-42 hours and it is transported in the body to the liver bound to albumin , where the 2 isomers by different pathways are metabolically transformed [25]. It is due to this long half life that even after starting warfarin , heparin or LMW heparin is continued as part of "bridging therapy".

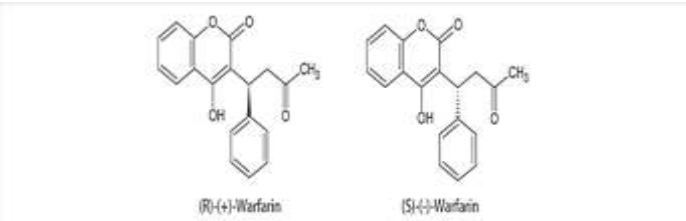


Figure 1. Structure of Warfarin Enantiomers

WARFARIN AND INR MONITORING

Warfarin has been for decades the drug of choice among the oral anticoagulants . After mechanical prosthesis, the standard of care lies in lifelong oral anticoagulation therapy. There is a reduction of nearly 75% of major embolic strokes when patients were treated with warfarin rather than isolated anti platelet therapy or no anticoagulation at all. The INR was developed by the World Health Organization's expert committee on Biologic Standardization in the year 1982. This

was done ' in response to variations in thromboplastin sensitivity and different ways of reporting prothrombin time across the world' [26] [27]. Previous recommendations suggest patients with mechanical valve replacement to have a therapeutic range of INR between 2.5 to 4.5. However this large range may be associated with risk for increased bleeding especially beginning from INR 3.5 . The goal of oral anticoagulation therapy post aortic valve replacement is to achieve an INR of 2.5 to 3.5 in the initial 3 months after surgery and later followed by 2.0 to 3.0 [28,29]. The risks of developing thrombosis and thromboembolism are found to be greater with mechanical valves in the mitral area than in the aortic area. Therefore target INR value of 2.5 to 3.5 are recommended for mitral valve prosthesis [11,30].

Recent Early Self-Controlled Anticoagulation Trial III conducted a safety and efficacy trial of very low dose INR self management which was compared with low dose INR self management. The enrolled patients in low dose INR self management had a target INR range of 1.8 to 2.8 in aortic valve replacement recipients and 2.5 to 3.5 in mitral or double valve replacement recipients for first six post operative months. Later the aforementioned INR target range was continued in the LOW group patients . However in the remaining population , the INR target value was kept at 2.0 (range, 1.6 to 2.1) in the aortic valve replacement group and 2.3 (range , 2.0-2.5) for the mitral and double valve replacement group. Study outcome showed that very low range INR self management resulted in low incidence of thromoboembolic events (<0.6%) and 1% rate of bleeding complications , showing safety and efficacy of this therapeutic approach[31].

WARFARIN IN PREGNANCY

Major controversy about oral anticoagulants lie in the topic related to pregnancy. Pregnancy itself with mechanical valve has a high probability of maternal complication due to alterations in hemostasis and coagulability leading to increased risk of thromboembolic events[32] and maternal mortality varying between 1% and 4%. Coumarin derivaties like warfarin carry the risk of embryopathy when used in 1st trimester which is dose dependent [33]. Cotrufo et al[34] in their study of 52 patients who had 71 pregnancies and on mechanical valve prostheses, were anticoagulated with warfarin for entire duration of pregnancy. Their results showed that out of 71 pregnancies, 23 pregnancy loss occurred, 5 still births and 4 developed embryopathy. There were no maternal deaths , haemorrhagic complications or thromboembolic complications. They concluded by stating that warfarin dosage over 5mg was considered as a risk for pregnancy
complications.

'According to the 2008 American College of Chest Physicians (ACCP) guidelines for antithrombotic therapy recommended one of three approaches for anticoagulation during pregnancy

1. Aggressive adjusted-dose UFH throughout the pregnancy; heparin is administered subcutaneously every 12 hours in doses adjusted to keep the mid-interval activated partial thromboplastin time (aPTT) at least twice control or to attain an anti-Xa level of 0.35– 0.70 U/mL. After a stable dose is achieved, the aPTT should be measured at least weekly.

2. Adjusted-dose subcutaneous LMWH therapy throughout the pregnancy in doses adjusted according to weight to achieve the manufacturer's recommended anti-Xa level 4 hours after subcutaneous injection.

3. Unfractionated heparin or LMWH therapy (as above) until the 13th week, a change to warfarin until the middle of the third trimester, and then restarting UFH or LMWH until delivery. [5,35],

During postpartum period, regardless of which regimen is used, long term anticoagulation should be resumed. Heparin can be restarted, 6 hours post- vaginal birth and 12 hours post cesarean, if there is no significant bleeding.

FACTORS AFFECTING WARFARIN DOSAGE

The number of dispensed outpatient prescriptions for warfarin in the year 2004 was nearly 31 million [36]. There are various factors which affect the relationship between warfarin dosage and the required biological responses. These include environmental and genetic factors and also includes mutations in the cytochrome P450 coding gene which is responsible for the oxidative metabolism of warfarin S- isomer. Because of these various factors, maintaining appropriate level of anticoagulation in patients on warfarin treatment is complex and always requires constant INR monitoring and adjustment of dosages. Patient noncompliance, miscommunication between the patient and physician and inaccuracies in laboratory testing also leads to variability in anticoagulant response. Pharmacokinetic and pharmacodynamics are the two categories into which warfarin drug interactions can be categorized. Pharmacokinetics as the name suggests are those that are involved with metabolism of warfarin and result in change in International Normalized Ratio (INR) whereas "synergistic" or additive effect form the basis for pharmacodynamic interactions.[37]

DETERMINANTS OF WARFARIN INTERACTIONS

1. ANTI INFECTIVE AGENTS

The most common cause of warfarin interaction clinically encountered is that between antimicrobial agents and warfarin which leads to fluctuation in INR values. The various mechanisms attributed to this interactions include interference with warfarin clearance , dietary changes of patients on antibiotic therapy resulting in reduction of vitamin K intake, imbalance of bacterial flora in the intestine leading to decreased amount of vitamin K production by intestinal bacteria.

Fisher et al [38] in their study on elderly patients receiving warfarin in combination with antibiotics for treatment of

urinary tract infections showed that there was a significant higher risk of upper gastrointestinal tract hemorrhage when patients were treated with cotrimoxazole than with other antibiotics (OR, 3.84; 95% confidence interval [CI], 2.33-6.33). The severity of fluctuation of INR is independent to the duration of initiation of cotrimoxazole treatment and even three days of treatment can increase INR to dangerously high levels [39] .

Among the antifungal drugs, many case reports have been reported regarding interactions between warfarin and fluconazole. Turrentine. M had described in their case report that even a single 150-mg oral dose of fluconazole can increase the prothrombin time to a clinically relevant level in women on chronic warfarin therapy [40]. In rare instances even spinal epidural haematoma have been noted due to warfarin/ fluconazole interaction [41]. Phamacokinetic modeling done by Miki et al [42] have shown that concomitant administration of warfarin and miconazole oral gel can lead to significant increase in warfarin concentration and requires proper monitoring.

By inhibiting CYP1A2, fluroquinolones have also been noted to interact with warfarin therapy [43] [44] [45] [46] [47] [48] [49]. In a retrospective evaluation, Gabriel et al [50] showed that patients concomitantly treated with warfarin and levofloxacin had a significant increase in INR values (P=0.001) which was comparable to the result found in our study.

Shrader et al [51] had published a case report in which their patient developed prolonged prothrombin time following treatment with azithromycin 500mg which later normalized after discontinuation of azithromycin. The possible explanations may be due to interaction occurring as a result of either 'infection induced changes in gastrointestinal flora, the inhibition of warfarin metabolism by the CYP450 system, and competitive protein binding.' Likewise Foster et al [52], in their paper report a case of 71 year old woman with prosthetic heart valve and normal INR value between 2.5 and 3.5 developing an increase in INR upto 15.16 after taking azithromycin for 5 days. Similarly several similar case reports have been published citing interactions between azithromycin and warfarin [53] [54] [55]. FDA published an update in February 2009 on azithromycin to warn the general public of potential drug interaction between warfarin and intravenous dosage form. According to FDA [56], concomitant use of azithromycin and warfarin may increase the INR values.

Among the different classes of anti retrovirals, non nucleotide reverse- transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) accounts for majority of interactions with warfarin as they are both metabolized by multiple CYP450 enzymes. Stefano Bonora et al [57] in their case report had documented INR elevation from 2.7 to 7.0 and gross haematuria in a patient with history of co administration of warfarin and efavirenz for a total duration of 3 weeks.

ANTI – INFECTIVE	CARDIOVASCULAR DRUGS	ANALGESICS, ANTI – INFLAMMATORIES & IMMUNOLOGICS
POTENTIATION (INCREASE INR)		
Amoxicillin/clavulanate	Amiodarone	Acetaminophen
Amoxicillin	Acetyl salicyclic acid	Acetyl salicyclic acid
Azithromycin	Atorvastatin	Allopurinol
Cefazolin	Diltiazem	Celecoxib
Chloramphenicol	Clofibrate	Indomethacin
Ciprofloxacin	Disopyramide	Interferon
Clarithromycin	Ezetimibe	Leflunomide
Cotrimoxazole	Fenofibrate	Dextropropoxyphene
Doxycycline	Glucagon	Methylprednisolone
Erythromycin	Propranolol	Phenylbutazone
Efavirenz	Propafenone	Piroxicam
Fluconazole	Lovastatin	Sulindac
Isoniazid	Quinidine	Tramadol
Itraconazole	Bezafibrate	Tolmetin
Levofloxacin	Rosuvastatin	Topical salicylates
Metronidazole	Simvastatin	
ANTI – INFECTIVE	CARDIOVASCULAR DRUGS	ANALGESICS, ANTI – INFLAMMATORIES & IMMUNOLOGICS
Nevirapine		
Norfloxacin		
Ofloxacin		

Voriconazole		
Terbinafine		
Ritonavir		
Saquinavir		
Moxifloxacin		
Tetracycline		

Adapted and updated from the following references [58] [59] [40] [60] [42] [61] [62] [63] [43] [44] [50] [45]

2. ANTIHYPERLIPIDEMIC AGENTS

In the current medical practice, the use of anti hyperlipidemic agents have increased dramatically due to its ability to decrease the risk of coronary events and stroke. Statistics have showed that approximately 30% of patients taking warfarin also take antihyperlipidemic agents. Schelleman et al [64] in an observational case control study by using Medicaid claims data , evaluated the risk of gastro intestinal (GI) bleeding in patients on warfarin after commencing statin or fibrate. Their results showed that chronic warfarin users had an increased odds ratio of GI bleeding upon starting of gemfibozil (1.88; 95% CI,1.00-3.54), simvastatin (1.46; 95% CI 1.03-2.07), atorvastatin (1.39; 95% CI 1.07-1.81). There was no increased risk seen with pravastatin (0.75; 95% CI,0.39-1.46). The reason may be attributed to the fact that simvastatin and atorvastatin are predominantly metabolized by CYP3A4 whereas pravastatin and rosuvastatin utilize CYP3A4 to a much lesser extend. Therefore if the need for statin therapy arises, physicians should judiously prescribe an agent with fewer documented interactions.

3. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) / SELECTIVE CYCLOOXYGENASE (COX)-2 INHIBITORS

NSAIDs ever since its discovery, is the most widely used drugs worldwide to control inflammation or musculoskeletal pain . NSAIDs apart from their antiplatelet function, by direct interactions can affect pharmacological action of warfarin. In a recent retrospective case control study using tertiary hospital medical records of 98 patients, Choi et al [65]concluded that after NSAID addition to warfarin, 39.8% of patients showed an increase in INR values of ≥15.0% with multivariate analysis revealing high maintenance dose (>40mg/week) of warfarin (P=0.025), the use of meloxicam (P=0.025), the presence of co administered medications(P=0.024) and low baseline INR value (P=0.03) as the risk factors for increase in INR values due to NSAID-warfarin interaction.

Similarly the risk of hospitalization for upper GI bleeding is increased in elderly patients when they took selective COX-2 inhibitors along with warfarin. A nested case-control analysis of multiple linked health care databases showed that out of 98821 elderly patients aged 66 years or more continuously receiving warfarin, 361 (0.3%) were admitted with upper GI hemorrhage [66]. The results after adjusting for potential confounders signify that case patients were more likely to be taking nonselective NSAIDS (OR, 1.9; 95% CI, 1.4-3.7), celecoxib (OR, 1.7; 95% CI, 1.2-3.6), or rofecoxib (OR, 2.4; 95% CI, 1.7-3.6) prior to hospitalization. As COX-2 inhibitors have rapidly gained acceptance in both Indian and Western clinical practice and accounts for fastest growing prescription medicine , care must be given by physicians and pharmacists when prescribing them to elderly patients on warfarin treatment due to possible interactions between both groups.

4. INTERACTION WITH ISONIAZID AND RIFAMPICIN

Isoniazid and rifampicin are the mainstay drugs used in the treatment of pulmonary and extrapulmonary tuberculosis. Rosenthal et al [67] in their case report record a 35 year old man admitted with coagulation abnormality after taking double dosage of isoniazid. Similarly by increasing the rate of warfarin clearance, rifampicin lowers plasma warfarin concentration. This could probably be due to a differential effect of warfarin stereoisomer metabolism or due to an altered dynamic effect [68].

5. GENETIC FACTORS

In the last decade, several studies were done in the area of warfarin dosage to genetic variants in genes involved in warfarin activity and metabolism and has shown consistent association with polymorphism in CYP2C9and VKORC1 gene variant. Direct association between warfarin dosage and CYP2C9 gene variant was first reported by Aithal and associates in the year 1999[69], whereas study on VKORC1 gene variant on warfarin doses were published in 2004[70].

CYP2C9*2 (430C>T) and CYP2C9*3(1075A>C) are the two most reported and studied polymorphism in CYP2C9 gene. Among this *2 allele has impaired hydroxylation of S-warfarin with 12% while *3 allele has less than 5% of wild type activity. As the result of these variations, there is a decrease in the degradation and warfarin clearance due to which a low dosage of warfarin is required to maintain therapeutic INR [71].

Another important factor affecting warfarin dosage is the promoter polymorphism VKORC1-1639G>A which is present withVKORC11173C>T. The binding site for VKORC1 transcription is altered and as a result of which there is lower VKORC1 mRNA expression in human liver. As the result of this , patients are more susceptible to inhibition by warfarin causing warfarin sensitivity[71,72]. Previously published articles [73-75] have showed that in Indians, presence of VKORC1 variant allele is 12-14% of the population. Natarajan.S et al. [76] in their study state that individuals were found to be sensitive to warfarin therapy even if there was presence of a single copy of variant allele.

76% of patients with VKORC1 variant in their study, within four standard dosage of warfarin doses of 5mg/day developed supra therapeutic INR (>4). In these patients, the INR values were brought down and maintained when their warfarin doses were decreased to 2-3 mg/day. According to this study , in patients carrying VKORC1 variation, the 'likelihood of developing supra therapeutic INR was found to be 13.96 times higher than wild types (OR=13.96:95% CI:4.85-44.65)' [76]. In patients with VKORC1 variations, lower than 5mg/day of warfarin dose is required to maintain INR within therapeutic range . In major population of patients with CYP2C9*2 heterozygotes and wild types, therapeutic INR was maintained with standard 5mg/day warfarin dosage.

Adequate knowledge of patient's genotype is also required to decide about initial warfarin dose required to maintain therapeutic INR which can invariably reduce the risk of developing supra-therapeutic INR and bleeding complications.

6. DRUG DIETARY INTERACTIONS

A. **CRANBERRY JUICE:-** Over the past few years , cranberry juice has been the rising trend in cystitis prevention and even treatment of urinary tract infections. Cranberry juice contains antioxidants which inhibit cytochrome P450 enzymes and since warfarin is predominantly metabolized in P450 CYP2C9, interactions with warfarin is biologically plausible. Griffiths et al [77] reported a case of fatal internal hemorrhage in an elderly man who consumed only cranberry juice (approximately 300–400 ml /day) for two weeks while maintain his usual dosage of warfarin. Similar such incident was seen in a 69 year old male admitted for revision of mechanical mitral valve and elevated INR value of 12. Patient had been drinking around two liters of cranberry juice for two weeks as prophylaxis for recurrent urinary tract infections. On discontinuing cranberry juice, his INR values dropped to 3.0 [78] . Based on these case reports and other published case reports [79] [80], UK medicines and health care products Regulatory Agency (MHRA)/Committee in Safety of Medicines (CSM) advised patients taking warfarin to avoid cranberry juice or products. In the wake of this precautionary statement issued by the FDA, many other larger studies were published which showed no significant interactions. Ansell et al. in their study of 30 patients on stable warfarin doses performed randomization and the patients received 240 ml of cranberry juice daily for 2 weeks [81]. At the end of the study there was no significant change in INR from the baseline. Another recent study prospective open labeled study [82] was conducted where 10 patients receiving warfarin was given 240ml of cranberry juice twice daily for 1 week. There was no significant changes noted in the INR values and there was no adverse events and no reported bleeding or bruising.

B. **GREEN TEA:-** Also known as Chinese tea is one among the most widely consumed beverages world wide. Various myths related to treatment of gastrointestinal disorders, enhancement of cognition and prevention of various cancers help to promote green tea consumption. The topic of concern is whether green tea contains vitamin K or not. James Taylor [83] had reported a case of 44 year old male who was on warfarin treatment for stroke prevention after receiving St Jude's mechanical heart valve presenting with significant decrease in INR value after patient consumed green tea. Patients previous records showed an INR of 3.2 while patient was on warfarin 7.5mg. following drinking one half to one gallon of green tea daily for 1 week, patient's INR dropped to 1.3 which returned to 2.5 after discontinuation of tea consumption. By using reverse- phase, vitamin K content of green teas was analyzed in an observational study [84] which revealed that dried green leaves contained 482mcg/100g of vitamin K and boiled green leaves contained 433 mcg/100g compared to only 0.03mcg/100g of vitamin K in brewed tea. Therefore significant interaction with warfarin is unlikely to happen with occasional consumption of brewed green tea.

C. **GREEN LEAFY VEGETABLES: -** As mentioned earlier, there are many drugs which can affect warfarin anticoagulation. To avoid dietary vitamin K- warfarin interactions, patients on warfarin therapy are advised to consume a constant dietary intake of vitamin K. The best sources of vitamin K are leafy vegetables which provide 50-800 plg vitamin K/100g [85]. Consumption of green leafy vegetables inconsistently is often the main cause of vitamin K fluctuation status [86]. As the result of which patients may present with evidences of anticoagulation and may receive increased doses of warfarin which may ultimately lead to over anticoagulation.

D. **FENUGREEK:-** It is one of the oldest medicinal plants originating in India where it is used mainly as a condiment[87]. 'It also contains alkaloids including trigonelle, gentian, and carpaine, as well as proteins rich in lysine, nucleoproteins rich in iron and phosphate, lecithin, steroids, coumarin glucosides, carbohydrates, mucilage, lipids, and saponins capable of hemolysis in aqueous solution.' [88,89] Fenugreek has many properties when taken orally. This includes lowering blood sugars in diabetics, stimulating appetite, reducing high cholesterol and triglyceride levels. The exact mechanism of its interaction with warfarin is unclear .However many case reports have been reported concomitant use of warfarin with fenugreek resulting in increase in INR values and by stopping the use, warfarin was seen to normalize [75].

7. **NON COMPLIANCE:-** One of the major factors found to attribute towards warfarin induced coagulation abnormality is the factor of non compliance to drug therapy especially in elderly patients. The different ways in which this can be manifested includes getting a prescription filled but failing to take the drug, failing to have a prescription filled, not following the dose or frequency of drug prescribed. Warfarin is a "double edged

sword" which requires good compliance with medication dose and prothrombin testing for optimal benefit or else may lead to coagulation abnormalities . Bridgen et al [90] in a retrospective study had concluded that 28% of INR values above 6 was due to poor compliance and may predispose patients to increased risk of hemorrhagic manifestations. Julian H [91] in a case control study concluded that non compliant cases were more likely to be younger (mean 53.7 years Vs 68.7 years, P 0.0001), male (OR 3.5, 95% CI 1.5, 8.2), and nonwhite (OR 6.4, 95% CI 1.9, 21.9).According to their study , non compliant patients considered regular blood testing as a big problem, warfarin usage adversely affecting their lives and failed to perceive health benefits from coagulation therapy. Therefore to tackle this problem ,the authors advise importance of patient education, physician involvement, and ease of prothrombin time monitoring.

MATERIALS AND METHODS

This was a prospective unmatched case control study . There were 50 patients recruited as case and an equal number of controls. The two groups had participants who had underwent post heart valve replacement and was on treatment with warfarin at the time of study. The first group recruited patients whose INR values were more than 4.5 and were termed as cases. The second group consisted of patients whose INR values were less than 4.5 and were termed as controls. Individual groups had appropriate tests done as detailed below. The data was then analyzed and association determined.

Details of Study Methods:

- Study involved:- Humans
- Type of study:- Prospective, case- control, observational
- Number of groups studied:- Two

Sample size in each group:

Total of 100 subjects. 50 in each group.

Study Period:- November 2013 to May 2015

Inclusion Criteria:

Cases: All patients who attended PIMS hospital on out patient department basis or patients who were admitted with INR values >4.5 or with bleeding manifestations and currently on warfarin therapy was assessed. Participants aged between 14 to 80 years were included in the study.

Controls: Participants in the age group of 14 to 80 years attending out patients in the department of cardiology with INR values <4.5 and with no evidence of bleeding and currently on warfarin therapy were included as controls

Exclusion Criteria:

Patients aged less than 14 or more than 80 years , on warfarin therapy for morbidities like atrial fibrillation, deep vein thrombosis prophylaxis were excluded in this study.

Parameters Studied:

The factors contributing or leading to coagulation abnormalities or INR more than 4.5 in post heart valve replacement patients receiving warfarin therapy in terms of:

Concurrent usage of antibiotics and other drugs:-This was done with the help of structured questionnaire. History of antibiotic/ NSAID use within past 1 week was taken into account which was verified by either outside prescription, medication cover or by telephonic confirmation with relatives of patients who were unsure of medication.

Compliance versus Non compliance: Patients were categorized as compliant and non compliant based on structured questionnaire which included last documented follow-up, last documented INR , dietary adherence in the past two months, documented versus actual warfarin dose that patient was taking and any history of double dosing of warfarin

INR monitoring:- This was done only at the time of study based on which patients were categorized as cases or controls. Liver function tests and platelet counts were also done to rule out other medical causes which could precipitate bleeding manifestations

Educational factors:- This was assessed based on Kuppuswamy's socioeconomic scale.

Dietary Factor :- This was done based on structured questionnaire of diet intake since past two months with regard to green leafy vegetables (e.g spinach, cabbage, Broccoli, green leafy lettuce) prior to last documented INR and prescribed warfarin dose. Patients were also asked about the intake of green tea and cranberry juice after the last documented INR and prescribed warfarin dose.

Distance to hospital Factor:- This was done by questionnaire and by plotting the distance with reference to map.

Brief Procedure:

Patients who attended PIMS hospital on OPD basis or patients who are admitted with INR more than 4.5 or with bleeding manifestations and currently on warfarin therapy were assessed in this study and were taken as the cases. Another group of unmatched patients who also underwent heart valve replacement and with INR values less than 4.5 were taken as controls. Patients were clearly explained about the study that is being done and was reassured about the maintenance of confidentiality . Questionnaires were handed out to the patients after obtaining their consent in the consent form. Patient's liver function test and INR test routinely done was noted for study purpose. Following participation in the study, patients were advised about how to prevent warfarin-induced coagulation in future.

Method of statistical analysis:

1. Number and percentage was used to describe characteristics of subjects.

2. Chi square test was used to assess the association.
3. Odds ratio , confidence interval and P value were used to assess risk in case control study. Odds ratio of > 1.0 was considered as risk and <1.0 was considered as protective effect.
4. Multivariate analysis to assess independent association of relevant variables found significant in the univariate analysis (less than 20% level).
5. P value <0.05 was considered as statistically significant

Ethical Considerations

1. Informed Consent was taken after clearing explaining to the participants about the study being done. As these patients were on lifelong oral anticoagulants any factors that could influence the outcome was of utmost importance to reduce the morbidity and mortality in this group.
2. Confidentiality of the information obtained from the patients as well as the biochemical parameters was maintained in both groups of patients.
3. The benefits of doing this study was duly informed to the study participants . All the patients were advised on how to improve the compliance to the treatment and maintain the INR values.
4. The participants were recruited in the study irrespective of the gender or socioeconomic status
5. Participants were not exposed to any increased risk as a result of the study and those participants who needed further management were subjected to the same.
6. No therapeutic intervention was done
7. The ethical approval was obtained from the P.I.M.S Institute Ethics Committee prior to the study .

RESULTS

There was a total of 100 participants who had underwent post heart valve replacement and currently on warfarin therapy. The first group consisted of 50 patients whose INR values were more than 4.5 or those with evidence of bleeding manifestations and therefore they were classified as cases. The second group also consisted of 50 patients whose INR values were less than 4.5 and were classified as controls. Both cases and controls were unmatched.

Table 1:- Demographic values among study participants (n=100)

Parameter	Case	%	Control	%	Total	ODDS RATIO	p value
GENDER							
Male	**23**	**54.8%**	**19**	**45.2%**	**42**	**1.38**	**0.418**
Female	**27**	**46.6%**	**31**	**53.4%**	**58**	**CI 0.62-3.08**	
AGE							
<40 years	**26**	**52%**	**24**	**48%**	**50**	**1.17**	**0.842**
> 40 years	**24**	**48%**	**26**	**52%**	**50**	**CI 0.53-2.57**	
DISTANCE							
Within Pondicherry	**15**	**51.7%**	**14**	**48.3%**	**29**	**1.00**	**1.00**
Outside Pondicherry	**35**	**49.3%**	**36**	**50.7%**	**71**	**CI 0.46-2.61**	
EDUCATIONAL STATUS							
Below high school	**34**	**57%**	**26**	**43%**	**60**	**1.96**	**0.15**
Above high school	**16**	**40%**	**24**	**60%**	**40**	**(0.87-4.42)**	

- There were 23 males and 27 females in the case group whereas the control group consisted of 19 males and 31 females [OR 1.38,(95% CI= 0.62-3.08), P=0.418].
- Similarly the number of participants whose age was less than 40 years were 26 and 24 in the case and control groups respectively and those who aged more than 40 years were found to be in the 24 and 26 in the case and control group respectively [OR 1.17(95% CI= 0.53-2.57), P=0.842].
- There were 15 patients in the case group and 14 in the control who resided within Pondicherry when compared with 35 patients in the case group and 36 patients in the control group who resided outside Pondicherry (OR 2.52 CI 0.72-8.81).

- Similarly in terms of educational status, case group had 34 participants who had completed below high school as compared to 24 participants who had passed high school seen in the control group.
- These results were not statistically significant stating that there is no difference between the cases and controls.
- Males were at increased chance of developing INR above 4.5 when compared with females. (OR : 1.38 CI : 0.62 – 3.08)
- Participants with age less than 40 years are 1.17 times at increased chance of developing INR above 4.5 when compared with participants above 40 years of age. But the result is not statistically significant due to null value in the confidence interval.(OR : 1.17 CI : 0.53-2.57)
- No association was found between deranged INR and distance of the patient from the treatment seeking centre
- Participants who are educated only upto high school have increased chance of developing INR above 4.5. (OR : 1.96 CI : 0.87-4.42). But the results are not statistically significant.

Table 2:- Educational Status in relationship with study participants (n=100)

Educational Status	CASES	%	CONTROLS	%	TOTAL
GRADUATE	3	100%	0	0	3
INTERMEDIATE	2	20%	8	80%	10
HIGH SCHOOL	11	40.7%	16	59.3%	27
MIDDLE SCHOOL	9	47.4%	10	52.6%	19
PRIMARY SCHOOL	13	59.1%	9	40.9%	22
ILLITERATE	12	63.2%	7	36.8%	19

P= 0.05

Table showing educational status among 100 participants.12 patients (63.2%) who were illiterate belonged to the case group whereas 8 patients (80%) in the control group had completed intermediate school. The results were found to be statistically significant (P=0.05)

Table 3:- Distribution of study participants based on intake of NSAIDS (n=100)

	Cases	%	Controls	%	Odds ratio	P value
NSAID taken	8	80%	2	20%	4.57	
NSAID not taken	42	46.7%	48	53.3%	C.I : 0.91-22.7	0.091

Participants who were taking NSAIDs were 4.57 times increased risk of having INR more than 4.5 when compared with participants not taking NSAIDs. (CI : 0.91 – 22.7). The result was not statistically significant.

Table 4:- Association of Antibiotics usage and INR (n=100)

	Cases	%	Controls	%	Odds ratio	P value
Antibiotics taken	9	69.2%	4	30.8%	2.52	
Antibiotics not taken	41	47.1%	46	52.9%	CI 0.72-8.81	0.233

Participants who were taking Antibiotics were 2.52 times at increased risk of having INR more than 4.5 when compared with participants not taking Antibiotics. (CI : 0.72 – 8.81). The result was not statistically significant.

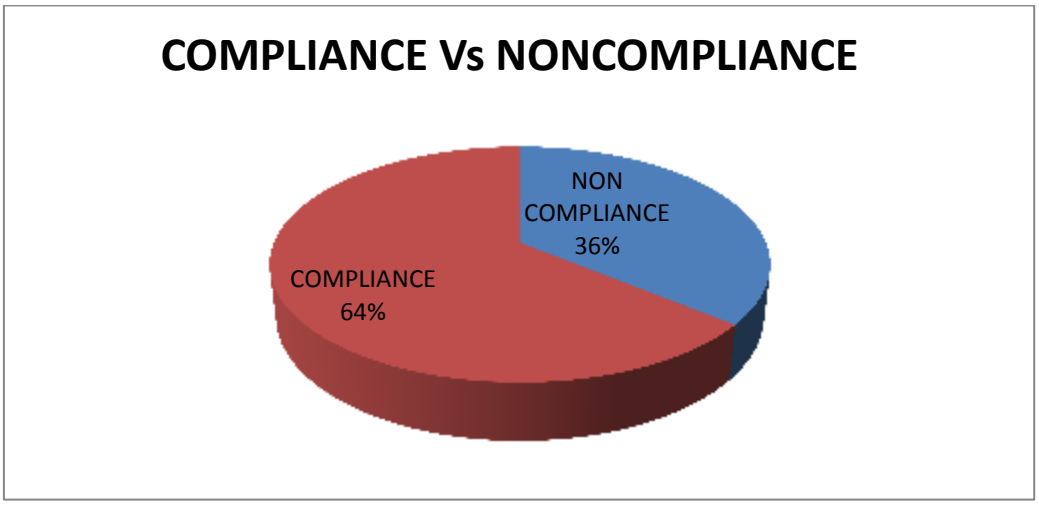


Table 5:- Distribution of study participants based on compliance (n=100)

Compliance	Cases	%	Controls	%	Odds ratio	P value
Non compliance	26	72.2%	10	27.8%	4.33 CI 1.78-10.52	0.001
Compliance	24	37.5%	40	62.5%		

Participants who were non compliant to medication were having an increased chance of having INR above 4.5 when compared with participants who are compliant to treatment.(OR : 4.33 CI : 1.78 -10.52). The results were statistically significant.
Among the 100 participants in the study , 36 % were found to be non compliant with treatment as compared to 64% who were compliant . Among the latter group, 40 patients (62.5%) belonged to the control group and only 24 (37.5%) belonged to the case group

Table 6:- Factors of elevated INR (n=100)

Parameters	Cases	Controls	Total	P value
Over anticoagulation	3	0	3	0.242
No Over anticoagulation	47	50	47	

Fisher Exact= 0.242

Parameters	Cases	Controls	Total	P value
CAD/ Liver disease	1	0	1	1.00
No CAD/Liver disease	49	50	99	

Fisher Exact =1.00

Table 7. Bleeding manifestation presented by participants with Elevated INR (> 4.5) (n=50)

Parameter	Frequency	%
Patients without clinical evidence of bleeding	33	66%
Gum bleeding	10	20%

Hematoma	**5**	**10%**
Per vaginal bleeding	**1**	**2%**
Haemoptysis	**1**	**2%**
Total	**50**	**100%**

Table 8. Bleeding manifestation present in the study Population (n=100)

Parameters	Cases	Controls	Total	P value
Bleeding	**17**	**0**	**17**	**<0.001**
No bleeding	**33**	**50**	**83**	

Fisher exact =<0.001

Table 9. Demographic table to compare compliant and non compliant population (n=100)

Parameters	Compliance	%	Non compliance	%	Total	Odds ratio	P value
Gender							
Female	**40**	**69.0%**	**18**	**31.0%**	**58**	**1.66**	**0.29**
Male	**24**	**57.0%**	**18**	**42.9%**	**42**	**(0.72-3.80)**	
Age							
Age>40 years	**33**	**66.0%**	**17**	**34.0%**	**50**	**1.18**	**0.835**
Age<40 years	**31**	**62.0%**	**19**	**38.0%**	**50**	**(0.52-2.69)**	
Distance							
Outside Pondicherry	**48**	**67.6%**	**23**	**32.4%**	**71**	**1.69**	**0.259**
Within Pondicherry	**16**	**55.2%**	**13**	**44.8%**	**29**	**(0.7-4.10)**	

- When compared with the compliance and non compliance population, there were 24 males and 40 females who were compliant with treatment when compared to 18 males and 18 females in the non compliant group.
- Similarly there were 31 participants who were less than 40 years and 33 participants who were aged more than 40 years in the compliance group when compared to 19 and 17 respectively in the non compliance group.
- There were 16 patients in the compliance group and 13 in the non compliance group who resided within Pondicherry when compared with 48 participants in the compliance and 23 participants in the non compliance group who resided outside Pondicherry
- Female gender have an increased chance of being compliant compared with male counterparts. (OR : 1.66 CI : 0.72-3.80).The result is not statistically significant.(P Value : 0292)
- Participants who are aged more than 40 years were more compliant to treatment than the those below 40 years. (OR : 0.84 P value : 0.835)
- Participants who were staying outside Puducherry were more compliant to treatment.(OR : 1.69 CI : 0.7 – 4.10). The results were not statistically significant.

Table 10. Educational Status in relationship with compliance and non compliance of patients (n=100)

Education	Compliance	%	Non Compliance	%	Total
GRADUATE	02	66.7%	01	33.3%	03
INTERMEDIATE	07	70%	03	30.0%	10
HIGH SCHOOL	16	59.3%	11	40.7%	27
MIDDLE SCHOOL	14	73.7%	05	26.3%	19
PRIMARY SCHOOL	12	54.5%	10	45.5%	22
ILLITERATE	13	68.4%	06	31.6%	19

Chi square = 0.0857

Educational status among 100 participants showed that 13 patients (68.4%) who were illiterate belonged to the compliance group whereas 11 patients (40.7%) in the non compliance group had completed high school. The results were found to be statistically insignificant (P=0.0857).

Table 11. Association of Non compliance with INR (n=100)

Parameter	Cases	%	Controls	%	OR	CI	P value	Total
Wrong dosage	7	77.8%	2	22.2%	3.90	0.76-19.83	0.15	9
Correct dosage	43	47 %	48	53%				91
Green leafy vegetables	9	64.3%	5	35.7%	1.97	0.61-6.37	0.388	14
Dietary adherent	41	48%	45	52%				86
Delay in follow up	10	77%	3	23%	3.91	1.00-15.22	0.07	13
Regular follow up	40	46%	47	54%				87

- Participants following wrong dosage was found to be at increased risk of having INR above 4.5 when compared with participants following correct dosage of warfarin. (CI 0.76-19.83; P Value : 0.15)
- Participants taking green leafy vegetables were found to be at increased risk of having INR above 4.5 . (OR : 1.97 CI 0.61-6.37; P Value : 0.38)
- Participants who delay in follow up and INR monitoring were 3.91 times increased risk of having INR above 4.5. (CI : 1.00 – 15.22 ; P Value : 0.07)

Table 12. Multivariate analysis to assess independent association of relevant variables with elevated INR (>4.5)

Parameters	Odds ratio	Confidence interval	P value
Age< 40 years	2.397	0.815-7.046	0.112
Male	1.756	0.680-4.533	0.244
Distance Within Pondicherry	1.391	0.496-3.899	0.531
Above high school	0.238	0.075-0.758	0.15
Compliance	0.228	0.089-0.583	0.002

On multivariate analysis, compliance to treatment was showing association with factors influencing warfarin interaction.

Table 13. Multivariate analysis to assess independent association of factors for patient compliance.

Parameters	Odds ratio	Confidence interval	P value
Age<40 years	1.530	0.565-4.142	0.403
Male	2.101	0.845-5.225	0.110
Within Pondicherry	2.207	0.837-5.817	0.109
Above High School	0.704	0.246-2.011	0.512

On multivariate analysis showed no factors of association for patient compliance.

DISCUSSION

Warfarin is a "double edged sword" , when used in its optimal range it can be beneficial for patients. But any deviation towards either extremes can lead to serious morbidity and even mortality. More than 2 million Indians take warfarin and it is more prescribed in the elderly population based on physician comfort due to years of usage[5].

The purpose of this study was to identify contributing factors for bleeding Manifestations or INR >4.5 in patients already on warfarin therapy and to address factors which increase patient compliance.

As there is a narrow therapeutic index existing among oral anticoagulants, therapeutic control is often difficult [92]. This makes compliance to treatment very crucial. Therefore the initial parameter that we studied was the level of non compliance. In our study, 36% of study participants among both cases and controls were found to be non compliant with the treatment as compared to 64% who were compliant. Among the latter group, 40 patients (62.5%) belonged to the control group and only 24 (37.5%) belonged to the case group which was statistically significant [OR= 0.23(95% CI=0.09-0.56), P=0.002].

In terms of finding the contributing factors, certain key issues related to warfarin had to be considered. To begin with our Indian population vary a lot when compared to the western population in certain issues with warfarin. One of the major factor that played a pivotal role in warfarin interaction was the dietary habits which differed from that of the west. Indian due to different dietary habits are more prone for warfarin interactions. The typical Indian diet is centered on consumption of wheat and green leafy vegetables like cabbage, cauliflower , spinach and other foods rich in Vitamin K. As a result of which target INR is not achieved due to lability in the INR values[86]. Similar results were also seen in our study . Out of 36 non compliant patients 14 patients (38.9%) had history of consumption of green leafy vegetables in the recent 2 months which included the last out patient visit. Majority of the subjects are not aware of which all green leafy vegetables to avoid while on warfarin or give history of consumption of green leafy vegetables at the time of study enrollment

Another major problem that we see in our society is the irrational use of over the counter medications especially non steroidal anti- inflammatory drugs or alternative herbal products for various symptoms like fever, joint pain, body ache. Choi .K.H. et al. in their study state that NSAIDs will lead to increase in the oral anticoagulant action of vitamin K antagonist and cause bleeding[65]. In our study, among the total 10 patients who had taken NSAIDS , 8 patients (80%) belonged to the case group [OR =4.57 ,(95% CI= 0.91-22.7), P=0.09]. To find out whether distance had any role in non compliance we calculated the number of cases presenting from within Pondicherry and those from outside Pondicherry. However no statistical significance was seen.

Lesser dose of Vitamin K antagonist is required for Indians with bony mass index and low body weight to achieve target INR compared to that of the west [5] . Similarly another factor worth noting is that large proportion of Indian population during any concurrent co- morbid illness like fever, diarrhea, vomiting etc tend to omit warfarin resulting in problems of low INR or more commonly take antibiotics like metronidazole or macrolides and may present with high INR/ bleeding [5]. This could be attributed to the fact that in majority of medical stores in our country, the pharmacist dispense medicines by themselves or patients tend to self medicate themselves without knowing the seriousness of drug – drug interaction. Similar trend was seen in our study where 13 patients presented with H/o taking antibiotic for fever and diarrhea out of which 9 (69.2%) had INR values more than 4.5 [OR= 2.52, (95% CI= 0.72-8.81), P=0.23]. All of these patients had been prescribed antibiotics by pharmacist for symptomatic treatment.

Kakkar et al [92] conducted a study based on the review of case records of 82 patients who were on anticoagulant therapy for a minimum duration of three months. Their study revealed that among outpatient , the overall therapeutic control was generally poor leading to a state of under anticoagulation of patients for most period of treatment. The rate of complication was also unacceptably high. This could be attributed to the fact that there is a lack of proper laboratories with standardized measurement of prothrombin time even in suburbs of large cities.

In the long run for optimal management of INR, not just the patients, but even physicians also have a large role to play in the general outcome of patients. Maintenance of optimal INR requires dosage regulation, frequent laboratory testing, , prompt diagnosis and treatment of thromboembolic or hemorrhagic complications in addition to compliance factor and patient education. Kakkar et al. [93] conducted over a 16

month period a retrospective review of 3152 consecutive INRs in patients on outpatient oral anticoagulant treatment of a well reputed teaching hospital. Study was performed by a questionnaire survey among 65 clinicians on various aspects of oral anticoagulant treatment. The results showed that in view of perceived risk of bleeding , there was a tendency to under coagulate. Moreover patient education was limited only to verbal information to patients on oral anticoagulation.

The need for regular INR monitoring is very crucial in those patients on warfarin therapy due o risks of thromboembolism or bleeding. SV Praveen [94] in their study reported that PT monitoring was irregular in 25% of patients. In our study , among 36 patient who were non compliant with warfarin treatment, 13 patients (36.1%) belonged to the category of delay in follow up and INR monitoring. Our study had patients ranging from 6 months since last follow-up up to 1.5 years of last follow up which clearly indicates the lapse in follow up.

Among area which needs to be addressed is the area of taking wrong dosage/ self medications. In our study out of 36 non compliant patients, 9 patients (25%) gave history of taking wrong dosage of warfarin. This could be attributed to the practice of taking double medicines in case of prior missing of regular dose. Wrong interpretation of dose prescribed could also lead to this.

Another parameter which we found significant in our study was the relation of educational status among the study subjects. Our study on educational status in concordance with Kuppasamy's scoring chart revealed that 63.2% of illiterate subjects belonged to the case group whereas 59.3% of subjects who had passed high school were seen in the control group (P=0.05) . This shows that literacy places a conclusive role as determinant in warfarin resistance.

Other contributing factors noted in our study is over anticoagulation. These were 3 such patients who had presented with h/o of struck valve and therefore their warfarin dosages were increased as a result of which , these patients developed iatrogenic induced coagulation abnormality. Similarly we had 1 patient who was a known case of coronary artery disease and chronic liver disease as a result of which had elevated INR values. Our study also had 3 patients for whom no reasons could be found for coagulation abnormality and hence were classified as with unknown causes.

Not all patients presenting with coagulation abnormality had bleeding manifestations. Among the 50 study populations enrolled as cases, only 17 patients (34%) had bleeding manifestations. Majority of patients (20%) presented with gum bleeding followed by hematoma (10%). There was 1 case each who presented with haemoptysis and per vaginal bleeding.

Our study had its drawbacks. First of all it was an unmatched case control trial. The possibility of whether genetic factors and phenotypes played a role in our study was not assessed .The study may have shown significant association in terms of age, gender and distance if the sample size in each group were more. Similarly the duration since valve replacement was not taken into account.

SUMMARY

- This is a case control study done in tertiary care teaching hospital in Pondicherry Institute of Medical sciences, Pondicherry with 50 cases and 50 controls
- There were 23 males and 27 females in the case group whereas the control group consisted of 19 males and 31 females
- Males were at increased chance of developing INR above 4.5 when compared with females. (OR : 1.38 CI : 0.62 – 3.08)
- Participants with age less than 40 years are 1.17 times at increased chance of developing INR above 4.5 when compared with participants above 40 years of age. But the result is not statistically significant due to null value in the confidence interval.(OR : 1.17 CI : 0.53-2.57)
- No association was found between deranged INR and distance of the patient from the treatment seeking centre
- Participants who are educated only up to high school have increased chance of developing INR above 4.5. (OR: 1.96 CI: 0.87-4.42). But the results are not statistically significant.
- Participants who were non compliant to medication were having an increased chance of having INR above 4.5 when compared with participants who are compliant to treatment.(OR : 4.33 CI : 1.78 -10.52). The results were statistically significant.
- Participants who were taking NSAIDs were 4.57 times increased risk of having INR more than 4.5 when compared with participants not taking NSAIDs. (CI : 0.91 – 22.7). The result was not statistically significant.
- Participants who were taking Antibiotics were 2.52 times at increased risk of having INR more than 4.5 when compared with participants not taking Antibiotics. (CI : 0.72 – 8.81). The result was not statistically significant.
- Female gender have an increased chance of being compliant compared with male counterparts. (OR : 1.66 CI : 0.72-3.80).The result is not statistically significant.(P Value : 0292)
- Participants who are aged more than 40 years were more compliant to treatment than the those below 40 years. (OR : 0.84 P value : 0.835)
- Participants who were staying outside Puducherry were more compliant to treatment.(OR: 1.69 CI : 0.7 – 4.10). The results were not statistically significant
- Participants following wrong dosage (non compliance to treatment) was found to be at increased risk of having INR above 4.5 when compared with participants following correct dosage of warfarin. (CI 0.76-19.83; P Value : 0.15).
- Participants taking green leafy vegetables (non compliance to treatment) were found to be at increased risk of having INR above 4.5. (OR : 1.97 CI 0.61-6.37; P Value : 0.38)

- Participants who delay in follow up and INR monitoring (non compliance to treatment) were 3.91 times increased risk of having INR above 4.5. (CI : 1.00 – 15.22 ; P Value : 0.07)
- On multivariate analysis, compliance to treatment was showing association with factors influencing warfarin interaction.

CONCLUSION

Non compliance to medication was found to be a risk factor for increased INR and was statistically significant. Gender, age, educational status, intake of NSAIDs and antibiotics were found to be a risk factor which increased INR but it was not statistically significant. Wrong dosage, intake of green leafy vegetables and delay in follow up were found to be risk factor for non compliance but it was not statistically significant.

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