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A Comparison of the Efficacy and Safety of Acenocoumarol and Warfarin in Valve Replaced Patients with Rheumatic Heart Disease

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ABSTRACT

Rheumatic valvular heart disease is a long term sequelae of rheumatic fever worldwide and the latter is the most common cause. Prevalence of rheumatic valvular heart disease is 15.7 million persons worldwide. To assess and compare the efficacy of Acenocoumarol and Warfarin in valve replaced patients with Rheumatic heart disease. To assess and compare the safety and tolerability of Acenocoumarol and Warfarin in valve replaced patients with Rheumatic heart disease. The present study was a randomized, prospective, open label, comparative study. This study was conducted from January 2018 to December 2018 at Department of Pharmacology in collaboration with Department of Cardio-Thoracic and Vascular Surgery (CTVS) at Institute of Post Graduate Medical Education and Research, Kolkata. RHD primarily affects the mitral valve (in approximately 2/3 rd of patients), as in this study, total 46.66% cases of MS, MR and MVR operations were noted due to RHD. As total 77.27% ADRs (100% in Acenocoumarol group and 58.33% in Warfarin group) were definitely preventable, precaution must be taken to prevent ADRs. As total 77.27% ADRs (100% in Acenocoumarol group and 58.33% in Warfarin group) were mild, it is important to follow-up for ADRs to prevent further complications. The study therefore concluded that Acenocoumarol and Warfarin are equally efficacious. After comparing overall safety in both groups or after comparing overall adverse drug reaction (ADRs) between Acenocoumarol group and Warfarin group, it is observed that according to severity of ADRs, Acenocoumarol is better and safer than Warfarin. This study showed that Vitamin K antagonists (VKAs) like Acenocoumarol or Warfarin must be administered as oral anticoagulants, after heart valve replacement surgery, in post-operative patients and both Acenocoumarol and Warfarin are equally effective in maintaining INR within therapeutic target range.

INTRODUCTION

Rheumatic valvular heart disease is a long term sequelae of rheumatic fever, it's most common cause worldwide. Prevalence of rheumatic valvular heart disease is 15.7 million persons worldwide. Acute rheumatic fever (ARF) is believed to be an autoimmune disease following Group A Streptococcus infection with multisystem involvement. Unless preventive measures are taken, episodes of ARF can recur in same person. Its recurrence increases the chances of damaging the heart valves called rheumatic heart disease (RHD)[1].

In 2015, prevalence of RHD was 3, 31, 94,900 in endemic countries and 2, 21,600 in non-endemic countries. The countries with the largest numbers of RHD cases in 2015 were India (13.17 million cases), China (7.07 million) and Pakistan (2.25 million)[2]. Group A Streptococcus (GAS) cause sore throat infection, which is followed by ARF after few weeks and may affect the skin, joints, heart and brain[3]. RHD is caused by the immune destruction of heart valves as aconsequence of the disease and associated with serious hemodynamic disturbances causing cardiac failure. It is also associated with other complications such as stroke and infective endocarditis. Rheumatic fever is caused by multiple factors and follows Group A Streptococcus pharyngitis (agent), in a susceptible individual (host), under deprived social conditions (environment).

Symptoms of RHD are heart failure, features like breathlessness, ankle swelling, fatigue and rapid heartbeat (due to abnormal rhythm resulting from dilated chambers). Blood stagnation in enlarged chambers result in clot formation, which breaks and obstructs the flow of blood to the CNS causing stroke, in addition to other body regions[3]. RHD primarily affects the mitral valve (in approximately 2/3 rd of patients) and secondarily affects the aortic valve (in approximately 1/3 rd of patients). Patients with valvular heart disease (VHD), with prosthetic heart valves (PHV) or with other comorbid conditions, are at high risk for thromboembolic complications and often require antithrombotic medications. Prothombin time (PT) guides treatment and varies across the world and among laboratories. Standardized PT is signified by International Normalized Ratio (INR). The therapeutic target range of INR for mechanical heart valve should be maintained between 2 and 3.5[1]. RHD can be prevented at different levels. As Primordial prevention: Development of socio-economic status, avoiding overcrowding and improving hygiene are necessary. As Primary prevention: Penicillin in treatment of sore throat infection is necessary. As Secondary prevention (or management): Prophylaxis with regular antibiotic (monthly long-acting penicillin injection) or lifelong, after an episode of ARF or diagnosed RHD[3]. For management of ARF: NSAIDS (prevent progression to the stage of polyarthritis from initial disease stage), bed rest, fluid restriction, cardiac medications, echocardiography, cardiology assessment, diuretics, ACE inhibitors etc. are required[4]. Best care involves penicillin prophylaxis as secondary prevention, timely specialist reviews, echocardiography assessment of left ventricular and valve function and timely surgical referral. Vitamin K antagonist Warfarin is the drug of choice for anticoagulation in patients with prosthetic heart valves with both rheumatic and non-rheumatic valve disease. Diet affects the absorption of warfarin, so INR must be measured regularly, with adjustments of the dose as necessary. Newer anticoagulants like Dabigatran inhibit thrombin or activated factor X dose-dependently but safety and efficacy of these drugs are still being studied and they are currently not recommended in patients with prosthetic valves[4].

In developed and developing countries like India, vitamin K antagonists like Acenocoumarol or Warfarin are frequently used as oral anticoagulants for management (prevention and treatment) of thromboembolic disorders like stroke, pulmonary embolism, myocardial infarction, recurrent infarction, deep vein thrombosis and systemic embolism in patients with prosthetic heart valves or atrial fibrillation. Coumarin derivative Acenocoumarol has pharmacological features closer to an ideal oral anticoagulant[5]. It is more efficacious than warfarin and maintains INR within the therapeutic target range (TTR). Vitamin K antagonists like acenocoumarol and warfarin are preferred in India for oral anticoagulation[5].

Efficacy and safety of acenocoumarol has been evaluated in treatment of deep vein thrombosis, atrial fibrillation, post myocardial infarction, after major surgeries, after cardiac valve replacement and after critical illness requiring prolonged hospitalization. In all age groups, Acenocoumarol is efficacious and safe. Over warfarin, it offers an advantage as better stability of anti-coagulant effect. In countries like India, due to its economic advantage, acenocoumarol may be a suitable oral anticoagulant for long term use[6].

MATERIAL AND METHODS

Source of data: The study was conducted by the Department of Pharmacology in collaboration with Department of Cardio-Thoraco-Vascular Surgery (CTVS) at Institute of Post Graduate Medical Education and Research, Kolkata. It is a tertiary care hospital equipped with modern diagnostic and treatment facilities. Patients visiting this hospital come from different geographical regions of West Bengal with a

fair representation of both urban and rural population belonging to varied socioeconomic status. The present study was conducted at the Cardio-Thoraco-Vascular Surgery (CTVS) Inpatients (IPD) and outpatients (OPD at Institute of Post Graduate Medical Education and Research, Kolkata, after replacement of heart valve for rheumatic heart disease.

Approval:

- This study was approved by the Institutional Ethics Committee

Study design and duration:

- This was a randomized, prospective, open label, comparative study
- The duration of the study was from January 2018 to December 2018

Sample size:

- Each study group included 30 participants. Total sample size was 60
- The participants were included in this study after obtaining written informed consent

Inclusion criteria:

- Age between 18-60 years
- Aortic valve replaced patients for Rheumatic heart disease
- Mitral valve replaced patients for Rheumatic heart disease
- Double valve replaced patients for Rheumatic heart disease
- Patients undergone valve replacement surgery where mechanical valve prosthesis used
- Patients who are willing to provide full written informed consent

Exclusion criteria:

- Patients with history of any combined Cardio-Thoraco-Vascular Surgery procedure including Valve replacement surgery.
- Patients with history of hypersensitivity to either drugs.
- Patients with previous history of embolic episode or hemorrhagic tendency

Methodology: Post-operative heart valve replaced patients for RHD, were recruited after visiting Cardio Thoraco Vascular Surgery (CTVS) Inpatients (IPD) of IPGMER. The eligible patients were screened for inclusion and exclusion criteria. Data was collected from eligible participants fulfilling inclusion criteria after obtaining written informed consent. The study objectives and process were explained to the patients and their relatives in their own language to obtain informed consent. Subjects who consented to participate were than interviewed, randomized and divided into two groups based on computer generated randomization schedule (http://www.randomizer.org).

- Each group comprised of 30 participants
- Group 1 or group A: Tablet Acenocoumarol, 1-4mg^{-1} day/oral for 3 months
- Group 2 or group B: Tablet Warfarin, 1-5mg^{-1}day/oral for 3 months

The initial and continuous doses of drug were decided on the value of Prothombin time (PT) and International normalized ratio (INR). PT guides treatment, varies across the world and among laboratories. Standard PT is signified by INR which depending on the type of mechanical heart valve should be maintained between 2 and 3.5. This was the TTR of INR values. The participants were followed up monthly after starting the drug, for 3 months. Total study duration was 1 year. Venipuncture for blood study was done.

Outcome measure

Primary outcome: Efficacy of both Warfarin and Acenocoumarol by testing:

- Value of Prothombin time monthly (every month) for 3 months
- Value of International normalized ratio monthly (every month) for 3 months

Secondary outcome:

- Safety and tolerability Adverse effects of Acenocoumarol other than bleeding are oral ulceration, gastro-intestinal tract disturbance, dermatitis, urticaria and alopecia. Adverse effects of Warfarin other than bleeding are alopecia, dermatitis and diarrhea
- Number of patients requiring dose adjustment
- Incidence of thromboembolism and major hemorrhage

Statistical analysis: Data collected were entered on Microsoft Office for Windows 2007 excel spread sheet. The baseline data like demography (IP/hospital number, age, sex etc.), efficacy, Safety and tolerability (adverse reactions) were subjected to descriptive statistical analysis and expressed as mean±SD, frequencies and percentages. The categorical variables were compared using Chi-square test. Comparison of

Table 1: Mean age and Standard deviation (SD) of participants completing study in groups

Drugs	N	Minimum	Maximum	Mean	SD
Acenocoumarol	25	22	58	44.44	11.787
Warfarin	24	20	60	37.71	11.830

Table 2: Diagnosis wise distribution of participants in both the groups

Diagnosis	No. of total subjects (n=60)	No. of subjects in Acenocoumarol group (n=30)	No. of subjects in Warfarin group (n=30)
MS, MR, AS and AR	14 (23.33%)	6 (20%)	8 (26.66%)
MS and MR	29 (46.66%)	17 (56.66%)	12 (40%)
AS and AR	17 (30%)	7 (23.33%)	10 (33.33%)

Table 3: Diagnosis wise distribution of participants in Acenocoumarol (n=25) study groups

		Frequency	Percent
Valid	MS, MR, AS and AR	5	20.0
	MS and MR	14	56.0
	AS and AR	6	24.0
	Total	25	100.0

Table 4: Diagnosis wise distribution of participants in Warfarin (n=24) study groups

		Frequency	Percent
Valid	MS, MR, AS and AR	7	28.0
	MS and MR	9	36.0
	AS and AR	8	32
	Total	24	96.0

continuous variables between groups was carried out using Independent sample t-test (or unpaired student's t-test). Statistical significance was set at $p<0.05$.

RESULTS

In Acenocoumarol the mean Drugs (mean±SD) of patients was 44.44±11.787. In Warfarin the mean Drugs (mean±SD) of patients was 37.71±11.830. In Acenocoumarol, 6 (20%) patients had MS, MR, AS and AR Diagnosis, 17 (56.66%) patients had MS and MR Diagnosis and 7 (23.33%) patients had AS and AR Diagnosis. In Warfarin, 8 (26.66%) patients had MS, MR, AS and AR Diagnosis, 12 (40%) patients had MS and MR Diagnosis and 10 (33.33%) patients had AS and AR Diagnosis. In our study, 5 (28.0%) patients had MS, MR, AS and AR, 14 (56.0%) patients had MS and MR and 6 (24.0%) patients had AS and AR.

In our study, 7 (20.0%) patients had MS, MR, AS and AR, 9 (36.0%) patients had MS and MR and 8 (32%) patients had AS and AR. In Acenocoumarol, 6 (20%) patients had DVR, 17 (56.66%) patients had MVR and 7 (23.33%) patients had AVR. In Warfarin, 8 (26.66%) patients had DVR, 12 (40%) patients had MVR and 10 (33.33%) patients had AVR. In our study, 5 (20.0%) patients had DVR, 14 (56.0%) patients had MVR and 6 (24.0%) patients had AVR.

In ADRs in Warfarin group, 3 (60.0%) patients had ADRs in Acenocoumarol group. In Acenocoumarol, 3 (30%) patients had Ecchymosis, 3 (30%) patients had Epistaxis, 2 (20%) patients had Hematuria, 2 (20%) patients had Bleeding in G.I.T. In Warfarin, 2 (16.66%) patients had Ecchymosis, 2 (16.66%) patients had Epistaxis, 2 (16.66%) patients had Hematuria, 2 (16.66%) patients had Bleeding in G.I.T , 1 (8.33%) patients had Alopecia, 1 (8.33%) patients had Dermatitis and 2 (16.66%) patients had Malaise or pain in chest, leg and thigh.

In our study, 18 (72.0%) patients had Type 1 ADRs, 3 (12.0%) patients had Type 2 ADRs, 2 (8.0%) patients had Type 3 ADRs, 1 (4.0%) patients had Type 4 ADRs and 1 (4.0%) patients had Type 5 ADRs in Acenocoumarol group. In our study, 19 (76.0%) patients had Type 1 ADRs, 1 (4.0%) patients had Type 2 ADRs, 1 (4.0%) patients had Type 3 ADRs, 1 (4.0%) patients had Type 4 ADRs,1 (4.0%) patients had Type 5, 1 (4.0%) patients had Type 6 ADRs , 1 (4.0%) patients had Type 7 ADRs , 1 (4.0%) patients had Type 8 ADRs and 1 (4.0%) patients had Type 9 ADRs.

In Acenocoumarol, 5 (50%) patients had developed Month wise ADRs in 1st month and 2 (20%) patients had developed Month wise ADRs in 2nd month and 3 (30%) patients had developed Month wise ADRs in 3rd month. In Warfarin, 8 (66.66%) patients had developed Month wise ADRs in 1st month and 4 (33.33%) patients had developed Month wise ADRs in 2nd month. In Acenocoumarol, 5 (71.42%) patients had developed Month wise ADRs in 1st month and 1 (14.28%) patients had developed Month wise ADRs in 2nd month and 1 (14.28%) patients had developed Month wise ADRs in 3rd month.

In Warfarin, 2 (40%) patients had developed Month wise ADRs in 1st month and 3 (60%) patients had developed Month wise ADRs in 2nd month. In Probable (In Warfarin group), 2 (100.0%) patients had Probable in Acenocoumarol group. In Possible (In Warfarin group), 1 (100.0%) patients had Possible in Acenocoumarol group. In Definitely preventable (In Warfarin group), 2 (100.0%) patients had Definitely preventable In Acenocoumarol group. In probably preventable (In Warfarin group), 1 (50%) patients had definitely preventable in Acenocoumarol group.

DISCUSSIONS

Duration: This present study was conducted from January 2018 to December 2018. This is comparable to a study done by Kulo *et al*. in which quality of treatment were evaluated between warfarin and acenocoumarol, in an observational, comparative, one-year clinical study, conducted in non-valvular atrial fibrillation (NVAF) patients[7].

Table 5: Treatment wise distribution of participants in both groups

Treatment	No. of total subjects (n=60)	No. of subjects in Acenocoumarol group (n=30)	No. of subjects in Warfarin group (n=30)
DVR	14(23.33%)	6(20%)	8(26.66%)
MVR	29(46.66%)	17(56.66%)	12(40%)
AVR	17(30%)	7(23.33%)	10(33.33%)

Table 6: Treatment wise distribution of participants in Acenocoumarol (n=25) study group

		Frequency	Percent
Valid	DVR	5	20.0
	MVR	14	56.0
	AVR	6	24.0
	Total	25	100.0

Table 7: Adverse drug reaction (ADRs) in both groups - Cross tabulation

			ADRs in Warfarin group		Total
			No ADRs	ADRs	
ADRs in Acenocoumarol group	No ADRs	Count	15	2	17
		% within ADRs in Warfarin group	78.9%	40.0%	70.8%
	ADRs	Count	4	3	7
		% within ADRs in Warfarin group	21.1%	60.0%	29.2%
Total		Count	19	5	24
		% within ADRs in Warfarin group	100.0%	100.0%	100.0%

Table 8: Types of adverse drug reaction (ADRs) in both the groups

ADRs	In both groups (out of total 22 ADRs)	In Acenocoumarol group (out of total 10 ADRs)	In Warfarin group (out of total 12 ADRs)
Ecchymosis	5 (22.72%)	3 (30%)	2 (16.66%)
Epistaxis	5 (22.72%)	3 (30%)	2 (16.66%)
Hematuria	4 (18.18%)	2 (20%)	2 (16.66%)
Bleeding in G.I.T	4 (18.18%)	2 (20%)	2 (16.66%)
Alopecia	1 (4.54%)	0	1 (8.33%)
Dermatitis	1 (4.54%)	0	1 (8.33%)
Malaise or pain in chest, leg and thigh	2 (9.09%)	0	2 (16.66%)

Table 9: Types of adverse drug reaction (ADRs) in Acenocoumarol group

		Frequency	Percentage
Valid	1	18	72.0
	2	3	12.0
	3	2	8.0
	4	1	4.0
	5	1	4.0
	Total	25	100.0

Table 10: Types of adverse drug reaction (ADRs) in Warfarin group

		Frequency	Percentage
Valid	1	19	76.0
	2	1	4.0
	3	1	4.0
	4	1	4.0
	6	1	4.0
	9	1	4.0
	Total	24	96.0

Table 11: Month wise, Number of ADRs developed in both groups

Month	In both group (out of total 22 ADRs)	In Acenocoumarol group (out of total 10 ADRs)	In Warfarin group (out of total 12 ADRs)
1st month	13 (59.09%)	5 (50%)	8 (66.66%)
2nd month	6 (27.27%)	2 (20%)	4 (33.33%)
3rd month	3 (13.63%)	3 (30%)	0

Table 12: Month wise, Number of patients developed ADRs in both the groups

Month	In both group (out of total 12 patients developed ADRs)	In Acenocoumarol group (out of total 7 patients developed ADRs)	In Warfarin group (out of total 5 patients developed ADRs)
1st month	7 (58.33%)	5 (71.42%)	2 (40%)
2nd month	4 (33.33%)	1 (14.28%)	3 (60%)
3rd month	1 (8.33%)	1 (14.28%)	0

Sample size or number of participants: In present study total 60 participants were recruited. A study by Undas *et al*. evaluated the effect of introducing warfarin in 68 subjects with unstable anticoagulation and variable INR values, previously treated with acenocoumarol[8]. The sample size was almost similar to that in the present study.

Follow up period: Follow up period for this study was 3 months, to evaluate safety and efficacy of Warfarin

Table 13: Cross tabulation of causality of ADRs (Naranjo scale)

			In Warfarin group					Total
			Not Applicable	Probable	Possible	Doubtful	Probable, Possible, Doubtful	
In Acenocoumarol group	Not applicable	Count	15	0	0	1	1	17
		% in Warfarin group	78.9%	0.0%	0.0%	100.0%	100.0%	70.8%
	Probable	Count	4	2	1	0 0	7	
		% in Warfarin group	21.1%	100.0%	100.0%	0.0%	0.0%	29.2%
Total	Count	19	2	1	1	1 24		
	% in Warfarin group	100.0%	100.0%	100.0%	100.0%	100.0%		

Table 14: Cross tabulation of preventability (Schumock & Thornton scale)

			In Warfarin group				
			Not applicable	Definitely preventable	Probably preventable	Definitely, Probably preventable	Total
In Acenocou marol group	Not applicable	Count	15	0	1	1	17
		% in Warfarin group	78.9%	0.0%	50.0%	100.0%	70.8%
	Definitely preventable	Count	4	2	1	0	7
		% in Warfarin group	21.1%	100.0%	50.0%	0.0%	29.2%
Total	Count	19	2	2	1	24	
	% in Warfarin group	100.0%	100.0%	100.0%	100.0%		

or Acenocoumarol therapy in post-operative valve replaced patients. Follow up period of 3 months was similar with another study by Thompson *et al*, evaluating early self-testing of INR which improved the quality of management[9].

Age: Mean age±SD was 44.44±11.787 in Acenocoumarol group and 37.71±11.830 in Warfarin group in this present study. This is comparable to a study done by Undas et al, in which mean age±SD was 57.4±12.3 and 58.3±13.3 in unstable and stable anticoagulation group's respectively[8].

Sex: In present study, out of total 60 participants 65% were male and 35% were female. In other study conducted by Ghufran *et al*, evaluated safety and efficacy of Warfarin or Acenocoumarol therapy in 52.4% male and 47.5% female patients[10]. These findings with male preponderance were almost similar in both studies.

In present study, out of total 30 participants in Acenocoumarol group 56.66% were male and 43.33% were female. This is comparable to a study done by Kulo et al, in which 56% male and 44% female in Acenocoumarol group, were compared with participants of Warfarin group[11].

Diagnosis: In this study, post-operative valve replaced cases of mitral stenosis (MS), mitral regurgitation (MR), aortic stenosis (AS) and aortic regurgitation (AR) due to rheumatic heart disease (RHD) were included in this study. Similar findings were noted in a study by Mirabel et al who mentioned that in rheumatic heart disease the immune system generates antibodies against the person's own heart valves leading to valve damage in the form of narrowed (stenotic) or leaky (regurgitant) valves[3]. In another study, Guilherme et al mentioned that rheumatic heart disease (RHD) leads to chronic valvular lesions[12]. Similar findings were noted in another study by Laudari et al mentioning that prolonged duration of medical treatment is required in RHD and many such patients also needed surgery[13].

Treatment: In the present study, after diagnosis of mitral or aortic valve stenosis or regurgitation, participants underwent valve replacement surgery and vitamin K antagonist/anticoagulants were given post-operatively after mechanical or prosthetic heart valve replacement. Similar treatment guidelines were noted in a study by Carapetis *et al*. who mentioned that referral for valve replacement cardiac surgery should be done in MS, MR, AS and AR cases and with RHD, for patients with prosthetic heart valves, the drug of choice for anticoagulation is vitamin K antagonist[4].

Operation or surgery: In this study, oral anticoagulants were given after mechanical heart valve replacement surgery like mitral valve replacement (MVR), aortic valve replacement (AVR) and double valve replacement (DVR) surgery. Similar findings were noted in a study by Leiria *et al*. who mentioned that depending on the anatomical position (mainly aortic or mitral valve) and type of prosthesis (mainly mechanical valves), chances of thromboembolic events or their estimated risk varies 48. Findings were almost similar in another study by Thompson *et al*. in which aortic, mitral and double valve recipients were evaluated for anticoagulation management[9].

Drugs: Vitamin K antagonists (VKAs) like Acenocoumarol or Warfarin were administered as oral anticoagulants after heart valve replacement surgery in post-operative patients in present study. In a study by Leiria *et al*. similar findings were noted and mentioned that, as risk of thromboembolic events are higher, use of VKAs are essential in patients with mechanical heart valves[14].

Dose range: In present study, dose range of tablet Acenocoumarol was 1-4 mg orally and that of Warfarin was 1-5 mg orally. In other study conducted by Ghufran *et al*. same dose range was used for Acenocoumarol and Warfarin[10].

Outcome of the study: Outcome of the study was evaluation of the value of PT and INR as efficacy and adverse effects as safety in post-operative mechanical heart valve replaced patients. These outcome findings are almost similar in other study by Thompson *et al*, in which number of INR tests, percentage of time in the therapeutic range were estimated after INR testing and adverse events were also evaluated, in mechanical heart valve recipients[9].

Statistical analysis: In this study, for statistical analysis, chi-square test was used for comparing two groups (Group A received Acenocoumarol and Group B received Warfarin). This is comparable to a study done by Kulo *et al*. in which therapeutic INR values were compared among groups using the chi-square test[11].

Investigation: In present study, venipuncture for blood study was done for measuring INR to compare the efficacy of Acenocoumarol and Warfarin. These findings were similar to study by Kulo *et al*. in which the blood samples were taken by venipuncture for measuring INR, to evaluate quality of treatment between warfarin and acenocoumarol groups[11].

INR therapeutic target range and frequency of INR measurement: In present study, efficacy of Acenocoumarol and Warfarin were compared by INR values in therapeutic target range (between 2 to 3.5). In this study, INR values were measured in every month. This is comparable to a study done by Kulo *et al*, in which blood sampling for INR control was performed on a monthly basis and also INR therapeutic target range was almost the same[11].

INR values: In present study, When INR values of 1st, 2nd and 3rd month were compared in both the study groups between Acenocoumarol group and Warfarin group, p values were 0.568, 0.386 and 1.000 respectively, all the p values were more than 0.05, so not significant. These findings are similar to study by Aida Kulo *et al*. in which no significant differences in the overall quality of treatment in warfarin and acenocoumarol groups were found, expressed by percentage of therapeutic INR values (51.77% vs. 53.62%, p = 0.548)[11].

Efficacy: In this study, both the drugs Acenocoumarol and Warfarin were equally efficacious. This is comparable to a study done by Kulo *et al*. in which both drugs Acenocoumarol and Warfarin have shown similar quality of individual anticoagulation control[11].

Safety and adverse drug reaction (ADRs): In this study, after comparing overall safety in both groups or after comparing overall adverse drug reaction (ADRs) between Acenocoumarol group and Warfarin group, it is observed that according to severity of ADRs, Acenocoumarol is better and safer than warfarin. This is comparable to a study done by Ghufran et al, in which Acenocoumarol is associated with lesser incidence of ADR's and is more effective and safer than Warfarin in a broad number of patients. Assessment of causality of ADRs was done according to Naranjo scale and assessment of severity of ADRs was done using the Modified Hartwig and Siegel scale, in both studies[10].

CONCLUSION

The study therefore concluded that Acenocoumarol and Warfarin are equally efficacious. After comparing overall safety in both groups or after comparing overall adverse drug reaction (ADRs) between Acenocoumarol group and Warfarin group, it is observed that according to severity of ADRs, Acenocoumarol is better and safer than warfarin. This study showed that Vitamin K antagonists (VKAs) like Acenocoumarol or Warfarin must be administered as oral anticoagulants, after heart valve replacement surgery, in post-operative patients and both Acenocoumarol and Warfarin are equally effective in maintaining INR within therapeutic target range. It is possible to suggest dose adjustments and accordingly both Acenocoumarol and Warfarin are equally effective, as requirement of dose adjustments was almost similar in both groups.

RHD primarily affects the mitral valve (in approximately 2/3 rd of patients), as in this study, total 46.66% cases of MS, MR and MVR operations were noted due to RHD. As total 77.27% ADRs (100% in Acenocoumarol group and 58.33% in Warfarin group) were definitely preventable, precautions must be

taken to prevent ADRs. As total 77.27% ADRs (100% in Acenocoumarol group and 58.33% in Warfarin group) were mild, it is important to follow-up for ADRs to prevent further complications. Counselling of patients by physicians on dietary habits and adherence to drugs can maintain INR within therapeutic target range, prevent ADRs and ensure patient's safety.

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