Original Research Paper

Cardiology

TIME IN THERAPEUTIC RANGE (TTR) PROFILE IN PATIENTS ON VITAMIN K ANTAGONISTS POST HEART VALVE REPLACEMENT SURGERIES

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ABSTRACT

INTRODUCTION: Oral anticoagulants have an important role in the long term anticoagulation following prosthetic valve replacement surgeries. The patients with mechanical prosthetic valves are at an increased risk of valve thrombosis and embolism. Anticoagulation usually started soon after mechanical valve replacement procedures as the risk of valvular thrombosis is high during the first 3 months after surgery. **TYPE OF STUDY:** Prospective Hospital based study **OBJECTIVES:** To calculate the Time in Therapeutic Range (TTR) in patients receiving VKA following prosthetic valve replacement surgeries. **MATERIAL AND METHOD:** 100 patients from 1st march 2016 onwards who had valve replacement surgery and were put on Vitamin K antagonists were studied in this prospective study. Only those patients who had mechanical valves were included in this study. **RESULTS:** The majority of the subjects were beyond 40 years of age. There was an equal gender distribution with majority of valve replacement for mitral position followed by aortic valve. The warfarin prescription rate was significantly higher in our study, possibly related to the practice pattern of the prescribing physicians (Warfarin in 80% vs. Acenocumarol in 20%). The 63% in our study group achieved a TTR >60%. The TTR levels did not differ with the different age groups of patients (p= 0.690) and the gender (p = 0.718).The TTR also didn't significantly differ in subjects with mitral vs. aortic position (mean TTR 53.77 ± 13.33 vs. 53.85 ± 13.88), however the patients with DVR had significantly lower levels of TTR (47.5 ± 15). **CONCLUSION:** Time in therapeutic range (TTR) is an excellent prognostic marker of the quality of anticoagulation treatment with vitamin K antagonists.

KEYWORDS : Time In Therapeutic Range (ttr), Warfarin , Acitrome, Prosthectic

INTRODUCTION:

Rheumatic Heart Disease (RHD) is endemic in India with a prevalence of <1 per 1000 and is one of the commonest cause of valve replacement. Many patients undergo mechanical valve replacement because of severely diseased valves, which are not suitable for surgical repair or percutaneous valvuloplasty.[1] The mechanical prosthetic valves require lifelong anticoagulation using vitamin K antagonists to lower the valvular thrombosis and the associated thrombo-embolic risk due to atrial arrhythmias. Anticoagulation usually started soon after mechanical valve replacement procedures as the risk of valvular thrombosis is high during the first 3 months after surgery. According to Antithrombotic Therapy for Prosthetic Valves by ACC/AHA guidelines 2014, anticoagulation with a VKA and international normalized ratio (INR) monitoring is recommended in patients with a mechanical prosthetic valve.[2] Anticoagulation with a VKA to achieve an INR of 2.5 is recommended in patients with a mechanical AVR (bileaflet or current-generation single tilting disc) and no risk factors for thromboembolism. An INR of 3.0 in patients with a mechanical AVR and additional risk factors for thromboembolic events (AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions) or an older-generation mechanical AVR (such as ball-in-cage). An INR of 3.0 in patients with a mechanical MVR with Aspirin 75 mg to 100 mg daily is recommended in addition to anticoagulation with a VKA in patients with a mechanical valve prosthesis. Aspirin 75 mg to 100 mg per day is reasonable in all patients with a bioprosthetic aortic or mitral valve. Anticoagulation with a VKA is reasonable for the first 3 months after bioprosthetic AVR, MVR or repair to achieve an INR of 2.5. Anticoagulant therapy with oral direct thrombin inhibitors or anti-Xa agents should not be used in patients with mechanical valve prostheses.[3] The maintenance of INR within a very narrow therapeutic range is a quite challenging task and at times difficult due to multiple factors. The number of complications increases when the INRs are outside this therapeutic range which is

termed as Therapeutic Time In Range or TTR. Hence assessment of TTR is a significant tool in reducing the thrombo-emboli complications associated with these mechanical heart valves and VKAs.

Methods to calculate Therapeutic Time In Range.
Three Different Methods
1.Percent of Visits in Range (Traditional Method)
2.Percent of Visits in Range on Given Date (Cross Section Method)
3.Percent of Days in Range (Rosendaal Method)

AIMS AND OBJECTIVE:

To calculate the Time in Therapeutic Range (TTR) in patients receiving VKA following prosthetic valve replacement surgeries. The study was conducted in the Department of Cardiology, Fortis health care Mohali. The study included 100 cases.

MATERIAL AND METHODS:

100 patients from 1st march 2016 onwards who had valve replacement surgery and were put on Vitamin K antagonists were studied in this prospective study. Only those patients who had mechanical valves were included in this study

SELECTION OF PATIENTS
Inclusion Criteria
Post mechanical heart valve replacement patients.

Exclusion Criteria
Pregnant patients.
Patients with Renal failure.
Patients with Liver failure.
Known coagulation disorder.

Method
• 100 patients with mitral and aortic valve replacement from the period starting from 1st March 2016 were studied.

- A written informed consent was taken.
- Detailed history as per performa was filled.
- INR was measured every month and plotted on a chart for that specific patient.
- At each of these visits patient was asked about any history of LOC, dizziness, syncope, weakness of any of limbs, abnormal bleeding- bruises/ hemoptysis/ hemetemesis/Bleeding per rectum and a routine cardiac examination was performed.
- Patients were followed up for 10 months after the surgery.
- TTR was calculated.

RESULTS:

TABLE 1: Age Distribution

Ageinyears	Numberofcases	Percentage
<20	18	18%
21-40	9	9%
41-60	35	35%
>61	38	38%

Among 100 patients maximum patients belonged to the age group of above 41 years. 35 % patients belonged to age group 41-60 and 38 % more than 61 years.

TABLE 2:Gender Distribution

	Frequency	Percentage
Male	51	51.00%
Female	49	49.00%
Total	100	100.00%

In the study the male and female patients were almost equally enrolled in the study.

TABLE 3: Nature Of Valve Replacement

	Number of patients	Percentage
AVR	39	39.00%
MVR	53	53.00%
DVR	4	4.00%
TVR	3	3.00%
PVR	1	1.00%
Total	100	100.00%

In this study 39% patients received anticoagulation after AVR, 53% After MVR, contributing to the major bulk of valve replacements. Only 4% patients had double valve replacement and 3 % patients had tricuspid valve replacement and only 1% had pulmonary valve replacement.

TABLE 4: Type Of Vitamin K Antagonist

	Frequency	Percentage
Warfarin	80	80.00%
Acitrom	20	20.00%
	100	100.00%

Of the total 100 patients 80% received warfarin and 20 % patients received Acitrome

TABLE 5: Number Of Patients With Ttr Equal To And Above 60%

TTRValue	Frequency	Percentage
<60	63	63%
≥60	37	37%

63% of the patients when were followed at one monthly interval with their INR values, they were shown to have a TTR of more than and equal to 60%.

TABLE 6: Percentage Of Patients With Ttr ≥60% In Different Age Groups

	<=20	21-40	41-60	>60	Pvalue
n, % of patients with TTR≥60% (total-63)	13,20.63%	6,9.52%	22,34.92%)	22,34.92%	0.769
Samplesize	18	9	35	38	
MeanTTR±SD	55.56±15.8	51.11±13.64	52.29±14.16	52.63±13.29	0.690

In the study there is no correlation between the age of the subject and the corresponding TTR levels. (p Value 0.769). However the TTR was better managed in the age groups 0f 41 -60 and > 60 years.

Table 7: Percentage Of Patients With Ttr ≥60% In Different Genders

	Male	Female	Pvalue
n, % of patients with TTR ≥60%(total-63)	33,52.38%	30,47.62%	0.718
Sample size	51	49	
Mean TTR ±SD	51.96±15.75	53.88±11.87	0.837

There is no correlation of age with TTR (p value 0.718)

Table 8: Percentage Of Patients With Ttr ≥60% In Those Taking Warfarin Vs Acitrome

	Warfarin	Acitrome	Pvalue
Samplesize	80	20	
MeanTTR±SD	50.38±13.45	63±11.29	0.0001
n,%ofpatientswith TTRabove60%(total-63)	46,73.02%	17,26.98%	0.023

The patients who were taking warfarin the mean TTR was 50.38% as compared to those on Acitrom whose mean TTR was 63%. This is statistically significant as Acitrom as longer half-life and less drug interactions it is easy to maintain TTR with it rather than warfarin. On the contrary as the number of patients receiving Acitrom is significantly less than warfarin; only 26.98% of those with TTR above 60% were receiving Acitrome.

Table 9: Percentage Of Patients With Ttr ≥60% In Different Valve Replacements

	AVR	MVR	DVR	TVR	PVR	Pvalue
Samplesize	39	53	4	3	1	-
n,%ofpatientswithTTRabove60%(total-63)	25,39.68%	35,55.56%	2,3.17%	1,1.59%	0	0.500
Mean TTR±SD	53.85±13.88	53.77±13.33	47.5±15	40±20	30±0	0.253

Of the total 39 patients who had AVR only 25 patients (39.68%) were able to maintain TTR above 60% with a mean TTR of 53.85%. In patients who had MVR 55.56% patients were able to maintain TTR above 60% with a mean TTR of 53.77%.

DISCUSSION:

The demographic analysis of our study revealed a mean age of 49.64 yrs and with M: F ratio of ~1:1. This may reflects the typical natural history of valvular heart diseases in our population and the gender differences. The subjects are generally younger as compared to other geographical regions. Comparison of the mean age of subjects, it appears that in our population, most of the patients are younger as compared to the other studies done at different

geographical areas. *(Vide table A,B.)*

Table A: Mean Age Of The Study Groups

STUDY	MEANAGE
Pokorneyetal[6]	75yrs.
RoseAJetal[12]	72yrs.
RanaIetal[10]	60.2yrs.
DhanyaP.S.[14]	39.48yrs.
Ourstudy	49.64 yrs.

Table B: Gender Distribution

STUDY	MALE	FAMALE
Pokorneyetal[6]	57%	43%
Schmittetal[4]	49%	51%
RanaIetal[10]	58.3%	41.7%
DhanyaP.S.[14]	47.27%	52.72%
Ourstudy	51%	49%

The spectrum of the anatomical locations of prosthetic valves in our study was different as compared to the study by Dhanya PS et al[14]. This may be related to the particular cross section of patient enrolled into the study group and the enrolled number of patients but it can't reflect the overall epidemiological incidences of valvular involvement in rheumatic or sclerodegenerative VHDs *(Vide Table no C)*

Table C: TYPE OF VALVE REPLACEMENT

STUDY	AVR	MVR	DVR	TVR	PVR
DhanyaPSet.al[14].	18.2%	70.9%	10.9%	NA	NA
AmbrosettiM[16]	43%	37%	20%		
Ourstudy	39%	53%	4%	3%	1%

The differences in the warfarin vs. Acenocumarol use in the two studies are different can be ascribed due to physicians' prescription pattern *(Vide table no: D).*

Table D: Type Of Drugs

STUDY	WARFARIN	ACITROME
DhanyaP.S.etal[14]	58.2%	41.8%
CotteF.E.[7]	62.2%	3.34%
Ourstudy	80%	20%

The comparison of the mean TTR value as compared to the other studies, revealed a lower mean TTR. The reason for such lower TTRs in our study is possibly due to significant differences in the TTRs among the participants. The possible reason for such differences in the TTRs among our participants could be related to different socio-economic status, awareness levels , suboptimal QA of the biochemistry laboratories in the patient's community, food habits , rural and urban patients, compliance to drug therapy , and concomitant use of drugs having interference with anticoagulation with VKAs *(Vide table no E).*

Table E: Mean Ttr Value In Study Groups

STUDY	MEANTTR
Patel.Uetal[17]	60.86%
Pakorneyetal[6]	65%
ErkensPMG[11]	67%
WielochMetal[15]	76.2%
ManjiIetal[13]	64.6%
Ourstudy	52.9%

The overall TTR achieved across all age group of patients were similar our study. This is in sync with the other studies. Although there has been data supporting the lesser TTR in older population, in our study, we encountered a similar TTR across all age. This may be related the level of patient care, education, and compliance to the drug. The other possible reason of such uniform TTR across age groups, is a very close anticoagulation follow up by the anticoagulation clinic in our hospital *(Vide table no F).*

Table F: Relation Of Age Groups With Ttr

STUDY	TTR IN AGE GROUPS				PVALUE
	<20	21-40	41-60	>60	
M wieloch et al[15]	>70%	>70%	>70%	>70%	
Marcatto R. L. et al[5]	<65yrs-60%		>65yrs-67%		<0.001
Singer D.E.[9]	<73-53.6%		>73-58.8%		<0.0001
Ourstudy	55.56 ± 15.8	51.11 ± 13.64	52.29 ± 14.16	52.63 ± 13.29	0.690

The TTR in both the gender in our study was uniform across both the groups. The explanation of such uniform TTRs among both the sexes is uniform access to healthcare services, family awareness, lack of gender bias in seeking medical assistance and education of the household*(Vide Table no G)*

Table G: Relation Of Gender With Ttr

STUDY	TTRINMALES	TTR IN FEMALES	PVALUE
Pokorneyetal[6]	-	46%	0.01
CaldeiraD[8]	>60%	<60%	0.01
SingerD.E.[9]	56.4%	53.3%	<0.0001
Ourstudy	51.96±15.75	53.88±11.87	0.837

CONCLUSION:

The Time in Therapeutic Range (TTR) is an optimal measure of INR control, and has a significant relationship with adverse outcomes . Thus TTR is an excellent prognostic marker of the quality of anticoagulation treatment with vitamin K antagonists.

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