Original Article

Nepalese Heart Journal 2024; Vol 22(2), 33-35

Percentage of Mitral Valve Replacement Patients on Warfarin within the Therapeutic Range of International Normalized Ratio (INR)

Amit Kumar Singh[1], Pranil Man Singh Pradhan[2], Rajesh Kumar Shah[1], Aditya Mahaseth[3]

[1] Consultant Interventional Cardiologist, Madhesh Institute of Health Sciences (MIHS), Madhesh Province
[2] Associate Professor IOM, Maharajgunj
[3] Senior Consultant Cardiologist, Kathmandu Medical College and Teaching Hospital

Corresponding author:
Dr. Amit Kumar Singh
Consultant Interventional Cardiologist
Madhesh Institute of Health Sciences (MIHS)
Madhesh Province
Email: dramitsgnhc@gmail.com
Contact: +9779851192239
ORCID ID: 0000-0003-4496-0436

Cite this article as: Singh AK, Pradhan PMS, Shah RK, Mahaseth A. Percentage of Mitral Valve Replacement Patients on Warfarin within the Therapeutic Range of International Normalized Ratio (INR). Nepalese Heart Journal. 2025;22(2):33–35.

Submission date: 30 August, 2025
Acceptance date: 19 October, 2025

Submitted using Strobe checklist

Abstract

Background: Nepal has a high prevalence of rheumatic heart disease and many patients undergo metallic valve replacement. Most of the time, the replaced valve is the mitral valve. It is more prone to getting stuck than a prosthetic aortic valve. It also requires a higher INR value to maintain the patient in the therapeutic range. There is limited data regarding patients' time in the therapeutic range (TTR). This study will help better manage such patients and know the shortcomings in management.

Methods: A total of 70 mitral valve replacement patients fulfilling the inclusion criteria having at least 3 months regular visit for INR underwent Rosendaal method to estimate TTR.

Results: The study conducted at Shahid Gangalal National Heart Centre, Janakpurdham, showed that only 58.5% of patients were within the INR therapeutic range.

The most frequent dose was approximately 6 mg with almost all patients requiring dose variation not in whole numbers but in decimals as daily warfarin dose.

Conclusions: A significant proportion of patients remain outside the therapeutic range. Dosing of warfarin is in decimal. This suggests a need for lower-dose warfarin formulations like 0.5mg to help patients staying in therapeutic INR. For uniform INR report throughout country, national level thromboplastin has to be introduced. Genetic study inclusion in warfarin dose will help in accuracy of dosage. A separate INR clinic will further improve patient care.

Keywords: International Normalized Ratio (INR), Time in Therapeutic Range (TTR), Mitral Valve Replacement (MVR),

DOI: https://doi.org/10.3126/nhj.v22i2.85791

Introduction

Nepal has a high prevalence for rheumatic heart disease as per the various researches conducted[1,2]. One of the studies carried out in the eastern part of Nepal showed the prevalence to be of 1%[3]. Most of the rheumatic heart disease requires mitral valve replacement and post operatively requirement of warfarin[4]. Mitral valve replacement is performed in most cases of rheumatic heart disease for its high rate of reoperation[5,6] The replaced valves are most frequently the mitral valve[7,8]. Patients require lifelong warfarin to maintain the therapeutic INR. As compared to the aortic valve, mitral valve is at high risk to undergo a stuck valve[9,10]. So, it becomes important to maintain the patient in the therapeutic range continuously. Knowing the time in therapeutic range (TTR) status would help improve the wellbeing of patients having mitral valve replacement. Warfarin targets especially two enzymes viz CYP2C9 and VKORC1 for its action for anticoagulation where Nepal currently lacks studies on genotype[11]. Its dosing varies with ethnicity[12]. Even among patients belonging to one ethnicity, there are various reasons for its variability[13]. As Nepal lacks such studies, to address the problem, we need to have study evaluating a mean dose of warfarin for Nepalese population. This study aimed to determine the percentage of MVR patients within the therapeutic INR range and to evaluate factors associated with warfarin dose variability.

Methods

Ethical approval was obtained from Shahid Gangalal National Heart Center ethical committee with Ref no: SGNHC/IRC No. 16- 2022

Patients attending Shahid Gangalal National Heart Centre, Janakpurdham for INR who also met the inclusion criteria were invited to participate in the study. The study was carried out for 6 months from 15th July 2022 to January 14th 2023. Using Cochrane formula with prevalence of 50%, the margin of error 8%, 95% confidence and an alpha 5%, the sample size of 151 was calculated. Patients taking warfarin for other valve replacement alone were excluded as per our inclusion criteria. Some patients failed to follow-up and went probably to other nearby centers for INR. Also, as our study was for only 6 months, we failed to collect projected numbers and was able to collect 70 samples. The study was hospital-based cross sectional study with retrospective record view The patients had at least 3 regular visits every month before getting enrolled in the study. INR was calculated with The International Sensitivity Index (ISI) of 1 in the hospital calorimeter. The patient's time in therapeutic range (TTR) was calculated using Rosendaal method of INR calculation[14]. Rosendaal interpolation method assumes that a linear relationship exists between two INR values with either increasing or decreasing trends in between and allows us to determine a specific INR value for each day for each patient[15]. This is one of the most frequently used methods for the measurement of TTR[16]. At least 3 INR were taken including the INR on the day of the visit to the hospital and the previous INR[17]. The patient had at least 3 months of consecutive visits to be included in the study. The INR of 2.5 to 3.5 with the tolerance of +/- 0.5 was considered to be in therapeutic range. As the formula is complex for the Rosendaal method, online calculator www.inrpro.com was used as in other studies[17]. Patient's TTR was divided into 3 categories viz, good control: TTR > 70%, Intermediate control: TTR 50 -70 %, and Poor control: TTR<50%. The patient's age was in years; height was measured in centimetres and weight were in kilograms.

Inclusion Criteria:

Patients of metallic mitral valve replacement with or without other valve replacements and between 18 years to 75 years of age were included in the study.

Exclusion criteria:

1. Patients of warfarin use for non-MVR cases
2. Patients using warfarin for Atrial Fibrillation (AF)
3. Recently operated cases of MVR at less than 3 months of surgery
4. Patients on amiodarone
5. Patient having Tricuspid Regurgitation (TR) velocity > 2.8m/s
6. Decreased Right Ventricle (RV) function having Tricuspid Annular Plane Systolic Excursion (TAPSE) <= 16mm.

Normality was assessed using Shapiro-Wilk test for continuous variables. The correlation between the various parameters with warfarin dose was measured using Pearson's correlation test. Statistical Package for Social Sciences (SPSS) version 25 was used to perform statistical analysis. P value of <0.05 was considered significant.

Results:

A total of 70 patients were selected out of which 44 patients were female. The average age of the patient was 39 years, the average height of 155 cm and the average weight was 55.126kg (Table 1). A total of 41.4% (29) patients were in subtherapeutic range (Table 2). The mean dose of warfarin was 5.81mg in male and 5.73mg in females (Table 3).

Table 1. Anthropometric parameters of the participants (n=70)

	Mean	Standard deviation	Minimum	Maximum
Age (years)	39.84	12.824	18	69
Weight (kg)	55.126	10.6856	32	84
Height (cm)	155.06	7.549	142	176
BMI (kg/m^2)	22.8839	4.01561	14.67	34.7

Table 2. Frequency of patients in various ranges of TTR

TTR Category	Frequency	Percent
Less than 50	29	41.4
50 to 70	8	11.4
Greater than 70	33	47.1

Table 3. Warfarin dose variable among male and female participants (n=70)

Sex	Mean (SD) warfarin dose	t	p-value
Male	5.81 (2.2)	0.138	0.891
Female	5.73 (2.4)	0.141	0.88

There was a weak negative correlation between warfarin dose with age (r=-0.256) and height (r=-0.007), and a weak positive correlation between warfarin dose with weight (r=0.202) and BMI(r=0.232). Similar warfarin dose variation was seen among males and females (Table 3).

Discussion:

The result showed that about 41.4% (29) of the patients were under sub-therapeutic INR. No significant relation was found with age or weight of the patients with dosing of warfarin. The mean requirement of male and female dose for the drug was similar and in decimal dosing. Similar studies in developed countries like Canada, patients had their TTR in a better range[14]. But one of the studies conducted in India showed TTR was lower as compared to our data[15]. So, data showed place for improvement. We have little knowledge regarding the therapeutic range of the patients who are not under our follow-up. One of the most advanced ways to have patients in TTR is to predict the dose as per the genetics of the patient[16]. The INR system is brought to bring down the variability in the value of prothrombin

time among various labs. ISI plays a vital role in the calculation of INR. Nepal does not have a system of standardization of ISI. The lower level of an ISI gives better report of the clotting condition of the patient[17]. The countries like Thailand have National Level Thromboplastin for uniformity in results

of INR (18) Another important finding in our study was that the dosing of warfarin had values in decimal. The lowest dose available in Nepal for warfarin is 1mg. Because of this problem, doctors have to alternate the dose of warfarin between one lower and the other higher dose of warfarin like alternate doses of 5mg and 6mg to make it on average 5.5mg. This gives erroneous results of INR. Introducing lower dose like 0.5mg warfarin in the market may help physicians keep the patients in therapeutic doses. Making a combination with a 0.5mg dose will further help in optimizing the dose to have the patient in TTR. Pharmaceutical companies in India produce 0.5mg warfarin which is definitely helping doctors and patients.

Future research is required for sub-therapeutic INR in patients who have undergone MVR. A more feasible way would be to have a separate INR clinic and follow-up patients in a scientific way as per the requirement for the monitoring of INR. Regular INR counselling sessions have to be conducted for patients undergoing valve replacement. This counseling should include the consequences of sub-therapeutic INR, interactions of food and antibiotics with INR values, and informing the attending physician regarding intake of warfarin during some non-cardiac problem.

Conclusions:

Only 58.6% of patients with MVR are having INR in the therapeutic range though having regular monitoring. The mean dose requirement of warfarin for TTR was having combination of whole number with decimals rather than whole number and so introduction of warfarin tablets in decimal dose like 0.5mg warfarin as in other countries may increase more patients in therapeutic range of INR. For uniformity in INR report, national level thromboplastin has to be introduced. Genetic study introduced will help in better calculation of warfarin dosage. A separate sINR clinic may help in better handling such patients.

Limitation:

This study had few limitations. This was a single center, hospital-based study with limited sample size. Due to short duration, the target sample size could not be reached which may limit the generalizability of the findings. Retrospective record review component of the study could have led to lack of data on important confounders

Acknowledgement:

We are very thankful to our medical officers and nurses and staffs who helped in carrying out the research.

References

1. Prajapati D, Sharma D, Regmi PR, Khanal H, Baidya SG, Rajbhandari S, et al. Epidemiological survey of Rheumatic fever, Rheumatic heart disease and congenital heart disease among school children in Kathmandu valley of Nepal. Nepalese Heart Journal. 2013;10(1):1–5.
2. Laudari S, Tiwari KK, Pazdernik M, Sharma SK. Rheumatic Heart Disease Screening Among School Children in Central Nepal. JACC Case Rep. 2019; (2):218.
3. Shrestha NR, Karki P, Mahto R, Gurung K, Pandey N, Agrawal K, et al. Prevalence of Subclinical Rheumatic Heart Disease in Eastern Nepal: A School-Based Cross-sectional Study. JAMA Cardiol. 2016;1(1):89–96.
4. Antunes MJ. The global burden of rheumatic heart disease: Population-related differences (it is not all the same!). Braz J Cardiovasc Surg. 2020;35(6):958–63.
5. Chen SW, Chen CY, Chien-Chia Wu V, Chou AH, Cheng YT, Chang SH, et al. Mitral valve repair versus replacement in patients with rheumatic heart disease. J Thorac Cardiovasc Surg. 2022;164(1):57-67.
6. Perier P, Hohenberger W, Lakew F, Batz G, Diegeler A. Rate of repair in minimally invasive mitral valve surgery. Ann Cardiothorac Surg. 2013;2(6):751.
7. Nepal R, Bista M, Dhungana SP. Patterns of Rheumatic Heart Disease and Treatment Practices at Tertiary Care Center in Nepal: A Descriptive Cross-sectional Study. JNMA J Nepal Med Assoc. 2020;58(230):784–8.
8. Manjunath CN, Srinivas P, Ravindranath KS, Dhanalakshmi C. Incidence and patterns of valvular heart disease in a tertiary care high-volume cardiac center: A single center experience. Indian Heart J . 2014;66(3):320.
9. Hirachan A, Roka M, Prajapati D, Adhikari CM, K.C. B, Khadka MB, et al. Prosthetic valve thrombosis in a tertiary cardiac centre. Nepalese Heart Journal. 2017;14(1):9–11.
10. Mahindru S, Pande S, Malhotra P, Thukral A, Kotwal AS, Gupta RP, et al. Mechanical prosthetic valve thrombosis in current era: 5-year follow-up. Indian J Thorac Cardiovasc Surg. 2021 Mar 1;37(2):140–6.
11. Li JX, Kim MH, Song K, Guo LZ, Jin EZ, Kim SJ, et al. Impact of VKORC1, CYP2C9, and CYP4F2 Polymorphisms on Optimal Warfarin Dose: Does Ethnicity Matters? Am J Ther. 2021;28(4):e461–8.
12. Huang JT, Chan YH, Wu VCC, Cheng YT, Chen DY, Lin CP, et al. Analysis of Anticoagulation Therapy and Anticoagulation-Related Outcomes Among Asian Patients After Mechanical Valve Replacement. JAMA. 2022;5(2)
13. Tatsuno SY, Tatsuno Ba EM. Does Ethnicity Play a Role in the Dosing of Warfarin in Hawai'i?; Available from: http://www.clinicaltrials.gov/ct2/show/NCT01119300.
14. Selby R, Kaus L, Sealey F, Koo M, Parpia S, Chan B, et al. Quality of anticoagulant control and patient experience associated with long-term warfarin in Canadian patients with non-valvular atrial fibrillation: A multicentre, prospective study. PLoS One. 2023;18(4).
15. Chebrolu P, Patil S, Laux T, Al-Hammadi N, Jain Y, Gage B. Quality of anticoagulation with warfarin in rural Chhattisgarh, India. Indian J Med Res . 2020;152(3).
16. Wei M, Ye F, Xie D, Zhu Y, Zhu J, Tao Y, et al. A new algorithm to predict warfarin dose from polymorphisms of CYP4F2, CYP2C9 and VKORC1 and clinical variables: derivation in Han Chinese patients with non-valvular atrial fibrillation. Thromb Haemost. 2012;107(6):1083–91.
17. Kitchen S, Preston FE. Standardization of prothrombin time for laboratory control of oral anticoagulant therapy. Semin Thromb Hemost. 1999;25(1):17–26.