ORIGINAL RESEARCH PAPER

Cardiac Surgery

TARGET INR IN PATIENTS WITH PROSTHETIC HEART VALVE REPLACEMENT: A RETROSPECTIVE STUDY

KEY WORDS: Anticoagulation therapy. Prosthetic heart valves, International normalised ratio (INR)

Dr Rakesh Kumar* Assistant Professor, Department of CTVS, Rajendra Institute of Medical Sciences, Bariatu, Ranchi-834009, Jharkhand India. *Corresponding Author

Hemant Narayan Roy Prof(Dr.)HOD, Department of Cardiology, Rajendra Institute of Medical Sciences, Bariatu, Ranchi-834009, Jharkhand India.

ABSTRACT

Objective: Despite various innovations, there is no ideal prosthetic heart valve; thus, patients with prosthetic heart valves still require anticoagulation therapy. This is a retrospective study to identify the optimum warfarin dose and international normalized ratio (INR) in Indian patients with prosthetic heart valves.

Methods: All patients who had prosthetic heart valves from September 2015 to February 2016 at the All India Institute of Medical sciences New Delhi were reviewed. Patient's data from the institution computer archive and case notes were imputed into Excel worksheet for data analysis.

RESULTS: One hundred and twenty-one Indian patients had prosthetic heart valves during this period, the mean age was 44.94 ± 15.70 (years) and mean body surface area was 1.59 ± 0.19 (kg/m2). The male/female ratio was 1:1.2. Seventy-seven patients had mechanical valves whilst 44 had tissue valves. St. Jude Medical bileaflet valve was the commonest mechanical valve used. Warfarin was the only anticoagulant used in all patients. Amongst the mechanical valve group, the mean warfarin dose was 4.9 ± 1.87 (mg) and mean INR was 2.16 ± 0.60. In patients with tissue valves, the mean warfarin dose was 3.77 ± 1.74 and mean INR was 2.3 ± 0.68. There was no significant difference in the INR of patients with mechanical valves and atrial fibrillation and those without atrial fibrillation. Warfarin was however discontinued at 3 months for patients with tissue valves. Five (4.13 %) patients died perioperatively. Haemorrhagic complications occurred in 5.2 %, noticed when INR was >3 whilst thrombotic complications occurred in 2.6 % of patients (INR < 1.5) in the mechanical valve group Conclusion Oral anticoagulants in Indian patients with mechanic heart valves can be maintained safely at a lower INR (1.56–2.76) as against the standard ranges in the guidelines by the American College of Chest Physicians.

INTRODUCTION

The burden of alular heart disease is on the increase worldwide; this is particularly due to an increase in degenerative aetiologies in the western world and increased prevalence of rheumatic heart disease (RHD) in the developing world. [1]

This increase in degenerative aetiologies is attributed to the increased life expectancy and ageing population in the west. RHD is endemic in the developing world especially in India, with a prevalence of 1.1/1000, and is one of the commonest causes of valve replacements. [2] Globally, India contributes nearly 25–50 % of newly diagnosed cases, deaths, hospitalization and burden of RHD [3].

Despite significant improvement, the quest for the ideal valve prosthesis still lingers. There are two families of prosthetic heart valves in use, mechanical and biological valves. These valves require some form of anticoagulant to prevent thrombosis and thromboembolism; however, the mechanical valves require lifelong anticoagulant therapy. The prevention of valvular prosthesis thrombosis and thromoembolism depends not only on effective antithrombotic therapy but also on the understanding of complex interplay between surgical procedure, individual type and site of valvular device, number of implanted prosthesis and patient's own risk factors. The ninth edition of the American College of Chest Physicians of evidence-based guidelines for antithrombotic and thrombolytic therapy recommends lifelong vitamin K antagonist (VKA), i.e. warfarin and antiplatelet (aspirin) therapy for patients with mechanical heart valves. [4] Warfarin requires international normalized ratio (INR) for monitoring and dose adjustments. It also recommends short-term (3 months) VKA as antithrombotic therapy for patients with bio prosthetic heart valves in the mitral position and lifelong antiplatelet therapy with aspirin (50–100 mg/day). Therapeutic INR ranges from 2.0 to 3.0 and 2.5 to 3.5 depending on the position of the valve [4]. However, despite the benefits of warfarin, there are several limitations such as bleeding complications, dietary and drug interactions and also claims of racial variability's with some studies showing reduced bleeding complications amongst Asian patients even at low INR [5, 6]. The aim of this study is to identify the optimum INR and warfarin dose amongst Indian patients with prosthetic heart valves.

Patients and methods

Objectives

1. To identify the optimum INR amongst Indian patients with prosthetic heart valves
2. To identify the optimum warfarin dose amongst Indian patients with prosthetic heart valves

This was a retrospective study from September 2015 to February 2016, conducted at All India Institute of Medical sciences New Delhi, India. All Indian patients with prosthetic heart valves and on oral anticoagulant were included in the study. Ethical approval was sought from the institution research and ethics committee. Patient's data extracted from the institutions computer data archive and case notes were imputed into Microsoft® Excel 2010 for data analysis.

RESULTS

One hundred and twenty-one (121) Indian patients had prosthetic heart valves during this period, the mean age was 44.94 ± 15.70 years and mean body surface area was 1.59 ± 0.19 (kg/m2). The male/female ratio was 1:1.2. Seventy-seven (77) patients had mechanical valves whilst 44 had bio prosthetic valves. St. Jude Medical bileaflet mechanical valve was the commonest type of mechanical valves used in our patients accounting for 63.6 %, whereas On-X valves were used in 15.6 % of patients with mechanical valves (Table 1). Warfarin was the only oral anticoagulant used in all patients. Amongst the mechanical valve group, the mean warfarin dose was 4.9 ± 1.87 (mg) and mean INR was 2.16 ± 0.60.

In patients with tissue (bio prosthetic) valves, the mean warfarin dose was 3.77 ± 1.74 and mean INR was 2.3 ± 0.68 (Table 2). There were no significant difference in the INR between patients who had atrial fibrillation and those without (p value 0.653). Also of note, the comparison between On-X and other mechanical valves in relation to INR values was not significant. All patients had concomitant antiplatelet therapy with 75 mg aspirin. Warfarin was however discontinued at 3 months for patients with tissue valves. Five (4.13 %) patients died perioperatively, none due to anticoagulant complications. Haemorrhagic complications occurred in 5.2 % which was noticed when INR was above 3 whilst thrombotic complications occurred in 2.6 % of patients when INR

was below 1.5 (Table 3). Discussion Oral anticoagulant therapy is an integral part of the management of patients with prosthetic heart valves, most especially as a lifelong medication in patients with mechanical valves. Warfarin is the most common oral anticoagulant used worldwide and the only one used in this study. The mean age of patients was 44.94 ± 15.70 years which was slightly higher than the mean age of 39.48 ± 11.67 in a study by Dhanya et al. [7]. It was also noticed that there were more female than male patients. Mitral valve was also the most commonly replaced valve which is similar to findings.

Table1 Epidemiological characteristics of study population
Characteristics Total (n = 121)
Age (mean years) 44.94 ± 15.7
Male 55 (45.5 %)
Female 66 (54.5 %)
BSA (mean) 1.51 ± 0.19
Mechanical valves 77
St. Jude 49 (63.6 %)
ATS 14 (18.2 %)
On-X 12 (15.6 %)
TTK-Chitra 2 (2.6 %)
Bio prosthetic valves 44

Indian J Thorac Cardiovasc Surg (2016) 32:174–177 175 in other studies, and most patients had mechanical valves placed. This could be attributed to the young age at presentation and the lower body surface area amongst this group of patients thus necessitating a mechanical valve which at smaller diameters still proffers good hemodynamic profile when compared to the bio prosthetic valves. Warfarin is a coumarin derivative which acts as a vitamin K antagonist. It decreases factors II, VII, IX and X as well as proteins S and C. Its half-life ranges from 20 to 60 h, with a mean plasma half-life of 40 h and duration of effect of 2 to 5 days. It has a narrow therapeutic range and shows large inter-individual variations in dose requirements. Factors such as age, body weight, dietary vitamin K intake, diseases and several medications are known to affect dose requirements and inter patient variability. All patients in our study group are given warfarin handbook on discharge which states amongst other things restrictions on some food items such as green leafy vegetables, cabbage, cauliflower, liver and egg yolk which are known to decrease the effectiveness of warfarin. It is noted that all our patients received low-dose antiplatelet therapy (aspirin 75 mg). This is supported by a systematic review by the Cochrane collaboration which showed that the combination of antiplatelet drugs to antithrombotic regimen in patients with prosthetic heart valves reduces the risk of thromboembolic events and mortality [8].

It is recommended by the American College of Chest Physicians that in patients with mechanical valves and associated risk factors such as atrial fibrillation, INR should be maintained between 2.5 and 3.5 [4]. However, we found that our patients with atrial fibrillation tolerated lower INR values (1.56–2.64) without any thrombotic complications. Furthermore, there was no significant difference (Table 4) in the mean INR of patients with atrial fibrillation and those without atrial fibrillation (p value 0.653). The mean INR of 2.16 ± 0.60 was maintained with a mean warfarin dose of 4.9 ± 1.87 in patients with mechanical valves; this is lower than values reported by Akhtar et al. in a similar study amongst Pakistani patients [9]. Several studies from Japan and India have advocated for lower INR levels 1.5–2.5 amongst Asian patients with low incidence of thromboembolic complications [5, 7, and 9]. We did not find any significant difference in the INR values between patients who had On-X and other types of mechanical valve (Table 5); this is in variance to the PROACT (Prospective Randomized On-X Anticoagulant Clinical Trial) which has shown significant difference in the INR values with the On-X aortic valve against other mechanical valves [10]. Although, a prospective study with a larger sample size and follow-up period will be required to substantiate this findings. Thromoembolic complications occurred in 2.6 % of the patients; this low incidence of thromboembolism despite a low INR supports the idea of maintaining most Indian patients on prosthetic heart valves at a lower INR levels compared to patients from the West.

Study limitations:-
This was a retrospective study, and thus, we are unable to randomize at the onset the patients into different groups (based on valve used) and compare them under similar conditions. A prospective study would be necessary in the future. We had a small sample size of 77 patients with mechanical valves; a larger group of patient would be essential to substantiate our findings. Also, a longer follow-up period of at least 5–10 years could help identify patients with late-occurring complications.

Table 2 Mean INR and warfarin doses in valve replacement surgeries
Surgery Mean INR Mean warfarin dose
AVR 2.09 ± 0.54 5.93 ± 2.26
MVR 2.22 ± 0.57 4.41 ± 1.90
DVR (MVR + AVR) 2.1 ± 0.7 5.08 ± 1.26

AVR -aortic valve replacement, MVR mitral valve replacement, DVR-double valve replacement

Table 3 Follow-up events
Variable N = 77 INR Warfarin dose (mg)
Thromboembolic events 2 (2.6 %)
Left hemiplegia 1 (1.29 %) 1.2 7
Valve thrombosis 1 (1.19 %) 1.5 5
Haemorrhagic events 4 (5.2 %)
Haematuria 3 (3.9 %) 3.6a 4
Haemoptysis 1 (1.29 %) 6.5 10 a Mean INR

Table 4 Comparison of associated atrial fibrillation with INR
N = 77 Mean INR ± SD p value
Patients with AF 18 2.10 ± 0.54
Patients without AF 59 2.18 ± 0.63 0.653 (not significant)
Significant p value is <0.05
AF atrial fibrillation

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Finally, our study was a single-centre study; thus, we hope this can be extended to other centres so as to have a multicentre data for analysis.

CONCLUSION
Oral anticoagulants in Indian patients with mechanic heart valves can be maintained safely at a lower INR as against the standard ranges in the guidelines by the American College of Chest Physicians. This also corroborates similar studies done amongst Asian patients reflecting lower INR levels. The reason for this low INR being tolerated in Indian patients with mechanical heart valves might be due to dietary and racial differences in comparison to western patients.

However, larger randomized study with a long-term follow-up would be required to substantiate these findings and also to find out the exact reasons why these patients tolerate lower INR levels.

Compliance with ethical standards- No external supports were received for this study.

Conflict of interest -The authors declare that they have no competing interests.

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