International normalized ratio monitoring in post surgical patients with mechanical prosthetic valve: Our experience.

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ABSTRACT Although the need for oral anticoagulant therapy in patients with mechanical heart-valve prostheses is not in dispute, the optimal intensity of anticoagulation has been a matter of debate and is measured in International normalized ratio (INR) value. We followed 161 patients with mechanical prosthetic valve on oral anticoagulants from June 2012 to December 2016. We used ATS-Medtronic (77 cases), TTK Chitra Tilting Disc (71 cases) were most common mechanical heart valve implanted at mitral (65.2%), both aortic and mitral (21.72%) and aortic (13%) positions. In our study we also observed that fluctuations in INR monitoring in patients on oral anticoagulants commonly exists either in range or below range in respect to ACCP guidelines at any types and positions of implanted mechanical heart valve. The below range and in range INR value were at mitral (38.38%, 49.49%), at aortic (52.63%, 31.57%), at both aortic and mitral (55.17%, 37.93%) positions respectively. In our study we found that proper monitoring of INR during follow-up period and protocol based appropriate timely action taken can enable safe long term anticoagulation.

Introduction-Surgical valve replacement or repair is currently the standard of care for treatment of valvular heart disease patients[1]. Rheumatic heart disease is endemic in India with a prevalence of 1.3/1000[2]. Worldwide, India contributes nearly 25-50 % of newly diagnosed cases, deaths, hospital admissions, and burden of disease.[3]On the basis of the leaflet material, two different types of surgical prosthetic cardiac valve exist- Mechanical and Biological[4]. Patients with mechanical heart-valve prostheses receive lifelong, high-intensity oral anticoagulant therapy to prevent thromboembolic complications, but this treatment is associated with an increased risk of bleeding[5]. The risk of prosthetic valve thrombosis and thromboembolic events is higher with mechanical than biological, more at mitral position and higher for right sided than left sided prosthetic valves[6]. The risk of thromboembolism and bleeding depends on the intensity of anticoagulation. The intensity of anticoagulation at which thromboembolism is effectively prevented without excessive bleeding is not known. It was not even possible to express the intensity in a standardized way until 1985, when the INR system was introduced[7].The current guidelines[1,8,9] for antithrombotic therapy after surgical valve replacement are outlined in table (1), but we followed the American College of Chest Physicians (ACCP) only because it express the intensity of anticoagulation in targeted international normalized ratio along with range .

Study design-Prospective study, single tertiary cardiac centre

Objective- Our aim of study is to know the safe level of INR range and their clinical outcome in patients with mechanical prosthetic valve on lifelong oral anticoagulant in follow-up period.

Material methods- In our prospective study we used protocols to monitor INR of patients with mechanical prosthetic heart valves on oral anticoagulant treatment in the outdoor department, which they visit regularly every four to six weeks. The study was conducted in 161 patients from June 2012 to December 2016 at our tertiary cardiac centre. We followed the ACCP guideline for INR monitoring in post surgical patients with mechanical prosthetic valve on oral anticoagulation.

Table1.Current guidelinesfor antithrombotic therapy

Prosthesis heart valve used	ACC/ AHA	ACCP	European society of cardiology
Mechanical prosthetic valve (Anticoagulation with VKA)	Target INR=2.5 for aortic and no risk factors for TE; Target INR =3.0 for aortic with risk factors for TE or mitral/both aortic and mitral) plus aspirin 75–100 mg daily (Class I)	Target INR =2.5 (range 2.0 to 3.0) for aortic and a target INR =3.0 (range 2.5 to 3.5 3.0) for mitral/ both aortic and mitral valve) (Grade 1B) Aspirin 50–100 mg indicated in patients at low risk of bleeding (Grade 1B)	Target INR according to prosthesis thrombogenicity and patient-related risk factor Class I) Aspirin 100 mg daily if concomitant atherosclerotic disease and/or TE despite adequate INR (Class IIa)

ACC American College of Cardiology; ACCP American College of Chest Physicians; AHA American Heart Association; ESC European Society of Cardiology; INR international normalized ratio; TE thromboembolism; VKA vitamin K antagonist.

Our protocols at every visit of patient are-

1. To verify anticoagulation card (name, address ,mobile number of patients and their one of family member ,doctor name and their mobile number, also having information that I am on blood thinning medication which cause me to bleed for larger than normal).

2. Verify INR monitoring chart (diagnosis and required INR)

3. Short history of any thromboembolic events / bleeding, hospital admission and any other adverse reactions.

4. Dietary history –avoid high vitamin- K rich foods such as green leafy vegetables (brussel sprouts-bandagobi, green onions-kacchapyaaz, mustard greens-sarsonkasaag, spinch-palak,turnip greens-shalagam), soyabean oil , lady finger.

5. Order PT & INR to laboratory, Electrocardiogram for atrial fibrillation /any other changes.

6. Echocardiography screening three monthly/ as when required.

7. Comparisons to previous visit PT &INR, dose and duration of oral anticoagulantand then prescribe optimal dose of oral anticoagulant accordingly to achieve required INR. In case of deranged PT &INR (very low / high/ out of range) then we repeat the blood sample within two days and manage oral anticoagulant treatment.

8. We used antiplatelet (low dose aspirin = 75 mg/day) in suboptimal INR patients.

9. Suboptimal INR is defined as that INR value less than the range in guidelines.

10. We used Warfarin as oral anticoagulant vitamin K antagonist (VKA) in majority of patients.

11. Pattern of complications in patients on oral anticoagulant is broadly divided into two categories- major requiring intervention (thrombosis, cerebrovascular events/bleeding) and minor (echymosis /skin discolouration, pedal oedema, epitaxsis, heavy menstrual periods, pericardial effusion, and headache) needs only dose reduction or temporarily stopping oral anticoagulant.

Results- A total of 161 patients undergoing elective surgical valve replacement with mechanical prosthetic valve were observed in outdoor patient department. Out of 161 patients, 84 (52.17%) were males and 77 (47.82%) were females. Age ranged between 10-62 years, with a mean age of 33.48 years. Atrial fibrillation (18%), LA/LAA clot (6.8%), and stroke (3.7%) were most common preoperative risk factors. We used ATS-Medtronic (77 cases), TTK Chitra Tilting Disc (71 cases) were most common mechanical heart valve implanted at mitral (65.2%), both aortic and mitral (21.72%) and aortic (13%) positions. Warfarin was most common oral anticoagulant used with dose ranging from 0.5 to 7mg. Antiplatelets (Aspirin 75 mg/day) was used in addition to oral anticoagulant in 53.74% cases who have INRValue < 1.5. Dietary restriction for vitamin K- rich foods and transthoracic echocardiography were done in 147 cases in regular follow-up period (table 2). In our study we observed that fluctuations in INR monitoring in patients on oral anticoagulants commonly exists either in range or below range in respect to ACCP guidelines at any types and positions of implanted mechanical heart valve. The below range and in range INR value were at mitral (38.38%, 49.49%), at aortic (52.63%, 31.57%), and at both aortic and mitral (55.17%, 37.93%) positions respectively (table 3).The major and minor complications of oral anticoagulant in mechanical heart valve

patients were common at mitral position in below range INR value <1.5group (n=4 cases) and in above range group (n=8 cases) respectively (table 4).

Table 2-Patient profile and clinical data

Serial number	parameters	Variables
1.	Age (mean in years) range 10-62 years	33.48
2.	Sex • Male • female	84 (52.17%0 77 (47.82%)
3.	Body surface area (mean mm3) range 0.89-2.17	1.47
4.	Preoperative risk factors (= n cases) • Atrial fibrillation • Stroke • LA/LAA Clot • Giant LA • LV dysfunction • Hypercoagulable state	29 (18 %) 06 (3.7%) 11(6.8%) 04(2.4%) 03 (1.8%) 00 (0.0%)
5.	Surgical procedure(= n cases) • MVR • AVR • DVR	105 (65.2 %) 21 (13.0%) 35 (21.72)
6.	Type of mechanical prosthetic valve used (= n cases) • ATS-Medtronic • TTK Chitra (Tilting Disc) • St. Jude • ON-X	77 71 12 01
7.	Oral anticoagulants • Warfarin- Range of dose (in mg) • Acenocoumarol (acitorm)-Range of dose (in mg)	0.5mg-7mg 1mg-4mg
8.	Antiplatelets therapy (Ecosprin dose 75 mg / day) in addition to oral anticoagulant (= n cases)	79 (53.74%)
9.	Echocardiography screening	147
10.	Dietary restriction (= n cases)	147
11.	Defaulter (irregular oral anticoagulants)	07 (4.7%)
12.	Complications- • Mortality • Lost to follow up	04 (2.7%) 03 (2.0%)

LA (left atrium), LAA(left atrial appendage), MVR (mitral valve replacement), AVR (aortic valve replacement), DVR (double valve replacement- aortic and mitral).

Table 3-Fluctuation in range of INR in patients on oral anticoagulant

Range of INR	MVR (= 99 n cases) 67.34 %	AVR (=19 n cases)12.92 %	DVR (= 29n cases)19.72 %
Below range	38.38 %	31.57 %	37.93 %
In range	49.49 %	52.63 %	55.17 %
Above range	12.12 %	15.78 %	6.89%

INR (international normalized ratio), MVR (mitral valve replace-ment), AVR (aortic valve replacement), DVR (double valve replacement - aortic and mitral).

Table 4– Pattern of complications in patients on oral anticoagulant

Extreme of Range of INR	MVR+ DVR (n =128 cases)		AVR (n =19 cases)	
	Major	Minor	Major	Minor
Below range • <1.5 • 1.5-2.0	 04 00	01 03 02	 02 00	 00
Above range/ Out of range	03	08	00	01

INR (international normalized ratio), MVR (mitral valve replacement), AVR (aortic valve replacement), DVR (double valve replacement- aortic and mitral).

Discussions-

INR monitoring for oral anticoagulant is the key part in treatment of patients with mechanical prosthetic valves during follow up period. Warfarin is the most common agent used today. Warfarin has a narrow therapeutic range and is associated with risk of thromboembolic events and bleeding. The annual rate of mechanical prosthetic heart valve thrombosis ranges from 0.1-5.7%,with higher rates observed with specific valve types with implanted position (mitral and tricuspid) and is strongly correlated with sub-therapeutic anticoagulation[6]. A number of trials have been conducted in which different levels of anticoagulation were compared, some in combination with antiplatelet therapy.In other recent studies combination therapy with coumarin derivatives and antiplatelet agents has been studied[10-11]. Turpie et al.[10] reported a beneficial effect of adding aspirin to warfarin, with a target INR of 3.0 to 4.5. In 1990, the British Society of Haematology recommended a target range of 3.0 to 4.5 for the INR, and in 1992 the American College of Chest Physicians recommended that the target range be 2.5 to 3.5. There seems to be a tendency to lower these recommended values, however, on the basis of the results of recent studies in which lower target ranges were used[12-15]. Pavani et al[16] developed a pharmaco-genomic algorithm, which explained 44.9% of the variability in warfarin dose requirements using age, gender, BMI, vitamin K intake, *CYP2C9* and *VKORC1* as predictors. *CYP2C9*8*, *CYP4F2* V433M, *GGCX* G8016A and thyroid status were added to an expanded genetic model (n = 243). Their result showed expanded genetic model explained 61% of the variability in warfarin dose requirement and has a prediction accuracy of ±11 mg/week and can differentiate warfarin sensitive and warfarin resistant groups efficiently (areas under receiver operating characteristic curves: 0.93 and 0.998, respectively; p < 0.0001). They found that in the warfarin-resistant group, primary hypothyroidism was found to induce more resistance while in the warfarin-sensitive group, hyperthyroidism was found to increase sensitivity. They concluded that expanded genetic model explains greater variability in warfarin dose requirements and it prolongs time in therapeutic range and minimizes out-of-range International Normalized Ratios. Factors especially age, body weight, associated diseases and interaction with drugs and food items also affect dose requirement and inter patient variability[17]. Akhtar et al found that the Asian population are less prone to complications on a low INR 2-2.5[18] which is also further established by other Asian studies[19-20].

In contrast to above studies, we found that fluctuations in INR monitoring in patients on oral anticoagulants commonly exists either in range or below range in respect to ACCP guidelines at any types and positions of implanted mechanical heart valve. We also noticed that, dietary factors, role of low dose antiplatelets in suboptimal INR and inter patient variability is the common reasons for requirement of dose adjustment of oral anticoagulants.

Conclusion-

In our study we found that proper monitoring of INR during follow-up period and protocol based appropriate timely action taken can enable safe long term anticoagulation. For patients receiving oral anticoagulanttreatment, deciding whether to add aspirin to their treatment is a common clinical scenario with no clear guidelines to aid practice. In our opinion, well-monitored anticoagulant treatment is preferable to combined therapy and addition of aspirin only be considered in suboptimal INR. The optimal intensity of anticoagulation in our patients without any major complications lies in between INR range values of 1.5 to3.0 and needs a guideline for Asian population.

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