Antithrombotic Therapy for VHD: An Eight Year Follow up Study

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ABSTRACT

Introduction: Incidence of valvular heart disease continues to grow in India and other developing countries as life expectancy is increased and incidence of Rheumatic heart disease is still prevalent in developing countries. Cerebrovascular catastrophes in the form of thromboembolic infarction and its consequences are devastating in patients with VHD; particularly patients with prosthetic heart valves. Therefore there is a need for antithrombotic therapy in patients with PHV even though the risk of bleeding is high in these patients. This prospective study was done on adult patients of valvular heart disease who were treated with antithrombotics to observe incidence of thrombotic events, haemorrhagic episodes and other adverse effects of anti thrombotic therapy.

Material and methods: The study period was from 1st January 2012 to 31st December 2019. Adult patients admitted in medicine wards with valvular heart disease, both males and females aged between 16 years to 80 years were taken up for study. These patients were treated with anti thrombotic therapy with a view to preventing thromboembolic events. All adult patients from 16 years to 80 years of age with VHD were followed up in our study starting from 1st January 2012 to 31st December 2019. All these patients were treated with VKA or LMWH as per the condition of the patients. Informed consent from the patients as well as permission from ethical committee was obtained. Proper history, thorough clinical examination as well as all relevant investigation were carried out.

Results: 143 patients qualified to be included in our study. Out of these 143 cases, we had thromboembolic episodes of CNS in 3 patients and 2 patients died due to intracranial haemorrhage. Hence, the number of patients having thromboembolic event was as low as in most of previous studies carried out by various authors.

Conclusion: Use of antithrombotic agent is not without complications like bleeding and thrombocytopenia. However, with the use of antithrombotic agent there is a huge benefit and reduction of incidence of thromboembolic event by more than 12%. There are no fixed dose of anticoagulants and each patients should be treated on the condition of the patient, presence of comorbid conditions and pregnancy. Ideally INR is adjusted to 2.5 to3. But in spite of this if there is evidence of increased risk, INR goal may be increased to 3.5 to 4.5.

Keywords: Antithrombotic Therapy, VHD, Rheumatic Heart Disease

INTRODUCTION

Worldwide incidence and burden of VHD is increasing day by day as the number of aged person is increasing. In India the prevalence of RHD is still high.[1] Patients with native valve with comorbid conditions like atrial fibrillation, CHF, hypertension, diabetes, old age, history of previous stroke and hypercoagulable state or with bioprosthetic valve or mechanical prosthetic valve are prone for stroke and are in need of antithrombotic agents despite having bleeding risk.[2] Even in non-valvular atrial fibrillation ischaemic stroke can be prevented by antithrombotic agents with 60% risk reduction when compared with placebo, and with antiplatelet therapy 40% risk reduction[3], The combination of aspirin and clopidogrel when compared to warfarin is non inferior in reduction of ischaemic stroke.[4] Data from contemporary trials have shown that stroke events are considerably reduced with antithrombotic therapy at a rate of 1.66 annually.[5]

Oral anticoagulant therapy is indicated in all patients with CHA2DS2-VASc (CHF,hypertension,Age>75 years,DM,stroke or TIA, vascular disease) score2 or more.[6] Newer anticoagulants like Dabigatran, Apixaban, Rivaroxaban are not indicated in Rheumatic MS with AF. MVR with mechanical or bioprosthetic valve.[2] Although it is not mandatory to continue with antithrombotic agent for more than 6 months with bioprosthetic valve it is mandatory for mechanical prosthetic heart valve for lifelong continuation of therapy along with monitoring of PT, platelet estimation, bleeding time and clotting time.[7]

Patients with MS and AF have got risks of stroke, 17fold whereas in non valvular AF the risk of stroke is 5fold irrespective of the severity.[8] The chances of thrombosis, embolism increase with aortic, mitral or double valve replacement to 1.4,4.0 and 8.6 respectively per 100 patients years. With warfarin this risk is reduced to 0.11,1.0 and 1.8 respectively.[9]

The addition of aspirin along with oral anticoagulant was a subject of controversy in the past and studies reported that there might be a decrease thromboembolic event but at an expense of increased bleeding.[10] ACCP guidelines recommend low dose aspirin if the bleeding risk is low and clopidogrel in lieu of aspirin if aspirin is contraindicated.[11] European Society of Cardiology 2012 clearly recommends addition of low dose aspirin in patients with atherosclerotic

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heart disease or after thromboembolism even if the INR is adequate.[12] Self monitoring of INR and adjustment of dose played major role in reducing thromboembolic episodes.[13] But this was refuted by a meta analysis which did not show any improvement of major bleeding or stroke.[14]
Direct inhibitors of Factor II and Factor X like Dabigartan, Apixaban or Rivaroxaban are contraindicated in mechanical prosthetic valve. The RE-ALIGN trial was prematurely terminated as excessive thromboembolic (9% vs 5%) and bleeding events(27% vs 12%) occurred in Dabigartan group when compared to warfarin group.[15]
In case of bioprosthetic valve implantation, risk of thromboembolic event seems to be high in first 3 months after implantation.[16] So antithrombotic therapy with VKA is advised for first 3 months.[12] After 3 months low dose aspirin(75mg) should be carried out in patients with AVR or MVR as there is a reduction in thromboembolic events.[16] In case of non cardiac major surgeries VKA should be stopped 48-72hours before surgery. When INR falls to 2 then UFH can be started 2500-5000units 12 hourly and this should be stopped 6 hours before surgery.[2] If there is no renal failure then Inj. LMWH can be administered 12 hourly after surgery as a bridging gap for 3-5 days.
Aspirin, prasugrel should be stopped 7 days prior to surgery and clopidogrel and Ticagrelor 5 days before surgery should be stopped.
Coronary artery stent implantation in VHD patients has generated lots of controversy as regards to use of Dual(VKA and Clopidogrel) or triple therapy(VKA, Clopidogrel and aspirin).
Patients with VHD undergoing stenting are better managed with VKA,Clopidogrel and Aspirin particularly when CHA2DS2-VASc score is more than 2.[17,18]
Triple antithrombotic therapy is associated with bleeding risk if continued for a long duration.[19]
While preferring triple therapy one should keep in mind

1. The duration should be short.
2. Low dose Aspirin(75mg) to be used.
3. Use of clopidogrel and not ticagrelor or prasugrel should be the 3rd option.
4. Prophylactic proton pump inhibitor to be used.
5. Lower target of INR to 2.5
6. Drug eluting stent for patients with low risk of bleeding.

After 12 months of therapy VKA should be continued along with low dose of aspirin to reduce events like AMI, thrombotic stroke or major bleeding events.[20]

Long Term Management: When patient is off anticoagulant and there is an embolic event then restart VKA and continue for a long time. When event occurs in patients on VKA then increase INR to 2.5 to 3.5 from 2 to 3. If INR is on 2.5 to 3.5 then increase to 3.5 to 4. Add aspirin(75mg) if not on Aspirin. If on 75mg of aspirin increase to 300mg and if required clopidogrel may be added.[21] For non urgent cases for cardiac catheterization stop VKA 72 hours prior to catheterization. For femoral access INR 1.8 is required and for radial or ulnar artery access INR should be <2.2.[22] In case of high risk patients of thromboembolism non avoidance of VKA prior to catheterization is a preferred choice as there is less events of bleeding as compared to bridging treatment with heparin.[23]
During pregnancy warfarin can be continued throughout pregnancy but recent data shows the adminitration of LMWH in late pregnancy yielded better results as there is less maternal and foetal morbidities and mortalities when the anti Xa level is kept between 0.9-1.2units/ml in pregnant females with MPHV.[24,25]
Study was aimed to observe the incidence of thrombotic events, haemorrhagic episodes, thrombocytopenia, major or minor bleeding. We will also observe maternal or foetal mortality in case of pregnant females with VHD.

MATERIAL AND METHODS

All adult patients from 16years to 80years of age with valvular heart disease were followed up in our study starting from 1st January 2012 to 31st December 2019.All these patients were treated with VKA(warfarin) or Injection Low Molecular Weight Heparin 1mg/kg of body weight twice daily as per their needs.[24,25] Low dose aspirin(75mg) was administered to patients who had evidence of thrombo embolism in spite of maintaining an adequate INR with VKA antagonist.[11] Informed consent was obtained from the patients and permission from ethical committee was also obtained. Patients were subjected to thorough clinical examination with particular reference to past history of Rheumatic fever, valvular heart disease, surgery, type of prosthetic valve implanted, site of implantation. We noted past history of diabetes, stroke including transient ischaemic attacks or any bleeding episodes.
Patients name, age, sex, address, ethnicity, family history of diabetes, hypertension, IHD were also noted. We also noted their personal habits of any alcoholism, smoking or substance abuse. We carried out CBC, Blood sugar tests, including HbA1C, Lipid Profile, Renal function, Liver function, BT, CT, Platelets, PT, APTT, CT Scan (As & when situation warranted), 2D Echo, Doppler study to exclude thromboembolism event in any artery and fundoscopy was done in all patients.

RESULT

Total numbers of 196 patients (Male-108, Females-88) were selected for our study. At the end of 1 year of our study we had 143 patients (males-85, Females-58) who qualified for the study. 20 males and 28 females were lost for follow up and hence were excluded. At the end of 1 year of study we lost 2 males for chronic liver disease, 1 male & 1 female died due to CHF and 1 female died due to diabetic nephropathy and sepsis and hence were excluded from the study. Finally, at the end of 1 year, we continued with our study with 143 patients; Male 85 & Females 58.
Table1: Total number of patients at the beginning of the study and qualified patients in the final group.
Table2: All these patients were treated with 5mg of warfarin in case of patients above 50kgs of weight and with 4mg in

patients who were less than 50kgs and patients who were treated with LMWH the dose was 1mg/kg of body weight. INR was maintained between 2.5 to 3.5 with adjustment of dose of warfarin. Anticoagulation with warfarin or Inj. LMWH as and when required were continued throughout our study. 4 of our patients became pregnant and we continued with warfarin till 30th week of pregnancy and from 31st to the end of 38th or 39th week replaced warfarin anticoagulation with LMWH. 2 patients developed infective endocarditis in which 3 patient was culture +ve(S. viridance) and 1 had classical echocardiographic evidence along with other major and minor criteria. These cases were treated with antibiotics and inj. LMWH was administered in lieu of warfarin. 3 cases required emergency abdominal surgery and hence warfarin was stopped 24 hours before surgery and after removal of stitches warfarin was continued. At the end of 24 hours of surgery Inj LMWH was administered for 5-7 days to bridge the gap. 3 patients had attacks of Acute Myocardial Infarction. We replaced warfarin with Inj LMWH and stopped aspirin and clopidogrel 5 days prior to coronary angioplasty. After 7 days of stenting we continued Inj LMWH for 7 days and then discontinued. We then started warfarin along with clopidogrel and after 1 year we continued with only warfarin only. 1 patient required implantation of permanent pacemaker and we stopped warfarin 3 days prior to implantation and after 3 days of implantation we started Inj. LMWH for 5 days for bridging and restarted warfarin 8 days after pacemaker implantation. After 1 month of warfarin we added aspirin as there was strong suspicion of thromboembolic phenomenon as evidenced by 3 episodes of transient ischemic attacks. CT revealed lacunar infarction near left horn of internal capsule. We encountered 3 cases of thromboembolic stroke all of

Sex	**Male**	**Female**	**Total**
Included	108	88	196
Lost for follow up	20	28	48
Died due to CLD	2	0	2
Died due to CCF	1	1	2
Died due to Nephropathy, Sepsis	0	1	1
Total number of exclusion	23	30	53
Total no. of patients qualified for the final study	85	58	143

Table-1: Data of patients at the beginning of study.

Age	**16-35**	**36-60**	**61-70**	**70 and above**
No. of patients 143	M-14/ F-10	M-46/ F-32	M-18/ F-13	M-7/F-0
Diabetes	M-3/ F-1	M-24/ F-6	M-4/ F-2	M-4/ F-0
Hypertension	M-0/ F-0	M-10/ F-2	M-3/ F-1	M-4/ F-0
Prosthetic Mitral Aortic DVR	 M-14/ F-12 M-4/ F-2 M-0/ F-0	 M-26/ F-22 M-8/ F-6 M-7/ F-3	 M-13/ F-8 M-3/ F-2 M-0/ F-0	 M-1/ F-0 M-2/F-0 M-0/ F-0
Bioprosthetic Mitral Aortic	 M-0/ F-0 M-0/ F-0	 M-2/ F-1 M-1/ F-1	 M-1/ F-1 M-0/ F-0	 M-0/ F-0 M-0/ F-0
Atherosctentic VHD	M-0/ F-0	M-0/ F-0	M-6/ F-3	M-4/ F-10
Renal failure	M-0/ F-0	M-2/ F-0	M-0/ F-0	M-0/ F-0
Thrombocytopenia	M-0/ F-2	M-1/ F-3	M-2/ F-3	M-0/ F-0
Stroke Embolic Thrombolic Haemorrhagic	M-2/ F-0 M-0/ F-0 M-0/ F-0	M-1/ F-1 M-1/ F-0 M-1/ F-0	M-2/ F-0 M-3/ F-2 M-0/ F-1	M-0/ F-0 M-0/ F-0 M-0/ F-0
Major bleeding	M-0/ F-0	M-1/ F-2	M-1/ F-1	M-1/ F-0
Trivial bleeding	M-2/ F-0	M-1/ F-3	M-3/ F-2	M-0/ F-0
LVEF<35	M-0/ F-0	M-2/ F-4	M-4/ F-4	M-2/ F-0
Hypercoagulable state	M-0/ F-2	M-1/ F-3	M-0/ F-2	M-0/ F-0
Artial Fibrillation	M-3/ F-51	M-10/ F-4	M-4/ F-4	M-5/ F-0
Bacterial Endocarditis Culture +ve Echo +ve	 M-1/ F-0 M-0/ F-1	 M-2/ F-0 M-0/ F-0	 M-0/ F-0 M-0/ F-0	 M-0/ F-0 M-0/ F-0
Acute MI	M-0/ F-0	M-0/ F-2	M-0/ F-1	M-0/ F-0
Pregnancy	F-3	F-1	F-0	F-0
Emergency Surgery	M-1/ F-0	M-1/ F-1	M-0/ F-0	M-0/ F-0
Implantation of PPM	M-0/ F-0	M-0/ F-0	M-1/ F-0	M-0/ F-0

Table-2: Data of the study group 1st January 2014- 31st December 2019 total no. 143

whom recovered and 2 cases of haemorrhagic stroke whom we lost.

DISCUSSION

Rheumatic heart disease is still very much prevalent in India. More over the ageing population also has led to atherosclerotic valvular heart disease with atrial fibrillation to a great extent.[1] Observational studies have clearly indicated that without anticoagulation/antithrombotic treatment there may be thromboembolic stroke upto 8% and limb amputation upto 4%.[2] But with anticoagulant(VKA Antagonist) and antithrombotic therapy(aspirin) the incidence can be reduced upto 60% and 20% with (VKA antagonist) and aspirin respectively.[3] Our observation is also in accordance with this opinion. In a native valve disease with atrial fibrillation with a CHA2DS2VASc score of 2 or more combination of warfarin with aspirin is recommended.[6] Till recently thrombolytics like aspirin, clopidogrel or anticoagulants like warfarin, UFH were recommended. But now with exception of LMWH, NoVKA(Non VKA antagonists) like apixaban, rivoroxaban or dabigatran are not recommended for use in VHD with or without prosthetic heart valves.[15] We did not use any of these NoVKA in our study. But with advent of LMWH and for their safety and rare need of monitoring LMWH is being used in many cases particularly in emergency situations.[11] Theoretically use of LMWH may increase the incidence of bleeding episodes but in our group there was much less events of bleeding(4.2%) and haemorrhagic stroke (1.4%). This is supported by the work of Kindo et al.[9] Only 3 months of anticoagulation is required for bioprosthetic valves as they cause less thromboembolic event after 3 months.[16] In our case we continued warfarin followed by aspirin with advice for lifelong aspirin supported by Merrie et al.[16,17] Some authors advocate self monitoring of INR and dose adjustment of warfarin by patients themselves but we did not resort to this method as there was every chance of overdose and underdose and error in recognizing early signs of thromboembolic phenomenon, bleeding etc by the patients. Our view in this regard was supported by Sharma et al.[14] As for elective surgery we stopped warfarin for 3 days prior to surgery which is supported by ACC/AHA guidelines 2006.[21] We also evaluated the risks of thromboembolism in our patients with particular reference to atrial fibrillation, LV dysfunction(LVEF<35%), previous thromboembolism, hypercoagulable state like pregnancy, sickle cell disease, sticky platelets in patients of prosthetic mechanical valves. We did not hesitate to use warfarin and aspirin(or clopidogrel if aspirin was contraindicated) in our patients. During pregnancy we continued with warfarin till 30th week and substituted with Inj LMWH which resulted in maternal and foetal benefits which are supported by previous studies.[24,25]

CONCLUSION

Use of antithrombotic agents is not without complications like bleeding, trivial or severe. In spite of the risks involved the benefits are huge. With the use of antithrombotic agents the overall reduction in thromboembolic event is 12%. The consequence of cerebral ischemia and subsequent hemiplegia is devastating. The consequent disability that remains can ruin the life of the patient as well as that of his family members both financially and socially. Many a times thromboembolic event can lead to amputation of a limb which is far more devastating physically and psychologically. Hence, it is worthwhile to accept the risks involved with the use of antithrombotic agents in all cases of valvular heart disease with high risk of thrombosis and all cases of VHD with MPHV. It is important to note that there is no guideline to use the type of antithrombotic agents and there is hardly any head to head trial with any agent against the other. There is no fixed dose for anticoagulants nor are there any fixed dose for injectable UFH or LMWH. Each patient must be treated according to their INR profile, age, pregnancy and renal profile. Of paramount importance is regular estimation of INR and to adjust the dose of anticoagulant accordingly. Ideally INR should be maintained between 2.5 to 3. But in spite of this level if there is evidence of thromboembolism INR can be maintained at 3.5 to 4.5 with addition of low dose aspirin and clopidogrel. Similarly at the time of an acute attack of CNS thromboembolism there is need for institution of LMWH or UFF. Preferably this should be carried out after ensuring that there is no intracerebral haemorrhage. Platelet count, BT, CT should be maintained besides controlling INR. Finally, it should be emphasized that in all cases of VHD with risk factors for thromboembolism and in all cases of MPHV antithrombotic therapy should be instituted and continued for lifelong and in case of bioprosthetic valve it should be continued for at least 3 months and if needed for a longer time if situation warrants its use.

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