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Role Of Acenocoumarol In Prosthetic Heart Valves

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Abstract:

Thromboembolic and anticoagulation related bleeding problems remain one of the most frequent complications of cardiac valvular prosthesis. Which and how much drug dose should be given depends on the individual response to the drug and the complications thereof. The aim of the study was to know the outcome of patients taking Acenocoumarol as anticoagulant drugs in prosthetic heart valves. The study was conducted on the patients who were on Acenocoumarol after heart valve replacement, and the dose was adjusted as per international normalized ratio (INR). Most of the patients were in the 4th decade of life and males were more. Seventy-three had mitral, 19 aortic, and 3 double valve replacements done. Medtronic Hall valve was the common prosthesis used in 78, followed by Bjork Shilley in 17. Acenocoumarol was the drug used in all. Seven patients developed central nervous system events, 6 patients had features of peripheral embolization of which two had surgical intervention done, two needed amputation. Complications occurred more in patients with mitral prosthesis, and were less in patients who maintained an acceptable INR of 2.5 to 3.5. Meticulous surgery, uneventful post-operative period, early anticoagulation, and maintaining an ideal INR are the gold standards in preventing thromboembolic and bleeding complications after valve replacement.

Key words: Acenocoumarol, International normalized ratio, mitral valve

Introduction:

One of the most fatal events after cardiac valve replacement surgery is valvular thrombosis [1]; prevalence of thromboembolism varies with the type of mechanical prosthetic heart valve and is lower with modern valves than first generation valves. Thromboembolism and bleeding are the consequence of inability to control the interaction between blood and synthetic material.[2] The causes of valvular thrombosis are surgical technique, prosthetic designs, systemic factors and the anticoagulation effect. To prevent the occurrence of such a complication, corrective measures are started immediately after surgery and some surgeons even advocate anticoagulation on the day of surgery; however some defer it for a day or two. It is not only to start anticoagulation and continue, but the problem of over-anticoagulation is equally disastrous, and the bleeding complications may be difficult to manage. With these facts in sight, it is very important to, not only start the right drug with the right dose at the right time, but also to monitor an ideal international normalized ratio (INR) for the best possible outcomes. The intensity of anticoagulation depends on the type of prosthesis, its position, and presence of atrial fibrillation and the individual's risk of thromboembolism. After the introduction of INR, oral anticoagulation has become more reliable, effective and relatively safe.[3] Thromboembolic events may be transient with recovery within 30 minutes or after 30 minutes, or permanent central nervous system deficiency, and the bleeding may be minor, moderate or severe. Risk factors for prosthetic valve thrombosis are periods of insufficient anticoagulation, mitral position, low cardiac output, atrial fibrillation, atrial thrombus, previous

embolic episodes, hypercoagulable state and pregnancy. The risk of thromboembolic events with ball cage, tilting disc and bileaflet prosthesis is estimated to be 2.5%, 0.7% and 0.5% per year respectively.[4] Though the advantages and disadvantages of anticoagulation are not clear and well defined, it is amply clear that in spite of all the problems, anticoagulation should be started and continued (except where absolutely contraindicated) in all the patients with mechanical prosthetic heart valve.

Materials & Methods:

The prospective study for two years was conducted on patients who had undergone cardiac valve replacement at other centers at least 3 months back. The patients were explained the advantages and disadvantages of follow-up, the limitations and lack of super specialized management. Only patients who wished to attend the department regularly, get the investigations done as directed and agreed to attend the higher centers in case of any problem for further management were included in the study. Patient with malignancy, pregnancy, multi-system diseases, coagulopathy, and those who had come by chance or compulsion and those who did not follow the guidelines were not included in the study. A detailed history, through general and systemic examination was done; all the patients were assessed for thromboembolic and/or bleeding complications at first visit. Patients with thromboembolic or bleeding complications, severe pain in limbs, any lateralizing sign, weakness of any limb, blurring of vision, slurring of speech, aphasia, vomiting, convulsions, change in vision, cranial nerve palsy, incontinence and inaudible prosthetic sound were referred to emergency department of the hospital or tertiary care centre and managed as per protocol. The investigation of choice was INR, prothrombin time though useful in assessment of congenital and/or acquired deficiencies of extrinsic coagulation pathways was done in all, but the bench mark was the INR, the use of which is universally recommended for the patients on oral anticoagulation therapy. The principal of this test, which measures the activity of extrinsic coagulation factors II, V, VII, and X, consists of use of calcium thromboplastin to measure the clotting time of patient's plasma and to compare it with that of a normal standard. Nine volumes of blood is collected in 1 volume of anticoagulant, that is 1.8 ml of blood in 0.2 ml of anticoagulant (3.2%) sodium citrate. As per international recommendations, the target INR was maintained between 2 to 3, preferably more than 2.5 to 3.5 for prosthesis in mitral position, and in patients with systemic embolization. The investigations were done from the hospital or a registered private laboratory. Acenocoumarol 1 to 8 milligram (mgm) in all, aspirin 75 mgm, and clopidogrel 75 mgm was also used in few patients. Acenocoumarol has shorter half life, a more rapid effect on prothrombin time, duration of action about two days, and a maintenance dose of 1 to 8 mgm.

All the patients with uneventful history, normal clinical examination, and with permissible INR of 2.5 to 3.5 were directed to continue the same drug in the same dose. In patients with less than 2.5 INR, the dose was increased by 1 milligram; in patients with more than 3.5 INR, the dose was decreased by 1 mg. Patients in whom dose was changed or adjusted, were asked to get the repeat INR done after 10 days, and the dose was modified accordingly. Patients with uneventful follow-up for three to six months, with acceptable INR were advised coagulations studies after 3 to 6 months in case there was no adverse sign or symptom suggestive of thrombosis or bleed. Echocardiography, X-Ray chest were done only in patients who had features of any

complication. All the complications, the morbidity and mortality were recorded.

Results:

Of the 127 patients, 32 (25.19%) did not follow the protocol and were excluded from the study. Majority were in 4th decade of life with more male patients. Time elapsed from surgery to starting of the study was 3 months to 3 years. Nine (9.47%) patients had already suffered a thrombotic, and 6 (6.31%) a bleeding episode. Seventy-three (76.84%) had mitral, 19 (20.00%) aortic, and 3 of the patients (3.15%) had double valve replacement done. Rheumatic heart disease was present in all. Initial INR was not within permissible limits in any. Medtronic Hall valve was the common prosthesis used in 78 (82.10%), followed by Bjork Shilley in 17 (17.89%), and Chitra valve in 3 (3.15%). Acenocoumarol was the drug used, with addition of aspirin, and clopidogrel in few patients only. The dose of acenocoumarol ranged from 1 to 8 mgm. In 71 (74.73%) patients, upto 4 mgm of acenocoumarol was sufficient to maintain an ideal INR. It took about two to three months to titrate the dose of anticoagulant at an ideal INR. Seven (7.36%) patients developed central nervous system events, of whom two had stroke and three recovered without any neural deficit; 6 (6.31%) patients had features of peripheral embolization of which three had surgical intervention done, two needed amputation and two recovered without any residual deformity. Ecchymotic spots, epistaxis and gastrointestinal tract (GIT) bleeding were recorded in 4 (4.21%), 3 (3.15%), and 2 (2.10%) patients respectively, none of whom had any abnormality in INR, and only patients with features of GIT bleeding were hospitalized; endoscopy did not reveal any evidence of bleed from upper GIT and after evaluation / management, anticoagulation was restarted. Twenty-three (24.25%) patients didn't maintain an ideal INR; probably were not taking drugs as prescribed, were looking for alternatives, even questioning that what difference has the surgery made, and this group suffered the most. In all, 22 patients (23.15%) developed one or the other complications, of which major events were recorded in 15 patients (15.78%). Three patients were re-operated for mitral and aortic valve malfunction, with two having residual neurological deficit. Eight patients (8.42%) died, 2.10% had amputation, 2.10% had permanent neurological deficit. Complications were seen, more in patients with INR of less than 1.5, and more than 3.5, and occurred more in patients with mitral prosthesis on 18 occasions, in aortic prosthesis on 3 occasions and in double valve replacement on one occasion. Ideal INR of 2.5 to 3.5 was maintained in 31.57% of the patients, who were followed for at least 2 years and had no problems. In addition to acenocoumarol, aspirin was used in patients who developed, or already had a thrombotic episode. Clopidogrel was used in only those patients who did not maintain an acceptable INR even with 8 mgms of acenocoumarol. Patients who maintained an ideal INR with acenocoumarol had no thrombotic or bleeding complications.

Discussion:

A seemingly benign problem, prosthesis related complications if not suspected, diagnosed and specifically managed in time can present with a grim phenomenon, increasing both the morbidity and the mortality. Management of valve prosthesis begins with selection of the optimal time point for valve replacement; aortic prosthesis-patient mismatch is prevented by choosing a properly sized prosthesis ring diameter. Generally, anticoagulation in patients with aortic bileaflet prosthesis should be kept at an INR 2.0- 3.0; other mechanical valves and bioprosthesis three months postoperatively at 2.5-3.5. An optimal intensity of oral anticoagulation

therapy is that at which the incidence of both thromboembolic and bleeding complications is lowest, and this level can be found at INR values between 2.5 and 4.9. Rheumatic heart disease being the common cause of valvular heart surgery is well known [5]; because of the extensive valvular damage, open repair or percutaneous valvuloplasty is not suitable and valve replacement becomes mandatory.[6] For lack of endothelialisation, the risk of thromboembolic complication is more in first three months after surgery. [7] Also, number of complications increase in parallel with time spent outside therapeutic range. [8] Addition of aspirin and dipyridamol results in reduction of anticoagulation therapy, thereby decreasing the incidence of thromboembolic and bleeding complications.[9] The oral anticoagulation should be started as early as possible, and not after 10 days as reported by others [10]. Normally, the INR should be titrated between 2.5 to 3.5, but should not be kept more than 3.5 in patients with prosthesis in mitral position and more than 3.0 in patients with prosthesis in aortic position. Majority of the patients are in fourth decade of life, and mitral valve being the most commonly replaced valve is well known. [6,11,12] It is a fact that acenocoumarol is not the commonly used anticoagulant in the world, instead warfarin is used more frequently. Risk of bleeding overweighs that of prosthetic valve thrombosis, thromboembolism, or peripheral ischemic complications [13]. Patients over 70 years of age have increased risk of bleeding as do patients recently anticoagulated or when anticoagulation is started.[14] Careful, consistent anticoagulant therapy, revisions of indications for surgery and improved thromboresistance of the new heart valves has decreased the complications rate of prosthesis. [15]

Mitral being the commonly replaced valve, and thromboembolism being five times higher in this position is reported from other studies also.[15,16] Medtronic Hall followed by Bjork-Shilley were the common implanted prosthesis, and the incidence of thromboembolism was more in Medtronic Hall valve; similar observations have been reported from other centres. [17] The dose of acenocoumarol was upto 4 mgm in 71 (74.73%), upto 6 mgm in 15 (15.78%) and upto 8 mgm in 9 (9.47%) of the patients. The results of this study differ from British Society of Hematology who recommended an INR of 3.0 to 4.5, and observed that addition of aspirin and dypyridamol results in reduction of intensity anticoagulation, thereby decreasing the incidence of thromboembolic and bleeding complications; we certainly are in agreement with the second part of the observations.[18] Our observations differ from those who observed that incidence of thromboembolism is low in low intensity oral anticoagulation [16]. Results of oral anticoagulation in combination with low dose aspirin is well known.[19] The incidence of complications from our study is very high when compared with other studies[20]; also thromboembolism in 0.9%, endocarditis in 1.2%, and hemorrhage in 2.3% is very low when compared to present study.[21] The results would differ as the present study has presented morbidity and mortality rate for two years, and not on yearly basis. Our observations are at variance to the results that even with an INR of 2.5 to 3.5, patients have thromboemboli [22] and with an INR of less than 3.0 have bleeding episodes. More than 60% of thromboembolic events leave no residual deficit and more than 75% of bleeding events require no treatment, and similar observations have been made by others.[16] The results of our study are in accordance to those of others who besides aspirin, also recommended an INR of 2.0 to 3.0 as safe compared to 3.0 to 4.5 with regard to thromboembolic and bleeding complications. [23]

The limitations of the study are that none of the patients were operated at our center, so it is not known what were the pre-operative and intra-operative problems, when was the anticoagulation started and when and what was the target value achieved. Patients with major bleeding complications were managed in the Department of Medicine, who used vitamin K, fresh frozen plasma, haemostatic drugs and whole blood. The various factors affecting the doses of the anticoagulant have not been studied. The complications were not recorded in individual valve; also warfarin and heparin were not used in any of the patients.

Conclusion:

The valve replacement is a commonly performed procedure; thromboembolic and bleeding complications can be fatal, optimal titration of INR during anticoagulation is a big challenge but can avoid disasters and Acenocaumarol can be used safely as an anticoagulant. If complications occur, early suspicion, quick diagnosis, and immediate, specific and precise multi-modality treatment prevents morbidity and mortality.

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