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Original Article

Is Bridging Anticoagulation with Heparin after Valve Replacement Surgery Mandatory? - A Prospective Observational Study in a Centre of Bangladesh

Kazi Shariful Islam; Ankan Kumar Paul

Department of Cardiac Surgery, NICVD, Dhaka

Key words:
Valvular heart disease, Mechanical valve, Anticoagulation, Bangladesh

Abstract:

Background: *This is a prospective observational single center study to determine whether bridging anticoagulation with heparin along with warfarin is mandatory in a heterogenous group of patients undergoing valve replacement surgery either single or multiple valve (with mechanical or tissue valve) in the post-operative period.*

Methods: *Perioperative data were collected in 41 patients undergoing multiple valve replacement at this center from July/2019 to September/2019 irrespective of age, sex, number and type of valve replaced. No bridging anticoagulation was given in preoperative and postoperative period in these patients. They were prospectively observed for the incidence of any thromboembolic end bleeding events with daily measurement of International Normalized Ratio (INR) till INR reached at therapeutic level for oral anticoagulant warfarin and complications of warfarin therapy.*

Results: *All the patient suffered from chronic Rheumatic heart disease. Single valve disease was in 70.73% and multiple valve disease was in 29.27% cases. Two patients had left atrial thrombus, seven patient (14.63%) had preoperative atrial fibrillation (AF). Postoperative new onset AF was present in 10 (24.39%) cases. No thromboembolism occurred in these patients and warfarin over anticoagulation was found in 1/41 patient.*

Conclusion: *Patients undergoing valve replacement surgery without concomitant postoperative bridging anticoagulation with heparin do not suffer from any thromboembolic and bleeding complications even at lower level of INR. This study also shows that single and multiple valve (both mechanical and tissue valve) have the same in hospital outcome in relation to thromboembolism and bleeding complications.*

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Introduction:

Patient who undergoes valve replacement surgery, warfarin is invariably given when the mediastinal bleeding decreases to an acceptable amount. We know that Warfarin does not work immediately, it takes 72 hours or more to exert its therapeutic effect. Most of the surgeons are not using bridging anticoagulation with heparin in the post-operative period. This issue aroused interest to know whether post valve replacement bridging anticoagulation with heparin is really necessary or not. This is the prime objective of this study.

After valve replacement the suture materials and sewing cuff is covered with biofilm and later endothelialized. This process takes few months after surgery. During this period anticoagulation is needed. Subsequently there may be thromboembolic events, valve thrombosis or impairment of valve function by subclinical thrombus.[1] Warfarin, antagonizes the actions of

Address for Correspondence: Dr. Kazi Shariful Islam, Department of Cardiac Surgery, NICVD, Dhaka, Bangladesh. Email- kazishariful_islam@yahoo.com

endogenous vitamin K-dependent coagulation factors. The half-life of warfarin is 36-42 hours and exerts its therapeutic effects up to five days in normal young person and sometimes longer in elderly person.[2] Warfarin shows its paradoxical thromboembolic effect by deactivating the two natural anticoagulant protein C and protein S in the body.[3] Although there is uncertainty regarding loading dose of warfarin, the common practice is 5 mg and a 10 mg loading dose of warfarin with lower initiation doses for elderly or age adjusted doses are appropriate.[4]

For the above reasons it takes longer time to achieve the therapeutic level of target INR for individual valve replacement patient unless the patient is over sensitive to warfarin or other factor potentiating the effect of warfarin, like drug and food.

One study on therapeutic dose vs prophylactic dose of I/V unfractionated heparin after mechanical valve replacement surgery found that almost equal risk of thromboembolism but significantly higher risk of bleeding in therapeutic dose group.[5] In some observational studies and a randomized trial have shown that there is remarkable perioperative or postoperative bleeding manifestation without decrease in thromboembolic incidence when bridging is done with heparin.[6,7]In a study carried out by Allou N et al., where they concluded that in spite of using intravenous unfractionated heparin as a bridging anticoagulation in the post-operative period the occurrence of thromboembolism remains elevated. They also mentioned that initial proper anticoagulation on day 3 lowers the incidence of thromboembolism.[12]

So, in patients with moderate to high thromboembolic threat, UFH or LMWH usually started on the second postoperative day for bridging. When the value of INR crosses the lower value of the therapeutic range for a period of 24 hours then the bridging is discontinued.[12]

The issue of bridging soon after valve replacement surgery is infrequently studied. So far, I know such kind of study was not done in our country. This is a very important area of cardiac surgery to be addressed in our country. If bridging anticoagulation is not done after valve replacement surgery there is a possibility to happen thromboembolic complication. Furthermore, if it can be established that post valve replacement bridging anticoagulation is not mandatory then it will be possible to avoid bleeding complications and to gain other benefits of doing it.

Methods:

This is a prospective observational study carried out at a tertiary cardiac center of Bangladesh. All the patients were selected purposively. A total of 41 patients were included in the study over a period of 3 months from July/2019 to September/2019 irrespective of age, sex number and type of valve replaced. All the patients underwent valve replacement surgery following standard protocol of this institute. Unfractionated heparin was used during surgery to do systemic anticoagulation before cannulation and initiation of cardio pulmonary bypass (CPB). Adequacy of anticoagulation was checked by Activated Clotting Time (ACT). It was commonly kept at e"480 seconds. At the end of operation, the heparin action was reversed with protamine sulphate. The reversal of heparin action was also rechecked by ACT, which was usually kept around 100 seconds. After proper hemostasis, hemodynamic stabilization and chest closure, patient was shifted to ICU for further care. Those patients had any significant peroperative event like massive air embolism, and those died on table for any reason were excluded from the study. Patient was observed and all the necessary parameters were recorded in the ICU flow chart by the Nurses.

Patients were extubated when fulfilled the criteria for extubation. After extubation when the mediastinal bleeding was minimum, then observing the result of post-operative INR report 5mg or 10mg or in few cases where bleeding risk was more 2.5 mg of warfarin was started.

Daily PT, INR was checked by (Model: Turbi Quick, Manufacture: AGAPPE Italy, Number: 21165920137) machine up to 5th postoperative day or more when necessary till the INR was within the therapeutic range. According to Anthony Carnicelli, regarding target INR of post valve replacement patients; for aortic valve replacement, target INR is 2.5 (Range 2-3), for mitral valve it is 3 (Range 2.5-3.5) and for double valve replacement, in aortic and mitral position in it is 3(Range 2.5-3.5).[7]

Whether patient received any bridging anti-coagulation was noted. Did the patient develop any warfarin related complications were noted. The warfarin initiation dose was decided by the respective consultant on the basis of clinical judgement of the individual patient as an institutional practice.

For study purpose a set of variables were selected. All the preoperative, peroperative and postoperative variables were recorded in a preformed data sheet. After that they were entered into the SPSS 24 program for statistical analysis. All the numerical variables were expressed in numbers, mean with standard deviation, median and range. All the categorical variables were expressed as number and percentage. Student's single sample, paired sample t-test and Chi-square test were done where applicable.

Results:

A total of 41 patients who underwent valve replacement surgery over a period of 3 months from July/2019 to September/2019 were selected for this prospective observational study. A total of 20 perioperative variables were selected for analysis.

The mean (SD) age of the patient was 36.66 (± 10.12) years. The number of female patients was higher in this study, female was 23 (56.1%) and male 18 (43.9%).

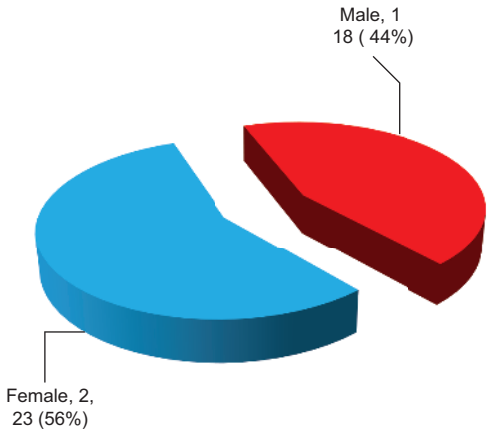

Fig.-1: *pie chart showing gender distribution of study population (n=41).*

Table-I

Preoperative primary diagnosis of the study population (n=41).

Preoperative diagnosis	Number (%)
CRHD+AS	7(17.1)
CRHD+AR	1(2.4)
CRHD+ASR	3(7.3)
CRHD+MS	11(26.8)
CRHD+MR	3(7.3)
CRHD+MSR	4(9.8)
CRHD+AVD+MVD	11(26.8)
CRHD+AVD+MVD+TR	1(2.4)
Single valve disease	29(70.73)
Aortic Valve disease	11(26.8)
Mitral Valve Disease	18(43.90)
Multiple Valve Disease,	12(29.27)

AS=Aortic stenosis; AR=Aortic regurgitation, ASR=Aortic stenosis with regurgitation; MS=Mitral stenosis; MR=Mitral regurgitation; MSR=Mitral stenosis with regurgitation; MVD=Mitral Valve Disease

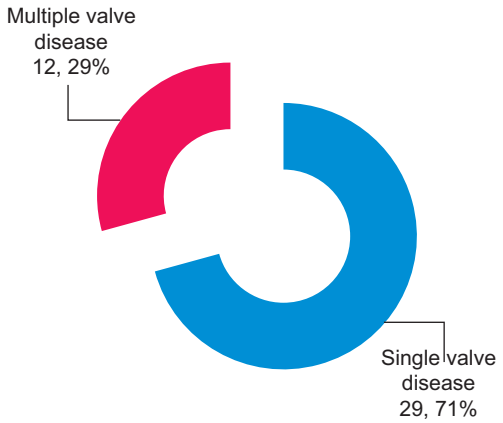

Fig.-2: *Doughnut showing number of valve involvement in CRHD needed valve replacement (n= 41).*

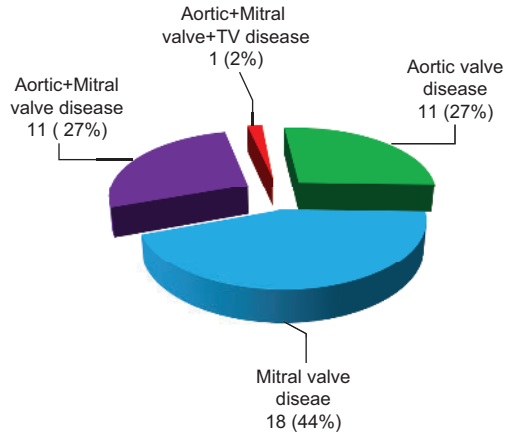

Fig.-3: *Pie chart showing pattern of valve involvement in CRHD requiring valve replacement (n= 41).*

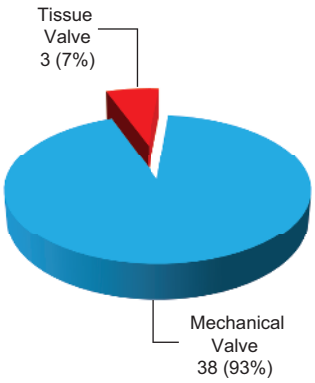

Fig.-4: *pie chart showing type of prosthetic valve used in the study population (n= 41).*

Regarding preoperative diagnosis of the patient all (41) had been suffering from chronic rheumatic heart disease. The echocardiographic diagnoses were as follows [Diagnosis, number (%)]:

Aortic stenosis, 7 (17.1%), Aortic regurgitation 1 (2.4%); Aortic Stenosis with regurgitation, 3 (7.3%); Mitral stenosis, 11 (26.8%); Mitral regurgitation, 3 (7.3%); mitral stenosis with regurgitation, 4 (9.8%); Aortic and mitral valve disease, 11 (26.8%); aortic, mitral and tricuspid valve disease, 1 (2.4%). Single valve involvement was in 29 (70.73%); Multiple valve involvement was in 12 (29.27%). (Table I)

Of the rheumatic valvular involvement mitral valve was highest in number, aortic and multiple valve involvement was similar in number.

Among all the patient 1 (2.4%) patient underwent prior PTMC. No post CMC patient was found in this series. Left atrial thrombus was found in 2 (4.9%) patients. Preoperative persistent AF was found in 7 (17.1 %). Other than 7 preoperative AF patient there were new 10 (24.39%) AF patient in postop period.

For preoperative AF patient and those having LA thrombus aspirin was given in 3(7.3%) and warfarin in 5 (12.2%) patients. For postop patient having AF aspirin was given in 6 (14.6%) and warfarin in 2 (4.9%). No heparin was used for them either preoperative or in the post-operative period.

All the patients underwent valve replacement surgery with normal preoperative CBC, liver and kidney function. In the post-operative period, there was raised serum level of bilirubin in 9 (22%), SGPT in 12 (29.3%) and creatinine in 16 (39%) patients.

The most common operation was MVR in 19(46.3) then DVR in12 (29.26) and at last AVR in 10 (24.4%) patients. Bileaflet mechanical valve was replaced in 38(92.68) and tissue valve in 3 (7.32%) patients.

After operation most of the patient was without warfarin for 2(0-4) days. The warfarin was started in most cases on 3rd (0-5th) post-operative day. Postoperative days without target INR, was 7 (4-13). Initially after operation warfarin starting dose was 5 (2.5-10) mg and to achieve target INR further dose added as 5 (0-10) mg. (Table II)

No postoperative bridging anticoagulation with heparin was done in these cases. There was no stroke or thromboembolic manifestation in these patients. One patient (2.4%) developed warfarin over anticoagulation. (Table IV) .

Table-II

Post-operative variables in the study population (n=41).

Name of the variables	Values
Postop days without warfarin, median(min-max)	2 (0-4))
Postop warfarin initiation day, median(min-max)	3 (0-5)
Postop days without target INR, median(min-max)	7 (4-13)
Initial dose of warfarin in mg, median(min-max)	5 (2.5-10)
Final dose of warfarin in mg, median(min-max)	5 (00-10)
Postop INR before Warfarin, mean (SD)	1.40 (0.27)
Postop INR after Warfarin, mean (SD)	2.87 (0.58)
Mechanical valve, mean (SD)	2.89 (0.60)
Tissue valve, mean (SD)	2.62 (0.15)

Table-III

Bridging anticoagulation, Thromboembolism and warfarin over anticoagulation.

Name of variables	Values
Bridging anticoagulation	00(00)
Postoperative stroke/ thromboembolism (Detected Clinically)	00(00)
Over anticoagulation (Detected clinically and by raised INR)	1(2.4)

Discussion:

According to ACC/AHA guidelines 2014 on the management of valvular heart disease regarding bridging anticoagulation therapy for patients undergoing intervention procedure, the recommendation is-

"CLASS I. Bridging anticoagulation with either intravenous UFH or sub-cutaneous LMWH is recommended during the time interval when the INR is sub-therapeutic preoperatively in patients who are undergoing invasive or surgical procedures with a 1) mechanical AVR and any thromboembolic risk factor, 2) older-generation mechanical AVR, or 3) mechanical MVR. (Level of Evidence: C)".[8]

Bridging therapy with UFH or LMWH can be done in patients with risk of thromboembolism during interruption of VKA or with sub-therapeutic INR to decrease thromboembolic event .It has been found in studies that with bridging anticoagulation the thromboembolic incidence is 0.62% and bleeding risk is 0.95%. Patients with mechanical MVR, tricuspid valve replacements or AVR and any risk factors for thromboembolism are at higher risk of thrombosis. These risk factors are AF, previous thromboembolism, hypercoagulable condition, older-generation mechanical valves, LV systolic dysfunction (LVEF <30%), or >1 mechanical valve.[8]

If the patient is on VKA, it is usually discontinued 2 to 4 days prior to the intervention (so that INR falls to <1.5 for major surgical intervention) and resumed when bleeding risk decreases, usually 12 to 24 hours later surgical intervention. Around 48 hours before intervention, bridging anticoagulation with intravenous UFH or subcutaneous LMWH is begun when INR is <2.0 and discontinued 4 to 6 hours (for intravenous UFH) or 12 hours (for subcutaneous LMWH) prior to the intervention. LMWH is given according to the weight-adjusted dose two times daily. Enoxaparin is used in most of the studies. After surgery bridging therapy with heparin should be individualized on the basis of thrombotic and bleeding risk.[8]

According to ESC/EACTS guidelines, 2017 it is a class I indication with level of evidence C that bridging using therapeutic doses of UFH or LMWH is recommended when VKA treatment should be interrupted.[9]

In a review article by Douketis,2011 there is a recommendation for bridging anticoagulation as follows: "In patients at high risk for thromboembolism, clinicians may consider using heparin bridging during interruption of warfarin therapy; in patients at moderate risk, clinicians may consider a bridging or no bridging approach based on an assessment of individual patient- and surgery-related factors; in patients at low risk for thromboembolism, clinicians may consider no heparin bridging during interruption of warfarin."[9]

Postoperative anticoagulation when necessary, oral anticoagulation is begun on the first postoperative day. Before the INR reaches at therapeutic level, for rapid anticoagulation usually intravenous UFH is used. Its action is monitored by aPTT (activated partial thromboplastin time of 1.5–2.0 times the control value).Low-molecular-weight heparin (LMWH) enoxaparin is mainly used and it is off-label use.[9]

There is no comparative study between early (≤24hrs) and late (>24 hrs.) initiation of weight-adjusted dose of enoxaparin as a bridging agent. In some studies it was shown that the incidence of major bleeding was 20% following major surgery and 5% after minor surgery with therapeutic dose of enoxaparin when given early. In some other studies it was shown that when enoxaparin was given late after surgery (>24 hrs. or 48-72hrs) depending on the bleeding risk, this incidence of major bleeding following major and minor surgery was 5%.[10]

In an article by Moesker et al. wrote that in 15.0 to 83.3% (mean = 41.8%) bridging therapy was practiced in each hospital. They also mentioned that AT9[The American College of Chest Physicians' Antithrombotic Therapy and Prevention of Thrombosis, Ninth Edition guideline (AT9) published in 2012 which contains risk assessment by classifying patients in low, moderate or high thromboembolic risk].They concluded that 31.5% of patients were noncompliant to AT9 for bridging anticoagulation. To explain practice of bridge therapy the individual risk factors were superior to AT9 risk factors. The hospitals were following AT9 guidelines heterogeneously. They recommended for further research on this issue. [11]

Most of the cardiac surgeons and cardiac hospitals of our country do not follow AT9 recommendations and post-operative bridge therapy. Their outcomes are reasonably good.

Cardiac surgery is a major surgical procedure which is done under cardiopulmonary bypass (CPB). Intra venous unfractionated heparin (UFH) is used for systemic anticoagulation before establishment and initiation of CPB. Although at the end of operation the action of heparin is reversed by protamine sulphate, there are factors related to CPB, operation itself and others which predispose the patients to higher post-operative bleeding risk. Use of heparin in the early post-operative period is associated with higher postoperative bleeding risk and chance of reopening and increased duration of hospital stay.

The findings of our study suggest that post valve replacement without bridging anticoagulation does not cause any thromboembolic event. So it is not mandatory to use bridging anticoagulation after valve replacement surgery.

Middle aged peoples underwent valve replacement surgery with increased number of female patients. Almost all patients had been suffering from chronic rheumatic heart disease. Total number of single valve involvement was greater than multiple valve involvement. Patient with mitral valve disease was higher in number than aortic valve and double valve involvement. Few patients received preoperative antiplatelet and warfarin but none of them received heparin as a bridging anticoagulation preoperatively. Regarding operative procedure mitral valve replacement was the highest in number. The replacement device was mostly mechanical heart valve AVR and MVR patient had almost equal cross clamp (XCT) and extracorporeal circulation time (ECCT) or cardiopulmonary bypass time. In case of DVR patients these times were longer because there was two valve replacement at the same operative procedure. Patients were maintaining a low level of INR immediately after operation and maintained for few days without warfarin and after giving warfarin till INR achieved at therapeutic level. No post-operative bridging anticoagulation was given to any of these patients. No thromboembolic manifestation occurred during this low level of INR and till the target INR was achieved few days after warfarin was given. There was very less incidence of warfarin over anticoagulation. Incidence of new onset of postoperative AF was higher in number than preoperative AF number without any incidence of thromboembolism.

Interestingly none of the patient developed any thromboembolic event in the postoperative period after valve replacement surgery despite not using bridging anticoagulation. In a review article of Yoshio Misawa, it is mentioned that all valve related complications were 0.7-3.5% per patient-year and the thromboembolic event rate was approximately 1% per patient-year.[12]It was also noticed that in the post-operative period before warfarin was given the mean (SD) of international normalized ratio (INR) was 1.40 (0.27). Literature search shows that no such estimation of INR within available online search. There was change in blood biochemistry report in terms of serum bilirubin SGPT and creatinine level which are indicative of hepatic and renal dysfunction. In this study it was found hepatic and renal dysfunction at a rate 0f 29% and 39%. These were in mild elevation of values greater than normal level. All were reversible. In a review article by Tan CW et al., where they mentioned that the incidence of hepatic and renal dysfunction was 47% and 7-13% it is transient. This dysfunction is associated with duration of Cardiopulmonary bypass. In the same article renal dysfunction was noted 7-13% and 1-1.5% patient needed some form of dialysis.[13] There was new onset of postoperative AF in 24% patients in this study group. This incidence of AF was a cumulative value for AVR, MVR and DVR in the

post-operative period. Bramer et al. found incidence of post-operative AF in MVR patient over a median follow-up of 3.1 year was 42%.[14] Troels H et al. mentioned in their article that "However, after SAVR and TAVI, the incidence of new-onset atrial fibrillation (NOAF) is 31%-64% and 4%-32%, respectively. NOAF is independently associated with adverse events such as stroke, death, and increased length of hospital stay".[15]

Postoperative days without warfarin, warfarin initiation days, days to reach target INR and postoperative bleeding complications were studied. Our study results are very close to the results of Guglielmett et al. in these respects except the post-operative complications.[16] The post-operative lower level of INR might be responsible for such kind of effect on the occurrence of thromboembolism.

The cardiopulmonary bypass causes systemic inflammatory response syndrome in the body. This causes some beneficial and some harmful effect in the human body through some inflammatory mediators which produces systemic dysfunction by various mechanisms. Hepatocellular malfunction is produced by TNF-á and IL6.[17] Salmane et al. wrote in their article that there are few patients who survived more than 30 years without oral anticoagulation after aortic valve replacement.[18] Mutation in the genes responsible for production of coagulation factors can elucidate the reason for long term survival without anticoagulation as described by Gül et al.[19] Certain mechanical valve can be maintained at low level of INR without any significant thromboembolic event like On-X valve. Our implanted valve may have similar effect. "International normalized ratios were safely maintained at 1.5 to 2.0 in high-risk patients, without differences in mortality or thromboembolic complications. (Randomized On-X Anticoagulation Trial [PROACT]; NCT00291525)".[20] St Jude valve has low thrombogenecity.[21] Brilliant outcome was also found by Van Nooten G V et el. in case of AVR with ATS mechanical valve patients having regular sinus rhythm with good ventricular function at a lower (1.5-2) INR level.[22] In this study post-operative INR without warfarin was very close to their lower level. Here in this cardiac center both the above-mentioned valves were replaced in the majority of the cases. This is the most likely fact which gave us such kind of result.

Conclusion:

This study shows that valve replacement surgery patients without concomitant bridging anticoagulation with heparin do not suffer from any thromboembolic and bleeding complications even at lower level of INR. This study also shows that single and multiple valve (both mechanical and tissue valve) have the same in hospital outcome in relation to thromboembolism and bleeding. Further study in this respect is needed with incorporating multiple centers, with increased sample size, individual procedure and valve type with long term follow up and RCT.

Conflict of Interest - None.

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