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Thromboembolic and Bleeding Complications following St. Jude Medical Valve Replacement

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Abstract

Introduction: The purpose of this study was to investigate the thromboembolic and bleeding complications following St. Jude Medical (SJM) mechanical heart valve replacement, maintaining an optimal target International Normalized Ratio (INR) between 2.5 to 3.5 in a rheumatic population.

Methods: Data from 217 patients following mitral valve replacement (MVR; n=58), aortic valve replacement (AVR; n=68), and combined aortic and mitral valve replacements (DVR; n=91) with SJM valve between January 2013 and December 2017 were analyzed, covering a total follow-up period of 420.14 patient-years. All complications were registered prospectively.

Results: Fifty-two thromboembolic events were documented (DVR: n=22; MVR: n=15; AVR: n=15). Major bleeding events requiring hospitalization or transfusion occurred in 7 patients (AVR: n=1; MVR: n=2; DVR: n=4). Twenty-five (11.5%) patients had prosthetic heart valve thrombosis. Eighteen (72%) patients had successful treatment, 5 (20%) patients had partially successful treatment, and 2 (8%) patients had unsuccessful thrombolysis. Five (2.3%) patients required reoperation due to failed thrombolysis of stuck valve (MVR: n=3; Aortic valve of DVR group; n=2). Significant variability of INR values were observed in DVR and AVR groups (DVR: p=0.001; AVR: p=0.04) and accounted for higher mortality, thromboembolism and bleeding complications. The actuarial survival at 68 months was 70.7 ± 0.01% (MVR), 66.9 ± 0.1% (AVR) and 59.6% ± 0.22% (DVR).

Conclusion: We conclude that despite attempting to maintain a target INR, there exists a statistically significant wide variability of warfarin effect among patients undergoing combined aortic and mitral valve replacements and isolated AVR, thereby predisposing then to a greater risk of thromboembolic and bleeding complications.

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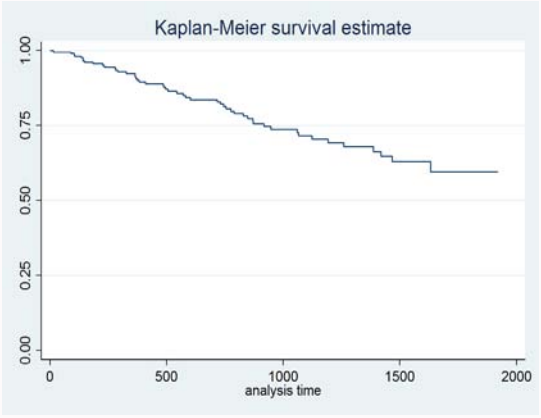
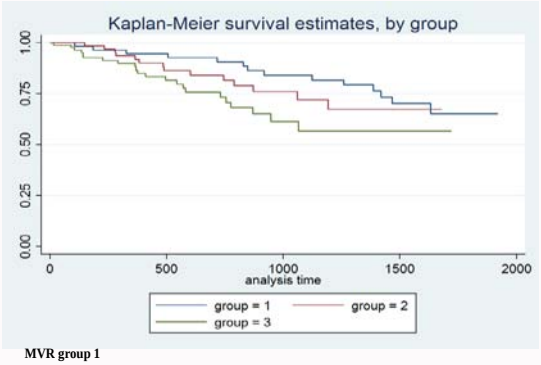
Introduction

Thromboembolic events and anticoagulant-related bleeding continue to account for 70-75% of all complications after mechanical heart valve replacement [1,2]. The risk of a major thromboembolic event without anticoagulation is around 4 per 100 patient years [1-4]. Isolated administration of aspirin decreases the risk of embolism by about 40%. Coumarin therapy reduces the incidence of major embolism by approximately 75% to an annual risk of about 1% [3]. Due to their inherent thrombogenecity, mechanical cardiac prosthetic valves necessitate life-long anticoagulation [1,2]. More effective prevention of thromboembolic events expected by a more intensive anticoagulation has to be weighed against an increase in bleeding complications [5]. The optimal intensity of oral anticoagulation is characterized by the lowest rate of both thromboembolic and bleeding complication [2]. The thromboembolic and bleeding hazard is not only related to the type of prosthesis implanted but to a variety of concomitant patient-related risk factors [6]. Published literature on the recommended target levels of oral anticoagulation to prevent both thromboembolic events and bleeding complications is limited and controversial [1-6]. Our second hypothesis is that the therapeutic intensity of oral anticoagulation may not be the same in the Western and Indian population. With this background, we evaluated all St. Jude mechanical valve recipients in our institution by a single surgeon (corresponding author) to identify the risk factors for complications that occur with warfarin therapy.



Time	Event free survivors (n=217)	Survival function (95% confidence limits)
1 YEAR	160	0.91(0.86-0.94)
2 YEAR	108	0.82(0.76-0.87)
3 YEAR	64	0.71(0.63-0.78)
4 YEAR	37	0.63(0.53-0.72)
5 YEAR	4	0.60(0.48-0.70)

Figure 1: Overall Event free survival of the study group.



MVR group 1

Time	Event free survivors (n=58)	Survival function (95% confidence limits)
1 YEAR	51	0.95(0.84-0.98)
2 YEAR	44	0.91(0.79-0.96)
3 YEAR	36	0.84(0.71-0.92)
4 YEAR	24	0.70(0.54-0.82)
5 YEAR	4	0.65(0.47-0.79)

AVR group 2

Time	Event free survivors(n=68)	Survival function (95% confidence limits)
1 YEAR	53	0.92(0.82-0.97)
2 YEAR	34	0.84(0.72-0.92)
3 YEAR	18	0.72(0.55-0.83)
4 YEAR	8	0.67(0.49-0.80)
5 YEAR	1	0.67(0.49-0.80)

DVR group 3

Time	Event free survivors(n=91)	Survival function (95% confidence limits)
1 YEAR	56	0.88(0.79-0.94)
2 YEAR	31	0.73(0.60-0.83)
3 YEAR	10	0.57(0.39-0.71)
4 YEAR	5	0.57(0.39-0.71)
5 YEAR	1	0.57(0.39-0.71)

Figure 2: Comparative Event free survival for MVR, AVR and DVR group of patients.

Patients and Methods

Selection criteria

Decision to perform surgery was made by physicians and was based on clinical, ecocardiographic and angiocardiographic criteria .Intraoperative transesophageal echocardiography was performed on all patients using a Hewlett-Packard Sonos 1500 or 5500 ultrasound system (Hewlett-Packard Co, Andover MA). The patients were eligible for study inclusion if they had Aortic Valve Replacement (AVR), Mitral Valve Replacement (MVR), or combined aortic and mitral valve replacement (DVR) with St. Jude Medical (SJM) cardiac valve (St. Jude Medical; St. Paul, MN) prosthesis. Patients with previous or concomitant coronary bypass surgery, reconstructive surgery of another cardiac valve, emergency operation, or valve replacement for infective endocarditis were included. Main exclusion criteria were contraindications for treatment with Coumarin, history of or current evidence of coagulation abnormalities, pre-existing anticoagulation therapy with a given intensity for indications unrelated to valve replacement, and/or implantation of a valve other than SJM prosthesis.

Patient characteristics

Institutional review board approval for this study protocol was available and informed consent was obtained from all patients. Two-hundred and seventeen consecutive patients undergoing prosthetic heart valve replacement with a St. Jude mechanical prosthesis from January 2013 to December 2017 operated by a single surgeon in All India Institute of Medical Sciences, New Delhi, India were included in the study. A total of 217 patients were included in the analysis: MVR: n=58, AVR: n=68, and Double Valve Replacements (DVR): n=91. Their demographic and clinical profiles are depicted in (Table 1). The average age was highest for patients undergoing isolated AVR (33.6 ± 14.6 years). The most common cause of valvular disease for the MVR, AVR and DVR groups was rheumatic heart disease (91.4%, 61.7% and 98.9%, respectively). There was male predominance in AVR and DVR groups compared to the MVR (88.2% and 79.1% vs. 55.2%; p=0.001). Dyspnoea on exertion was the predominant symptom and was present in majority patients. Two-hundred and five patients (94.5%) were in NYHA functional class III or IV. Congestive Heart Failure (CHF) was present in 18(8.5%) patients. Although the majority of patients in all three groups were in sinus rhythm at the time of the operation (79.8% overall), approximately one-third of the MVR (37.9%) and DVR (24.2%) recipients had preoperative atrial fibrillation as compared with 2.9% of the patients undergoing AVR. The preoperative Left Ventricular (LV) ejection fraction was 53.61 ± 8.00 for all patients and did not differ significantly by the valve location (p = 0.88). 77.5% of patients undergoing isolated MVR (n=45) and 82.4% of patients undergoing DVR (n=65) had either posterior, or total chordal preservation of the mitral valve. The technique of preservation of chordopapillary apparatus was made after intraoperative visual assessment of the mitral valve. The patients were divided in three groups: group1-MVR with complete excision of native valve with sub valvular apparatus (nil preservation), group2-MVR with preservation of the posterior chordo-papillary apparatus, group 3-MVR with complete preservation of chordae and papillary muscle.

Valve pathology

Seventy-three (33.6%) patients had stenotic lesion and sixty-two patients had regurgitant lesion (28.6%), while eighty-two patients (37.8%) had mixed lesions. Stenotic lesion was more common in patients undergoing MVR (51.7%), regurgitant lesion in patients undergoing AVR (45.6%), while mixed lesion were more prevalent in patients undergoing DVR (54.9%). Total chordal preservation was possible in 65% patients undergoing DVR and 55% in patients undergoing MVR. Subtotal chordal preservation was done in 18 % patients undergoing DVR and 13 % in patients undergoing MVR. Almost half the valves 105(48.39%) were severely calcified. Severe calcification was more prevalent in patients undergoing AVR (50%)

Table 1: Demographic details of the study group.

Profile	MVR	AVR	DVR	TOTAL	P VALUE
No of patients,n (%)	58(26.7)	68(31.3)	91(41.9)	217	
Age in years(mean± SD)	30.20±12.10	33.6±14.6	30.1±10.4	31.25±12.36	0.16
Height in cm (mean ± SD)	153±13.8	161.6±11.1	160.8±11.9	159.06±11.95	**0.001**
Weight in kg (mean ± SD)	45.7±10.3	55.05±11.13	49.73±10.89	50.34±11.36	**0.001**
Male population n(%)	32(55.2)	60(88.2)	72(79.1)	164(75.58)	**0.001**
Etiology					
Rheumatic	53(91.4)	42(61.7)	90(98.9)	185(85.25)	**0.001**
Calcific	1(1.72)	12(17.65)	1(1.10)	14(6.45)	
Other	4(6.90)	12(17.65)	0	16(7.37)	
Stuck	2(2.94)	0	0	2(0.92)	
Valve pathology Stenosis	30(51.72)	21(30.88)	22(24.17)	73(33.64)	0.16
Regurgitation	12(20.68)	31(45.58)	19(20.87)	62(28.57)	
Mixed	16(27.58)	16(23.52)	50(54.94)	82(37.78)	
CCF	5(8.62)	2(2.94)	11(12.09)	18(8.29)	0.1
AF	22(37.93)	2(2.94)	22(24.19)	46(21.20)	**0.001**
LA Clot	7(12.07)	0	7(7.69)	14(6.45)	**0.019**
CT Ratio(mean ± SD)	0.63±0.07	0.72±0.08	0.62±0.07	0.65±0.51	0.4
LAES(mean ± SD)	49.47±10.77	40.68±12.00	50.08±10.06	48.48±11.03	**0.005**
LV Function%(mean ± SD)	53.87±6.21	53.82±8.42	53.29±8.73	53.61±8.00	0.8
Preoperative NYHA class					
II	3(13.54)	4(5.88)	5(5.49)	12(5.52)	0.4
III	3(13.63)	43(63.23)	65(71.42)	147(67.74)	
IV	16(72.72)	21(30.88)	21(23.07)	58(26.72)	
Chordal preservation					
Nil	13(22.41)	68(98.53)	16(17.58)	96(44.24)	**0.001**
Posterior	13(22.41)	0	16(17.58)	30(13.82)	
Total	32(55.17)	0	59(64.84)	91(41.94)	
LAA Ligation	16(27.59)	0	31(34.07)	47(31.54)	0.5
Calcification					
No	12(20.69)	18(26.47)	17(18.68)	47(21.66)	0.6
Mild	19(32.76)	16(23.53)	30(32.97)	65(29.95)	
Severe	27(46.55)	34(50)	44(48.35)	105(48.39)	
AOXC(mean ± SD)(min)	49.32±15.13	57.45±19.00	85.90±12.86	67.21±22.46	**0.001**
CPB(mean ± SD))(min)	76.32±17.96	84.5±28.66	115.42±20.16	95.28±28.52	**0.001**
PT/INR AT DIS	2.40±0.60	2.29±0.50	2.42±0.65	2.37±0.59	0.4

Data in bracket denote percentage, data denotes mean standard deviation, p<0.05 suggests the difference is statistically significant.
CCF=congestive cardiac failure, AF=atrial fibrillation, LA =left atrium, CT=cardiothoracic ratio, LV= left ventricle, LAA= left atrial appendage, AOXC=aortic cross clamp time, CPB= cardiopulmonary bypass time

while 48% patients undergoing DVR and 47% patients undergoing MVR were severely calcified.

Surgical technique

All operations were performed by single surgeon; standard Cardio Pulmonary Bypass (CPB) was established using membrane oxygenator and moderate hypothermia (28°C to 32°C). Cold blood cardioplegia using St. Thomas II solution (1:4) was used for myocardial protection and topical cooling was done using cold saline. After debriding the valve annulus, the prosthesis was secured using interrupted sutures of 2-0 Ethibond (Ethicon, Cincinatti, OH) reinforced with polytetrafluroethylene pledgets in mitral position. Sutures were carefully placed from above and through the annulus so that the valve annulus would be everted when the sutures were tied, thus inserting the prosthesis in an intra-annular position. MVR was performed with the valve placed in the antianatomic position and AVR with one of the pivot guards positioned against the ventricular septum and the other between the left coronary and non-coronary cusps. The mitral sub valvular apparatus was left intact to the maximum extent possible and partial or subtotal chordal preservation was done if severe calcification of sub valvular deformity was present. The sub valvular apparatus of the mitral valve was preserved whenever technically feasible. Valve sizes for the 3 groups ranged from 19 to 33 mm (Table 2). The mean aortic cross-clamp time was 67.21 ± 22.46

Table 2: Distribution of the sizes of the St Jude mechanical prosthesis in three groups of patients.

Valve sizes (mm)	Mitral valve replacement (Number)	Aortic valve replacement (Number)	Aortic and mitral valve replacement (Aortic number)	Aortic and mitral valve replacement (Mitral number)
19	-	8	10	-
21	-	45	74	-
23	-	15	4	-
25	10	-	3	5
27	14	-	-	23
29	27	-	-	40
31	6	-	-	21
33	1	-	-	2

Table 3: Comparative data of short-and long-term postoperative outcome of the study group.

Profile	Mitral valve replacement	Aortic valve replacement	Aortic and mitral valve replacement	Total	P value
Number (%)	58(26.7)	68(31.3)	91(41.9)	217	
Deaths	9(14.24)	10(10.95)	17(10.81)	36	**0.04**
Early(<30 Days)	2(5.55)	1(2.77)	6(16.67)	9	
Late	7	9	11	27	
Valve related death	3	4	5	13	
Other causes	4	5	6	15	
Events	14 (19.83%)	14(15.39%)	22(14.78%)	50	**0.05**
Thromboembolic events	2	8	3	13	
Stuck Valve	8	5	12	25	
Repeated Stuck Valve	2	0	3	5	
Bleeding Events	2	1	4	7	
Patient follow up(months) (mean ± SD)	28.44±16.92	40.3 ±17.52	21±15	28.81±22.8	
Lost to follow up	2(3.44)	1(1.47)	3(3.29)	6(2.76)	

p <0.05 statistically significant

minutes and the CPB time was 95.28 ± 28.52 minutes.

Mitral valve replacement

The mitral valve was analysed intra operatively in a systematic manner to allow the optimal techniques to be chosen. The sub valvular apparatus was preserved using the technique described by Miki and colleagues [7]. The technical details of mitral valvular total and posterior chordal preservation, annular decalcification and reconstruction have already been mentioned in our earlier publication [8]. Extensive scarring, shortening, and thickening of the chordopapillary apparatus precluded the use of artificial Gore-Tex sutures (WL Gore and Associates, Flagstaff, AZ) to resuspend the remnant papillary muscle base to the mitral annulus. The left atrial appendage was routinely ligated. No surgical procedure was performed for atrial fibrillation.

Aortic valve replacement

The leaflets of the aortic valve were excised to the level of the annulus and the annulus was thoroughly debrided of any calcium, if present. Calcification was dealt with by excision of the calcified segment, shaving off the calcified leaflet margin, squeezing or milking out the calcific debris from the annulus. Aortic valve was replaced using St. Jude mechanical prosthesis placing the pivot guard perpendicular to the non-coronary cusp.

Postoperative Studies

These included three-monthly clinical examinations, electrocardiograms, chest radiographs, cinefluoroscopy and echocardiography. The functional class at follow-up was noted. Results were reported according to prescribed criteria [9]. At each visit, a short history was taken and patients were asked about thromboembolic or bleeding complications, other diseases, and hospital admissions. Prothrombin Time (PT) was measured and the results were expressed in terms of the International Normalized Ratio (INR). All patients received warfarin and aspirin (100 mg/day) for anticoagulation to maintain INR between 2.5 to 3.5. The warfarin dose was regulated by the surgical team while the patient is in the hospital and by the referring physician after the patient was discharged.

Follow-up

Patients were followed up in the outpatient department as well as through telephone and mail. All valve-related complications were identified according to the guidelines for reporting morbidity and mortality after cardiac valve operations [9]. Apart from preoperative investigation each patient was followed up with cinefluoroscopy before discharge, within first three months then at least at 6-months interval. Regular PT/INR was measured in every 3-monthly follow-up. People coming from far areas were asked to get their PT/INR checked every 3 monthly and to come for follow-up every 6 months. They were asked to report immediately if any complications occurred

Echocardiographic Studies and Measurements

Transthoracic two-dimensional (2D), color flow and Doppler echocardiography was performed using a Hewlett-Packard-Sonos-5500 with 2.7 or 3.5 MHz transducer. Prosthetic valve function was assessed on 2D apical four-chamber view, and M-mode

Table 4: Univariate associations with operative and late deaths.

Variables	Alive (Number, %)	Dead (Number, %)	P value
Age >30 years	88(81.5)	20(18.5)	0.3
Left ventricular ejection function <0.55	67(75.3)	22(24.7)	**0.007**
Aortic cross clamp time > 50 min	91(82.7)	19(17.3)	0.5
Cardiopulmonary bypass time >75 min	96(83.5)	19(16.5)	0.6
Cardiothoracic ratio >0.55	156(85.3)	27(14.7)	**0.08**
NYHA >II	55(79.7)	14(20.3)	0.2
Left atrial diameter >50 mm	68(81.9)	15(18.1)	0.4
International normalized ratio >2.5 at discharge	64(87.7)	9(12.3)	0.5
Usage of Ecosprin	155(85.6)	26(14.3)	0.3
Preoperative Warfarin	19(76)	6(24)	0.3
Calcification			
Absent	38(80.8)	9(19.1)	0.8
Moderare	54(83.1)	11(16.9)	
Severe	89(84.7)	16(15.2)	
Atrial fibrillation	38(20.9)	8(22.2)	0.9
Congestive heart failure	11(6.1)	7(19.4)	**0.008**
Left atrial clot	11(6.1)	3(8.3)	0.6
Emergency surgery	178(98.3)	33(91.6)	**0.02**
Chordal preservation			
Nil	81(44.7)	15(41.6)	0.9
Posterior	25(13.8)	5(13.9)	
Total	75(41.4)	16(44.4)	
Left atrial appendage ligation			
No	85(69.1)	17(65.4)	0.8
Yes	38(30.9)	9(34.6)	

Table 5a: Relationship between the indexed prosthetic valve size and mortality (early and late) in the study.

Variables	Valve	Alive	Death	p value
BSA/MVR SIZE	MVR	0.049±0.006	0.053±0.010	0.9
	DVR	0.005±0.006	0.05±0.006	0.1
BSA/AVR SIZE	AVR	0.07±0.008	0.07±0.012	0.7
	DVR	0.07±0.009	0.06±0.007	0.07

Table 5b: Relationship between the indexed prosthetic valve size and postoperative events (early and late) in the study.

Variables	Valve	Nil event	Supraventricular tachycardia	Thromboembolism and bleeding	p value
BSA/AVR	AVR	0.07±0.008	0.08±0.007	0.06±0.005	0.7
	DVR	0.07±0.008	0.07±0.011	0.06±0.008	0.5
BSA/MVR	MVR	0.05±0.006	0.04±0.002	0.04±0.006	0.1
	DVR	0.05±0.006	0.05±0.010	0.04±0.007	0.2

parasternal long-axis view. Preoperative studies were performed within 7 days before surgery. Postoperatively, all survivors were followed echocardiographically at the time of follow-up.

Statistical Analysis

Statistical analysis was performed using Stata 11.0 software (College Station, Texas, USA). All variables were defined in compliance with the guidelines established by The American Association for Thoracic Surgery and the Society of Thoracic Surgeons [9]. Variables analyzed included valvular thromboembolism (including episodes of embolism, transient ischemic attacks, and valve thrombosis), anticoagulant-related haemorrhage (defined as episodes resulting in death, stroke, surgery, hospitalization, or transfusion), prosthetic heart valve thrombosis and valve-related mortality. Variables were compared between groups by unpaired *t* tests /one way ANOVA, Fisher exact test, or X^2 analyses as appropriate. Life table methods were used to analyze actuarial freedom from death and thromboembolic and bleeding events. Survival curves were compared between groups by the log rank test for censored survival data. Repeated measures ANOVA were used to compare the difference in PT/INR values over

period of follow up among the groups. Statistical significance was set at p<0.05.

Results

Survival

Overall, there were 9 (4.1%) early and 27 (12.4%) late deaths. In the MVR cohort, there were 2 operative and 7 late deaths (3 valve -related, 2 cardiac and 2 sudden or unknown).In the AVR group, there were 1 operative and 9 late deaths (4 valve related, 2 cardiac and 3 non cardiac) (Table 3). In the DVR group, there were 6 operative and 11 late deaths (5 valves- related 3 cardiac and 3 non-cardiac). The overall hospital mortality was lowest for the patients undergoing an isolated AVR (2.7%) followed by those having MVR (5.5%) and highest for the DVR group (16.7%).

Follow-up was 97.3% complete (range 1-68 months) and yielded 420.14 patient-years of data with mean follow-up of 28.81 months (standard error ± 22.8 months). The closing interval for this study was 6 months. The actuarial survival at 68 months was 70.7 ± 0.1% (MVR), 66.9 ± 0.1 %(AVR) and 59.6 ± 0.22% (DVR), respectively One-year survival was highest for patients who had MVR (100%) followed by survival for AVR (94% ± 3%) and DVR (88% ± 3%) groups respectively. Cox proportional hazard analysis revealed preoperative NYHA class 4, poor left ventricular function (EF <0.40), cardiothoracic ratio > 0.55, presence of preoperative CHF at presentation and emergency surgery were predictors of late death (Table 4).

Reoperations

Two patients with isolated AVR were re operated due to thrombosed aortic prosthesis. Three patients with isolated MVR were re operated due to thrombosed mitral prosthesis. There were no structural deteriorations.

Valve-related complications

In this study, at 5-years only 59 ± 5% patients were free from thromboembolism and bleeding events. The actuarial freedom from thromboembolism and bleeding events and linearized event rates of thromboembolism are shown in (Figures 1,2) respectively.

Thromboembolic complications

In the AVR cohort, 8 patients had 15 total thromboembolic episodes (cerebrovascular accidents: n=4; transient ischemic attacks: n=4; systemic embolism: n=2; prosthetic valve thrombosis: n=5). In the MVR cohort, 2 patients had 15 thromboembolic episodes (cerebrovascular accident: n=1; transient ischemic attack: n=1; systemic embolism: n=8; prosthetic valve thrombosis: n=5). In the DVR cohort, 3 patients had 22 thromboembolic episodes (cerebrovascular accidents: n=2; transient ischemic attacks: n=2; systemic embolism: n=3; valve thrombosis: n=7; recurrent thrombosed mitral prosthesis: n=8).

Bleeding Events

Major bleeding events requiring hospitalization or transfusion occurred in 7 patients (AVR: n=1; MVR: n=2; DVR: n=4). In the AVR group, one patient had intra-cerebral bleeding. In the MVR group, 1 patient had gastrointestinal bleeding and 1 patient had cerebral bleeding (1 fatal). In the DVR group, 1 patient had lower gastrointestinal bleeding and 2 patients had cerebral bleeding, (1 fatal) while 1 patient had massive epistaxis.

Prosthetic Valve Endocarditis

None of the patients in the study group developed prosthetic valve endocarditis.

Valve-Related Mortality

Out of 27 late deaths, 12 were valve related (preceded by valve-related complications while 15 died due to other reasons). In the AVR cohort, 3 patients died of valve-related causes (systemic embolism: n=2; prosthetic valve thrombosis: n=1) and 5 patients died of unknown causes. In the MVR group, 3 patients died of valve-related causes (systemic embolism: n=1; massive intra-cerebral bleeding: n=1; and 4 patients died of unknown causes). In the DVR cohort, 5 patients died of valve-related causes (systemic embolism: n=2; thrombosed mitral prosthesis: n=2; intra-cerebral haemorrhage: n=1) and 6 patients died of unknown causes. Overall, freedom from valve-related mortality was 64.36% ± 7.71% at 5 years. Actuarial freedom from valve-related mortality was 70.76 ± 10.92%, 66.95 ± 12.22%, 59.67 ± 14.18% at 5 years in the AVR, MVR and DVR groups respectively.

Valve related morbidity

Bleeding complications: Evacuation of Sub Dural Hematoma (SDH) was done in 3 patients; out of them 2 improved post-surgery and are on regular follow up, three patients had small SDH in the immediate post-operative period. These patients were managed without administering any anticoagulation or antiplatlet drugs for a period of 3 weeks following surgery. Subsequently they had been kept on warfarin and aspirin (100 mg / day) maintaining INR between 2.5-3.0. There are no neurological deficits in the follow-up. The 3 patients who had intra cerebral hemorrhage died within 40 days. Two patients with upper gastrointestinal bleeding due to gastric erosion and one patient with lower gastrointestinal bleeding were managed medically.

Prosthetic heart valve thrombosis: In this study patients with prosthetic valve thrombosis (n=25) were initially treated with the thrombolytic agents. Nineteen (76%) patients had restricted leaflet motion involving both leaflets and 6 (2.7% patients had immobility of one leaflet. The treatment was considered successful if the prosthetic valve leaflets resumed > 90% of mobility. Eighteen (72%) patients had successful treatment and 5 (2.3%) patients had partially successful treatment. Two (8%) patients with unsuccessful thrombolysis underwent redo-MVR using SJM. During follow up, 5 patients had cinefluoroscopic evidence of recurrent prosthetic heart valve thrombosis. They also received either streptokinase or urokinase or heparin alone on an individual basis. Of these 5 patients, 3 had partial improvement and are awaiting redo MVR; 2 patients with recurrent thrombosis died of progressive CHF and massive gastrointestinal bleeding respectively. Older age, longer CPB time, presence of atrial fibrillation or LA clot were not predictors of long-term survival for any group (Table 4). There was no statistically significant correlation of patient prosthesis mismatch with mortality as well as postoperative events (Table 5). When the serial PT/INR values were analyzed there was significant variability in the INR values in AVR and DVR groups (AVR p=0.04, DVR p=0.001). Variability was observed in the whole group between the six values of PT/INR (P= 0.02). On comparing the three groups separately it was observed that the patients who died had more fluctuations in PT/INR values (p value not statistically significant). In the DVR subset even the patients who are alive had high fluctuation in PT/INR values; this may be one of the reasons of finding more events in this group. Patients taking warfarin preoperatively (p =0.03), had significant risk of developing thromboembolic and bleeding complications. Patients with preoperative AF (p=0.08) and

Table 6a: Relationship between events and patient variables of the study group.

Variables	Nil event	Supraventricular tachycardia	Thromboembolism and bleeding	p value
Age >30 years	83(76.8)	13(12.0)	12(11.1)	0.2
Left ventricular ejection fraction < 0.55	66(74.1)	11(12.3)	12(13.4)	0.4
Aortic cross-clamp time > 50 min	87(79.0)	11(10)	12(10.9)	0.5
Cardiopulmonary bypass time >75 min	91(79.1)	12(10.4)	12(10.4)	0.3
Cardiothoracic ratio >0.55	143(78.1)	14(7.6)	26(14.2)	0.2
NYHA >II	49(71.0)	11(15.9)	9(13.0)	0.8
Left atrial diameter >50 mm	63(78.3)	7(8.4)	11(13.2)	0.8
International normalized ratio >2.5 at dis	58(79.4)	8(10.9)	7(9.5)	0.4
Uses of Ecosprin	140(77.3)	16(8.8)	25(13.8)	0.4
Preoperative warfarin therapy	18(72)	0	7(28)	**0.04**
Calcification				
Nil	40(85.1)	2(4.3)	5(10.6)	0.3
Moderate	49(75.3)	4(6.2)	12(18.4)	
Severe	78(74.2)	14(13.3)	13(12.3)	

Table 6b: Relationship between events and patient variables of the study group.

Variables	Nil event	Event	P Value
Atrial fibrillation	31(18. 6)	15(30.0)	0.08
Congestive heart failure	17(10.2)	1(2.0)	0.06
Left atrial clot	10(5.9)	4(8.0)	0.6
Emergency surgery	161(96.4)	50(100.0)	0.2
Chordal preservation			
Nil	79(47.3)	17(34.0)	0.07
Posterior	25(14.9)	5(10.0)	
Total	63(37.7)	28(56.0)	
Left atrial appendage ligation			
No	77(68.1)	25(69.4)	0.8
Yes	36(31.8)	11(30.5)	

those with chordal preservation (p=0.07) had more incidences of events. (But was not statistically significant) (Table 6).

Discussion

The major findings of this investigation are:

1. Absence of structural deterioration of the St. Jude mechanical valve prosthesis in both aortic and mitral position. 2. Preserved (particularly complete) chordopapillary apparatus did not predispose patients with MVR or DVR to an increased risk of prosthetic valve thrombosis.

3. There exists a wide fluctuation of INR values despite attempting to maintain a therapeutic INR between 2.5 and 3.5 adjusting the warfarin dosage, in the absence of administration of interactive drugs. The fluctuations of INR values are more profound among patients undergoing combined aortic and mitral valve replacements followed by that undergoing isolated aortic valve replacement.

4. Bleeding and thrombotic complications are more pronounced among patients undergoing combined aortic and mitral valve replacements. Although the INR values were abnormal (high/low) at the time of thromboembolic/ hemorrhagic events, the fluctuations were profound among patients undergoing combined aortic and mitral valve replacements, thus predisposing them to recurrent thromboembolic/ hemorrhagic events.

Despite central flow design of St Jude Medical mechanical prosthetic valve, thromboembolism and anticoagulant-induced haemorrhage after surgery continue to account for 75% of all valve-related complications [4,7-18]. These complications occur most frequently during the first 6 months after operation. The risk then becomes low where it remains constant for years [19-21]. It is important to achieve an anticoagulation balance which prevents both adverse thromboembolic events and bleeding [22-24]. There can also been variability of warfarin effects which when out with a predetermined 'target' INR range is associated with higher risk of valve-related thromboembolic or haemorrhagic mortality[22-24]. In the past 20 years, several investigators have attempted to identify an 'optimal' target INR for patients with mechanical heart valves. Unfortunately, the reported results varied greatly because of differences in patient selection, definitions of end points, and methods of follow-up and statistical analysis, type, intensity, and efficacy of anticoagulation therapy [25]. Besides, with a scarcity of large randomized trials, most guidelines are based on cohort studies and case series, a fact acknowledged by the groups themselves. McGoon DC and colleagues examined 51 reports on this subject and concluded that none of these gave complete information [26]. Consequently, from the information of the individual studies, it is hardly possible to establish the risks of thromboembolism and bleeding with any reliability. Assessing the influence of factors such as position and model of the valve is even more difficult. The patient profile and the increased incidence of rheumatic fever population make a study in Indian population unique. Risk levels in conjunction with on-going anticoagulation therapy are considerably higher in cases in which International Normalized Ratio (INR) values fluctuate strongly. Several investigators have demonstrated that at the time of anticoagulation related events, as many as 60% of the coagulation values controlled are not within the therapeutic range [10,11]. In this study, we also found a wide variation in INR values, possibly accounting for high incidence of these events. In our study, 5-year freedrom from thromboembolism and bleeding events was 59.5 ± 5.6%. The actuarial 5-year freedom from thromboembolic events was 65.3 ± 8.23%, 67.3 ± 8.1% and 56.72 ± 8.2% in the AVR, MVR and DVR

groups respectively. The thromboembolic hazard is not only related to the type of prosthesis implanted, but to a variety of concomitant patient-related risk factors [6,9,10,27]. Low left ventricular ejection fraction, older age, and a history of thromboembolism also are associated with an increased risk of thromboembolic complications. In this study, patients taking warfarin preoperatively (p =0.04), had significant risk of developing thromboembolic and bleeding complications. Although an increased incidence of thromboembolic events were noted in patients with atrial fibrillation in this study, it was not statistically significant. In this study the mortality was high in patients with poor left ventricular function, increased cardiothoracic ratio, presence of CHF at presentation and those undergoing emergency surgery ($p < 0.05$). Older age, long cardiopulmonary bypass time, presence of atrial fibrillation or left atrial clot was not predictors of death for any group. Doppler echocardiography and cinefluoroscopy have complementary roles in assessing prosthetic valve function during thrombolytic therapy [15]. Medical treatment of thrombosed St. Jude valves is safe, has a low complication rate. Doppler echocardiography may overestimate gradients in St. Jude valves as well as underestimate valve areas [18]. Cinefluoroscopy is the preferred method for diagnosis and follow-up of St. Jude valve thrombosis at our institution. Since the St. Jude valve is only slightly radiopaque, a side or pivot view with the disks parallel to the x-ray beams is required for optimal leaflet visualization and measurement of leaflet angles [12-14]. Thrombolysis was the initial treatment offered for patients with thrombosed prosthetic heart valve. Initially, the patients were treated using streptokinase1.5 mu over 30-45 min, (250,000 units bolus i.e. injection over 30 minutes followed by a maintenance infusion of 100,000 units/hr for 72 hours). Patients with recurrent prosthetic valve thrombosis were treated with urokinase at a dose of 4,400 units/kg given over 10-15 minutes followed by maintenance dose of 4,400 units/kg/hr. Patients with contraindication of thrombolytic therapy received only heparin. Thrombolytic therapy was considered successful in the event of cine fluoroscopic evidence of restoration of leaflet motion. These patients were subsequently heparinized and discharged on warfarin and aspirin maintaining an INR between 2.5-3.5. Patients who do not respond within 48-72 hours should be referred for surgery, because these patients may have tissue ingrowth obstructing the valve (pannus formation) and probably will not respond to continued thrombolytic treatment. Patients who return with repeated episodes of thrombosis can usually be treated successfully with thrombolytic therapy. However, these patients may be at a continuing risk for further thrombotic episodes, probably related to patient factors (senility, noncompliance, etc.), and consideration should also be given to prosthetic valve replacement with a tissue valve. Patients with residual limitation of leaflet motion after thrombolytic therapy remain a clinical challenge. In our experience, they may be managed conservatively, with stringent monthly follow-up but this decision should be individualized. Thrombosis of a St. Jude prosthetic valve is a rare but potentially lethal clinical situation. The clinical presentation varies from minimal or absent symptoms to circulatory collapse, and prompt diagnosis is essential. Many patients with prosthetic valve thrombosis give a recent history of stopping anticoagulation to undergo surgery. Thrombolysis may be used as the first line of therapy in patients with thrombosed St. Jude valves and appears to be an effective and safe treatment. We believe that surgery should be reserved for patients who cannot be stabilized medically and for patients who have contraindications to thrombolytic therapy.

Conclusions

We conclude that despite excellent biocompatibility and absence of structural failure of St Jude mechanical prosthesis in either mitral or aortic position, lifelong therapeutic anticoagulation with warfarin and antiplatelet drugs are mandatory. Secondly, despite attempting to maintain a therapeutic INR, there exists a statistically significant wide range of fluctuation of PT/INR values among patients undergoing combined mitral and aortic valve replacements, thereby predisposing them to greater risk of thromboembolic and bleeding complications. Based on these findings, we think it should be possible to reduce the risk for complications by attending to modifiable risk factors such as intensity of treatment and PT/INR variability and considering modifiable risk factors such as co-morbidity, when deciding to identify an 'optimal' target INR for patients with mechanical heart valves. As variability in Prothrombin time is an important risk factor, a patient with highly erratic PT/INR should be aggressively treated with his/her assigned target range to avoid unexpected periods of excessive or inadequate anticoagulation.

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