Comparison between Percutaneous Coronary Intervention versus Coronary Artery Bypass Graft with Mitral Valve Replacement in Patients with Single Vessel and Mitral Valve Disease

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April 25, 2022

Abstract

Background: We compared staged percutaneous coronary intervention (PCI) versus coronary artery bypass graft (CABG) with mitral valve replacement (MVR) in patients with combined single vessel and rheumatic mitral valve disease. *Methods:* We prospectively evaluated 80 patients with combined single coronary artery (requiring revascularization in non-LAD (Left Anterior Descending artery) territory) and rheumatic mitral valve disease, divided into two groups; Group I consisting of 40 patients who underwent staged PCI, and mitral valve replacement 3 months later, and Group II consisting of 40 patients who underwent combined CABG (using saphenous venous graft) and mitral valve replacement. We compared between both groups. *Results:* The median aortic cross-clamp and cardiopulmonary bypass times were 44 and 62 minutes for Group I, versus 60.5 and 82 minutes for Group II, that difference between groups is statistically significant. 8 patients (20%) in Group I needed inotropic support versus 12 patients (30%) in Group II, which is not statistically significant. No patients in both groups did need any mechanical support in the form of intra-aortic balloon pump (IABP). None of the patients in both groups had intraoperative ECG (electrocardiogram) changes in the form of ischemia or arrhythmias. The median intensive care unit (ICU) length of stay (hours) and hospital length of stay (days) were 39 hours and 5.5 days for Group I, versus 56.5 hours and 8.5 days for Group II, that difference between groups is statistically significant. The median blood loss (ml) postoperatively was 925 in group I versus 1075 in group II, which is statistically significant. However, the rate of re-exploration for bleeding did not differ significantly between both groups, with 1 case only (2.5%) in group I versus 2 cases (5%) in group II, and no postoperative delayed cardiac tamponade noted in any of the two groups. The post-operative complications for groups I and II included 0 (0%) versus 3 (7.5%) prolonged mechanical ventilation (>24 h), 0 (0%) versus 1 (2.5%) respiratory complications, 0 (0%) versus 2 (5%) wound infection, 0 (0%) versus 1 (2.5%) cerebrovascular accidents, 2 (5%) versus 1 (2.5%) acute kidney injury, respectively. There is no statistically significant difference between both groups regarding these previous post-operative complications. None of the patients in both groups died within the first 30 days after surgery. None of the patients in both groups had major cardiac events or CCU (Cardiac Care Unit) admission. Regional wall motion abnormalities were noted in 15 patients (37.5%) of group I versus 17 patients (42.5%) of group II, who all undergone stress ECG, of whom 9 patients (22.5%) in group I versus 11 patients (27.5%) in group II showed positive results, and qualified for diagnostic coronary angiography, which confirmed the need for reoperation for myocardial ischemia/infarction within the first year of follow up post-operatively in 4 patients (10%) of group I versus 8 patients (20%) of group II. All these follow up outcomes showed no significant difference between both groups. *Conclusions:* A staged approach of PCI followed by MVR is an alternative to the conventional combined CABG and MVR, can be performed safely in some patients with single coronary artery and MV disease, and is associated with good short and follow-up outcomes

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Conclusions: A staged approach of PCI followed by MVR is an alternative to the conventional combined CABG and MVR, can be performed safely in some patients with single coronary artery and MV disease, and is associated with good short and follow-up outcomes.

Keywords: PCI, CABG, MVR

Background

Combined coronary artery mitral valve disease is a major cause of morbidity and mortality in the adult patient population. Traditional treatment involves combined mitral valve and CABG surgery using a median sternotomy. However, this combined surgical approach confers a higher risk when compared with isolated MV surgery, the risks of such a combined surgical procedure may outweigh the benefits. Thus, the concept of parsing the total risk of a single major procedure to the lesser individual and summed risks of 2 smaller procedures—percutaneous coronary intervention (PCI) plus the mitral valve operation—has been applied in clinical practice and reported by various groups.

Interest in hybrid procedures, defined for the purpose of this thesis as Mitral valve surgery and percutaneous

coronary intervention (PCI), has intensified with improved coronary stent technology, increased collaboration between cardiac surgeons and interventional cardiologists, and the introduction of hybrid operating suites. The complementary goals of minimizing the morbidity of surgical procedures and optimizing resource utilization have driven development of new solutions for concurrent valvular and coronary heart disease (1).

Methods

The study was a prospective comparative review, of 2 years duration, of 80 patients with combined single coronary artery (requiring revascularization in non-LAD territory) and rheumatic MV disease, divided into two groups; Group I consisting of 40 patients who underwent staged PCI, and mitral valve replacement 3 months later, and Group II consisting of 40 patients who underwent combined CABG (using saphenous venous graft) and mitral valve replacement. The study centers were Cardiothoracic Surgery Department of Ain Shams University Hospitals, and National Heart Institute (NHI). PCI was done at Cardiology Department of Ain Shams University Hospitals, and National Heart Institute (NHI).

Included were patients with combined single vessel and mitral valve disease, of age between 35 and 60 years old. Excluded were patients with Ejection Fraction (EF) less than 45%, concomitant aortic or tricuspid valve disease requiring surgery, concomitant congenital heart disease requiring surgical correction, redo cardiac surgery, acute coronary syndrome requiring primary PCI together with mitral valve disease, renal/hepatic failure, Chronic Obstructive Pulmonary Disease (COPD) or other respiratory disease, any neurological deficit or previous cerebrovascular event, or hematological disorders.

In all patients, the coronary and valvular lesions were documented by diagnostic catheterization and echocardiography, respectively. Patients were selected to undergo a hybrid approach after a comprehensive Heart Team evaluation. Baseline variables, operative characteristics and outcomes, and major adverse cardiovascular events during the follow-up period were analyzed using our institutional medical records, outpatient surgical and cardiology office visits, and a follow-up survey at 3-month intervals within the first postoperative year.

All patients were clinically stable for both PCI and the operation. Preoperative medication regimens were similar. Once the treatment plan was established, the interventional cardiologist proceeded with PCI of the significant lesion in the native vessel. Drug-eluting stents were placed in all of Group I patients. A loading dose of 600 mg clopidogrel and 325 mg aspirin was administered at the time of stent placement, followed by clopidogrel 75 mg daily and aspirin 81 to 325 mg daily thereafter (dual antiplatelet therapy). Management of antiplatelet therapy between the PCI and the operation was at the discretion of the interventional cardiologist. The patients had their antiplatelet agents stopped 5 days before surgery. All patients resumed their antithrombotic regimen within 24 to 48 hours after surgery, which comprised of single antiplatelet (clopidogrel 75 mg daily) and an oral anticoagulant dose adjusted according to target International Normalized Ratio (INR), because of the mechanical mitral valve prosthesis inserted in all patients.

In all patients, standard median sternotomy was performed, followed by inverted T-shaped pericardiotomy, Aorto-bicaval cannulation, conduction of cardiopulmonary bypass, and application of aortic cross-clamp. Warm blood antegrade cardioplegia was given. Mitral valve was accessed through left atriotomy via Sondergaard's groove, preservation of the posterior leaflet was done, and the mechanical mitral prosthesis inserted using 2-0 interrupted Ethibond sutures with pledgets sitting on the atrial surface of the mitral valve. Closure of left atrium, deairing through aortic root vent, and removal of aortic cross-clamp. Weaning off bypass, hemostasis, and anatomical closure in layers. In group II patients, the distal and proximal anastomoses using 7-0 and 6-0 Prolene sutures, respectively, were done in addition to the previous steps of mitral valve replacement, using the saphenous venous graft harvested simultaneously with the median sternotomy at the start of the operation.

The intraoperative variables prospectively assessed as per our study included total cardiopulmonary bypass time, total cross-clamp time, the need for inotropic support, and ECG changes in the form of ischemia or arrhythmias. The postoperative outcomes included bleeding, cerebrovascular accidents, renal failure, respiratory complications, duration of mechanical ventilation, duration of ICU stay, wound infection, duration

of hospital stay, and 30-day mortality. All patients underwent postoperative routine trans-thoracic echo (TTE) follow up upon discharge, after 3 months, 6 months, and 1 year, postoperative stress ECG and/or coronary angiography if needed. The follow-up outcomes included major cardiac events or CCU admission within first year, and the need for reoperation for myocardial infarction or ischemia within first year.

Statistical Analysis

The Community, Environmental and Occupational Medicine Department of Ain Shams University suggested a minimum sample size of 36 patients in each group to get reliable results. The collected data was revised, coded, tabulated, and introduced to a PC using the Statistical Package for the Social Sciences (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). The variables are reported as mean ± standard deviation (SD), median and interquartile range (IQR), or number (N) and percentage. Suitable analysis is done according to the type of data obtained. An independent t-test, chi-square test, and Mann-Whitney U test are used to analyze data accordingly. P-value <0.05 is considered statistically significant.

Results

Baseline demographic, clinical, angiographic, and echocardiographic information was prospectively collected for all patients. There was no statistically significant difference between both groups in the baseline characteristics, including age, sex, BMI, hypertension, diabetes mellitus, and dyslipidemia (Table 1). There were 23 (57.5 %) men in the staged PCI + MVR group (Group I) and 25 (62.5 %) in the CABG + MVR group (Group II) (P= 0.648), with a mean age of 51.1±3.2 and 52.1±4.6 years (P= 1.000), and body mass index (BMI) of 27.2 ± 1.7 and 27.3 ± 2.1 (P= 0.819), respectively. The incidence of hypertension, diabetes mellitus, and dyslipidemia for both groups were 82.5 versus 87.5% (P= 0.531), 37.5 versus 42.5% (P= 0.648), and 77.5 versus 82.5% (P= 0.576), respectively.

Table (1)

Characteristic	**Group I (n=40)**	**Group I (n**
Age		
Mean± S.D.	51.1	±
Range	45.0	-
Sex	**N**	**N**
Males	23	23
Females	17	17
BMI		
Mean± S.D.	27.2	27.2
Range	24.0	24.0
Hypertension	33	33
Diabetes Mellitus	15	15
Dyslipidemia	31	31
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The median pre-operative creatinine in group I and group II were 1.2 and 1.1 (P= 0.299), respectively, which is not statistically significant (Table 2). None of the patients in both groups had cerebrovascular disease, peripheral vascular disease, prior Myocardial Infarction (MI), congestive heart failure, liver disease, chronic lung disease, prior cardiac surgery or PCI, preoperative aspirin administration, preoperative clopidogrel administration, or preoperative dual-antiplatelets administration.

Table (2)

Characteristic	**Group I (n=40)**	**Group I (n=40)**	**Group I (n=40)**
Pre-operative creatinine			

Characteristic	Group I (n=40)	Group I (n=40)	Group I (n=40)
Median	1.2	1.2	1.2
IQR	1.0	-	-
**t: Independent Samples t-test*	**t: Independent Samples t-test*	**t: Independent Samples t-test*	**t: Independent Sample*

The median left ventricular ejection fraction (EF) was 56% (IQR, 54-60%) in Group I and 55% (IQR, 52-60%) in Group II (P=0.579). 9 patients (22.5%) in Group I had atrial fibrillation (AF) versus 11 (27.5%) in Group II (P=0.606). Median pulmonary artery pressure (PAP) was 25 in both groups (P=0.330). There was no statistically significant difference between both groups regarding EF, AF, and median PAP (Table 3). No left ventricular dilatation or right ventricular dysfunction were noted in both groups preoperatively.

Table (3)

Characteristic	Group I (n=40)	Group I (n
Ejection fraction %		
Median	56.0	56.0
IQR	54.0	-
Atrial fibrillation		
N - %	9	9
Median PAP		
Median	25.0	25.0
IQR	23.0	-
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The most treated coronary arteries were the right coronary in 24 patients (60%) of Group I versus 20 patients (50%) of Group II (P=0.369), and the left circumflex in 16 patients (40%) of Group I versus 20 patients (50%) of Group II (P=0.369). None of the patients in both groups had left anterior descending or ramus intermedius artery lesions. Regarding the mitral valve lesions, mitral stenosis was found in 24 patients (60%) of Group I versus 16 patients (40%) of Group II (P=0.074), mitral regurgitation in 8 patients (20%) of Group I versus 4 patients (10%) of Group II (P=0.210), and mixed mitral lesions (stenosis + regurgitation) in 8 patients (20%) of Group I versus 20 patients (50%) of Group II (P=0.005). There was a statistically significant association between groups regarding mixed mitral valve lesions only. However, the association was not statistically significant regarding left circumflex artery lesions, right coronary artery lesions, mitral valve stenosis, and mitral valve regurgitation. The median time interval between PCI and mitral valve surgery in Group I was 93 days (IQR, 91-95) (Table 4).

Table (4)

Characteristic	Characteristic	Group I (n=40) N %	Group I (n=40) N %	Group I (n=40) N %	Group I (n=40) N %	Group II (n=40) N %	Group II (n=40) N %	Group II (n=40) N %	Group II (n=40) N %	χ2*
Coronary artery lesions	**Left circumflex artery lesions**	16	16	40.0	40.0	20	20	50.0	50.0	**0.808**

Characteristics	Characteristics	Group I (n=40) N %	Group I (n=40) N %	Group I (n=40) N %	Group I (n=40) N %	Group II (n=40) N %	Group II (n=40) N %	Group II (n=40) N %	Group II (n=40) N %	χ2*
	Right coronary artery lesion	24	24	60.0	60.0	20	20	50.0	50.0	**0.808**
	Left anterior descending lesions	0	0	0.0	0.0	0	0	0.0	0.0	**-**
	Ramus intermedius lesions	0	0	0.0	0.0	0.0	0.0	0.0	0.0	**-**
Mitral valve lesions	**Mitral valve stenosis**	24	24	60.0	60.0	16	16	40.0	40.0	**3.200**
	Mitral valve regurgitation	8	8	20.0	20.0	4	4	10.0	10.0	**1.569**
	Mixed mitral valve lesions	8	8	20.0	20.0	20	20	50.0	50.0	**7.912**
Time of PCI to valve surgery (days)	**Time of PCI to valve surgery (days)**									
	Median	93.0	93.0	93.0	93.0	-	-	-	-	**-**
	IQR	91.0	-	-	95.0	-			-	

Characteristic	Characteristic	Group I (n=40) N %	Group I (n=40) N %	Group I (n=40) N %	Group I (n=40) N %	Group II (n=40) N %	Group II (n=40) N %	Group II (n=40) N %	Group II (n=40) N %	χ2*
	*χ2: ῆι-σχυαρϵ τϵστ **: στατιστιςαλλψ σιγνιφιςαντ	*χ2: ῆι-σχυαρϵ τϵστ **: στατιστιςαλλψ σιγνιφιςαντ	*χ2: ῆι-σχυαρϵ τϵστ **: στατιστιςαλλψ σιγνιφιςαντ	*χ2: ῆι-σχυαρϵ τϵστ **: στατιστιςαλλψ σιγνιφιςαντ	*χ2: ῆι-σχυαρϵ τϵστ **: στατιστιςαλλψ σιγνιφιςαντ	*χ2: ῆι-σχυαρϵ τϵστ **: στατιστιςαλλψ σιγνιφιςαντ	*χ2: ῆι-σχυαρϵ τϵστ **: στατιστιςαλλψ σιγνιφιςαντ	*χ2: ῆι-σχυαρϵ τϵστ **: στατιστιςαλλψ σιγνιφιςαντ	*χ2: ῆι-σχυαρϵ τϵστ **: στατιστιςαλλψ σιγνιφιςαντ	*χ2: ῆι-σχυαρϵ τϵστ **: στατιστιςαλλψ σιγνιφιςαντ

The median aortic cross-clamp and cardiopulmonary bypass times were 44 (IQR, 39-48) and 62 minutes (IQR, 59-68) for Group I, versus 60.5 (IQR, 55-65) and 82 minutes (IQR, 75-88) for Group II (P=0.001), this difference between groups is statistically significant. 8 patients (20%) in Group I needed inotropic support versus 12 patients (30%) in Group II (P= 0.302), which is not statistically significant. No patients in both groups did need any mechanical support in the form of intra-aortic balloon pump (IABP). None of the patients in both groups had intraoperative ECG changes in the form of ischemia or arrhythmias (Table 5). The AF patients preoperatively in both groups went through several changes in the rhythm and rate intraoperatively before returning to baseline AF again.

Table (5)

Characteristic	Group I (n=40)
Aortic cross-clamp time (min)	
Median	44.0
IQR	39.0
Cardiopulmonary bypass time (min)	
Median	62.0
IQR	59.0
Operative need for inotropic support	**N**
Yes	8
No	32
ECG changes in the form of ischemia or arrhythmias	0
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The median intensive care unit (ICU) length of stay (hours) and hospital length of stay (days) were 39 hours (IQR, 32-45) and 5.5 days (IQR, 5-6) for Group I, versus 56.5 hours (IQR, 49-69) and 8.5 days (IQR, 7-13) for Group II (P=0.001), that difference between groups is statistically significant. The median bleeding loss (ml) postoperatively was 925 (IQR, 650-1200) in group I versus 1075 (IQR, 900-1400) in group II (P= 0.021), which is statistically significant, with a median of 2 units of packed red blood cells (RBCs) transfused (IQR, 1–2) in group I compared to a median of 2 packed RBCs units transfused (IQR, 2-3) in group II (P= 0.002), which is statistically significant also. However, the rate of re-exploration for bleeding did not differ significantly between both groups, with 1 case only (2.5%) in group I versus 2 cases (5%) in group II (P= 0.556) (Table 6), and no postoperative delayed cardiac tamponade noted in any of the two groups.

The post-operative complications for groups I and II included 0 (0%) versus 3 (7.5%) prolonged mechanical ventilation (>24 h) (P= 0.077), 0 (0%) versus 1 (2.5%) respiratory complications (P= 0.314), 0 (0%) versus 2 (5%) wound infection (P= 0.152), 0 (0%) versus 1 (2.5%) cerebrovascular accidents (P= 0.314), 2 (5%) versus 1 (2.5%) acute kidney injury (P= 0.556), respectively. There is no statistically significant difference between both groups regarding these previous post-operative complications. None of the patients in both groups died within the first 30 days after surgery (Table 6).

Table (6)

Outcome	**Group I (n=40)**	**Group I (n=40)**	**Group I (n=40)**	**Group I (n=40)**	**Group I (n=40)**	**Group II (n=40)**	**Group II (n=40)**	**Group II (n=40)**	**Group II (n=40)**	**Sig.**
ICU length of stay (hours)										**U***
Median	39.0	39.0	39.0	39.0	39.0	56.5	56.5	56.5	56.5	
IQR	32.0	-	-	45.0	45.0	49.0	-	-	69.0	**-8.379**
Blood loss (ml)										
Median	925.0	925.0	925.0	925.0	925.0	1075.0	1075.0	1075.0	1075.0	**-2.316**
IQR	650.0	-	-	1200.0	1200.0	900.0	-	-	1400.0	
Packed RBCs units transferred										
Median	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	**-3.091**
IQR	1.0	-	-	2.0	2.0	2.0	-	-	3.0	
Hospital length of stay (days)										
Median	5.5	5.5	5.5	5.5	5.5	8.5	8.5	8.5	8.5	**-6.571**
IQR	5.0	-	-	6.0	6.0	7.0	-	-	13.0	
Prolonged mechanical ventilation (>24 h)	0	0	0	0	0.0	3	3	7.5	7.5	**χ2*** 3.117**

Outcome	Group I (n=40)	Group I (n=40)	Group I (n=40)	Group I (n=40)	Group I (n=40)	Group II (n=40)	Group II (n=40)	Group II (n=40)	Group II (n=40)	Sig.
Respiratory complications	0	0	0	0	0.0	1	1	2.5	2.5	**1.013**
Wound infection	0	0	0	0	0.0	2	2	5.0	5.0	**2.051**
Cerebrovascular accidents	0	0	0	0	0.0	1	1	2.5	2.5	**1.013**
Re-operation for bleeding	1	1	1	1	2.5	2	2	5.0	5.0	**0.346**
Acute kidney injury	2	2	2	2	5.0	1	1	2.5	2.5	**0.346**
30-day mortality	0	0	0	0	0.0	0	0	0.0	0.0	**-**
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After one year of follow-up, none of the patients in both groups had major cardiac events or CCU admission. Postoperative routine trans-thoracic echo (TTE) follow-up was done upon discharge, as well as after 3 months, 6 months, and 1 year for all patients in both groups. Regional wall motion abnormalities were noted in 15 patients (37.5%) of group I versus 17 patients (42.5%) of group II (P=0.648), who all undergone stress ECG, of whom 9 patients (22.5%) in group I versus 11 patients (27.5%) in group II showed positive results (P=0.606), and qualified for diagnostic coronary angiography, which confirmed the need for reoperation for myocardial ischemia/infarction within the first year of follow up post-operatively in 4 patients (10%) of

group I versus 8 patients (20%) of group II (P=0.210). All these follow up outcomes showed no significant difference between both groups (Table 7).

Table (7)

Outcome	**Group I (n=40)**	**Group I (n=40)**	**Group**
	N	**%**	**N**
Major cardiac events or CCU admission	0	0.0	0
Echo regional wall motion abnormalities	15	37.5	17
Positive stress ECG	9	22.5	11
Need for reoperation for myocardial infarction or ischemia	4	10.0	8
*χ2: ήι-σχυαρϵ τϵστ	*χ2: ήι-σχυαρϵ τϵστ	*χ2: ήι-σχυαρϵ τϵστ	*χ2: ήι-

Discussion

The STS adult cardiac surgery database cites the operative mortality of isolated MV replacement at 4.7%. When performing concomitant CABG, the operative mortality increases to 9.8%, with a significantly greater occurrence of post-operative complications and major morbidity occurring in 7.0% to 11.6% (1). Thus, it is hypothesized that the operative risk of combined CABG and MV surgery may be reduced by partitioning the operation into the two lower-risk, less invasive procedures of PCI + MVR. The present study demonstrated a low morbidity and mortality with staged PCI + MVR for significant single coronary artery and MV disease, compared to combined CABG and MVR.

Given the trends toward increases in minimally invasive cardiac surgery, the broad applicability of the hybrid approach described here may be particularly appealing. Gammie and colleagues (2) reported that from 2004 to 2008 the percentage of mitral valve operations that were done via a minimally invasive approach increased from 11.9% to 20.1% (P<.0001). With this progression, it is most likely that a hybrid approach will increase as well. On the other hand, the short-term benefits of a hybrid approach are not without potential long-term hazards.

Fortunately, in-stent restenosis, one of the major limitations of percutaneous revascularization, has decreased with each new generation of coronary stent (3). PCI, however, has yet to match CABG with regard to long-term benefits (4). Multiple studies have consistently demonstrated that for patients with multi-vessel disease and/or left main disease, regardless of the presence of diabetes, CABG yields better outcomes than PCI in terms of mortality, myocardial infarction and need for repeat coronary revascularization (5). Even when comparing CABG versus PCI for patients with proximal LAD disease, Hannan et al., showed that CABG patients had lower rates of repeat revascularization (6). The benefit of CABG over PCI involves the long-term effects of Internal Mammary Artery (IMA) to LAD anastomosis, the potential ability of bypass grafts to 'treat' lesions that subsequently develop and resultant downstream effects of cytokines on arterial disease (7). On the other hand, PCI offers lower rates of morbidity and shorter hospital stay.

The primary purpose of a hybrid valve/PCI is to substitute PCI for bypass grafting with saphenous vein grafts (SVGs), particularly for lesions not in the left anterior descending (LAD) coronary artery (8). With the current excellent performance of drug-eluting coronary stents (DES), restenosis and thrombosis rates of DES may be less than the estimated rate of SVG failure of 20 % at 12 months (9). The two most common clinical objectives of hybrid procedures are to reduce overall operative morbidity and mortality by transforming a single, high-risk surgery into two less risky procedures, and to facilitate minimally invasive surgery (8).

Hybrid procedures offer a reasonable alternative to traditional surgery for patients who meet the following basic criteria: non-LAD coronary lesions, not amenable to internal mammary bypass grafting; PCI that is technically feasible and likely durable from a procedural standpoint; and ability to tolerate the required antiplatelet and anticoagulation regimens.

Our study was a prospective comparative review, of 2 years duration, of 80 patients with combined single coronary artery (requiring revascularization in non-LAD territory) and rheumatic MV disease, divided into two groups; Group I consisting of 40 patients who underwent staged PCI, and mitral valve replacement 3 months later, and Group II consisting of 40 patients who underwent combined CABG (using saphenous venous graft) and mitral valve replacement. Our Aim was to compare intraoperative, postoperative, and follow-up outcomes of staged PCI versus CABG with mitral valve replacement in patients with combined single vessel and mitral valve disease.

Reoperative coronary bypass grafting in a patient with valvular disease poses a particular challenge in cardiac surgery. The hybrid approach is of particular benefit in reoperative patients who have had prior CABG with patent grafts. The technical difficulty of accessing lateral wall targets, safely dissecting patent bypass grafts, and obtaining exposure often precludes safe surgery, and these risks are not reflected in traditional scoring systems. Hybrid valve/PCI may be particularly useful in this regard and can dramatically simplify a challenging open valve and CABG surgery by substituting PCI for reoperative bypass grafting in lesions amenable to PCI (9). However, we excluded redo patients from our study, as this cohort is extremely high risk, and would have affected the results in a different way.

Although DES have shown excellent results in clinical trials, their effectiveness in clinical practice with more complex patients and complex lesions (high Syntax score, totally occluded coronary vessels, bifurcated lesions, small vessels, long lesions requiring multiple stents, ostial stenosis, calcified vessels) remains to be seen. Patients with diabetes, who comprise 30% of the surgical population and 37.5% of Group I in our study, have higher restenosis rates with DES (10). Late stent restenosis and thrombosis is another concern.

The most recent data from STS (Society of Thoracic Surgeons) demonstrate that in those undergoing isolated MV surgery, the rate of MV repair was 57.4%, and MV replacement was 42.6% (1). In the cases where MV pathology and etiology were documented, 56.6% were identified as having mitral regurgitation due to annular or degenerative disease, without stenosis, of which repair was performed in 75.0% of patients. In the present study, regarding the mitral valve lesions, mitral stenosis was found in most of the patients; 24 patients (60%) of Group I versus 16 patients (40%) of Group II (P=0.074), mixed mitral lesions (stenosis + regurgitation) come in the second place with 8 patients (20%) of Group I versus 20 patients (50%) of Group II (P=0.005) (statistically significant association between groups regarding mixed mitral valve lesions only), and mitral regurgitation in the minority of study groups with 8 patients (20%) of Group I versus 4 patients (10%) of Group II (P=0.210). This means that mitral repair could have been feasible in a minority of patients with pure mitral regurgitation, as the reparability of other pathologies varies markedly. That encouraged us to exclude mitral repair and standardize mitral replacement as the uniform approach for mitral valve surgery in this study.

Although one needs to be cautious when making direct comparison with other studies, reductions in the parameters of morbidity were noted when compared with data from the most recent STS adult cardiac surgery database outcomes. In patients undergoing CABG plus MV replacement, the most common complication is new-onset atrial fibrillation, which occurs in 44.2%, and increases peri-operative morbidity and hospital length of stay (11). This figure is higher than the 16.1% noted in present cohort of PCI + MIMVS (Minimally Invasive Mitral Valve Surgery) and is consistent with prior studies suggesting a reduced incidence of post-operative atrial fibrillation when utilizing a minimally invasive approach for valve surgery (12). In our study, we compared staged PCI + conventional MVR (Group I) to combined CABG + MVR (Group II). We noticed no ECG changes in the form of arrhythmias in both groups, the AF patients preoperatively in both groups went through several changes in the rhythm and rate intraoperatively before returning to baseline AF again. This may be due to the less morbid group of patients in our study, with good EF, low median PAP, relatively good clinical status, and nearly no comorbidities.

The staged strategy ensures optimal myocardial protection during the mitral correction. It is our belief that myocardial protection is greatly enhanced with hybrid procedures. By achieving 100% completeness of revascularization before cross-clamping in all of our valve-PCI patients, cardioplegia administration to all regions of the heart was possible. In contrast, if surgeons are reluctant to attempt revascularization

on high-risk or technically difficult to reach lesions, cardioprotection may be compromised, leading to low cardiac output postoperatively, and worsened outcomes. The reduction in cross-clamp time for a hybrid procedure also provides significant myocardial protective benefit, as the heart is faced with a lower overall ischemic time, and potentially less dysfunction upon reperfusion.

By performing PCI to treat the coronary artery disease, one obviates the necessity of performing concomitant CABG at the time of surgery, significantly reducing the complexity of the surgery and shortening the operative times, which was noted in our study when compared with conventional combined CABG and MVR. In our study, the median aortic cross-clamp and cardiopulmonary bypass times were 44 (IQR, 39-48) and 62 minutes (IQR, 59-68) for Group I, versus 60.5 (IQR, 55-65) and 82 minutes (IQR, 75-88) for Group II (P=0.001), that difference between groups is statistically significant.

The less traumatic nature of isolated MVR and reduced operative times in Group I likely conferred lower bleeding and transfusion requirements, the median bleeding loss (ml) postoperatively was 925 (IQR, 650-1200) in group I versus 1075 (IQR, 900-1400) in group II (P= 0.021), which is statistically significant, with a median of 2 units of packed red blood cells (RBCs) transfused (IQR, 1–2) in group I compared to a median of 2 packed RBCs units transfused (IQR, 2-3) in group II (P= 0.002), which is statistically significant also. However, the rate of re-exploration for bleeding did not differ significantly between both groups, with 1 case only (2.5%) in group I versus 2 cases (5%) in group II (P= 0.556). All reoperation for bleeding cases were related to sternal wire placement, and no postoperative delayed cardiac tamponade was noted in any of the two groups.

Although, our study was not powered to detect a statistically significant difference, shorter operative times and less blood product use during cardiac surgery are associated with fewer infections, and a lower morbidity and mortality (13, 14). However, composite post-operative complications (prolonged mechanical ventilation (>24 h), respiratory complications, wound infection, cerebrovascular accidents, re-operation for bleeding, acute kidney injury, and 30-day mortality) occurred less frequently in group I than in group II.

With the goal being to optimize stent patency while minimizing the risks of bleeding, there is concern regarding the risk of bleeding if the surgery is performed after the PCI and the possibility of stent thrombosis with protamine reversal. Of particular concern is the risk of bleeding with dual antiplatelet therapy, largely based on known higher rates of bleeding after CABG in patients receiving clopidogrel (15). In the current study, median time of PCI to mitral valve surgery was 93 days, the patients had their antiplatelet agents stopped 5 days before surgery and resumed their antiplatelet regimen within 24 to 48 hours after surgery.

In the previously mentioned study by Byrne and colleagues (16), because of the use of dual antiplatelet therapy, a high incidence of bleeding occurred, with 22 (85%) of the 26 patients requiring blood transfusions. In an attempt to reduce the incidence of bleeding, Brinster and colleagues (17) performed the PCI the day of, or evening before, the scheduled minimally invasive aortic valve replacement in 18 patients. There were no reoperations for bleeding, and only 8 (44%) patients required blood transfusions.

Santana O, et al. compared the outcomes of patients taking clopidogrel with those who were not taking clopidogrel. In the intraoperative period, there were no differences in the requirement of blood products, whereas in the postoperative period, there was a significantly higher number of patients taking clopidogrel who required blood products compared with those not taking clopidogrel. Out of concern for the possible development of stent thrombosis, they prefer the continuation of antiplatelet therapy at the time of valve operation (18).

In the study of Mihos CG, et al. (19), even though there was a higher use of pre-operative clopidogrel in those undergoing PCI+MIMVS, there were fewer intraoperative transfusions required, when compared with CABG+MVS. The lower need for blood products in the PCI+MIVS group is most likely due to the fact that, by its less traumatic nature, minimally invasive valve surgery is associated with less blood loss. Also, by virtue of the fact that there was no need to place bypass grafts, the operative times were much shorter in this group, thereby having less bleeding (20). Importantly, there were no cases of acute stent thrombosis peri-operatively. In their previous work, they evaluated 222 patients who had PCI+MIMVS, 183 of which

were on clopidogrel and were compared with 38 who were not (18). In the intra-operative period, there were no differences in the requirement of blood products between the two groups. Post-operatively, there was a higher proportion of patients on clopidogrel requiring blood products compared with those who did not take it (50.5% versus 26.3%, P=0.005); however, there was no significant difference in the need for re-operation for bleeding. Because clopidogrel use perioperatively appears to be safe (21), their clinical practice has been to continue anti-platelet therapy at the time of valve surgery to minimize the risk of acute stent thrombosis.

Ideally, these patients would be best managed by either a longer staging duration so that the clopidogrel can be stopped (three to six months with drug-eluting stents), or by a very short staging duration (under 6 h), so that clopidogrel's actions are just beginning to take effect once the surgery has been completed. Our study differs from the previously mentioned studies in that we had a significant variation on the use of antiplatelet agents, our Group I patients had their antiplatelet agents stopped 5 days before surgery. The median time of PCI to mitral valve surgery in our study was 93 days, so we feel it is safe to withhold the antiplatelet therapy.

In these hybrid procedures, the optimal timing of the valve operation once PCI has been performed is not known. At our institution, the time delay between PCI and the valve operation is mainly driven by a desire to reduce the incidence of acute kidney injury counterbalanced with the urgency of the operation. It has been noted that the closer the 2 procedures are in time, the higher the incidence of acute kidney injury. Data from 4,440 patients undergoing coronary angiography and cardiac operation on the same day demonstrated this approach to be an independent predictor for the development of acute kidney injury (22). Another study evaluated the incidence of acute kidney injury in patients who had cardiac catheterization and cardiac operations during the same admission and compared it with a group of patients who had cardiac catheterization followed by operation at a later admission (23). The incidence of acute kidney injury in the patients who had same-admission cardiac catheterization and operations was 50.2% compared with 33.7% in those who had operations at a later date (p = 0.009). To reduce the incidence of acute kidney injury, several institutes prefer to wait at least 3 weeks after PCI to perform valve operations (22, 23).

We decided to wait 3 months after PCI to perform MVR, to avoid renal failure, and to be able to stop the antiplatelet therapy safely. We have got 2 patients (5%) in group I versus 1 (2.5%) in group II of acute kidney injury (P= 0.556), in the form of elevated creatinine levels, which resolved medically, without the need for dialysis. This difference was not statistically significant. We attribute this to the period of 3 months between PCI & MVR, which provide us with the protection window against acute kidney injury.

Santana O, et al (24) compared 65 patients who had a hybrid approach with 52 matched control patients who underwent conventional bypass grafting and valve operation. The results demonstrated a significant reduction in composite complications and hospital lengths of stay in the hybrid group when compared with conventional group. This is similar to the results per our study which showed fewer composite complications in Group I, as well as statistically significant lower median intensive care unit (ICU) length of stay (hours) and hospital length of stay (days); 39 hours (IQR, 32-45) and 5.5 days (IQR, 5-6), versus 56.5 hours (IQR, 49-69) and 8.5 days (IQR, 7-13) for Group II (P=0.001), respectively.

The postoperative complications were comparable with no statistically significant difference for groups I and II, with less prolonged mechanical ventilation (>24 h) 0 (0%) versus 3 (7.5%), and less respiratory complications 0 (0%) versus 1 (2.5%) for group I. This may be due to less aggressive and less time consuming is the isolated MVR than the combined CABG + MVR, which paves the way for faster extubation with less respiratory complications. The 3 patients of Group II eventually got extubated, one of them got chest infection which has been resolved using appropriate antibiotics. However, both approaches did include a sternotomy.

By virtue of avoiding a sternotomy, minimally invasive surgery results in less thoracic surgical trauma and alterations in pulmonary physiology and biomechanics, which contributes to an enhanced post-operative recovery and faster extubation, with a reported significantly lower incidence of prolonged mechanical ventilation occurring in 18.3% of the PCI + MIMVS cohort, and 29% in CABG plus MV replacement, leading to

shorter intensive care unit length of stay with the PCI + MIMVS approach, when compared with sternotomy. We don't see this significant difference in our study, because both groups were approached through a median sternotomy, with low incidence of prolonged mechanical ventilation, most probably due to exclusion of any lung disease or other comorbidities from our study groups.

Our present study showed slightly less wound infection in group I; 0 (0%) versus 2 (5%), most probably due to less operative time, ICU & hospital stay, blood transfusion requirements, & other postoperative complications which usually encourage infection. However, this difference is not significant, probably due to the similar approach used in both groups; sternotomy, and similar baseline characteristics between both groups.

The cerebrovascular accidents encountered in our study was one stroke patient in group II without any residual deficit. No other cases were reported in both groups, probably due to relatively good baseline characteristics of the patients included in our study, with good carotid duplex preoperatively, and exclusion of old patients above 60 years old with any central or peripheral vascular disease.

Several groups have investigated hybrid approaches of PCI combined with valve operations. In 2014, Santana et al., published the results of over 200 patients who underwent PCI for coronary revascularization followed by a minimally invasive valve procedure. They found a mortality rate of 3.6% and an all-cause mortality rate of 12% at 4.5 years. They also demonstrated a decreased complication rate and length of stay for the hybrid group compared to those undergoing conventional sternotomy (24).

In 2015, George et al. described a series of 26 patients who underwent a single-stage hybrid procedure involving PCI of a non-LAD vessel followed by a valve operation (21). Recalculating the STS risk after the PCI was performed, they found a 35% risk reduction in the re-operative group and a 17% risk reduction in the non-reoperative group. In addition, they had no in-hospital mortalities and very few complications. No coronary-stent thromboses were noted during a follow-up period of two years.

Specific to mitral valve, Umakanthan et al. described the Vanderbilt experience with 32 consecutive patients who underwent a hybrid procedure, including PCI and mitral valve surgery. Of these procedures, 28 (89 %) were performed as a single-stage procedure in a hybrid operating room (25). The observed in-hospital mortality rate was 3 % (1/32) and survival at one and two years was 96 % and 89 %, respectively. The series was expanded to 39 patients and reported by Solenkova et al., noting a predicted mortality for conventional CABG/ mitral of 14.1 % versus an observed in-hospital mortality of only 2.6 % (1/39). (26)

This is different from our study which showed no operative/30-day mortality in both groups. This may be attributed to the baseline characteristics of our group of elective patients who are low risk patients with few or no comorbidities.

As demonstrated by 5-year outcomes from the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) trial (27), a strong argument can now be made for PCI in patients with left main or multivessel disease with low SYNTAX scores (less than 23). However, the SYNTAX trial also clearly demonstrates a survival benefit of CABG for patients with a higher burden of disease, as reflected by a high SYNTAX score (greater than 33), and in specific patient subsets, such as patients with diabetes mellitus (28). The benefit of CABG is primarily attributable to left IMA grafting to the LAD, and the patency of IMA grafting consistently exceeds 95% at 10 years, setting the gold standard with which other revascularization strategies should be compared. Yet, significant limitations of both PCI and CABG persist. Whereas PCI is burdened by the need for repeat target lesion interventions, saphenous vein graft failure for non-LAD targets in CABG can reach 30% at 1 year, and at 10 to 15 years, only 50% to 60% of the SVGs have been reported to be patent (29). Conversely, the early restenosis and thrombosis rate of the drug-eluting stents (DES) in non-LAD vessels is lower than that reported for SVG failure (30).

This is to a great extent in line with the results per our study. Postoperative routine trans-thoracic echo (TTE) follow-up was done upon discharge, as well as after 3 months, 6 months, and 1 year for all patients in both groups. Follow-up was completed after one year. Regional wall motion abnormalities were noted in

15 patients (37.5%) of group I versus 17 patients (42.5%) of group II (P=0.648), who all undergone stress ECG, of whom 9 patients (22.5%) in group I versus 11 patients (27.5%) in group II showed positive results (P=0.606), and qualified for diagnostic coronary angiography, which confirmed the need for reoperation for myocardial ischemia/infarction within the first year of follow up post-operatively in 4 patients (10%) of group I versus 8 patients (20%) of group II (P=0.210). However, all these follow up outcomes showed no significant difference between both groups within the first year of follow up. None of the patients in both groups had major cardiac events or CCU admission. We attribute this to the nature of our patients in both groups, who have single non-LAD vessel disease supplying limited heart territories with good functional reserve. Long term data are needed for more informative conclusion.

As more hybrid PCI/valve procedures are being performed, many questions remain unanswered, including the optimal order for the procedures, their timing, the management of dual antiplatelet therapy, and the optimal costs and logistics of the procedures (8).

Limitations

The primary limitation of the present study is the associated potential for treatment selection bias. The patients who underwent PCI were selected on the basis of favorable coronary anatomy for this procedure, which is an important selection bias. Also, all patients had single-vessel coronary artery disease with normal left ventricular ejection fractions, and few or no comorbidities. High risk patients were excluded from this study.

The follow-up of the patients was limited to 1 year, and thus no statement may be made regarding long-term differences in outcomes, as might be expected when comparing PCI and CABG.

Conclusions

In conclusion, a staged approach of PCI followed by MVR is an alternative to the conventional combined CABG and MVR, can be performed safely in some patients with single coronary artery and MV disease, and is associated with good short and follow-up outcomes. As per our study, it was associated with: (I) significantly less operative time, (II) significantly faster post-operative recovery, as evidenced by a shorter intensive care unit and hospital lengths of stay, (III) significantly less bleeding & blood transfusions, with no significant difference regarding re-exploration for bleeding, (IV) comparable morbidity, mortality, and early follow-up outcomes. Although our valve-PCI cohort primarily underwent surgery through conventional sternotomy, we expect to see even greater clinical benefits with regard to lower transfusion, pain, and length of stay when undergoing minimally invasive, robotic, or small incision valvular surgery.

Nevertheless, important questions remain, including the optimal timing of the individual procedures, and the optimal antiplatelet therapy after PCI. With ongoing advances in stent technology, procedural techniques, and anticoagulation strategies, as well as the accumulation of long-term outcomes data, hybrid approaches to concomitant coronary artery and mitral valve disease will likely become increasingly common. Tailoring the approach to individual patient pathology and comorbidities is feasible and offers potentially better treatment paradigms.

List of abbreviations

PCI : Percutaneous Coronary Intervention

CABG : Coronary Artery Bypass Graft

MVR : Mitral Valve Replacement

LAD : Left Anterior Descending artery

IABP : Intra-Aortic Balloon Pump

ECG : Electrocardiogram

ICU : Intensive Care Unit

CCU : Cardiac Care Unit

NHI : National Heart Institute

EF : Ejection Fraction

COPD : Chronic Obstructive Pulmonary Disease

INR : International Normalized Ratio

TTE : Trans-Thoracic Echo

BMI : Body Mass Index

MI : Myocardial Infarction

AF : Atrial Fibrillation

PAP : Pulmonary Artery Pressure

IMA : Internal Mammary Artery

SVG : Saphenous Vein Grafts

DES : Drug-Eluting Stent

STS : Society of Thoracic Surgeons

MIMVS : Minimally Invasive Mitral Valve Surgery

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Table Legends

Table (1): Baseline characteristics of the study patients.

Table (2): Baseline characteristics of the study patients "continued".

Table (3): Baseline characteristics of the study patients "continued".

Table (4): Baseline characteristics of the study patients "continued".

Table (5): Operative characteristics of the study patients.

Table (6): Postoperative outcomes of the study patients.

Table (7): Follow-up outcomes within first year of the study patients.

Declarations

Ethics Approval and Consent to Participate

The study was conducted according to the Helsinki Declaration and approved by the Research Ethics Committee of the Faculty of Medicine of Ain Shams University. Informed written consent was obtained from all participants.

Consent for Publication

This manuscript has been reviewed and approved by all the co-authors and has not been submitted to any other journals for consideration for publication.

Availability of Data and Material

The data sets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

No competing interests exist.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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Acknowledgements

None.