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Original Article

Effectiveness of Milrinone in Preventing Myocardial Infarction After Coronary Artery Bypass Graft Surgery

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ABSTRACT

Objective: To study the effectiveness of Milrinone in prevention of Myocardial Infarction (MI) after Coronary Artery Bypass Grafting (CABG) surgery.
Study Design: Quasi experimental study.
Place and Duration of Study: Armed Forces Institute of Cardiology & National Institute of Heart Diseases, Rawalpindi Pakistan, from Jun to Dec 2023.
Methodology: One hundred and twenty patients who underwent CABG irrespective of age and gender were enrolled through non probability consecutive sampling. Patients were divided equally into two groups non-randomly: Milrinone-Group (Group- M) and Saline-Group (Group-S). Before coming off bypass in on pump cases and after completion of grafting in off pump cases, bolus dose of Milrinone 50µg/kg was administered in Group- M and same volume of normal Saline in Group-S. The primary endpoint of the study was the occurrence of postoperative myocardial infarction (PMI), as determined by Electrocardiography (ECG) and cardiac biomarkers (CK and CKMB).
Results: Out of 120 patients, 106(88.37%) were males and 14(11.60%) were females with median age of 58.00(53.00-68.75) years. In Group-M and Group-S, raised CKMB levels was observed in 7(11.7%) and 20(33.3%) patients respectively (p=0.008). Regarding ECG changes, both groups demonstrated statistically insignificant difference (Group-M: 4(6.7%) patients vs. Group-S: 7(11.7%) patients; p>0.05).
Conclusion: Milrinone may have some cardioprotective effects, by lowering CKMB level but it was not consistently effective in prevention of MI following CABG surgery.

Keywords: Cardiac biomarkers, Electrocardiography, Milrsinone, Myocardial infarction.

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INTRODUCTION

Coronary artery disease (CAD) is a leading cause of morbidity and mortality and is estimated that it is associated with nearly 7 million deaths globally.[1] Many patients with CAD present for coronary artery bypass grafting (CABG) surgery which is associated with minor complications such as blood loss, dysrhythmias, renal dysfunction, stroke, infection, respiratory complications, myocardial ischemia and infarction.[2] Perioperative Myocardial Infarction (PMI) remains a significant complication after CABG surgery. A meta-analysis showed that incidence of PMI after CABG surgery was 5-30% which was confirmed by repeat angiography.[3] Patients with PMI require high inotropic support, intra-aortic balloon pump (IABP) insertion or graft revision, prolonged ICU stay, increased cost of treatment and eventually suffer high morbidity and mortality.[4]

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PMI after CABG is diagnosed by raised cardiac biomarkers in addition to ECG changes (ST segment changes, new Q waves or LBBB) or new regional wall motion abnormalities on echocardiography or evidence on angiography.[5] Confirmatory investigation is angiography but it is time consuming and not feasible routinely due to limited resources in most setups.[6] A previous study reported that Milrinone use in CABG patients was associated with reduced complications, such as difficulty weaning from CPB, the requirement for IABP insertion, vasopressor support, CPB re-initiation, and extended stays in the intensive care unit.[7]

Milrinone, a phosphodiesterase III inhibitor, is a potent inodilator agent that has been shown to improve myocardial contractility and decrease afterload, thereby improving coronary blood flow. Several studies have investigated the role of Milrinone in low cardiac output state, diastolic dysfunction and heart failure after cardiac surgery.[8] It causes pulmonary and systemic vasodilation and is being

used in patients with pulmonary hypotension.[9] It also has dilatory effect on coronaries, but this effect is not directly studied in prevention of PMI. A meta-analysis showed that there was no significant difference between placebo and Milrinone group in terms of mortality but occurrence of PMI was lower in Group-M.[10]

Milrinone is routinely used in pediatric and adult cardiac surgery patients with diastolic dysfunction and low cardiac output. In Pakistan, the effectiveness of Milrinone in preventing PMI after CABG surgery has yet to be investigated. CABG is a frequent surgical procedure for patients with CAD, although it increases the risk of PMI due to ischemia-reperfusion injury. This study aimed to determine whether administering Milrinone, can effectively reduce the frequency of PMI in CABG patients by lowering cardiac biomarker levels and minimizing ECG changes, thereby providing insight into its potential role in improving surgical outcomes.

METHODOLOGY

It was a quasi-experimental study conducted in department of Adult Cardiac Anesthesiology And Intensive Care Department, Armed Forces Institute of Cardiology & National Institute of Heart Diseases, Rawalpindi Pakistan, from June 2023 to December 2023 after formal approval from Institutional Ethical Review Board (IERB) (ltr#. 9/2/R&D/2023/259; Dated: 25th May 2023). Data was collected using non probability consecutive sampling technique.

A sample size of 100 (50 for each group) was calculated using the WHO sample size calculator. In the Group- M, the postoperative myocardial infarction (PMI) prevalence was 15.6%, while in the placebo group it was 44.4%.[11] the calculations were performed at 80% power, and a 5% margin of error. However, data was collected from120 patients.

Inclusion Criteria: Elective CABG surgeries performed by surgeons with at least 10 years of experience were included, regardless of the patients' age or gender.

Exclusion Criteria: Patients undergoing emergency surgery redo surgery, combined CABG and valvular surgery, poor LV function, recent MI, severe renal or hepatic dysfunction, allergic to Milrinone or any of its components, reopening and use of IABP were excluded from study

All eligible patients who met the inclusion requirements were enrolled after taking informed consent from them or their guardians. Patients were allocated non-randomly into two groups, Group-M & Group-S as shown in figure below.

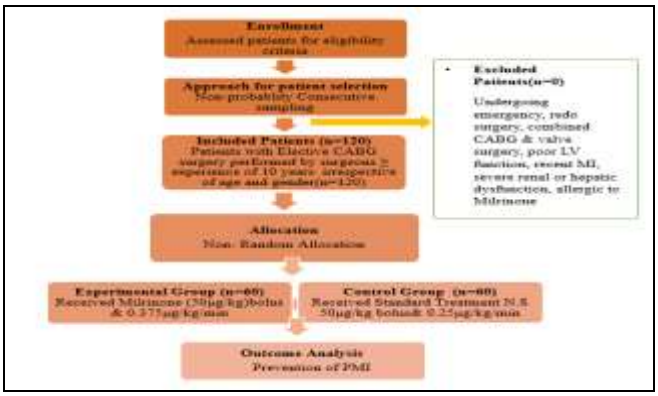

Figure: Consort Flow Diagram

Standard management of anesthesia was done in all patients. Inotropic and vasopressor support if required was provided with Adrenaline and Noradrenaline in addition to Milrinone. Before coming off bypass in on pump cases and after completion of grafting in off pump cases, bolus dose of Milrinone 50µg/kg was administered in Group- M and same volume of normal Saline in Group-S. Milrinone or Saline was continued for 24 hours in similar volumes. Infusion was started at 0.375µg/kg/min and titrated up and down, from 0.375 µg/kg/min to a maximum dose of 0.75µg/kg/min as per mean arterial pressure. The placebo, consisting of saline, was administered following the same protocol and manner as the Milrinone infusion. Hypotension was countered by volume infusion or increasing Noradrenaline support. The primary endpoint of the study was the prevention of PMI, as determined by electrocardiography (ECG) and cardiac biomarkers (CK and CKMB). ECG and cardiac biomarkers were done after surgery. Evidence of PMI by elevated.CK-MB more than 125U /L or CK-MB/CPK ratio more than 6% with ECG changes (new ST depression at least 0.1 mV or new ST elevation at least 0.2 mV, new Q waves or LBBB in 2 or more leads) was considered PMI. Patients were monitored for PMI during the 48 hours following CABG surgery. Data regarding frequency of other postoperative complications such as arrhythmias was also recorded. Data was collected by anesthesia registrar who was unaware of the infusion.

Data analysis was performed by using Statistical Package of Social Sciences (SPSS) version-28:00. Normality of all quantitative variables (age and

ejection fraction) was evaluated and both variables were not normally distributed thereby Median (IQR) was reported and for categorical data (Gender, comorbid, raised CKMB, IABP insertion, no of grafts, ECG changes and PMI), frequencies and percentages were calculated. Chi-square test/Fisher's exact test and Mann Whitney U test were applied to find the association and median differences for qualitative and quantitative variables among study groups respectively. A *p*-value ≤0.05 was considered as statistically significant.

RESULTS

A total of 120 participants with a median age of 58.00(53.00–68.75) years were included in the study. Of these, 106(88.3%) were males and 14(11.7%) were females. Arrhythmias were observed in 9(7.5%) patients, diabetes mellitus in 72(60.0%) cases, and hypertension in 62(51.7%) patients. ONCAB was performed in 111 patients (92.5%), while OPCAB was carried out in 9(7.5%) cases. Elevated CKMB levels were noted in 27(22.5%) patients as shown in Table-I.

Table-I: Demographic, Comorbid and Pre/Post-Operative Parameters of Study Participants (n=120)

Variables		Frequency (%)
Demographics		
Gender	Male	106(88.3%)
	Female	14(11.7%)
Age(years)		Median(IQR)
		58.00(53.00-68.75)
Comorbid		Frequency (%)
Hypertension		62(51.7%)
Diabetes Mellitus		72(60.0%)
Pre-operative parameters		Frequency (%)
Type of Surgical Procedure	ONCAB	111(92.5%)
	OPCAB	9(7.5%)
EF%		Median(IQR)
		50.00(47.25-56.00)
Grafts		Frequency (%)
	3	99(82.5%)
	4	21(17.5%)
Post-operative parameters		Frequency (%)
Hypotension		24(20.0%)
Inotropic Support	1	14(11.7%)
	2	84(70.0%)
	3	22(18.3%)
IABP insertion		9(7.5%)
CKMB Level	Raised	27(22.5%)
	Normal	93(77.5%)
ECG Changes	ST Elevations	11(9.16%)
	No ST Elevations	109 (90.83%)
PMI		8(6.67%)
Arrhythmias		9(7.5%)

EF= Ejection Fraction; IABP= Intra- Aortic Ballon Pump; CKMB= Creatine kinase Myocardial Band; ONCAB= On Pump Coronary Artery Bypass Grafting; OPCAB= Off Pump Coronary Artery Bypass Grafting; ECG=Electrocardiography

Each group included 60 patients, with a slightly higher proportion of males in Group-M than in Group-S [54(90.0%) vs. 52(86.7%); *p*=0.77]. Off-pump CABG was performed in 1 (1.7%) patient in Group-M and 8 (13.3%) in Group-S (*p*=0.03). Higher median EF was reported in Group-S [52.00% (48.00–54.00) % vs. 50.00(47.00–56.00) %.;*p*=0.85].

Hypotension was twice as common in Group M compared to Group S [16 (26.7%) patients vs. 8 (13.3%); *p*=0.10]. The need for an intra-aortic balloon pump (IABP) was similar between groups, [Group-M: 5 (8.3%) patients vs. Group-S: 4 (6.7%) *p*=1.00].

Statistically significant raised CKMB levels were noted in Group-S compared to Group-M [20 (33.3%) vs. 7 (11.7%) patients; (*p*=0.008). No significant difference in ECG changes were observed in both groups (*p*=0.52). The frequency of patients meeting PMI criteria was 4 (6.67%) in each group, which was statistically insignificant. (Table-II).

Table-II: Comparison of Demographics, Pre-operative, Post-operative Parameters and Complications Between Study Groups (n=120)

Variables		Group- M (n=60)	Group-S (n=60)	*p*-value
Demographics				
Age	Median(IQR)	61.00(53.00-71.00)	51.00(45.00-56.00)	0.01
Gender	Male	54(90.0%)	52(86.7%	0.77
	Female	6(10.0%)	8(13.3%)	
Comorbid		Frequency (%)		
Hypertension	Yes	34(56.7%)	28(46.7%)	0.36
	No	26(43.3%)	32(53.3%)	
Diabetes Mellitus	Yes	36(60.0%)	36(60.0%)	1.00
	No	24(40.0%)	24(40.0%)	
Pre-operative parameters		Median(IQR)		
`EF%		50.00(47.00-56.00)	52.00(48.00-54.00)	0.85
		Frequency (%)		
Type of Surgical Procedure	ONCAB	59(98.3%)	52(86.7%)	0.03
	OPCAB	1(1.7%)	8(13.3%)	
Post-operative parameters				
Hypotension	Yes	16(26.7%)	8(13.3%)	0.10
	No	44(73.3%)	52(86.7%)	
IABP	Yes	5(8.3%)	4(6.7%)	1.00
	No	55(91.7%)	56(93.3%)	
CKMB Level	Raised	7(11.7%)	20(33.3%)	0.008
	Normal	53(88.3%)	40(66.7%)	
ECG Changes	ST Elevations	4(6.7%)	7(11.7%)	0.52
	No ST Elevations	56(93.3%)	53(88.3%)	
PMI	Yes	4(6.7%)	4(6.7%)	1.00
	No	56(93.3%)	56(93.3%)	
Arrhythmias	Yes	4(6.7%)	5(8.3%)	1.00
	No	56(93.3%)	55(91.7%)	

EF= Ejection Fraction; IABP= Intra- Aortic Ballon Pump; CKMB= Creatine kinase Myocardial Band; ECG=Electrocardiography; PMI= Perioperative Myocardial Infarction; ONCAB= On Pump Coronary Artery Bypass Grafting; OPCAB= Off Pump Coronary Artery Bypass Grafting

DISCUSSION

This study showed that Milrinone successfully lowered CK-MB levels and improved coronary and

conduit blood flow, but it did not reduce the frequency of PMI, arrhythmias, or ECG changes in CABG patients. PMI in CABG patients was generally related with poor outcomes. Current study demonstrated no significant difference in occurrence of PMI between the control and experimental group (6.67% vs. 6.67%, p=1.00), indicating that Milrinone was ineffective at preventing PMI. A previous study found a substantial difference for PMI in both groups (4.7% versus 18%; p=0.002 in the Group-M and Group-C respectively).[8] The difference from the previous study may be attributed to variations in patient characteristics, dosing regimens, or postoperative management protocols.

Quintero-Altare *et al*.[11] found that Milrinone reduced arrhythmias (p=0 .01) whereas our study discovered no significant difference in arrhythmias between the groups (p>0.05). However, fewer individuals with arrhythmias were observed in Group-M. Kram *et al*.[12] found that 81(41.1%) patients developed new arrhythmias after cardiac surgery. This study cited overall nine (7.5%) patients had arrhythmias after CABG. Another study found a statistically significant difference in occurrence of arrhythmias between the Milrinone and Control group (p=0.01).[13]

Previous study found that new ST elevation occurred in 5 of 15 patients in the Group-M (33.3%) and 13 of 15 patients (86.7%) in the Nifedipine group (p<0.05).14 However, our study found ST elevation in 4(6.7%) patients in Group- M and 7(11.7%) patients in control group. You Z *et al*. concluded in their meta-analysis of randomized controlled trials that continuous infusion of Milrinone in perioperative period is effective in lowering the frequency of myocardial ischemia and myocardial infarction in patients after CABG, however, they found that it was unable to improve the overall morbidity and mortality or decrease the duration of intensive care unit stay.[15] Mehdi *et al*., found a significant difference in CK-MB levels immediately after surgery and 24 hours later between the two groups (p=0.03), with the Control-Group had higher levels than the Group- M.[14] This is consistent with our data, in which significant difference was observed in both groups, where CK-MB was raised in 20(33.33%) patients in Group-S compared to 7(11.71%) patients in Group-M (p=0.008).

Similarly, another recent meta-analysis showed that as compared to placebo or standard treatment, Milrinone was associated with reduced myocardial ischemia, infarction and arrhythmias However, use of IABP in both groups was similar which is comparable to our study. They reported no statistically significant difference in incidence of AKI, use of inotropic support, ICU stay and mortality with Milrinone.[10]

Literature has demonstrated a lower frequency of PMI after CABG in patients treated with Milrinone.[15,16] Previous study was conducted on the flow of blood in grafts after CABG surgery. It was shown that bolus of Milrinone was associated with increased blood flow in coronaries and conduits.[17] Milrinone use in patients undergoing CABG surgery was associated with better oxygenation and mixed venous saturation as compared to placebo group.[18,19] These factors are likely to be involved in reducing incidence of PMI. Previous study had also suggested that Milrinone be used to treat patients with heart failure, pulmonary congestion, and open heart surgery after myocardial infarction because to its beneficial and vasodilator effects.[20] Milrinone and other dilators have some role in increasing the blood flows in conduits and coronaries.

This study provided useful insights into the use of Milrinone in CABG patients, including its impact on PMI. Milrinone significantly reduced CK-MB levels, implying a potential cardioprotective effect that could affect postoperative care measures to decrease myocardial injury. Furthermore, the study demonstrated that Milrinone may not be beneficial in reducing PMI or arrhythmias, providing evidence that somehow contradicts previous studies. This information is critical for improving clinical decisions and optimizing treatment procedures in CABG patients.

However, Milrinone had certain benefits, such as lowering CK-MB levels and enhancing coronary and conduit blood flow after CABG, but it did not significantly reduce the risk of PMI, arrhythmias, or ECG changes in this study. These findings were in contrast to certain previous research and meta-analyses that found Milrinone to produce better results.

LIMITATIONS OF STUDY

The non-randomized approach may add selection bias, reducing the generalizability of the results. The limited sample size restricted the ability to detect statistically significant changes in outcomes such as myocardial infarction and arrhythmia. Furthermore, the single-center setting may limit the application of the findings. This study had no data on cardiac index.

CONCLUSION

Based on our study, we conclude that Milrinone may have some cardioprotective effects, by lowering CKMB level but it was not consistently effective in preventing PMI following CABG surgery. Additionally, no significant difference was found among study groups in prevention of PMI, arrhythmias, requirement of intra-aortic balloon pump and new ECG changes.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MAA & WA: Data acquisition, data analysis, critical review, approval of the final version to be published.

RM & SARAS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MN & KHQ: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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