

# Effect of milrinone on short-term outcome of patients with myocardial dysfunction undergoing coronary artery bypass graft: A randomized controlled trial

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## Abstract

**Background:** Myocardial dysfunction needing inotropic support is a typical complication after on-pump cardiac surgery. In this study, we evaluate the effect of milrinone on patients with ventricular dysfunction undergoing coronary artery bypass graft (CABG).

**Methods:** Seventy patients with impaired left ventricular function [left ventricular ejection fraction (LVEF) < 35%] undergoing on-pump CABG were enrolled. Patients were randomized to receive either an intraoperative bolus of milrinone (50 µg/kg) or saline as placebo followed by a 24-hour infusion of each agent (0.5 µg/kg/min). Hemodynamic parameters and transthoracic echocardiographic measurement of systolic and diastolic functions were the variables evaluated.

**Results:** Serum levels of creatine phosphokinase (CPK), the MB isoenzyme of creatine kinase (CK-MB), occurrence of myocardial ischemia or infarction, and mean duration of using inotropic agents were significantly lower in the milrinone group ( $p < 0.05$ ). There were no significant differences between the two groups regarding the development of ventricular arrhythmia, duration of cardiopulmonary bypass, intra-aortic balloon pump and inotropic support requirement, duration of mechanical ventilation, duration of intensive care unit stay and mortality rate. Although mean pre-operative LVEF was significantly lower in the milrinone group, there was no significant difference between post-operative LVEFs.

**Conclusions:** We suggest that perioperative administration of milrinone in patients undergoing on-pump CABG, especially those with low LVEF, is beneficial. (Cardiol J 2010; 17, 1: 73–78)

**Key words:** on-pump coronary artery bypass graft, low output syndrome, left ventricular dysfunction, milrinone, low left ventricular ejection fraction

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## Introduction

Myocardial dysfunction requiring inotropic support is a typical complication following on-pump cardiac surgery [1]. Low-output syndrome (LOS) is a major complication in approximately 30% of patients with reduced ventricular function undergoing coronary artery bypass graft (CABG) with cardiopulmonary bypass (CPB) [2]. This condition leads to delayed recovery, organ failure, increased duration of intensive care unit (ICU) stay, and higher hospital costs [3]. Furthermore, in patients with weak ventricular function, the LOS adds to the risk of early post-operative mortality [2].

Reversal of the LOS is needed to improve myocardial contractility and tolerate cardiac loading conditions which are achieved by instituting appropriate inotropic drugs and fluid management plans [4].

Myocardial  $\beta_1$ -receptor desensitization occurs chronically in patients with congestive heart failure [5, 6] and acutely following CPB [7], therefore limiting the efficacy of  $\beta$ -agonists for post-CABG cardiac failure. Phosphodiesterase-III inhibitors, including milrinone and amrinone, provide an alternative means of inotropic support via non  $\beta_1$ -adrenergic pathways and vasodilatation [8, 9]. These agents also improve hemodynamic parameters and increase blood flow of the grafted internal mammary arteries as well as middle cerebral arteries during CABG [2].

Previous studies have revealed that both milrinone and amrinone improve ventricular function and hemodynamic status after CPB in patients who have been treated with catecholamines and nitroglycerin for a long time [10–12].

There are limited studies evaluating the effects of milrinone on cardiac function in patients with LOS who undergoing CABG. The present study was designed to test the hypothesis that milrinone can reduce the risk of developing myocardial ischemia and infarction after CABG in patients with pre-existing myocardial dysfunction.

## Methods

### Patients

This study was reviewed and approved by the local ethical committee of Tehran University of Medical Sciences. All participants gave written informed consent pre-operatively. Seventy consecutive patients with left ventricular ejection fraction (LVEF) lower than 35% [13, 14] who were selected

for elective isolated CABG, enrolled in a randomized, double-blind, placebo controlled trial at Shariati Hospital. Patients who underwent emergency CABG, those with myocardial infarction (MI) or ventricular arrhythmias within 72 hours before the operation, and those requiring inotropic support prior to the surgery were excluded. Concomitant valvular heart disease and left bundle branch block were other exclusion criteria.

Seventy eligible patients were randomly assigned to receive milrinone ( $n = 35$ ) or a placebo ( $n = 35$ ) intravenously within 24 hours after CABG. Milrinone or a saline placebo was administered as a bolus dose ( $50 \mu\text{g}/\text{kg}$ ) immediately after CABG and continued as an infusion ( $0.5 \mu\text{g}/\text{kg}/\text{min}$ ) for 24 hours later.

A need for inotropic support was defined as observation of diminished cardiac contractility by using transthoracic echocardiography and inspection of the right ventricle during and after weaning [15]. Inotropic support was provided by using a second inotrope without vasodilator activity (dopamine). Second inotropic agents were administered after giving milrinone if needed.

All operations were done by the same cardiac surgery team. Utilizing visual inspection, LVEFs were measured 24 hours before and 24 hours after each operation by a single expert cardiologist who was blind to the study.

### Surgical technique

In both groups, a standard CPB technique was used. Median sternotomy and harvesting of the internal mammary artery as pedicled fashion were followed by full exposure of the coronary artery branches to be revascularized. Then, the left internal mammary artery was used as the main graft on the left anterior descending artery and the saphenous vein was utilized as a conduit for other coronary arteries.

All patients underwent on-pump CABG with moderate hypothermia and simultaneous retro- and ante-grade blood cardioplegia.

Following aortic clamp removal, milrinone or saline (placebo) administered as an intravenous (IV) bolus dose of  $50 \mu\text{g}/\text{kg}$  followed by infusion of  $0.5 \mu\text{g}/\text{kg}/\text{min}$  during the next 24 hours.

### Measurement of variables

Creatine phosphokinase (CPK) and creatine kinase MB (CK-MB) were measured immediately after the surgery and four and 24 hours later. Required data including demographics, pre- and post-operation LVEF, CPK and CK-MB levels, CK-MB/

**Table 1.** Comparison of baseline characteristics of patients between two groups.

	Milrinone (n = 35)	Control (n = 35)	P
Age	56.9 ± 9.7	58.2 ± 8.4	0.57
Sex (male/female)	25/10	28/7	0.58
Diabetes (%)	25.7	20	0.77
Hypertension (%)	54.3	60	0.80
Prior myocardial infarction (%)	42.9	51.4	0.63
Three vessels CAD (%)	40	45.7	0.80
≥ 3 grafts (%)	63	49	0.22
Pre-operative LVEF (%)	31.8 ± 3.2	34.5 ± 1.4	0.001*
Post-operative LVEF (%)	34.7 ± 4.5	33.1 ± 3.2	0.098

Data presented as mean ± standard deviation; LVEF — left ventricular ejection fraction; CAD — coronary artery disease; \*significant difference (independent samples t-test)

/CPK ratio, CPB time, duration of inotropic support, length of ICU stay as well as appearance of ventricular arrhythmia, and the need for an intra-aortic balloon pump (IABP) were recorded for each patient.

Evidence of myocardial ischemia and development of MI were also recorded. New ST depression (at least 0.1 mV) or new ST elevation (at least 0.2 mV) on electrocardiography were considered as evidence of myocardial ischemia. Development of MI was defined as rising in CPK, CK-MB or CK-MB/CPK ratio more than 6% concomitant with electrocardiography changes (appearance of new Q wave or conductive abnormality) or echocardiographic evidence of ischemia (new wall motion abnormality) were also recorded.

### Statistical analysis

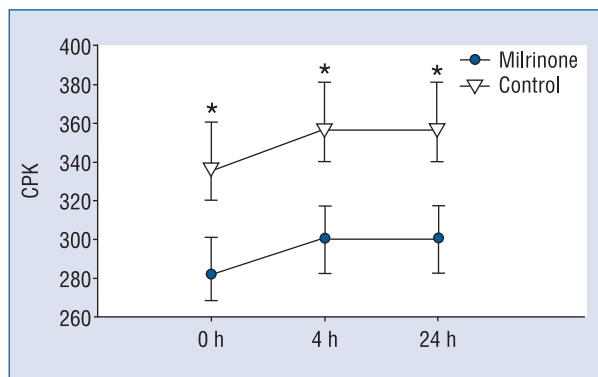
The primary endpoint of this study was development of myocardial ischemia and/or MI. Other endpoints were cardiac enzyme levels and duration of inotropic support. Sample size and power were estimated by determining the number of patients required to show the significant difference between risk ratio of the ischemic evidence development by eight hours after CABG. It was determined that 33 patients in each group (66 in total) would be required to show a statistically significant difference between the two groups using an alpha of 0.05 and power of 80%. We enrolled two extra patients in each group in case a patient dropped out of the study. SPSS software (SPSS Inc., Chicago IL. version 11.5) was used for statistical analysis. Independent samples t-test,  $\chi^2$  and Fischer’s exact test were used for statistical analysis. A p value < 0.05 was considered statistically significant.

### Results

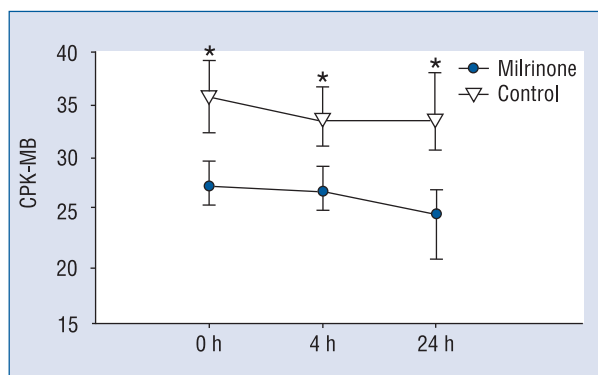
Data was collected for 70 consecutive patients meeting the inclusion criteria, with 35 in each study group. A comparison of baseline demographic information, as well as pre-operative and post-operative variables by treatment group, is presented in Table 1. Mean age of the patients was 57.6 ± 9.1 (mean ± standard deviation) and ranged from 33 to 75 years. Of the 70 patients, 53 were male. There were no significant differences between the two study groups regarding age and sex distributions.

The number of grafts which were used ranged from one to six. Although the mean duration of CPB was longer in the control group (96.5 min for control and 92.9 for milrinone), it was not statistically significant (p > 0.05).

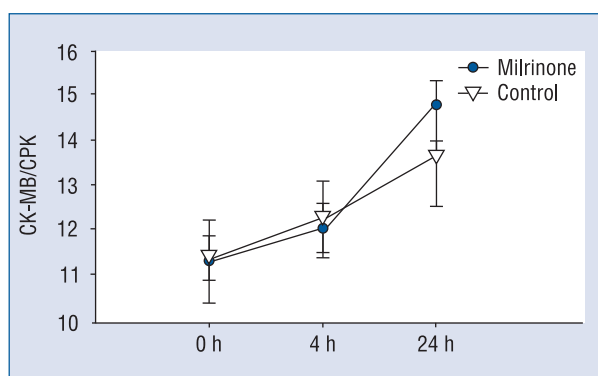
The values of CPK (Fig. 1) and CK-MB (Fig. 2) measured immediately after operation, four hours, and 24 hours later, were significantly lower in the milrinone group, while the CK-MB/CPK ratio was comparable in both groups (Fig. 3). Evidence of myocardial ischemia on electrocardiography after 24 hours was found in 16 patients of the placebo group and in four patients of the milrinone group (p = 0.003, odds ratio: 6.53 with 95% confidence interval: 1.90–22.45). Evidence of MI after 24 hours was found in eight patients, all belonging to the placebo group (p = 0.005). Ventricular arrhythmia occurred in five and ten patients in the milrinone and control groups respectively, which was not statistically significant (p = 0.244). In addition, there was no significant difference between the two groups regarding IABP requirement (one in the milrinone and four in the control group, p = 0.35). Inotropic support



**Figure 1.** Creatine phosphokinase (CPK) concentrations among study groups measured immediately after surgery (0 h), at four hours (4 h), and at 24 hours (24 h) following the procedure; \*indicates the significant difference between milrinone and control groups.



**Figure 2.** Creatine kinase MB (CK-MB) concentrations among study groups measured immediately after surgery (0 h), at four hours (4 h), and at 24 hours (24 h) following the procedure; \*indicates the significant difference between milrinone and control groups.



**Figure 3.** Creatine kinase MB (CK-MB) to creatine phosphokinase (CPK) — CK-MB/CPK ratios among study groups measured immediately after surgery (0 h), at four hours (4 h), and at 24 hours (24 h) following the procedure.

was used in 33 patients in the milrinone group and 32 patients in the control group ( $p = 0.99$ ), while duration of inotropic support was longer in the control group ( $p = 0.007$ ). The mean pre-operative LVEF was lower in the milrinone group ( $p = 0.001$ ), while the difference between post-operative LVEFs was not significant ( $p = 0.098$ ; Table 2). The mean ICU stay was 2.4 (range from one to four) days and 2.1 (range from one to three) days in the control and milrinone groups respectively ( $p > 0.05$ ). No re-sternotomy, stroke or renal failure occurred. Post-operative death occurred in two patients (both in the control group, due to cardiogenic shock) while no death occurred among patients treated with milrinone. However, the difference was not statistically significant ( $p > 0.05$ ).

### Discussion

Our results revealed that administration of bolus doses of milrinone, followed by continuous maintenance infusion for about 24 hours post-operatively, will reduce the serum level of CPK, CK-MB and evidence of myocardial ischemia and infarction in patients with impaired left ventricular function undergoing CABG. We used a bolus milrinone dose of  $50 \mu\text{g}/\text{kg}$  with an infusion at the rate of  $0.5 \mu\text{g}/\text{kg}/\text{min}$  because it had previously been found that it maintains plasma concentrations at the threshold of therapeutic effects or above [16].

Myocardial ischemia and infarction are major complications immediately after coronary artery bypass grafting. They may be due to incomplete surgical revascularization, perioperative anesthetic management or vasospasm of arterial grafts, e.g. the internal mammary artery [17]. The efficacy and safety of milrinone for treatment of LOS are well known [18, 19]. Furthermore, it has been shown that milrinone lessens myocardial ischemia and cell damage after elective CABG [17]. We also observed high rates of MI and myocardial ischemia in the placebo group (eight and 16 cases respectively) which shows that milrinone protects against serious myocardial ischemia. There are also several experimental studies that suggest protective effects of phosphodiesterase III inhibitors against myocardial ischemia on both right and left ventricles [20, 21]. Sanada et al. [21] suggested that pretreatment with phosphodiesterase III inhibitors such as milrinone has cardioprotective effects in canine hearts. These cardioprotective effects are exerted via cAMP-, protein kinase A-, and p38 mitogen-activated protein kinase-dependent but protein kinase C-independent mechanisms in canine hearts.



**Table 2.** Comparison of operative and post-operative parameters between two groups.

Variable	Milrinone (n = 35)	Control (n = 35)	P
Myocardial ischemia	4 (11.4%)	16 (45.7%)	0.003*
Myocardial infarction	0	8 (22.8%)	0.005*
Duration of CPB [h]	92.9 ± 16.9	96.5 ± 22.9	0.47
Duration of inotropic support [h]	13.9 ± 3.3	17.9 ± 7.6	0.007*
ICU stay (days)	2.1 ± 0.5	2.4 ± 0.9	0.16
Duration of mechanical ventilation [h]	12.3 ± 7.3	14.3 ± 4.5	0.18
Need for IABP	1 (2.9%)	4 (11.4%)	0.35

CPB — cardiopulmonary bypass; ICU — intensive care unit; IABP — intra-aortic balloon pump; \*significant differences

Our results are consistent with previous studies suggesting that milrinone decreases post-operative deterioration of cardiac function after weaning from CPB [10, 11]. Kikura et al. [10] reported that milrinone reduces inotropic support (dopamine) after surgery. In our study, there was no difference between the two groups regarding inotropic support requirement. However, duration of inotropic support was significantly lower in patients treated with milrinone, which agrees with the report by Levy et al. [22] which suggested that milrinone is an alternative to other inotropic drugs.

In our study, pre-operative LVEF was significantly lower in the milrinone group, while there was no difference between post-operative LVEFs in the two groups. Reduction in LVEF after cardiac surgery can be explained by the stunning effect, but increased post-operative LVEF in patients treated with milrinone is an important issue, which has been reported by Konstam et al. [23]. They suggested that short-term infusion of positive inotropic agents such as milrinone or dobutamine will usually result in a transient increase in left ventricular systolic performance and cardiac output, George et al. [24] also showed that milrinone has inotropic and vasodilator effects, increases cardiac performance and corrects low cardiac output in all patients. Moreover, they reported a rise in the cardiac index, systolic index and left ventricular stroke work index by using milrinone. Similar to a previous report [23], we could not find significant differences between the two groups regarding using IABP.

This study had some limitations that readers should bear in mind. A very short follow-up was one of the limitations. We did not measure cardiac troponin in this study, and that can be considered as a limitation of our study. However, our findings showed significant changes in serum level of other enzymes. Absence of data on cardiac index, blood urea nitrogen and creatinine values which can be

used for end organ perfusions are other limitations. Also we had no data on Swan-Ganz measurements of cardiac function.

### Conclusions

The present study demonstrates that administration of milrinone in patients undergoing on-pump CABG, especially those with low LVEF, may decrease MI rate and duration of inotropic support.

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The authors do not report any conflict of interest regarding this work.

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