

Cardio-Protective Effects of Oral Nicorandil in Patients Undergoing Cardiac Valve Surgery

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Abstract

Background: Reduction of myocardial reperfusion injury during cardiopulmonary bypass is an essential requirement for increasing the success rate, decreasing morbidity and mortality of open-heart surgery. **Aim:** To study the role of pre-operative oral nicorandil in decreasing reperfusion cardiac injury in patients subjected to cardiac valve surgery. **Patients and Methods:** The study included 62 patients, who were equally randomized into two groups: nicorandil group and control group. Pre-operative, intra-operative and post-operative data were reported and analyzed. Left Ventricle Ejection Fraction (LVEF) was estimated pre-operatively and postoperatively for both groups. Troponin I, creatine kinase-muscle/brain (CK-MB), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) were measured before surgery by 24 hours then 4, 12 and 48 hours after aortic cross clamp removal. **Results:** Nicorandil considerably decreased TNF- α and IL-6 after 4 and 12 hours following the removal of aortic clamping. It also reduced troponin-I and CKMB at the same time points. However, there were no important changes in IL-6, TNF- α , troponin-I and CK-MB levels in control group in comparison to nicorandil group in the next 48 hours following the removal of aortic clamping. **Conclusions:** Pre-operative oral nicorandil expressively decreased myocardial reperfusion damage during open heart valve operations, this evidenced by the decrease in the postoperative use of inotropic drugs, considerable reduction of postoperative elevation of cardiac enzymes and inflammatory cytokines with no reported complications.

Keywords

Nicorandil for Myocardial Protection, Cardiopulmonary Bypass,

1. Introduction

Myocardial Ischemia-reperfusion (IR) injury is a known complication of cardiac operations with the use of heart lung machine [1]. Because the rate of operations on older individuals and high risk score patients increases, many methods have been tried to advance cardiac protection during open heart surgeries [2]. IR injury is defined as the myocardial damage due to restoration of blood stream following a transient period of coronary flow occlusion [3].

Systemic inflammatory response syndrome (SIRS) which may occur with myocardial ischemia reperfusion injury during cardiopulmonary bypass (CPB), can be responsible for complications and mortality events in open heart surgery [4] [5]. Therefore, it is continuously required to look for new methods for improving myocardial function while performing heart surgeries to improve outcome and reduce complications and mortality [6].

Clinical studies have established that nicorandil, which has an action similar to nitrate, protects the heart from ischemic reperfusion injury through improvement of the post-ischemic myocardial dysfunction [7].

Many articles have been published since 1992 till now discussing the safety and cardio-protective effect of Nicorandil; most of the authors studied the effect of intravenous use of nicorandil during cardiopulmonary bypass in patients undergoing CABG surgery [8] [9] [10]; others discussed the cardio-protective effect of intravenous nicorandil during cardiopulmonary bypass regardless the procedure which may be CABG or valve surgery [11] [12]; others discussed the effect of pre-operative oral nicorandil on myocardial protection in comparison to remote ischemic pre-conditioning through limb ischemia [13]; here in our study we tried to explore the effect of pre-operative oral nicorandil on myocardial ischemia/reperfusion injury and record its effect in patient subjected to open heart valve surgery.

2. Patients and Methods

This controlled prospective randomized study has been carried out on 62 patients at the Department of Cardiothoracic Surgery, Sohag University Hospital, Sohag, Egypt; between January 2018 to November 2018. The study was carried out. The research protocol has been agreed by the research and investigations ethics board of the University. Patient consent has been fulfilled. Adult Patients with rheumatic heart valve lesions undergoing valve surgery either replacement and /or repair were enrolled in the study.

We have excluded patients, who associated with congenital heart diseases, coronary artery disease, severe other system disorders (pulmonary, renal, hepatic,

and, endocrine) patients with severe pulmonary artery hypertension, patients with infective endocarditis, also redo and emergency surgery were excluded. The study included 62 patients who were randomized to two groups: control group (31 patients) who did not receive nicorandil and nicorandil group (31 patients); who received oral nicorandil for 10 days pre-operatively; Nicorandil was administered as 10 mg twice daily, the last dose was at the night before surgery.

Pre-operative data: including patient characteristics, clinical history, laboratory findings, echocardiography reports and electro-cardiographic findings were recorded and studied.

Operative data: we have used the same surgical technique to both groups, Medline sternotomy incision was performed. Heparin was used to achieve and maintain Activated clotting time (ACT) above 470 seconds. Cardio-pulmonary by-pass (CPB) has been established with modest hypothermia (28°C to 32°C). Antegrade cold crystalloid cardioplegia was used for achieving myocardial protection, average arterial blood pressure between 50 and 70 mmHg was maintained. Valve replacement with a mechanical prosthesis and/or valve repair was done. Cardiopulmonary by-pass (CPB) time, aortic cross clamp time (ACC) and the intra-operative use of inotropic drugs were recorded in all cases.

Post-operative data: the patient's requirements of inotropic drugs in the intensive care unit were recorded, Echocardiographic examination was performed for every patient; left ventricular ejection fraction (LVEF%) was recorded 24 hours preceding and next to the operation. Samplings of five milliliter of Venous-blood from each patient were reserved 24 hours before surgery, and then four, twelve and forty-eight hours post aortic cross clamp removal. From these blood samples, CKMB, troponin I, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α) were estimated and recorded for all cases.

Plasma level of troponin I was measured, utilizing Enzyme-linked immunosorbent assay (ELISA) kits (Monobind Inc., Lake Forest, USA). Measurement of CK-MB: Serum iso-enzyme of CK-MB concentration was determined by kinetic method utilizing a commercially available assay kits (Spectrum diagnostics, Hannover, Germany); the mean reading of serial readings everyone minute for 4 readings was considered. Determination of Serum concentration of TNF- α and IL-6: Using ELISA kits (Orgenium Laboratories, Vantaa, Finland and Ray Biotech Inc., Norcross, USA respectively). Duration of post-operative hospital admission with attention to post-operative intensive care admission days was recorded for every patient.

Statistical analysis: was conducted using SPSS (Version 20) statistical software for Windows (IBM Corporation, Chicago, IL, USA). The data were calculated as mean \pm standard deviation or range for continuous variables and as numbers with percentages for categorical variables. Concerning qualitative data, Chi-square test was used for comparison between two or more than two groups, while student's t-test has been used to compare the quantitative data among means of two groups. A p-value was considered statistically considerable (significant) if it was less than 0.05.

3. Results

Data from nicorandil group (31 patients) and control group (31 patients), collected pre-operatively which include age, gender, associated co-morbidities, LVEF, serum CKMB, Troponin I, TNF, IL6 and intra-operatively which include CBP, ACC and intra-operative use of inotropes. statistical work up and comparison of the data between the two groups, revealed that, there is no considerable differences (P value > 0.05) which may affect the myocardial status, this finding is indicative of the pre and intra-operative similarity of both groups, as shown in **Table 1**.

Nicorandil decreased cardiac ischemic injury after open heart valve operations; this finding was evidenced by measurement of troponin I, CKMB, interleukin six (IL 6) and tumor necrosis factor alpha (TNF- α) values at four, twelve and forty-eight hour post release of aortic cross-clamp as depicted in **Table 2**.

Table 1. Patient demographics, Pre-operative and intra-operative variables that may affect myocardial function.

Variable	Control group (n)31	Nicorandil group (n)31	p value
Age (y)	38.9 \pm 11.18	39.8 \pm 12.71	0.548
Sex	Male	13 (42%)	0.844
	Female	18 (58%)	
DM	Yes	4 (13%)	0.735
	No	27 (87%)	
Hypertension	Yes	6 (19%)	0.875
	No	25 (81%)	
Smoking	Yes	5 (16%)	0.978
	No	26 (84%)	
pre-op LVEF%	63.55 \pm 4.23	65.4 \pm 5.42	0.495
pre-op R-wave amplitude in V5 (mm)	24 \pm 0.66	25 \pm 0.57	0.338
pre-op CKMB	6.55 \pm 0.57	6.66 \pm 0.76	0.753
Preop Troponin I	0.210 \pm 0.10	0.217 \pm 0.08	0.873
Preoperative TNF- α	12.38 \pm 1.19	13.04 \pm 1.28	0.124
Preoperative IL-6	18.55 \pm 1.31	17.11 \pm 1.58	0.184
Type of valve surgery	MVR	16 (51.6%)	0.876
	MVR + TR	6 (19.3%)	
	AVR	5 (16.1%)	
	DVR	4 (13%)	
CPB time (min)	76.5 \pm 11.13	79.14 \pm 10.87	0.245
ACC time (min)	56.75 \pm 11.18	54.9 \pm 13.51	0.384
Operative use of inotropes	yes	24 (77.5%)	0.315
	No	7 (22.5%)	

LVEF: left ventricular ejection fraction, MVR: mitral valve replacement, TR: tricuspid repair, AVR: aortic valve replacement, DVR: double valve replacement. CPB: cardiopulmonary bypass, ACC: aortic cross clamp.

Table 2. Postoperative Effect of nicorandil on indicators of myocardial ischemic reperfusion injury.

Variable		Control group (n)31	Nicorandil group (n)31	p value
Post-op uses of inotropic drugs	yes	18 (59%)	9 (29%)	0.018*
	No	13 (41%)	22 (71%)	
Overall number of inotropic drugs		1.48 ± 1.07	0.66 ± 0.73	0.048*
Post-operative R-wave amplitude reduction in V5 (4 h) mm		4.6 ± 0.85	3.63 ± 0.89	0.011*
post-op LVEF%		56.48 ± 3.66	62.22 ± 3.55	0.048*
	4 hours	51.76 ± 3.87	38.67 ± 3.44	0.031*
Post-operative CKMB	12 hours	43.08 ± 2.43	34.75 ± 2.33	0.001*
	48 hours	14.05 ± 2.66	13.05 ± 3.55	0.816
Post-operative Troponin I	4 hours	1.36 ± 0.18	1.12 ± 0.16	0.017*
	12 hours	1.54 ± 0.31	1.18 ± 0.22	0.006*
Post-operative tumor necrosis factor alpha (TNF- α)	48 hours	0.54 ± 0.44	0.52 ± 0.45	0.741
	4 hours	20.3 ± 2.44	15.17 ± 1.56	0.001*
Post-operative interleukin 6 (IL-6)	12 hours	16.36 ± 2.37	13.17 ± 1.55	0.081*
	48 hours	12.33 ± 1.44	12.1 ± 1.25	0.649
Intensive care unit stay	4 hours	36.71 ± 2.99	27.06 ± 3.4	0.021*
	12 hours	29.84 ± 5.66	23.18 ± 3.46	0.004*
Length of post-operative hospital stay	48 hours	22.66 ± 1.99	21.77 ± 2.36	0.162
		2.66 ± 0.55	2.49 ± 0.33	0.588
		11.10 ± 1.35	10.85 ± 1.20	0.964

*: Statistically considerable (significant) difference compared to control ($p < 0.05$).

Estimation of Troponin I Levels post-cardiac surgery for both groups showed an obvious increase with a peak value at twelve hours after removal of the aortic clamp, and then it decreased gradually in both groups. However, troponin I levels (mean), four hours (1.12 ± 0.16) and twelve hours (1.18 ± 0.22) after removal of the aortic clamp in nicorandil group were statistically considerably less than their respective values in control group which was 1.36 ± 0.18 at four hours and 1.54 ± 0.31 ng·L at 12 hours (p value < 0.05), but there was no important variance in troponin I levels in both groups after 48 hours (p value = 0.741) following the removal of aortic clamp (**Table 2 & Figure 1**).

CK-MB levels increased post-operatively in both groups and showed a peak value at 4 hours after removal of aortic clamping then it decreased gradually in both groups. However, CK-MB mean levels, four hours (38.67 ± 3.44 ng·L) and twelve hours (34.75 ± 2.33 ng·L) following aortic clamp release in nicorandil group were statistically important lower (p value < 0.05) compared to their respective values in control group which was 51.76 ± 3.87 ng·L, 43.08 ± 2.43 ng·L at four and twelve hours respectively, but there was no important difference in CK-MB levels in the two groups after 48 hours following the removal of aortic clamping (**Table 2 & Figure 2**).

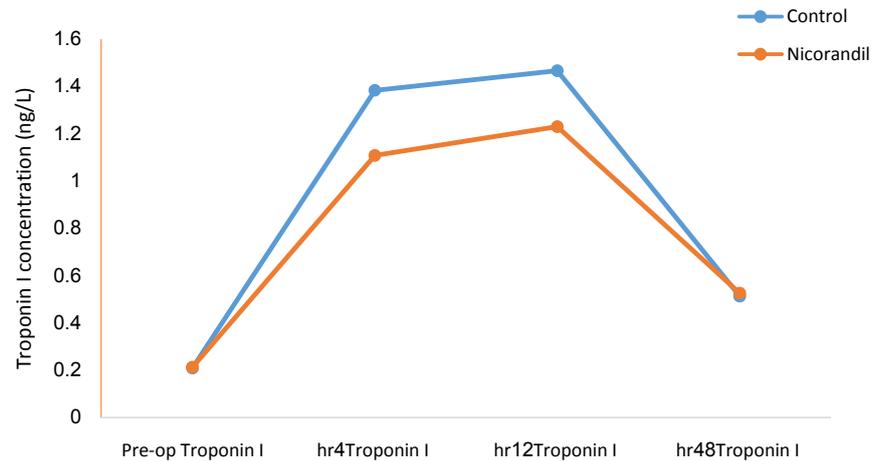


Figure 1. Pre-operative and serial post-operative Troponin I value in control & nicorandil groups.

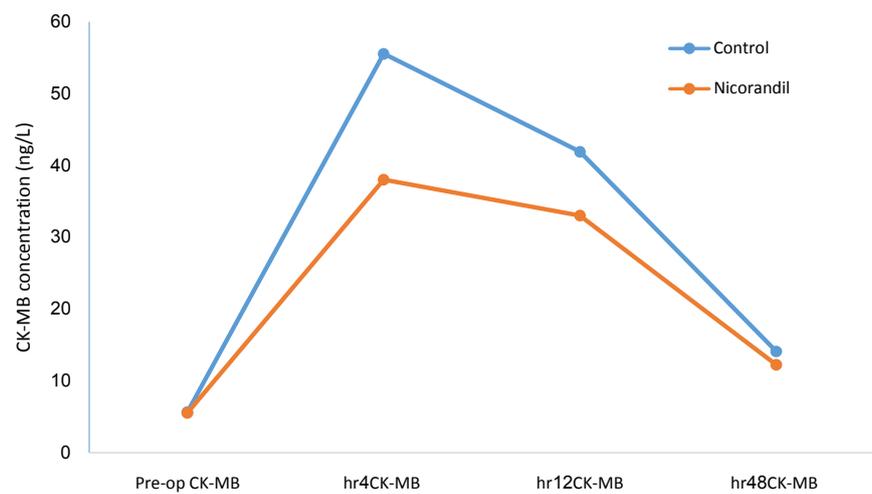


Figure 2. Pre-operative and serial post-operative CKMB values in control & nicorandil groups.

As regard the pre-operative LVEF%, No considerable difference was detected among both control and nicorandil groups (P value = 0.495). Post-operatively, the LVEF% values were higher considerably in nicorandil group compared to control group (P value = 0.048) as shown in **Figure 3**. This also indicates that nicorandil reduced injury of myocardium after valvular cardiac surgery.

The pre-operative baseline values of the mean levels of IL-6 were 18.55 ± 1.31 ng-L, 17.11 ± 1.58 ng-L for control and nicorandil groups respectively. The pre-operative baseline values of the mean levels of TNF- α were 12.38 ± 1.19 ng-L, 13.04 ± 1.28 ng-L for control and nicorandil groups respectively. It is found that, there is no statistically significant difference between the pre-operative measurements of IL-6 and TNF- α for both groups (p value > 0.05).

TNF- α and IL-6 levels were increased after surgery in both groups showing peak values at four hours after aortic unclamping, then the values of both IL-6 and TNF- α decreased gradually in both groups.

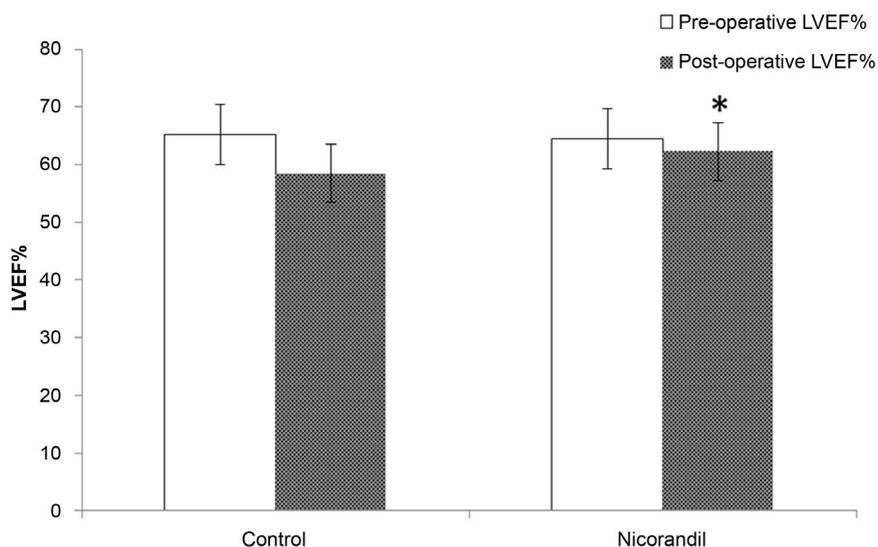


Figure 3. Pre-operative and post-operative LVEF% values in control & nicorandil groups. Values are shown as mean \pm standard deviation. *Means statistically considerable (significant) difference compared to control $p < 0.05$.

However, serum levels of IL-6 and TNF- α at four hours and twelve hours after aortic unclamping were statistically considerable (P value < 0.05) lower in the nicorandil group compared to their respective values in control group, but there was no important variance in IL-6 and TNF- α levels in both groups after 48 hours from aortic unclamping. There is a statistically considerable decrease in the post-operative need of inotropic drugs in nicorandil group; however, there is no important variance in both groups as regard ICU stay and hospital stay (Table 2). No complications were reported in this study interrelated to nicorandil use.

4. Discussion

Nicorandil is a dual action anti-anginal drug. It is the unique potassium channel agent with an anti-anginal properties, has an active role in the dilatation of the coronary arteries and other blood vessels [14] [15]. Moreover, no bad consequences on the contractile function, conductive system or heart rhythm has been reported [16]. Ischemia-reperfusion (IR) injury after open heart surgery is usually associated with more complications that can reach mortality, so adequate myocardial protection is very important to prevent myocardial injury after CPB [17].

In the present study nicorandil showed a statistically considerable improvement in post-operative LVEF% compared with control group which means that nicorandil provided myocardial protection after valvular cardiac surgery, and this was proved laboratory by detecting the postoperative decrease in CK-MB and troponin I levels compared to control group. Other studies concluded the same effect of nicorandil (either in oral or intravenous) on the myocardium during coronary angioplasty [18] [19].

During open heart surgery and after discontinuation of CPB, the R-wave am-

plitude usually reduced which results from ischemic myocardial reperfusion injury [20]. In our study, a statistically considerable increase in the R wave amplitude in V5 was observed in the nicorandil group than control group after four hours and 24 hours, this result is in agreement with the results published in the literature [13].

CK-MB concentration after CABG surgery showed a considerable decrease after coronary surgery in patients subjected to ischemic limb preconditioning [21]. other studies disclosed that Remote ischemic preconditioning and nicorandil pretreatment, equally, reduced ischemic myocardial reperfusion damage during open heart valve surgery which were noticed by consecutive troponin I and CK-MB concentrations postoperatively [13].

A recent Meta-analysis performed on 1616 patients subjected to percutaneous coronary intervention (PCI) concluded that; Nicorandil can reduce the level of CK-MB and troponin T after, at six hours, twelve hours, eighteen hours and twenty-four hours. Also Nicorandil can decrease the incidence of adverse reactions post percutaneous coronary intervention [22].

Teoh L. K. *et al.* had compared the outcome of Adenosine preconditioning versus ischemic preconditioning on myocardial reperfusion injury post open heart surgery for coronary artery bypass grafting (CABG), They concluded that ischemic preconditioning has an extra effect than pharmacological preconditioning in reducing myocardial damage during coronary surgery [23].

On the other hand, Blanc P. and his colleagues in their study; concluded that no statistically important variance between placebo group and nicorandil group on cardiac enzymes release and hemodynamic variables in patients undergoing CABG surgery. The authors assumed that nicorandil, was safe for usage as a medication but there was uncertainty about its cardio protective result [24]. We agree with Blanc P. and as regard the safe use of nicorandil but there is a controversy as regard the levels of post-operative myocardial enzymes concentration. The difference between results may be attributed to the nature of surgery, myocardial injury more pronounced in valve surgery than CABG.

Our results are in accordance with the results of the previous work of Abdel-Hady and his colleagues who compared the post-operative LVEF and cardiac enzymes of three group of patients (control, remote-ischemic pre-conditioning and Nicorandil groups), all of them subjected to open heart valve surgery by the same techniques, they found that both groups (Nicorandil group, remote ischemic preconditioning group) show a considerable decrease in the immediate post-operative elevation of cardiac enzymes than control group, considerable increase of the postoperative LVEF than the control group and considerable decrease in the post-operative need of inotropic drugs which matched with our results [13].

In a recent systematic meta-analysis about the clinical trials studying the prevention of contrast-induced acute kidney injury (CI-AKI) in high-risk adult patients undergoing coronary artery catheterization through drug pre-conditioning

by using nicorandil. the results revealed a statistically considerable decrease in the incidence of CI-AKI [16]. In open heart surgery; the contact of the blood to tubes used in cardiopulmonary circuit, the operating trauma, and abrupt excessive variations in the human temperature lead to systemic inflammatory response (SIR) [25]. The syndrome of systemic inflammatory response, involves leakage of inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNF- α) which have an important effect on myocardial IR injury and cause damage to the myocardium [26]. Our study showed high values of serum IL-6 and TNF- α after valvular surgery, however this increase in IL-6 and TNF- α values after 4 and 12 h was considerably higher in control group in comparison to nicorandil group.

The ability of nicorandil to decrease the pro-inflammatory cytokines may be related to nitric oxide that is liberated from nicorandil and may be involved in suppression of atomic factor, named κ B factor, it controls the expression of many genetic factors including those responsible for the release of IL-6 and TNF- α and therefore decreasing the level of these pro-inflammatory cytokines by blocking their mRNA expression [27].

Our results were in accordance with the results of Wei and his colleagues; who focused on the outcome of nicorandil effect and they found that, it modulate the inflammatory mediators release and inhibited the release of TNF- α from lymphocytes [25].

5. Conclusion

Our study outcomes suggest that nicorandil reduces the ischemia and reperfusion injury, evidenced by an improvement of post-operative LVEF% and a decrease in CKMB and troponin I enzymes, the cardiac enzymes that reflect myocardial muscle injury. The effect of nicorandil is attributed to its ability to suppress pro-inflammatory cytokine production such as TNF- α and IL-6. Finally, we conclude that nicorandil may be a promising useful agent for cardio-protection during open heart valve surgery.

Limitation of the Study

The small size sample and different surgeons doing the procedures may affect the results.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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