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Original Article

Nicorandil reduces myocardial injury and improves cardiac function in valve replacement surgery

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Abstract

Background: Myocardial injury during cardiac surgery is associated with increased morbidity and mortality, and proper myocardial protection improves surgical outcomes. We aimed to study the role of preoperative nicorandil in myocardial protection during valve replacement surgery.

Methods: The study included 40 patients who were randomized into two groups: control group, and nicorandil group. Preoperative, intraoperative, and postoperative data were collected. Creatine kinase- MB (CK-MB), troponin I, malondialdehyde (MDA), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were measured 24-hours before surgery then 4, 12 and 48 hours after aortic cross-clamp removal.

Results: Nicorandil significantly decreased MDA (p=0.005 and 0.036), TNF-α (p< 0.001), IL-6 (p<0.001 and 0.003) 4 and 12 hours following the removal of aortic clamp compared to the control group. Additionally, It significantly reduced CK-MB (p< 0.0001 and 0.0002) and troponin-I (p= 0.0002 and < 0.0001) 4 and 12 hours after the removal of the aortic clamp, respectively. However, there was no significant difference in MDA, TNF-α, IL-6, CK-MB, and troponin-I levels between the nicorandil and the control group after 48 hours following the removal of aortic clamping (p= 0.084; 0.64; 0.12; 0.12; 0.75; respectively).

Conclusions: Nicorandil reduced myocardial injury significantly in valve replacement surgery. Nicorandil decreased CK-MB and troponin I and improved postoperative left ventricular ejection fraction.

KEYWORDS

Nicorandil; Ischemia-reperfusion injury, Cardiopulmonary bypass, Heart valve surgery, Myocardial protection, Oxidative stress, Inflammatory cytokines

Article History

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Introduction

Ischemia-reperfusion (IR) injury is a known complication of cardiopulmonary bypass (CPB) and cardiac surgery [1]. IR injury is defined as the myocardial damage that occurs because of the restoration of blood flow after a period of coronary occlusion [2]. IR injury to multiple organs may also occur in association with a systemic inflammatory response syndrome (SIRS), which is

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responsible for the increased morbidity and mortality after open heart surgery [3].

The elevated levels of the circulating free radicals that occur during IR injury result in metabolic, functional, and structural alterations [1]. Moreover, IR injury and CPB can trigger an inflammatory response, which may have a role in increasing postoperative complications [4]. Several biomarkers were evaluated clinically to measure the degree of myocardial injury after cardiac surgery, and the most commonly used markers are creatine kinase-MB and troponin I [5].

Nicorandil, a drug used in the management of angina, has a potassium channel (K-ATP) opening action, in addition to its nitrate like action [6]. The effect of this drug on the outcomes after valve surgery has not been evaluated. The objective of our study is to evaluate the effect of the potassium channel opener (nicorandil) on the oxidative stress, proinflammatory cytokines during myocardial ischemia/reperfusion injury and its impact on the outcomes after heart valve surgery.

Patients and Methods:

Design and Patients:

The study is a prospective randomized controlled trial and was carried out on 40 patients who underwent valve replacement surgery in the Cardiothoracic Surgery Department, Tanta University. The study was approved by the Research Ethics Committee, Faculty of Medicine, and was performed from January 2018 till June 2018. We excluded patients with a concomitant surgical procedure (ischemic heart disease or congenital anomalies) or those with severe systemic (endocrine, hepatic, renal, and pulmonary) disorders (Figure 1).

The patients were randomized by block randomization into two groups: control group (20 patients) and nicorandil group (20 patients); the last group received nicorandil for a period ranged from 5 to 15 days; starting from the first day of preparation for surgery and ending in the night before surgery. The dose of nicorandil was 20 mg daily divided into two doses.

Surgical technique:

Surgery was carried out to both groups using the same techniques. Cardiopulmonary bypass with moderate hypothermia (28°C to 32°C) was applied, and antegrade or retrograde cold crystalloid cardioplegia was used for myocardial protection. The average arterial blood pressure was maintained between 50 and 70 mmHg, mechanical prostheses were used in all patients, and total bypass time and ischemic time were recorded.

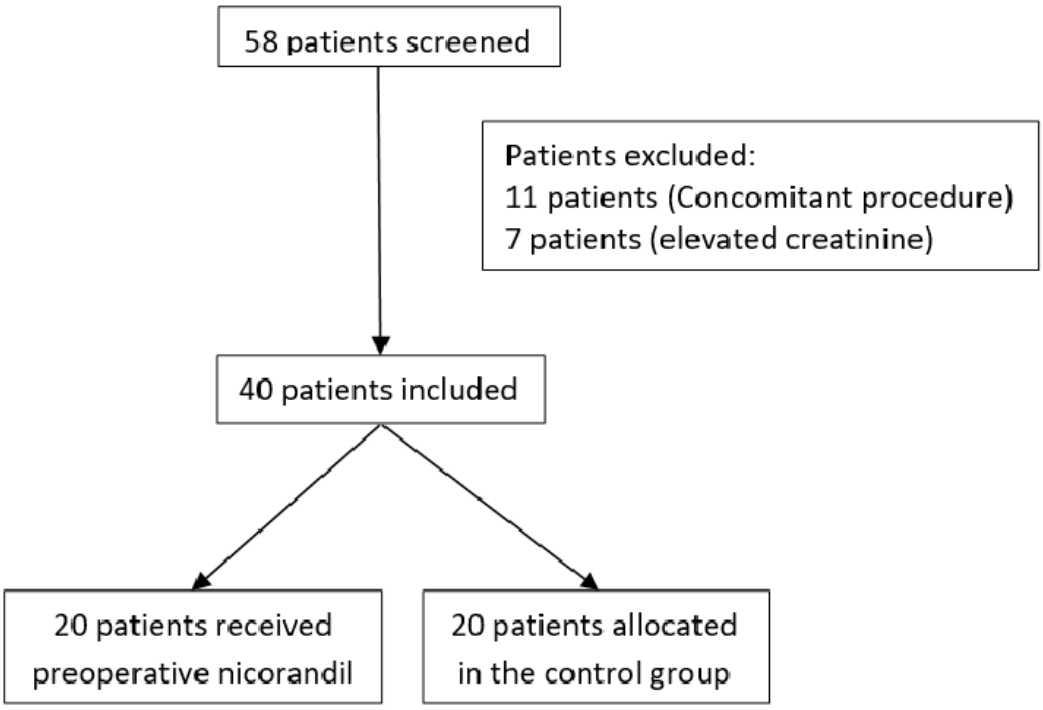

Figure 1: Study flowchart

Table 1: Pre- and intraoperative data (Continuous variables are presented as mean± standard deviation and categorical variables as number and percent)

		Control group	Nicorandil group	p. value
Age (years)		40.8±12.19	37.9±11.81	0.449
Sex	Male	8(40%)	9(45%)	0.749
	Female	12(60%)	11(55%)	
Diabetes mellitus		2(10%)	3(15%)	0.633
Hypertension		3(15%)	4(20%)	0.677
Preoperative LVEF (%)		65.85±5.25	64.5±4.62	0.393
preoperative CK-MB (ng/L)		5.65±0.55	5.56±0.66	0.652
Preoperative Troponin I (ng/L)		0.209±0.07	0.213±0.07	0.855
Type of valve surgery	DVR	3(15%)	4(20%)	0.913
	AVR	3(15%)	3(15%)	
	MVR+TR	2(10%)	3(15%)	
	MVR	12(60%)	10(50%)	
Total bypass time (Minutes)		73.7±13.04	80.15±12.67	0.121
Ischemic time (Minutes)		54.75±11.18	57.9±10.52	0.365

AVR: aortic valve replacement; CK-MB; Creatine kinase- MB; DVR: double valve replacement; LVEF%: left ventricular ejection fraction; MVR: mitral valve replacement; TR: tricuspid replacement

Study outcomes:

Left ventricular ejection fraction (LVEF %) was assessed before and after surgery by echocardiography. Venous blood samples for creatine kinase- MB (CK-MB), troponin I, malondialdehyde (MDA), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were measured 24 hours before surgery then 4, 12 and 48 hours after aortic cross-clamp removal.

Measurements of malondialdehyde:

Serum malondialdehyde (MDA) was measured using the Draper and Hadly method [7]. The pink color is formed because of the reaction between MDA and thiobarbituric acid in an acidic medium at high temperature and then extracted and measured at 535 nm.

Measurement of CK-MB:

Serum isoenzyme of CKMB concentration was determined by a kinetic method utilizing a commercially available assay (Spectrum diagnostics, Hannover, Germany). The mean reading of serial readings every 1 minute for 4 readings at 340 nm was considered.

Measurement of TNF- α, Il-6, and troponin-I:

The serum concentration of TNF- α, Il-6 and troponin-I were determined using enzyme-linked immunosorbent assay (ELISA) kits (Orgenium Laboratories, Vantaa, Finland; Ray Biotech Inc., Norcross, USA and Monobind Inc., Lake Forest, USA respectively).

Statistical analysis:

We analyzed data using SPSS version 18 (IBM Corp- Chicago- IL- USA) and presented the continuous variables as mean ± standard deviation (SD). Concerning qualitative data, Chi-square test (X2) was used to compare the two groups, and data were presented as number and percentage. Student's t-test or Man-Whitney test was used to compare quantitative data between the two groups. A p-value was considered statistically significant if it was less than 0.05.

Results

There was no statistically significant difference between the two groups regarding the pre- and intraoperative data (Table 1).

CK-MB and troponin I levels at 4, 12, and 48 hours after removal of aortic cross-clamp were significantly lower in the nicorandil group. CK-MB levels increased postoperatively in both groups and showed a peak value at 4 hours after removal of aortic clamping then it decreased gradually. However, CK-MB levels at 4 hours and 12 hours after cross-clamp removal were significantly lower

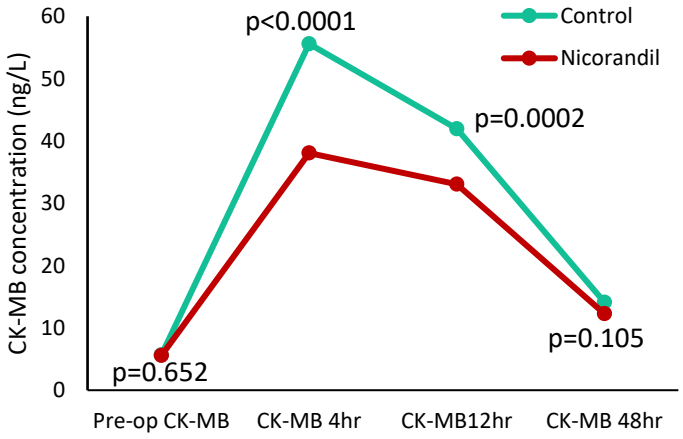

Figure 2: Creatine kinase- MB (CK-MB) change in both groups

in nicorandil group, and there was no significant difference in CK-MB levels in both groups after 48 hours following the removal of aortic clamp (Figure 2). Troponin I levels increased after surgery in both groups and peaked at 12 hours after removal of the aortic clamp then decreased gradually. Troponin I levels 4 hours and 12 hours after removal of cross-clamp were significantly lower in the nicorandil group compared to their respective values in the control group, and there was no significant difference in troponin I level in both groups after 48 hours following the removal of aortic clamp (Figure 3).

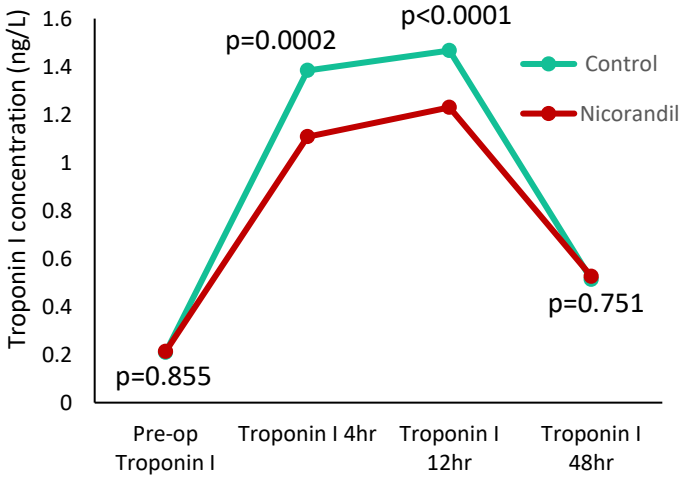

Figure 3: Troponin I change in both groups

The preoperative LVEF of both groups were not significantly different, while postoperative LVEF was higher in the nicorandil group compared to the control group, as shown in Figure 4.

The baseline values of the mean levels of MDA, IL-6, and TNF-α were not significantly different in both groups (Table 2). After aortic unclamping, the mean levels of MDA and TNF-α and IL-6 were elevated in both groups. MDA concentrations increased after surgery in both groups showing a peak value at 4 hours then decreased gradually. MDA levels at 4 hours and 12 hours after de-clamping the aorta were significantly lower in the nicorandil group. There was no significant difference in MDA levels after 48 hours of aortic de-clamping in both groups. TNF-α and IL-6 increased after surgery and peaked at 4 hours after aortic unclamping then the levels of both TNF-α and IL-6 decreased gradually in both groups. However, TNF-α and IL-6 concentrations at 4 hours and 12 hours after cross unclamping were significantly lower in nicorandil group compared to their respective values in control group, and there was no significant difference in TNF-α and IL-6 levels in both groups after 48 hours from aortic unclamping (Table 2).

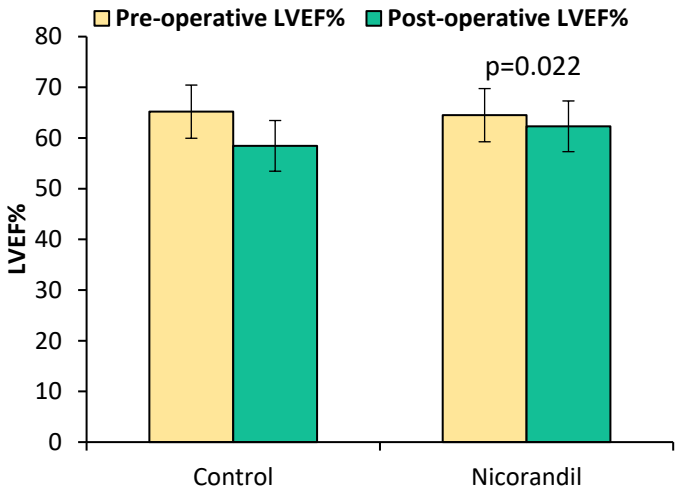

Figure 4: Preoperative and postoperative left ventricular ejection fraction (LVEF%) levels in both groups. (Values are shown as mean ± standard deviation

Discussion

Ischemia-reperfusion (IR) injury after open heart surgery is usually associated with increased complications and mortality; therefore, adequate myocardial protection is critical to prevent myocardial injury after CPB [8]. In the present study, nicorandil showed a significant improvement in postoperative LVEF compared to the control group which indicates a myocardial protecting effect of nicorandil after valvular cardiac surgery, and this was proved laboratory by detecting the decrease in the postoperative CK-MB and troponin I levels compared to the control group. These findings are in agreement with other

Table 2: Effect of nicorandil on malondialdehyde (MDA), tumor necrosis factor- α (TNF-α), interleukin-6 (IL-6) measured in ng/L

	Control	Nicorandil	p. value
Preoperative MDA	4.05±0.49	4.09±0.52	0.825
MDA (4hours)	5.74±0.66	5.13±0.63	0.005
MDA (12 hours)	5.21±0.68	4.76±0.62	0.036
MDA (48 hours)	4.42±0.54	4.38±0.55	0.836
Preoperative TNF-α	11.38±1.17	12.04±1.3	0.101
TNF-α (4 hours)	19.4±2.42	15.08±1.43	<0.001
TNF-α (12 hours)	15.37±2.26	13.07±1.48	<0.001
TNF-α (48 hours)	12.29±1.26	12.1±1.25	0.638
Preoperative IL-6	18.42±1.41	19.08±1.55	0.165
IL-6 (4 hours)	35.61±2.89	28.06±3.4	<0.001
IL-6 (12 hours)	28.84±5.47	24.17±3.36	0.003
IL-6 (48 hours)	22.62±1.54	21.65±2.25	0.122

MDA: malondialdehyde, TNF-α: tumor necrosis factor alpha, IL-6: interleukin 6

studies that showed that nicorandil provided myocardial protection in different situations, such as during coronary angioplasty [9, 10].

Oxidative stress that arises from the overproduction of oxygen free radicals during the reperfusion of ischemic myocardium is the leading cause of IR injury [11]. The burst of reactive oxygen species (ROS) starts in the first minutes after reperfusion. ROS are generated from many sources; leakage of the mitochondrial electron, lipoxygenase, xanthine oxidase, and NADPH-oxidases [12-14]. ROS result in many detrimental processes as peroxidation of lipid membranes, macromolecule oxidation, membrane dysfunction, altered calcium homeostasis, DNA lesions, the attraction of neutrophils, apoptosis which is triggered by the opening of the permeability transition pores in mitochondria which all result in myocardial damage [13-15].

Direct measurement of oxygen free radicals that proves the presence of oxidative stress is difficult in humans because of their transient nature and difficulty of the measurement techniques. That's why an indirect marker of oxidative stress such as MDA is used in the present study to reflect the extent of oxidative stress. MDA is a known product of polyunsaturated fatty acid peroxidation, and oxidative stress leads to depletion of antioxidant capacity of plasma resulting in higher lipid peroxidation and increases the production MDA [16].

In the present study, the serum MDA concentration increased after valvular surgery, but this increase in MDA levels after 4 and 12 h was lower significantly in the nicorandil group in comparison to the control group. This may be explained by the ability of nicorandil to reduce the mitochondrial formation of ROS by opening the mitochondrial ATP-sensitive K channel, that evokes a mitochondrial depolarization and suppresses ROS formation [17]. In addition; nicorandil is thought to have free radical scavenging action [18].

There is a close relation between ROS production and IR injury and systemic inflammatory response during cardiopulmonary bypass [19]. In cardiac surgery; the mechanisms causing oxidative stress and SIR are similar; including the exposure of blood to tubes used in CPB, the surgical trauma itself, and sudden excessive changes in body temperature [20].

The systemic inflammatory response involves leakage of cytokines, such as IL-6 and TNF-α, which play an important role in myocardial IR injury and cause damage to the myocardium [19]. Reperfusion of the ischemic tissue leads to higher chemotactic factors concentrations that attract macrophages, monocytes, and

polymorphonuclear leucocytes (PNL) and that initiate an inflammatory response and tissue damage [21]. Migration of PNLs leads to increased endothelial damage and increase the secretion of IL-6 and TNF-α. Excessive inflammatory cytokine production activates further neutrophils and exacerbates tissue damage [22].

Our study showed high levels of serum TNF-α and IL-6 after valvular surgery. However, this increase in TNF-α and IL-6 levels after 4 and 12 h was lower in the nicorandil group compared to the control group. Nicorandil is reported to modulate the inflammatory mediators' release and inhibit the release TNF-α from a lymphocyte by Wei and associates [23] which is in agreement with our results.

The ability of nicorandil to decrease the proinflammatory cytokines may be related to nitric oxide that is liberated from nicorandil and may be involved in suppression of nuclear factor-κB which regulates the expression of many genes including pro-inflammatory cytokines (TNF-α and IL-6) and therefore decreasing the level of these proinflammatory cytokines by blocking their mRNA expression [24,25].

Limitations:

There are several limitations of the study, including the inability to study the effect of different durations and routes of administration of nicorandil on myocardial protection, which can be assessed in further studies. The preoperative duration of nicorandil varied from 5-15 days, and the optimal period was not evaluated. Additionally, the study did not evaluate whether the effect of nicorandil is related to a specific dose since all patients had the same daily dose. Another issue is masking the treatment since we did not use a placebo. However, the endpoints used were objective and included laboratory measurements, and the person who performed the analyses was blinded to patients' assignment.

Conclusion

Our study suggests that nicorandil reduces the ischemia and reperfusion injury presented in an improvement of postoperative LVEF and the decrease in CK-MB and troponin I enzymes. Nicorandil may exert this effect through its ability to suppress oxygen free radicals and proinflammatory cytokine production such as TNF-α and IL-6. Nicorandil may be a promising agent for cardioprotection during heart valve surgery.

Conflict of interest: Authors declare no conflict of interest.

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