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# Evaluation of Cardioprotective Effect of a Single Oral Dose of Nicorandil before Primary PCI in Patients Presenting with Anterior STEMI

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## ABSTRACT

**Background**: Nicorandil has been demonstrated to have a cardioprotective effect, when used in conjunction with primary percutaneous coronary intervention (PCI). Even over the long term, PPCI using intravenous and intracoronary forms have evidence that it improves cardiac function and lessen the effects of reperfusion injury. There is however little data on role of oral form in ST segment elevation myocardial infarction (STEMI) patients.

**Objective**: The purpose of this trial was to determine whether giving a single oral dosage of nicorandil before primary PCI had any cardioprotective effects on patients who had their first anterior STEMI following the onset of symptoms by six hours.

**Patients and Methods**: 80 patients who had undergone primary PCI as a mean of reperfusion for first attack of anterior STEMI were enrolled in the study. The patients were split into two equal groups: Nicorandil 20 mg single oral dose was given to group A, the study group, and group B, the control group, didn't receive nicorandil.

**Results:** Group A had higher left ventricle ejection fraction, (43.550 % ± 5.114) compared to control (40.325 % ±5.753), (P=0.010), lower peak values of cardiac enzymes, CK total levels peaked at 1899.1 U/L ± 601.000 compared to control [2386.300 U/L ± 844.318, (P=0.004)], peak level of CK MB was 264.100 U/L ± 86.982 compared to control [329.325 U/L ± 147.404 (P=0.018)].

**Conclusion:** Before reperfusion with primary PCI, giving 20 mg single oral dose of nicorandil in the first six hours in patients presenting with a first attack of anterior STEMI, had a significant cardioprotective effect, as shown by higher left ventricular ejection fraction and lesser release of cardiac enzymes, indicating less myocardial damage caused by reperfusion and greater myocardial salvage of the area at risk.

**Keywords:** Primary PCI, Nicorandil, Reperfusion injury.

## INTRODUCTION

Prompt and efficient myocardial reperfusion using either primary PCI or thrombolytic treatment reduces ischemic injury, limits the size of myocardial infarction (MI), maintains left ventricular function, and prevents the onset of heart failure in patients with an acute STEMI [(1)].

In acute STEMI, effective reperfusion of the occluded coronary artery significantly improved prognosis and reduced myocardial necrosis [(2)], largely as a result of advancements in accessibility and effectiveness of reperfusion therapies, in particular PPCI. Modern rapidly acting antiplatelets and anticoagulants have been widely used in clinical practice, in addition to primary PCI, significantly enhancing the patency of the infarct-related artery and the efficiency of reperfusion [(3)].

A lot of research work was dedicated to investigate the role of many therapeutic strategies (both pharmacological and non-pharmacological) when used as adjuvant to reperfusion therapy to protect the heart from RI. Pharmacological treatments as an adjuvant to reperfusion therapy were also shown to attenuate myocardial dysfunction associated with AMI [(1, 6)].

Nicorandil, a dual mechanism action nicotinamide ester, combining opening of ATP-sensitive potassium channels with nitrate like actions, has favorable effects on patients with ischemic heart disease when used as an additional therapy [(7)]. Studies show that these effects are brought on by its impact on the preconditioning pathway's end effector, mitochondrial (K-ATP), and plays an important role in cardioprotection [(8)].

An earlier study showed that giving nicorandil intravenously to patients with anterior AMI increases tissue perfusion, speeds up the restoration of cardiac function, and lowers in-hospital complications [(9)]. In acute MI, intracoronary nicorandil treatment decreased the incidence of no-reflow, sluggish reflow, and reperfusion arrhythmia, enhanced TIMI flow during PCI, hence improving clinical outcomes [(10)]. There were few reports known concerning the cardioprotective effect of orally administered nicorandil and they addressed its use mainly in patients with NSTACS or in elective PCI setting in which nicorandil administration was associated with less incidence of periprocedural myocardial injury [(11, 12)].

Our goal was to determine whether a single oral dosage of 20 mg of nicorandil administered prior to primary PCI had any cardioprotective effects on individuals who had their first anterior STEMI within six hours of the beginning of symptoms.

## PATIENTS AND METHODS

80 patients, who presented with a first attack of anterior wall STEMI following the onset of symptoms by six hours and had primary PCI as a cardiac reperfusion technique were included in this prospective multicenter research. The included patients were presented to emergency rooms and coronary care units of Ain Shams University Hospitals and National Heart Institute. Patients were considered eligible for the study



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if they had a first attack anterior STEMI, and presented within 6 hours from commencement of symptoms, and the selected reperfusion method was primary PCI.

**Exclusion criteria:** if onset of symptoms was more than 6 hours, past history of CABG, PCI to LAD or previous myocardial infarction, procedural complications such as sizable side branch occlusion, unsuccessful primary PCI as in case of failure to pass PCI wire or have been referred for an urgent CABG surgery, diabetic patients treated with sulphonyl urea group of drugs such as glibenclamide, which is potent inhibitor of K-ATP channels [(13)], renal impairment, history of nicorandil use in the last 5 days, patients with contra-indications for nicorandil therapy such as known hypersensitivity, oral or genital ulcers (either as a past history or active ulcers) as nicorandil was shown to induce gastrointestinal or genital ulceration [(14)], borderline systolic blood pressure or those in cardiogenic shock, advanced diseases that may affect life expectancy e.g. Cancer etc....

**Methods:**

All patients were subjected to full history and examination with the initial 12 lead ECG obtained within 10 minutes from patient arrival at the emergency room and STEMI was diagnosed based upon presentation with typical chest pain > 20 minutes irresponsive to nitrates coupled with ST-segment elevation suggestive of ongoing coronary artery acute occlusion in the following cases: in the absence of LBBB, at least two consecutive chest leads with ST-segment elevation of 2.5 mm in men younger than 40 years, 2 mm in men 40 years of age, 1.5 mm elevation in leads V2-V3 and/or 1 mm in the other leads for females [(15)].

Blood sampling for baseline cardiac enzymes levels on admission was done. Then, the patients were split into two groups: Group A (40 patients), the study group, was given single dose of oral nicorandil 20 mg soon as they were admitted, along with loading doses of aspirin and clopidogrel. Group B (40 patients), didn't receive nicorandil.

The PPCI procedures were done by experienced Interventional Cardiologists via a transfemoral artery approach applying Seldinger method and using the standard techniques. The use of balloon predilatation, thrombus aspiration catheter and GP IIb/IIIa receptor blockers were left to the operator preference. All patients received the following medications immediately after diagnosis: aspirin 300 mg, clopidogril 600 mg and nicorandil in the study group. Heparin 100 u/kg IV was given on table after gaining the arterial access and at the end of diagnostic coronary angiography. Hemodynamic data monitoring was continuously followed during procedure coupled with continuous ECG monitoring.

TIMI thrombus grade assessment was done after PCI wire crossing and patients were categorized either as having no or low thrombus burden (grades 0-2) or having high thrombus burden (grades 3-5)[(16)].The occurrence of slow flow or no-reflow phenomena during the procedure was observed. Final TIMI flow at the end of the procedure was recorded for all patients [(3)]. Myocardial Blush Grade (MBG) at the end of the primary PCI procedure was recorded for all patients and patients were categorized either as having high blush grade (grades 2-3) that correlates with good perfusion at the microcirculation level or having (grades 0-1) that correlate with poor perfusion [(3)]. The occurrence of malignant reperfusion arrhythmias during or within 24 hours after primary PCI was observed [(25)].

After Primary PCI procedure 12-lead electrocardiography (ECG) was done at 90 minutes post procedure to detect degree of ST Segment resolution with the improvement classified as > 50% or < 50% from the initial ECG [(17)]. All patients were subjected to serial blood sampling for CKT and CK MB with the first sample withdrawn 8-12 hours and the second sample 20-24 hours post-procedure to determine their peak levels. Standard trans-thoracic echocardiography done within 72 hours post procedure by experienced Echocardiographers, who were blinded of study protocol, for assessment of left ventricle ejection fraction that was evaluated by Simpson's method.

All patients continued their care in the coronary care units of the above mentioned hospitals and they all received (except if there were contraindication for use) high intensity statins, beta adrenoreceptors blockers (BBs), angiotensin converting enzyme inhibitors or angiotensin receptor blockers and diuretics (according to haemodynamics and LVEF% on Echocardiography) and all patients were maintained on dual antiplatelet therapy in the form of ASA 100 mg and clopidogril 75 mg daily according the guidelines of the European society of cardiology [(18)]. All patients in their hospital stay were observed for occurrence of arrhythmias, reinfarction and cardiovascular mortality. Follow up after one month after discharge was done for all patients to evaluate occurrence of arrhythmias, reinfarction, rehospitalization for heart failure and cardiovascular mortality.

**Ethical consent:**

**An approval of the study was obtained from Ain Shams University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

***Statistical analysis***

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc., Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative

data were represented as frequencies and relative percentages. Chi square test ($\chi^2$) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value ≤ 0.05 was considered significant.

## RESULTS

80 patients were included in the study, the mean age was 56.250 ± 9.358 in the study group vs 54.350 ± 8.490 years in the control group, there were no statistically significant difference between the 2 groups regarding demographic data and cardiovascular risk factors (Table 1).

**Table (1):** The research population's baseline characteristics

| Variable | | Groups | | |
|---|---|---|---|---|
| | | Group A N=40 | Group B N=40 | P-value |
| Age (years) Mean ±SD | | 56.250± 9.358 | 54.350± 8.490 | 0.345 |
| Sex | Male | 32 (80%) | 35 (87.5%) | 0.363 |
| | Female | 8 (20%) | 5 (12.5%) | |
| Hypertension | | 21 (52.5 %) | 20 (50% ) | 0.823 |
| Diabetes | | 13 (32.5 %) | 16 (40%) | 0.485 |
| Smoking | | 23 (57.5 %) | 20 (50 %) | 0.501 |
| Dyslipidemia | | 12 (30 %) | 12 (30 %) | 1.000 |
| Family History of CAD | | 10 (25 %) | 12 (30 %) | 0.617 |

The pain to wire crossing time was 222.875 ± 59.440 vs 230.125 ± 51.931 minutes in the study group, the presence of proximal LAD occlusion, significant other vessel affection, heavy thrombus, the use of predilatation or thrombus aspiration catheter were similar between both groups, post-procedural there were no significant difference between both groups in the achievement of TIMI III flow, high MPG the occurrence of reperfusion arrhythmias or achievement of > 50 % ST segment resolution (Table 2).

**Table (2):** Procedural and reperfusion data

| Procedural data | Groups | | |
|---|---|---|---|
| | Group A | Group B | |
| | N | N | P-value |
| Pain to wire crossing (minutes) (Mean ± SD) | 222.875± 59.440 | 230.125± 51.931 | 0.563 |
| Proximal LAD occlusion | 33 (82.5 %) | 35 (87.5 %) | 0.531 |
| Significant other vessels lesions | 11 (27.5 %) | 12 (30 %) | 0.805 |
| Heavy Thrombus Burden | 12 (30 %) | 16 (40 %) | 0.348 |
| Aspiration Catheter use | 3 (7.5 %) | 4 (10 %) | 0.692 |
| Balloon Predilatation | 13 ( 32.5%) | 16 (40 %) | 0.485 |
| IIb/IIIa receptor blockers use | 10 (25 %) | 13 (32.5% ) | 0.459 |
| Slow/No Reflow occurrence | 7 (17.5 %) | 12 (30 %) | 0.189 |
| Final TIMI III | 36 (90 %) | 33 (82.5 %) | 0.529 |
| High MBG | 34 (85 %) | 30 (75 %) | 0.264 |
| Reperfusion arrhythmias | 4 (10 %) | 8 (20 %) | 0.210 |
| >50% ST segment resolution | 35 (87.5) | 31 (77.50) | 0.239 |

When compared to group B, group A had higher left ventricle ejection fraction, (43.550 ± 5.114%) compared to (40.325 ± 5.753%), (P=0.010) (Table 3).

**Table (3)**: LV EF % between 2 groups.

| EF | Groups | | T-Test | |
|---|---|---|---|---|
| | Group A | Group B | t | P-value |
| Range | 25-51 | 28-50 | 2.650 | 0.010* |
| Mean ±SD | 43.550±5.114 | 40.325±5.753 | | |

There were statistically significant lower peak levels of cardiac enzymes in group (A) compared to group (B). The mean peak level of CKT in group (A) was 1899.100 ± 601.000 compared to 2386.300 ± 844.318 in group (B), (P=0.004). The mean of the peak level of CK MB in group (A) was 264.100 ± 86.982 compared to 329.325 ± 147.404 in group (B) (P=0.018) (Table 4).

**Table (4):** Peak cardiac enzymes levels between 2 groups

| | | Groups | | T – Test | |
|---|---|---|---|---|---|
| | | Group A | Group B | t | P - Value |
| CK T | Range | 1270 - 3973 | 1312 - 4894 | -2.973 | 0.004* |
| | Mean | 1899.100± 601.000 | 2386.300± 844.318 | | |
| CKMB | Range | 166-530 | 188-723 | -2.410 | 0.018 * |
| | Mean | 264.100± 86.982 | 329.325± 147.404 | | |

**In-hospital and 1 month follow up** showed that In-hospital arrhythmias occurred in 1 patient in group (A) in the form of atrial fibrillation compared to 3 patients in group (B) who experienced (ventricular tachycardia-frequent pvcs -atrial fibrillation) with no statistically significant difference between the two groups. There were no cases of reinfarction during in-hospital follow up in group (A) compared to 1 case in group (B) and no cases of in-hospital mortality occurred in both groups. After 1 month follow-up, 2 patients in group (A) were admitted for worsening symptoms of heart failure compared to 3 patients in group (B) with no statistically significant difference between the two group (P=0.644). No cases of reinfarction were reported in group (A) compared to 1 case in group (B). Neither arrhythmias nor cardiovascular mortality were reported in both groups (Table 5).

**Table (5):** Data from in-hospital and one-month follow-up

| In-hospital follow-up | Groups | | | | | | Chi-Square | |
|---|---|---|---|---|---|---|---|---|
| | Group A | | Group B | | Total | | | |
| | N | % | N | % | N | % | $X^2$ | P-value |
| **Arrhythmias** | 1 | 2.50 | 3 | 7.50 | 4 | 5.00 | 1.053 | 0.305 |
| **Reinfarction** | 0 | 0.00 | 1 | 2.50 | 1 | 1.25 | 1.013 | 0.314 |
| **Mortality** | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | x | x |
| **One Month follow up** | | | | | | | | |
| **Arrhythmias** | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | x | x |
| **Reinfarction** | 0 | 0.00 | 1 | 2.50 | 1 | 1.25 | 1.013 | 0.314 |
| **Rehospitalization for HF** | 2 | 5.00 | 3 | 7.50 | 5 | 6.25 | 0.213 | 0.644 |
| **Mortality** | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | X | x |

## DISCUSSION

Beside reducing infarct size, early reperfusion of completely occluded coronary arteries in STEMI patients using thrombolytics or primary PCI also minimizes cardiac death rates and in-hospital events [(6)]. However, these benefits were not experienced in all patients even when early reperfusion was achieved successfully, mostly due to reperfusion injury. It is generally recognised that the location of the infarction affects clinical outcomes, this was proven by **Gibbons *et al.*** [(19)] who used tomographic imaging with technetium-99 m sestamibi to indicate that patients with anterior wall myocardial infarction would benefit from enhanced reperfusion therapy significantly more than those with inferior wall MI, primarily because the area at risk in anterior MI is larger and therefore more likely to be detected. Being the largest epicardial coronary artery, LAD occlusion induces a large area of jeopardized myocardium. A substantial left ventricular impairment and a clinically diminished functional capacity may result from inability to successfully revascularize LAD [(20)].

Many drugs were investigated to evaluate their cardioprotective effects in conjunction with PPCI such as adenosine [(21)], exentide [(22)], cyclosporin A [(23)] and nicorandil [(9-12)].

When administered orally, the peak plasma level (Cmax) of nicorandil is achieved within 30 minutes [(14)], and it was rapidly and extensively absorbed from the gastrointestinal tract with no hepatic first pass metabolism in contrary to organic nitrates also it achieves bioavailability of 75%-100% of the administered dose [(14)].

Nicorandil was proven to exert benefits for individuals with ischemic heart disease as an adjuvant therapy. Several potential mechanisms can be considered, nicorandil enhances coronary perfusion especially to small diameter vessels (<100um) leading to pharmacological prevention of slow flow [(24)], also it prevents coronary spasm [(8)].

The pharmacological action of nicorandil is similar to that of preconditioning effect. It has been shown that mitochondrial K-ATP is the end effector of preconditioning pathway and this channel openers, including nicorandil, protect heart against reperfusion injury [(25)]. It also reduces infiltration and activity of neutrophils into the ischemic myocardium in a concentration-dependent manner [(26)], and reduces ROS production in cardiac mitochondria at reoxygenation [(27)]. Reduction of preload and afterload adds to decreased myocardial oxygen demand [(14)]. Moreover, it was shown experimentally to have antiarrhythmic effects, which aids in prevention of reperfusion arrhythmias [(28)]. It was studied in multiple trials previously, with the orally administered nicorandil investigated in patients undergoing elective PCI [(11)] and in patients with unstable angina undergoing PCI [(12)].

The intravenous administered [(29)] and the intracoronary [(10)] administered nicorandil were studied in patients with STEMI. Based on the above studies and pharmacokinetics of nicorandil, the present study used single dose of nicorandil 20 mg (which is 5 times higher than intracoronary doses and nearly twice as high as the single IV dose in the above-mentioned studies) was chosen to achieve the most possible blood concentration prior to reperfusion as all the included patients were presenting with STEMI. Moreover, oral route is much easier compared to other routes and widely accepted in clinical practice.

**Effect of oral nicorandil on peak levels of CKT and CK MB:**

Peak levels of CKT that reflects infarct size were significantly lower in the study group (1899.100 ± 601) compared to the control group (2386.3 ± 844.318), (P=0.004). The present study results are similar to the results of a randomized, double-blinded trial done by **Ishii *et al.*** [29] in 2005, which showed that a single 12 mg IV dose of nicorandil before reperfusion in patients presenting with first STEMI led to serum peak CKT levels in the nicorandil group being considerably lower than those in the placebo group (P=0.03). That study was conducted among 368 patients who were divided into two groups to receive either nicorandil, 185 patients - in 89 of whom the LAD was the culprit vessel or placebo, 183 patients - in 85 of whom the LAD was the culprit vessel with time to reperfusion being 4.8 ± 2.9 hours in nicorandil group versus 4.5 ± 2.8 hours in control group [29].

On the other hand, Nicorandil effect on CKT peak levels in the present study contradicted with another study published in 2003 that was done by **Sugimoto *et al.*** [30]**.** In that study they evaluated the effect of intravenous nicorandil infusion in conjunction with coronary reperfusion therapy in 272 patients with acute myocardial infarction. The nicorandil group received a 4 mg bolus injection, a 24 hours infusion of 6 mg/h, and then 15 mg/day of oral nicorandil for at least one month. Nicorandil and control groups did not differ statistically from one another in relevance to the peak CKT levels, even in subgroup analysis that included only patients with anterior STEMI [30]. This contradiction could be attributed to many factors: first, it was done retrospectively with the control group cases (n=114) dating back to the period between November 1995 and April 1996 and nicorandil group cases (n=158) dating back to the period between November 1997 and April 1998. Secondly, reperfusion was done in the first 24 hours post symptoms onset compared to the 6 hours cut off time that was adopted in the present study and in the subgroup analysis in patients with anterior STEMI that included 86 patients from nicorandil group versus 59 patients from control group, reflow onset time was 8.6 ± 7.3 hours for nicorandil group compared to 7.1 ± 5.3 hours in control group. Finally PTCA was done to the majority of patients rather than stenting [30].

In this study the peak levels of CK MB were significantly lower in the study group (264.100 ± 86.982) compared to control group (329.325 ± 147.404), (P=0.018). The present study result as regards nicorandil effect on the CK MB peak levels match the result of a study published by **Qi *et al.*** [31]**,** which assessed the efficacy of intracoronary nicorandil in patients with acute STEMI for prevention of the no-reflow during primary PCI and it included 120 patients presenting with acute STEMI who underwent primary PCI and were randomly assigned to three equal groups. The first group received 2 mg injection of the medication into the coronary artery at a distance of 2 mm after the occlusion site along with balloon pre-dilation. The second group, was given 200 μg sodium nitroprusside. Finally, the control group underwent PCI and balloon pre-dilation alone [14]. The first and second groups had significantly lower peak levels of CK-MB (P=0.001) following PCI.

Conversely, in 2008 **Lee *et al.*** [10] assessed the effect of intracoronary nicorandil administration before reperfusion in acute STEMI. The study included 73 patients presented within 12 hours from symptoms onset and underwent primary PCI. They were randomly assigned to the nicorandil group (n=37) and the control group (n=36) with the subjects in the nicorandil group given 2 mg intracoronary nicorandil prior to coronary angiography and an additional intracoronary dose of 2 mg nicorandil before stent implantation. They reported that there was no statistical difference in peak CK MB levels between the two groups [10]. What could explain the difference in the results is that, they included patients with symptoms onset within 12 hours and this is nearly twice our pain to door time cut off that was used in the present study. Additionally, the time to reperfusion in their study was higher than the present study being 354 ± 165 minutes in nicorandil group versus 346 ± 135 minutes in the control group. Moreover, the number of patients who had LAD occlusion was 20 patients in either group with the remaining patients represented non-anterior STEMI coupled with that they did not perform subgroup analysis addressing CK MB levels in anterior STEMI. Finally, in the present study a 5 times higher dosage with a different route was used [10].

**Effect of oral nicorandil on LV EF:**

In the present study, the left ventricle ejection fraction in the study group (43.550 ± 5.114) was significantly higher than in the control group (40.325 ± 5.753) (P=0.010). This finding matches the result of the study done by **Qi *et al.*** [31] where the LVEF% in the nicorandil-treated group was significantly higher than the sodium nitroprusside-treated group following PCI at one week (P=0.031) and at one month (P=0.005) when compared to the control group (P0.05). But for all of the aforementioned, there was no difference (P>0.05) between the nicorandil-treated group and the sodium nitroprusside-treated group [31]. In contrast, the present study result concerning LV EF% is different in the early phase post STEMI than another study done by **Ito *et al.*** [9]. This trial evaluated role of intravenous nicorandil on preserving myocardial viability in patients with reperfused anterior wall myocardial infarction and included two groups: nicorandil group (40 patients) got an injection of 4 mg nicorandil followed by continuous infusion at a rate of 6 mg/h for 24 h before being taken orally 15 mg/day and control group (41 patients). All patients underwent PTCA and achieved effective coronary reflow (TIMI II or III) within 12 hours from the beginning of symptoms.

**Ito *et al.*** [9] reported that there was no statistical significance in the difference in the effect on LV ejection fraction between the two groups though LV EF% was higher in nicorandil group nearly at 3 weeks post procedure compared to control. Also, they performed subgroup analysis including the patients presenting within less than 6 hours and similar non-significant results were obtained [9]. The differences could be attributed to the fact that this study was conducted nearly 20 years ago with coronary intervention technology was still evolving as regards tools and drugs used. Moreover, they performed only PTCA to patients rather than stent implantation compared to the present study and used different drugs regimen (ASA or ticlopedine and coumadin). Additionally, they considered the procedure successful based on final TIMI flow with no comment on residual diameter stenosis post PTCA. Also, time to reperfusion was higher in their study and even the subgroup analysis of patient presenting within less than 6 hours included 31 patients in the nicorandil group and 27 patients in the control group. The smaller size of the subgroups could alter the statistical results [9].

The present result is in accordance with a systematic review and meta-analysis including 964 patients undergoing primary PCI and received nicorandil, and showed that using nicorandil was associated with significant increase in LVEF after one to 12 months [32]. The present study result as regards LV EF % match the result of an abstract that was published in October 2018 by **Peng *et al.*** [33]. They studied the effects of nicorandil on microcirculation of coronary artery and short-term prognosis in patients with STEMI after PPCI in 106 patients divided randomly in 2 groups. The nicorandil group received intracoronary 4 mg of nicorandil then it was continuously infused at 4 mg /hour for 24 hours. They reported that LVEF % at 1 week after primary PCI was statistically significantly higher in the nicorandil group compared to the control group (P= <0.05) [33].

Another similar result to the present study was reported by **Shehata** [11] using orally administered nicorandil but in elective PCI at Ain Shams Cardiology Department, oral nicorandil was associated with lower risk of coronary procedure related myocardial injury in terms of cardiac biomarkers elevation post procedure and the improvement of LV EF% after 6 months in diabetic patients undergoing elective PCI.

**Effects of oral nicorandil on TIMI flow, MBG and reperfusion arrhythmias:**

The results of this study as regards effect of nicorandil on achieving higher TIMI flow and higher MBG and limiting the occurrence of slow flow, no reflow and reperfusion arrhythmias did not have statistical significance. This is in contrary to what was reported by **Lee *et al.*** [10] and **Ishii *et al.*** [29]**.** Both of these studies showed statistical significance in the role of nicorandil in the above mentioned areas of reperfusion parameters and this may be explained partly by the fact that they both used parenteral routes rather than the oral route that was used in the present study for drug administration and this could play a role in the direct effect of nicorandil on coronary microcirculation during reperfusion.

**Effects of oral nicorandil on in hospital MACE and follow up of the patients:**

No statistical significance was found in our study as regarding MACE during in-hospital stay and after 1 month follow-up between the 2 groups, this meets the results of **Lee *et al.*** [10] when they reported no difference between the control and nicorandil-treated group as regards occurrence of in-hospital MACE. In neither groups, there were any fatalities. There was no substantial difference between the two groups regarding the incidence of MACE at 30 days.

According to **Ishii *et al.*** [29] study, patients with STEMI who received a single IV dosage of nicorandil prior to reperfusion experienced a reduction in both early and late clinical events. They showed that the treatment with nicorandil proved to have a substantial impact on the risk of cardiovascular death or hospital readmission for CHF. The contrast with the present study result could be attributed to the fact that the follow-up median duration in their study was 2.4 years compared to 1 month in our study and the much larger sample of patients they investigated [29].

## CONCLUSION AND RECOMMENDATION

Before reperfusion with primary PCI, giving 20 mg single oral dose of nicorandil in the first six hours in patients presenting with a first anterior STEMI, had a significant cardioprotective effect, as shown by higher left ventricular ejection fraction and lesser release of cardiac enzymes, indicating less myocardial damage caused by reperfusion and greater myocardial salvage of the area at risk. Oral nicorandil has cardioprotective effects in anterior STEMI patients, yet larger sample studies with relatively longer follow-up period is recommended. Further studies to evaluate oral nicorandil in non-anterior STEMI is to be considered. Also, to determine the optimal nicorandil dose and frequency of administration when given orally in STEMI patients.

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