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(RESEARCH ARTICLE)

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A prospective study on efficacy of nicorandil and isosorbide mononitrate in coronary artery disease

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Abstract

Background: The aim of this prospective study was to assess the efficacy of Nicorandil (NR) and Isosorbide Mononitrate (ISMN) in coronary artery disease (CAD). Nicorandil strengthens CAD treatment by inhibiting cardiac fatty acid oxidation, easing aggravation and improving heart function, which is critical for preventing heart failure and other significant consequences.

Methods: 110 patients with CAD were selected as research subjects and randomly assigned to two groups: observational (Group O) and control (Group C), with 55 patients in each. The control group was given traditional CAD treatment, whereas the observational group received NR and ISMN in addition to conventional treatment. The blood pressure, CRP, left ventricular ejection fraction (LVEF), troponin T, and ST-segment levels of two groups were assessed and compared at baseline, as well as after the second and fourth months, respectively.

Results: This study found significant differences ($P<0.05$) between the observational and control groups in terms of BP, CRP, troponin T, and ST segment levels after the second and fourth months, whereas LVEF rose significantly ($P<0.05$) using one-way ANOVA. Similarly, an independent t-test was used to assess significant improvements in each group.

Conclusions: The addition of Nicorandil and Isosorbide Mononitrate to a standard CAD regimen was found to have an important association with LVEF and inflammatory mediators, which can significantly improve cardiac functions while also preventing other cardiovascular complications in patients with coronary artery disease.

Keywords: Nicorandil; Isosorbide Mononitrate; Coronary Artery Disease

1. Introduction

Every year, coronary artery disease (CAD) results in over 7 million deaths worldwide and is one of the major causes of cardiovascular morbidity and mortality [1]. The primary symptom of angina is CAD, which is becoming more common in India and is cause for serious concern. Angina also increases the chance of major adverse cardiovascular event (MACE) outcomes, which include heart failure, stroke, hospitalisation for myocardial infarction, and cardiovascular mortality. When heart failure progresses, coronary heart disease can cause a number of serious complications, including the possibility of death [2]. Therefore, in order to prevent heart failure and other dangerous problems, it is imperative to increase the treatment of coronary heart disease in order to reduce disease progression and improve heart function. Through hemodynamic processes, conventional anti-anginal medication relieves myocardial ischemia [3]; however, the

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use of hemodynamic agents in combination has a higher risk of side effects and drug interactions. As the first-line treatment for angina, the recommendations suggest using a beta-blocker or calcium channel blocker, with additional medications for more severe symptoms [4]. One such medication is nicorandil (NR), which has been demonstrated to enhance exercise tolerance and lessen the frequency of anginal episodes without altering hemodynamic parameters [5-6]. By inhibiting heart fatty acid oxidation, NR treats angina and myocardial ischemia either on its own or in combination with hemodynamic medications. The goal of this study was to prevent further cardiovascular problems while also observing the effects of isosorbide mononitrate and nicotinamide on coronary artery disease using cardiac function evaluation [7].

2. Material and methods

2.1. Study Population

A total of 110 patients, both inpatients and outpatients, with coronary artery disease who had post-acute myocardial infraction, hypertension, hyperlipidemia, systolic heart failure, type 2 diabetes mellitus, and stable or chronic angina were included in the study [8]. The individuals were all diagnosed with coronary artery disease according to the guidelines. Exclusion from the study was granted to patients with clinical findings such as malignant tumours (which can cause cardiac events related to chemotherapy), psychiatric disorders (which can lead to treatment nonadherence), parkinsonism, restless leg syndrome, and renal dysfunction (GFR > 30 ml/min) [9]. At the time of enrollment, all eligible patients were made aware of the study and asked for their written consent. Patients receiving standard treatments for coronary artery disease, such as anti-platelet, hypolipidaemic, and anti-anginal medications, continued to receive them over the study period [10].

2.2. Study Design

2.2.1. Two groups were included in the prospective cohort research design

The control group (Group C) and the observational group (Group O).Every group had fifty-five patients [11]. Both groups were given standard medication therapy; however, Group O also received oral treatment with isosorbide mononitrate (5 mg BD) and nicorandil (35 mg SR BD) [13]. Age, sex ratio, and illness distribution did not significantly differ between the two groups (P>0.05), suggesting that Tables 1 and 2 represent comparable populations [12].

Table 1 Demographics and Co-Morbid Characteristics of the Study Population

Characteristics	Group O (n = 60)	Group C (n= 60)
Age	62 (51%)1	60 (47%)1
Male	36 (60.7%)1	31 (52.3%)1
Female	22 (37.3%)1	27 (45.7%)1
Hypertension	31 (49%)1	23 (41%)1
Heart failure	5 (11%)1	4 (8.5%)1
Post MI	3 (3.5%)1	3 (6.8%)1
Type 2 DM	21 (35.71)1	26 (44%)1

[1]Data were shown as number (%) appropriate to show age, gender, and co-morbidities distribution.

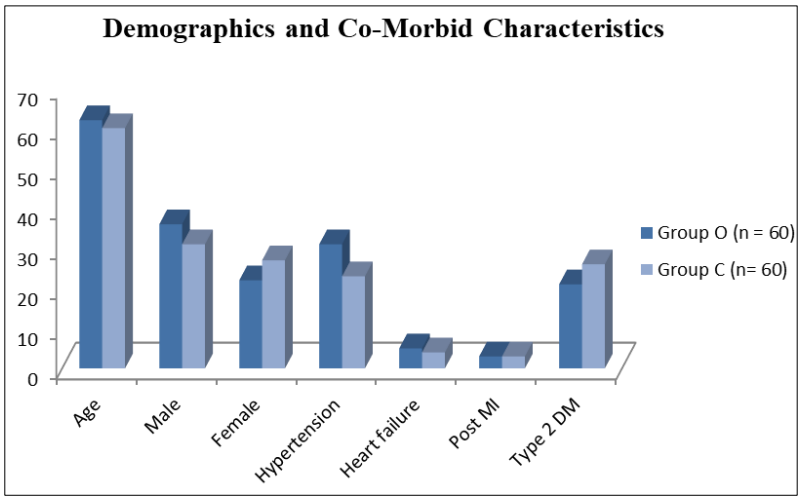

Figure 1 Demographics and Co-Morbid Characteristics of the Study Population

Table 2 Baseline Characteristics of the Study Population

Characteristics	Group O (n = 60)	Group C (n= 60)	P value
Age	64.9 ± 5.4[2]	64.3 ± 7.1[2]	0.6205
Systolic BP	141.1 ± 4.01[2]	143.1 ± 19.5[2]	0.5220
Diastolic BP	88.1 ± 4.8[2]	91.1 ± 8.7[2]	0.4424
CRP	2.11 ± 0.4[2]	3.51 ± 0.2[2]	< 0.0001
LVEF	56.4 ± 4.4[2]	55.2 ± 3.7[2]	0.0004
Troponin T	0.013 ± 0.004[2]	0.015 ± 0.003[2]	0.1155
ST segment	98.4 ± 7.6[2]	102.08 ± 6.8[2]	0.2108

[2]Data were shown as mean ± SD and independent t-test were used to determine significance (p>0.05).

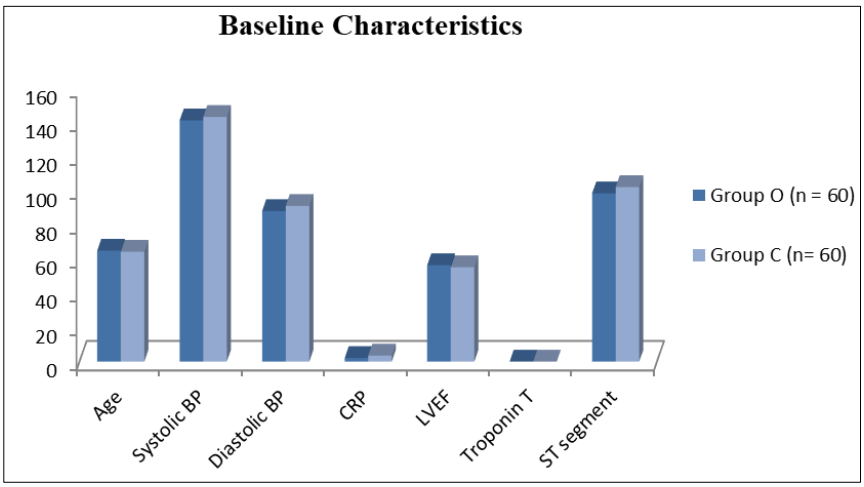

Figure 2 Baseline Characteristics of the Study Population

2.3. Observation Indexes

Each group was followed up with every two months following an initial assessment of all research data, and any changes in parameters like blood pressure, inflammatory mediators, ECG parameters, and heart function were evaluated [13]. To measure study parameters like systolic and diastolic blood pressure, C-reactive protein (CRP), left ventricular ejection fraction (LVEF), troponin T, and ST-segment at the end of the second and fourth month, and to assess the effectiveness of the treatment given, each patient underwent echocardiography, electrocardiography, laboratory testing, and an ELISA (enzyme-linked immune sorbent assay) kit [14].

2.4. Statistical Analysis:

The SPSS 21.0.0 version and Graph Pad Prism with 95% confidence interval were used to analyse the data that was collected. Because the data were parametric, the independent t-test and one-way ANOVA (analysis of variance) were used to examine the statistical differences between and within the groups. The measurement data were presented as mean ± SD. P values less than 0.05 are regarded as statistically significant differences in both intragroup and within-group comparisons [15].

3. Results

110 patients with coronary artery disease who met the study's inclusion criteria were admitted. For this investigation, male persons with concomitant type 2 diabetes mellitus are more likely to have CAD; demographic and baseline clinical characteristics in Tables 1 and 2 indicated an approximate age of above 60 years.

3.1. Effect of Nicorandil and Isosorbide Mononitrate

After two months, patients with coronary artery disease treated with nicorandil demonstrated a substantial difference in study parameters when compared to patients receiving conventional medication; in contrast, the control group (Group C) exhibited only weakly significant changes when compared to baseline values. After four months, similar substantial differences were seen in the research parameters, as Tables 3 to Table 8 demonstrate. Figures 3, 4, 5, 6, 7, and 8 show a significant difference ($p<0.05$) between the systolic and diastolic blood pressure, C-reactive protein, Troponin T, and ST-segment in patients treated with Isosorbide Mononitrate and Nicorandil compared to those receiving conventional therapy from the 2nd to the 4th month, although the observational group's left ventricular ejection fraction significantly increased (from 60.3 ± 3.1 to 65.4 ± 2.3) in comparison to the control group Figure 6. There was only a slight variation in blood pressure between the two groups, and there was a significant difference ($P<0.05$) between the two groups. The control group's research parameters differed only slightly.

Table 3 Comparison ofSystolic BP (mmHg) Within and Between The Two Groups at the 2nd Month and 4th Month

Characteristics	Group O (n = 60)	Group C (n= 60)	P-value
Systolic BP (mmHg)			
2 nd month	132.16 ± 15.08[3]	135.33 ± 13.20[3]	0.2236
4 th month	120.16 ± 7.70[3]	126.33 ± 11.92[3]	<0.0001
P	<0.0001	<0.0001	

[3]Data were shown as mean ± SD and independent t-test & analysis of variance were used to determine significance (P<0.05).

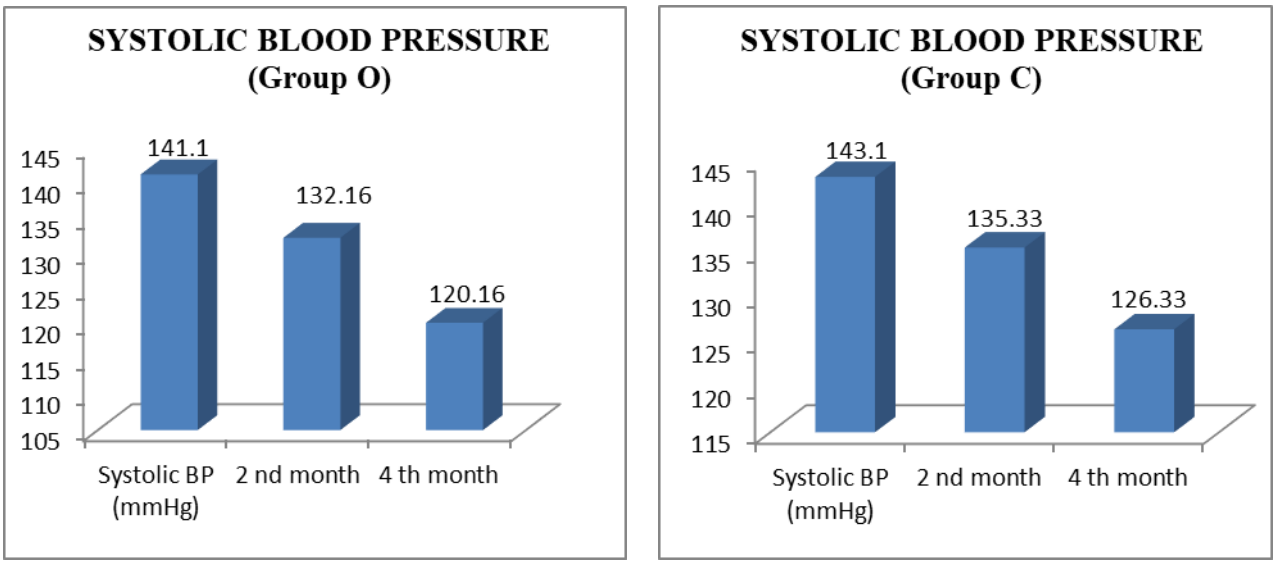

Figure 3 Systolic Blood Pressure of O - Observational Group And C - Control Group in Coronary Artery Disease

Table 4 Comparison ofDiastolic BP (mmHg) Within and Between The Two Groups at the 2nd Month and 4th Month

Characteristics	Group O (n = 60)	Group C (n= 60)	P-value
Diastolic BP (mmHg)			
2 nd month	86.1 ± 6.9[3]	88.3 ± 5.8[3]	0.0667
4 th month	80.1 ± 7.4[3]	8.3 ± 5.0[3]	<0.0001
P	<0.0001	0.0568	

[3]Data were shown as mean ± SD and independent t-test & analysis of variance were used to determine significance (P<0.05).

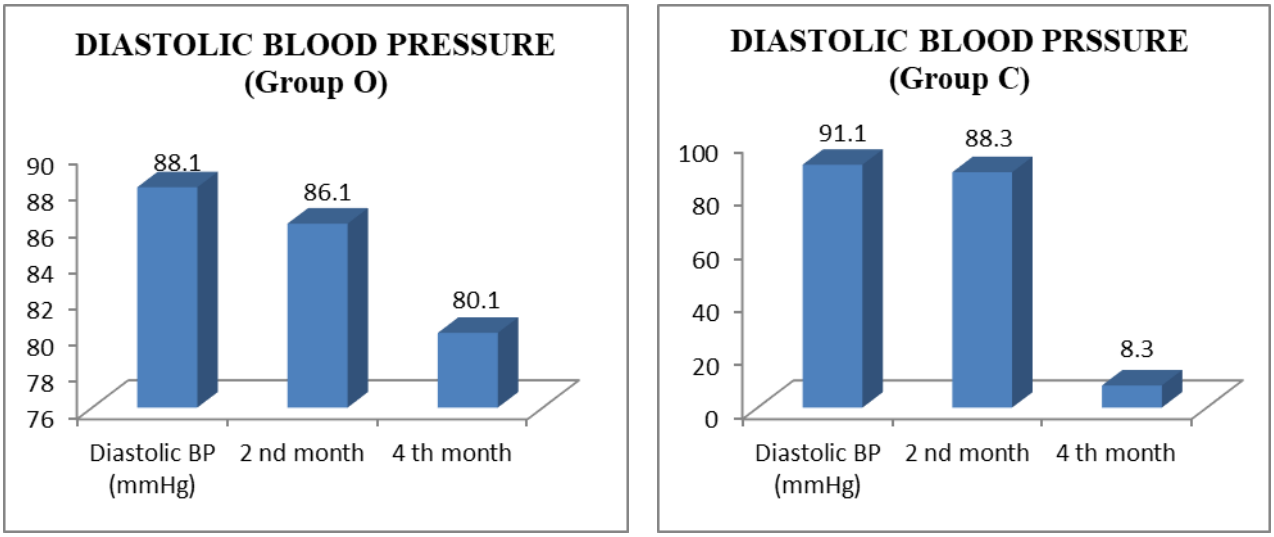

Figure 4 Diastolic Blood Pressureof O - Observational Group And C - Control Group in Coronary Artery Disease

Table 5 Comparison ofC - reactive protein (mg/L) Within and Between The Two Groups at the 2nd Month and 4th Month

Characteristics	Group O (n = 60)	Group C (n= 60)	P-value
C - reactive protein (mg/L)			
2 nd month	86.1 ± 6.9[3]	88.3 ± 5.8[3]	<0.0001
4 th month	80.1 ± 7.4[3]	8.3 ± 5.0[3]	<0.0001
P	<0.0001	<0.0001	

[3]Data were shown as mean ± SD and independent t-test & analysis of variance were used to determine significance (P<0.05).

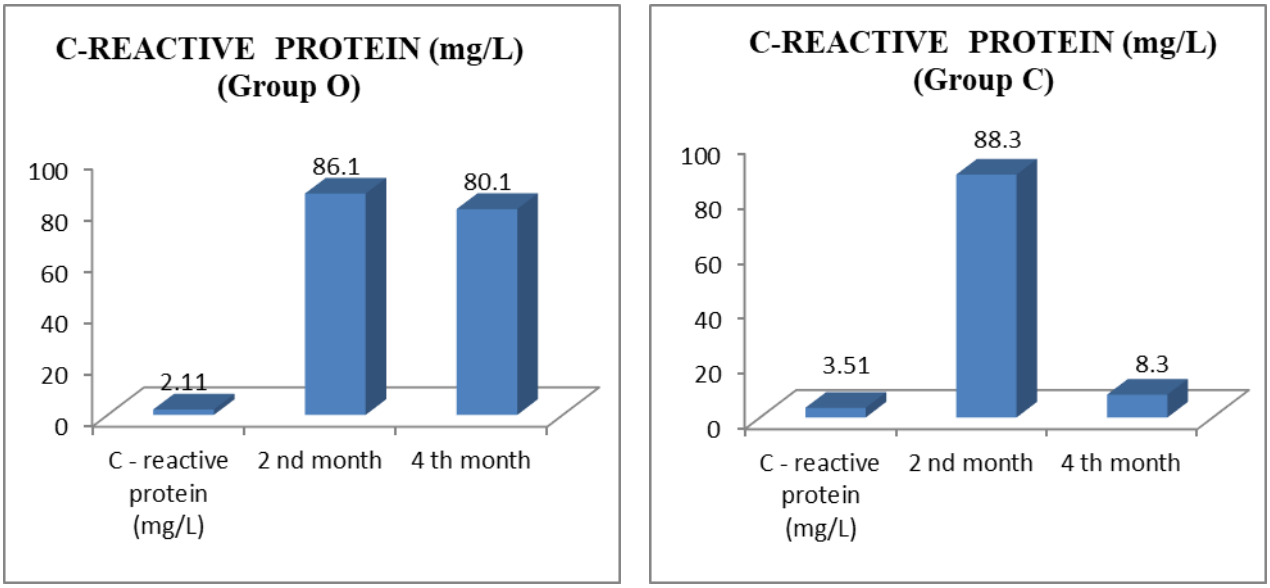

Figure 5 C Reactive protein (mg/L) of O - Observational Group and C - Control Group in Coronary Artery Disease

Table 6 Comparison ofLVEF (%) Within and Between The Two Groups at the 2nd Month and 4th Month

Characteristics	Group O (n = 60)	Group C (n= 60)	P-value
LVEF (%)			
2 nd month	60.3 ± 3.1[3]	57.4 ± 2.5[3]	<0.0001
4 th month	65.4 ± 2.3[3]	60.0 ± 3.5[3]	<0.0001
P	<0.0001	<0.0001	

[3]Data were shown as mean ± SD and independent t-test & analysis of variance were used to determine significance (P<0.05).

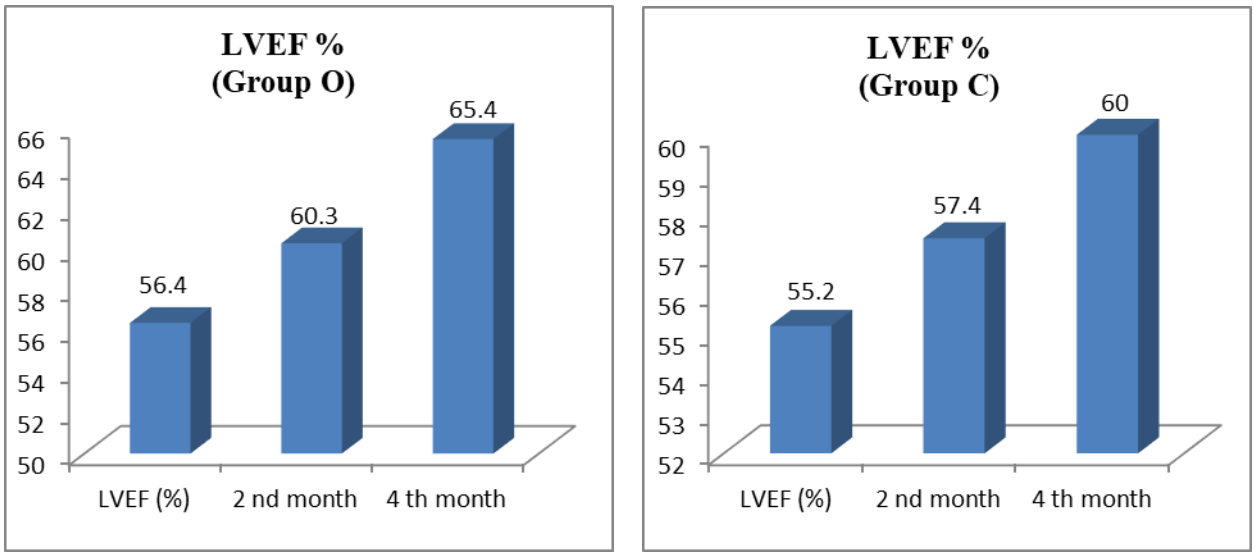

Figure 6 LVEF (%) of O - Observational Group and C - Control Group in Coronary Artery Disease

Table 7 Comparison ofTroponin T (ng/ml) Within and Between The Two Groups at the 2nd Month and 4th Month

Characteristics	Group O (n = 60)	Group C (n= 60)	P-value
Troponin T (ng/ml)			
2 nd month	0.008 ± 0.003[3]	0.013 ± 0.003[3]	<0.0001
4 th month	0.004 ± 0.001[3]	0.007 ± 0.003[3]	<0.0001
P	<0.0001	<0.0001	

[3]Data were shown as mean ± SD and independent t-test & analysis of variance were used to determine significance (P<0.05).

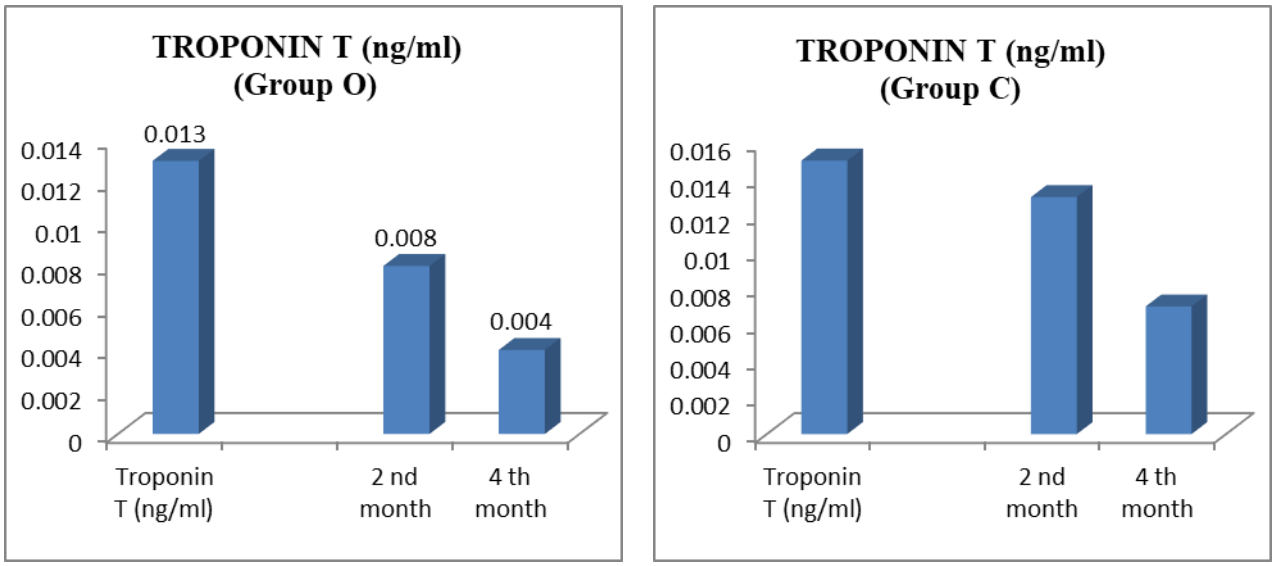

Figure 7 Troponin T (ng/ml) of O - Observational Group and C - Control Group in Coronary Artery Disease

Table 8 Comparison of ST segment (ms) within and Between The Two Groups at the 2nd Month and 4th Month

Characteristics	Group O (n = 60)	Group C (n= 60)	P-value
ST segment (ms)			
2 nd month	95.2 ± 5.0[3]	97.1 ± 6.8[3]	<0.0006
4 th month	86.1 ± 2.7[3]	92.0 ± 5.2[3]	<0.0001
P	<0.0001	<0.0001	

[3]Data were shown as mean ± SD and independent t-test & analysis of variance were used to determine significance (P<0.05).

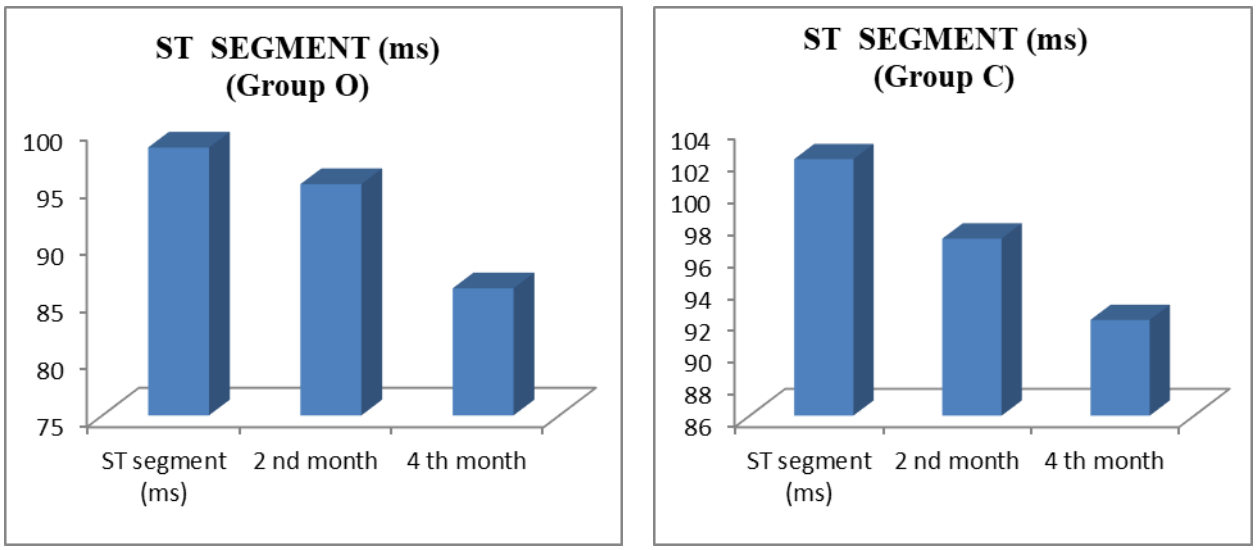

Figure 9 ST segment (ms) of O - Observational Group and C - Control Group in Coronary Artery Disease

3.2. Adverse Reactions

All patients completed the clinical trial. During the therapy period, routine urinalysis indicated no noticeable differences in liver and kidney function, as well as blood lipid and glucose levels in the two groups. There were two patients with muscle cramps and a moderate headache in the observation group, and one patient with abdominal discomfort in the control group; no major problems occurred in either group.

4. Discussion

An imbalance between the oxygen demand and blood supply of the heart (ischemia or hypoxia) results in coronary artery disease (CAD), which reduces blood flow to the heart muscle as a result of plaque accumulation in the heart's arteries. Exercise, emotional stress, cold or heavy meals, and effort are the main causes of the symptoms (absent at rest), which might show as pressure-like feelings, heaviness, or substernal discomfort that can radiate to the jaw, shoulder, back, or arm. As a result of CAD, there may be electrocardiographic evidence of ST-T alterations during rest or after exercise, as well as conduction abnormalities [16]. More specifically, it implies that the likelihood of a heart attack increasing in the future. Anti-anginal or vascular protecting medicines are those used in coronary angiography, the standard inquiry used to diagnose CAD in conventional medical treatment. Antianginal chemicals decrease the primary factors, such as the severity and frequency of anginal episodes and the time to commencement of exercise producing S-T depression of myocardial work, improving exercise duration until the onset of angina and reducing myocardial ischemia. Conversely, vascular protective drugs have the potential to slow down the advancement of atherosclerosis and intracoronary thrombi growth/rupture while stabilising coronary plaques, which would ultimately lower the frequency of subsequent cardiovascular events [17]. In the presence of CAD, standard anti-ischemic medications may not always be enough to alleviate symptoms. However, when conventional medications alone proved ineffectual, their combination with agents that work through pathways distinct from those of classic antiischemic substances, including nicorandil (second line of treatment), may prove beneficial. Orally administered isosorbide mononitrate was quickly

absorbed from the digestive system and had long-lasting hemodynamic (vasodilatation resulting in a decrease in preload) and antianginal (relaxation of vascular smooth muscles) effects [18]. Nicorandil's anti-ischemic action is achieved at the cellular level through selective inhibition of 3-ketoacylCoA thiolase (3-KAT), which prevents the production of oxygen free radicals in cardiomyocytes. This results in a shift in energy substrate preference from fatty acid oxidation to glucose oxidation. However, when conventional medications alone proved ineffectual, their combination with agents that work through pathways distinct from those of classic antiischemic substances, including nicorandil (second line of treatment), may prove beneficial. Orally administered isosorbide mononitrate was quickly absorbed from the digestive system and had long-lasting hemodynamic (vasodilatation resulting in a decrease in preload) and antianginal (relaxation of vascular smooth muscles) effects. Nicorandil's anti-ischemic action is achieved at the cellular level through selective inhibition of 3-ketoacylCoA thiolase (3-KAT), which prevents the production of oxygen free radicals in cardiomyocytes. This results in a shift in energy substrate preference from fatty acid oxidation to glucose oxidation, decrease the damage of inflammatory substances to myocardial cells while simultaneously improving cardiac systolic and diastolic function, coronary blood circulation, and myocardial function [19]. Less oxygen is needed for a given quantity of labour when glycogen is the substrate because it produces more ATP per oxygen consumed than fatty acids do. Because it speeds up the restoration of phosphorylation processes, shields cardiac cells from hydrogen ion buildup, and prevents intracellular calcium and sodium ion accumulation, nicotinamide has been demonstrated to have a cardioprotective effect during myocardial ischemia in experimental in vitro studies. Nicorandil increases the activity of the sodium-potassium ATPase and the sarcoplasmic reticulum's calcium uptake pump, which are in turn in charge of left ventricular diastolic relaxation and systolic depolarization, due to the preferential enhancement of glucose and pyruvate oxidation. Therefore, nicotinamide exhibited significant effects in CAD, particularly when administered in conjunction with nitrates.

The results of this study demonstrate that the effectiveness of isosorbide mononitrate and nicotinamide in Group O was significantly higher than in Group C, suggesting that these treatments are far more effective than other conventional therapies in the treatment of CAD, which primarily involve increasing the capacity of the myocardium to supply oxygen to the heart [20]. Additionally, this study saw an improvement in the cardiac functions of Group O by lowering cardiac function indexes like C-reactive protein (CRP), a significant inflammatory factor that influences the development of coronary artery disease and can trigger the formation of foam cells, which in turn releases the formation of lipid plaques, activate the complement system for atherosclerotic plaque intima, and impair the function of vascular endothelial cells, In comparison to Group C, Troponin T is a crucial biomarker for assessing acute MI, ST-segment, and an increase in left ventricular ejection fraction (LVEF), which improves myocardial ischemia, metabolism, and lowers cardiac stress. The study had certain drawbacks, such as raising treatment costs due to the large range of medications required and limited follow-up duration, as well as burdening patients with various pharmacological treatments [21].

5. Conclusion

The results of this study show that Nicorandil (NR) and Isosorbide Mononitrate (ISMN) can be effective in conjunction with conventional therapy in patients with coronary artery disease by improving cardiac function, decreasing inflammatory mediators that promote CAD progression, and lowering future cardiovascular complications.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflict of interest, financial or otherwise.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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