



A prospective observational study on comparison of safety and efficacy of Nitrates and Nicorandil in anginal pain

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ABSTRACT

A prospective observational study to compare the safety and efficacy of Nitrates and Nicorandil in anginal pain and to track the occurrence of headache, giddiness and SGPT variations. Patients were randomly arranged into 2 groups, each group receiving either nitrates or nicorandil directed on 110 patients during a study period of 6 months. Comparison was done among both the groups using Visual Analog Scale (VAS) and Numerical Pain Relief Score. Appraisal was done in patients with anginal discomfort being treated with either nicorandil or nitrates within one hour of admission into hospital Emergency Department. Results: Severity of pain was significantly reduced in patients treated with Nitrates, compared to that of Nicorandil. Blood pressure and pulse maintenance were comparatively efficient with Nitrate administration. However, during the 6-month study period, 24% of patients treated with Nitrates developed Side effects, compared to 26% of patients using Nicorandil. Significant SGPT variations were observed with both the medications. Nitrates has greater efficacy compared to that of Nicorandil. Incidence of side effects were also observed to be slightly greater in Nicorandil treatment group than in Nitrates treatment group. Consequently, this study supports the use of Nitrates over Nicorandil as the initial treatment for anginal pain in patients admitted to the Emergency Department.

INTRODUCTION

Angina pectoris, or simply angina is the most common symptoms of IHD. Angina is the discomfort in the chest that occurs when the blood supply to the myocardium is compromised. Chronic stable angina is defined as the chronic occurrence of chest discomfort due to transient myocardial ischemia with physical exertion or other conditions that increase oxygen demand. Angina is characterised by an uncomfortable pressure, fullness, squeezing, or discomfort in the centre of the chest. This discomfort can be felt in the neck, jaw, shoulder, back, or arm^[1].

IHD affects over 16 million Americans and is the leading cause of death for both men and women in the US. The incidence of IHD is higher in middle aged men compared with women. However, the rate of IHD increases two-to-threefold in women after menopause. Chronic stable angina is the initial manifestation of IHD in 50% of patients, whereas unstable angina or MI is the first sign of IHD in other patients^[2,3].

Short acting nitrates are the first line treatment to terminate

acute episodes of angina. All patients with a history of angina should have sublingual nitro-glycerine tablets to spray and relieve acute ischemic symptoms. Nitrates undergo biotransformation to nitric oxide. Nitric oxide activates smooth muscle guanylate cyclase, leading to increased intracellular concentrations of cyclic guanosine monophosphate, release of calcium from muscle cells, and ultimately to smooth muscle relaxation. Nitrates primarily cause venodilation, leading to reduction in preload. Myocardial oxygen demand is reduced as a result of the decrease in ventricular volume and wall tension^[4]. Nitrates cause arterial dilation and lower afterload and blood pressure at higher doses. Nitrates increase myocardial oxygen supply by dilating epicardial coronary arteries and collateral vessels, as well as relieving vasospasm, in addition to lowering oxygen demand^[5].

Nicorandil is a balanced vasodilator that acts as a nitric oxide (NO) donor as well as a K⁺ ATP channel agonist^[6]. N-[2-(Nitro-oxy) ethyl]-3-pyridine carboxamide is a nicotinamide derivative with a nitrate moiety in its chemical structure^[7]. Nicorandil undergoes de-nitration and bio-activation via the nicotinamide/nicotinic acid pathway. The nitrate-like action of nicorandil

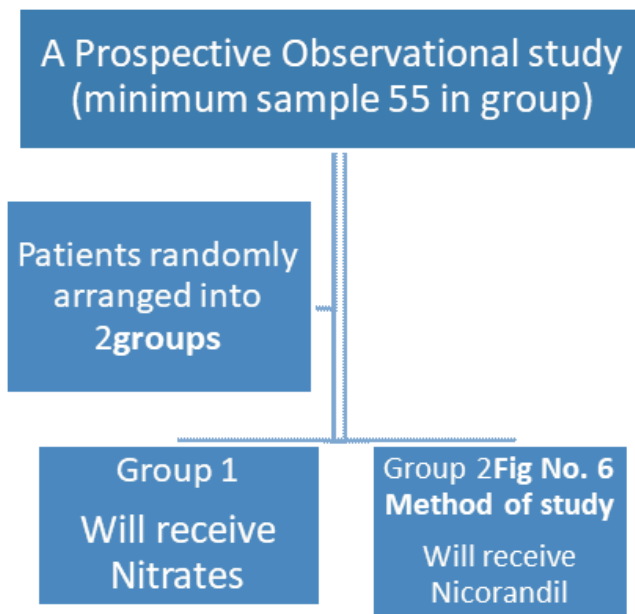


Fig 1 : Method of study for the comparison of Nitrates and Nicorandil.

possibly accounts for the majority of its clinical efficacy in angina, which is mediated via NO activation of cyclic guanosine-3', -5'-monophosphate (cGMP)^[8] signal pathways within vascular smooth muscle cells, causing peripheral venous and coronary arterial vasodilatation^[7]. When administered orally, as a single intravenous injection, or as a continuous infusion, nicorandil has been shown to improve hemodynamic in patients with chronic congestive heart failure who have a relatively stable hemodynamic condition by lowering preload and afterload and increasing cardiac output^[9].

In acute and emergency cases, sublingual nitrates are the drug of choice for angina management. They alleviate angina symptoms by veno-dilating capacitance vessels and preferentially dilating coronaries, lowering myocardial oxygen demand^[10]. Nicorandil works by relaxing and widening your

blood vessels, which increases the supply of blood and oxygen to your heart. This helps to reduce the chest pain that angina causes.

While nitrates and nicorandil are effective pharmacological agents for prevention of anginal symptoms, when prescribing these drugs, it is important to consider that unwanted and poorly tolerated hemodynamic side-effects such as headache and SGPT variations can often occur owing to systemic vasodilatation. It is necessary to ensure a dosing schedule to avoid nitrate tolerance, which can lead to not only a loss of drug efficacy but also endothelial dysfunction and an increase in long-term cardiovascular risk^[11,15].

MATERIALS AND METHODS

The prospective observational study was designed to evaluate the safety and efficacy of Nitrates compared to Nicorandil,^[12] the

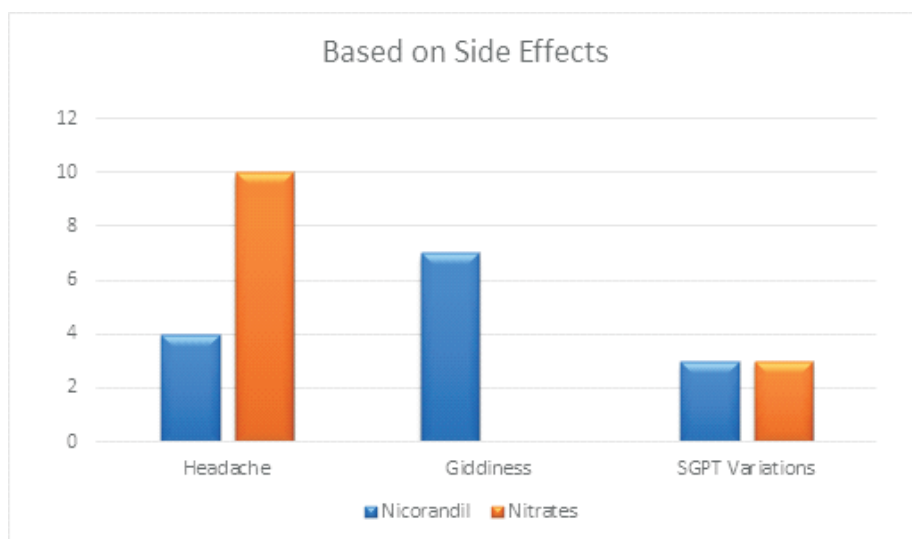


Fig 2 : Comparison of incidence of side effects

current standard therapy for Anginal pain and to track the occurrence of side effects in both medications which was carried out in a 700-bedded tertiary care teaching hospital in the Department of Emergency Medicine, KMCT Medical college, Kerala in India, with a total duration of the study was 6 months and 110 number of patients were enrolled into the study. Patients were selected based on the inclusion and exclusion criteria stated in the protocol.

The entire study population was divided into two groups. Group A constituted 55 patients treated with Nitrates, whereas Group B constituted 55 number of patients treated with

Nicorandil. Study was conducted for a period of 6 months. Each patient or bystander (if the patient is unable to answer) was interviewed at the time of admission, during the treatment, and at the time of discharge to assess the pain severity and other important details (fig. 6). The entire study was designed to be conducted in three phases^[14]. Phase I includes (1) Detailed literature review, done extensively using tertiary resources, secondary resources, primary resources. (2) Procure the necessary documentation: Designing of data entry form, informed consent document, patient information sheet. (3) Ethical committee approval: Ethical clearance was obtained from the Institutional Ethics Committee of National College of

Table 1 : Categorization based on side effects

| GROUP | Headache | Giddiness | SGPT Variation | Total |
|------------|----------|-----------|----------------|-------|
| Nicorandil | 4 | 7 | 3 | 14 |
| Nitrates | 10 | 0 | 3 | 13 |
| Total | 14 | 7 | 6 | 27 |

Table 2 : Chi-Square tests for categorization based on side effects.

| | Value | DF | Asymptomatic significance |
|-----------------------|---------------------|----|---------------------------|
| Pearson Chi-square | 12.494 ^a | 3 | 0.006 |
| Number of Valid Cases | 30 | | |

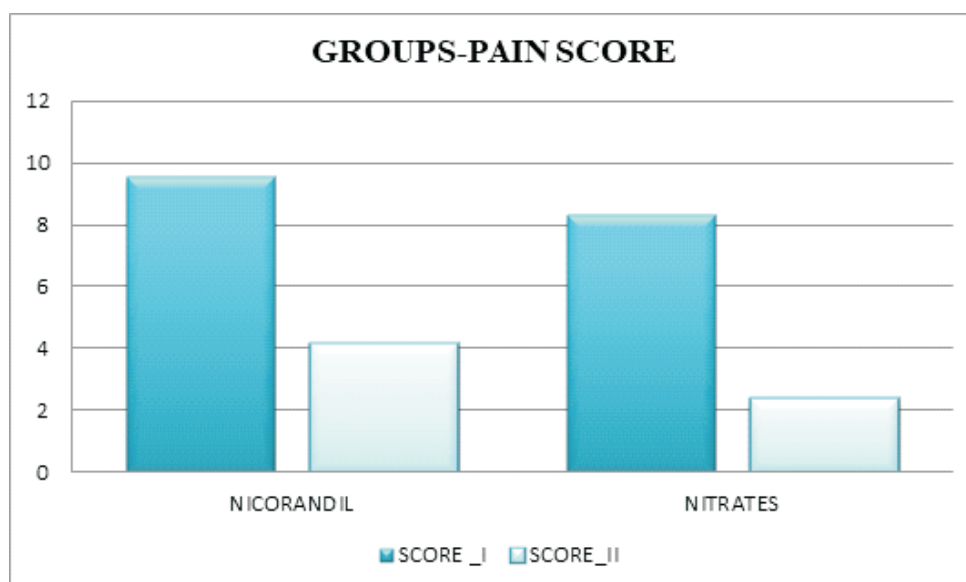


Fig 3 : Comparison of pain response in two treatment groups

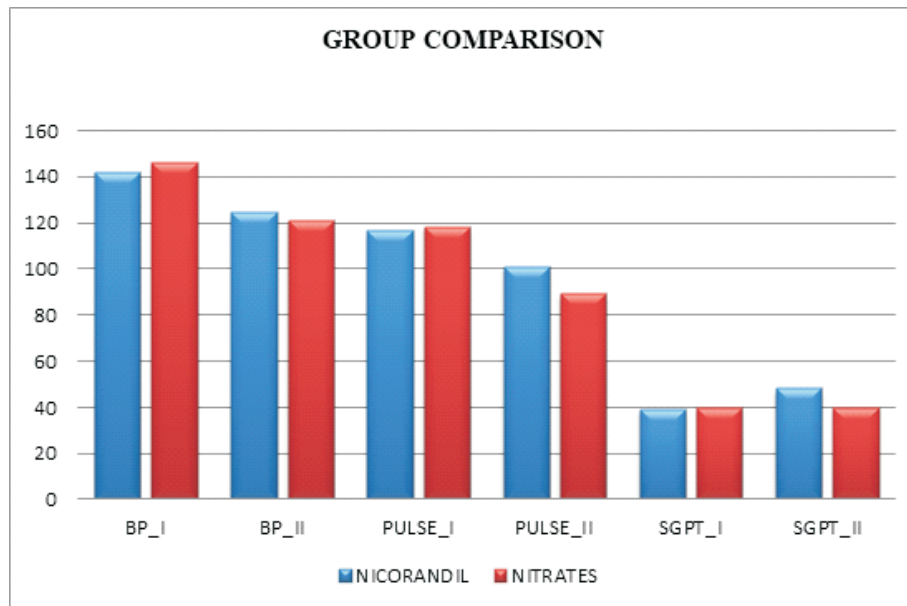


Fig 3 : Group Comparison between Nitrates and Nicorandil

Pharmacy. Phase II includes (1) The sample size was collected which comes under the inclusion and exclusion criteria at the time of enrolment. (2) Data was collected using data entry form after explaining patient information sheet and signing informed consent document Phase III includes Reports were analyzed using various statistical tools and reporting of results and presentation.

Inclusion Criteria includes Adult men/women aged between 20-75 presenting to ED with: Chronic stable angina with typical pain and definitive ECG changes (ST depression > 2mm, 80 milliseconds after J- point), Acute typical anginal pain, Typical pain and definitive ECG changes developed during Tread Mill Stress Test.^[14] Exclusion Criteria includes Cardiac Arrhythmia II- or III-degree AV block, Systolic BP < 120mmHg, Pregnant women and nursing mothers, Known hypersensitivity to nitrates and patients with Known history of Valvular heart disease,

cardiomyopathy, Myocardial infarction < 6 months, unstable angina, CHF, Anaemia (Hb < 7 g/dl), Significant liver dysfunction or renal dysfunction^[13]

The patients were selected during the time period from November 2019 to June 2020. From the 900 patients who visited Emergency department, 110 patients who satisfied the inclusion, as well as exclusion criteria, were allotted to study. The sample population was requested to answer at the time of their admission and relevant information were collected. Patient/Bystander interview and patients case records which contain the patient's demographics, history, laboratory investigation reports and prescribed drugs. Informed Consent Form and Patient Information Sheet was used to enroll patients in the study, informed consent and patient information sheet in the local language (Malayalam) was prepared. For collecting the necessary data obtained from the sources, separate data entry form was designed by including demography of patients, date of admission, past medical and medication history, diagnosis, current medication, visual analog scale and Numerical pain scale score. Patients were randomly arranged into 2 groups. Group 1 received Nitrates, whereas the other received Nicorandil. The comparison was done among both the groups to assess efficacy using VAS (Visual Analog Scale). Visual Analog Scale is a uni-dimensional measure of pain intensity, which is a single 11-point numeric scale. Score ranges from 0-10, in which the score "0" resembles "No pain", and that of "10" resembles "worst pain imaginable". Respondent is asked to indicate the scale that best describes their pain intensity, after which, the corresponding percentage is calculated (0-100%; 0 signifying "No pain", and 100 signifying

Table 3 : Comparison of pain response in two treatment groups

| GROUP | SCORE I | SCORE II |
|------------|---------|----------|
| Nicorandil | 9.5418 | 4.1364 |
| Nitrates | 8.3236 | 2.4018 |

Table 4 : Paired sample test of Nitrates and Nicorandil for the association of pain.

| | Mean | SD | P- Value |
|------------|---------|----------|----------|
| Nicorandil | 5.40545 | 10.64199 | 0.000 |
| Nitrates | 5.92182 | 1.26296 | 0.000 |

Table 5 : Comparison of blood pressure in Nitrates and Nicorandil group

| | Mean | SD | P- Value |
|------------|----------|----------|----------|
| Nicorandil | 30.89636 | 12.68405 | 0.000 |
| Nitrates | 33.82182 | 15.18889 | 0.000 |

“Worst pain”).^[14]

Statistical analysis

Data entry and statistical analysis were done using software SPSS version. A p value of < 0.05 was considered to be statistically significant. Chi-square test is used to determine where the association between the variables is statistically significant and examine difference between expected counts and observe counts to determine which variable levels may have the most impact on association.

RESULTS

Patients were assessed in terms of their blood pressure, pulse and incidence of side effects like headache, giddiness and SGPT variations. In this study, the entire study population was categorized into 4 groups based on age, (30 40), (40 50), (50 60) and >60 age groups. Majority of study population was distributed in the 60 above and (50 60) age groups. In the study population, male gender constituted majority in both the treatment group since the incidence of Angina is observed to be more in males than in females. Hypertension and Diabetes Mellitus was the most common comorbid condition observed in the entire study population followed by COPD, Asthma, Dyslipidaemia, Alzheimer's Disease and Arthritis being the rarest. The entire study population is classified into 21 categories based on trigger. it was observed that 18% of the study population were Smokers and another 18% of the study population were Alcoholics. This, Smoking and Alcohol consumption are found to be the most common triggers of Angina followed by tobacco and obesity. Assessment of side effects in both treatment groups reveals that 26% of the study group administered with Nicorandil developed side effect and 24% of the patients enrolled in the Nitrates treatment group were presented with side effects, (Table 1)

significance data in Table 2. From (Fig. 2) Nitrates treatment group showed few occurrences of side-effects compared to Nicorandil treatment group so that justifies the safety of the Nitrates over Nicorandil. In this study population headache was the most common side effect, seen in patients treated with Nitrates. Patients treated with Nicorandil showed giddiness as well as headache as common side effects' variations were observed in both study groups^[15]. Severity of pain was assessed in the patients who were enrolled in the study. Each patient was asked to rate the pain in 0 to 10 score, to assess the severity of pain. Reduction of the pain in the patients reflects the efficacy of the drug to reduce pain are shown in Table 3, Fig. 3 By Comparing the pain response in two treatment groups, patients treated with Nitrates showed a significant reduction in the pain. Patients treated with Nicorandil showed a less significant reduction in pain compared to Nitrates. The patients in the Nitrates treatment group showed major reduction in the pain score i.e., Mean pain score (5.92182). Nicorandil treatment group showed only less reduction in the pain score compared to that of Nitrates. i.e., Mean pain score (5.40545). Association of Pain by using Paired Sample test mean score shows comparison of pain in Nitrates and Nicorandil groups showed significance as the p-value is <.05 in Table 4, Fig. 4 Considering the maintenance of blood pressure, Nitrates treatment group showed a significant reduction in the BP, i.e., Mean (33.82182). On the other hand, Nicorandil treatment group exhibited less reduction in BP compared to that of the Nitrates group, i.e., Mean (30.89636). comparison between both the BP values before and after the administration of Nicorandil showed a significant association as the p- value is <0.05. Blood pressure values were reduced following the administration of Nicorandil. comparison between both the BP values before and after the administration of Nitrates showed a significant association as the p- value <0.05. From the graph, blood pressure

Table 6 : Comparison of pulse in Nitrates and Nicorandil group

| | Mean | SD | P- Value |
|------------|----------|----------|----------|
| Nicorandil | 15.43636 | 3.03537 | 0.000 |
| Nitrates | 29.27273 | 10.69346 | 0.000 |

Table 7 : Comparison of pulse in Nitrates and Nicorandil group

| | Mean | SD | P- Value |
|------------|----------|----------|----------|
| Nicorandil | -9.37500 | 28.69016 | 1.000 |
| Nitrates | .00000 | 2.64575 | 0.386 |

values were more significantly reduced following the administration of Nitrates compared to nicorandil (Table 5). From the graph, pulse values were more significantly reduced with Nitrates administration compared to Nicorandil administration. Assessment of pulse in the study population during the study revealed that significant pulse reduction and maintenance is associated with Nitrates study group (Mean 29.27273) compared to that of Nicorandil (Mean 15.43636). The comparison between the pulse values before and after the administration of Nicorandil showed a significant association as the p-value is <0.05 . Pulse values were reduced following the administration of Nicorandil, rejecting the null hypothesis. The comparison between the pulse values before and after the administration of Nitrates showed a significant association as the p-value <0.05 in Table 6. The comparison between the SGPT Variations before and after the administration of Nicorandil showed negative association as it accepts the null hypothesis that states "there is no association between the variables". SGPT values were significantly altered following the administration of Nicorandil. The comparison between the SGPT Variations before and after Nitrates administration also showed a negative association as the p-value is >0.05 and accepts the null hypothesis. SGPT Variations are observed in patients administered with Nitrates in Table 7. The statistical analysis by paired t test generated a p value that was <0.05 . Thus, it shows the significance in the comparison of pain severity between Nitrates and Nicorandil. Null hypothesis, stating the equal efficacy of Nitrates and Nicorandil in the pain reduction gets rejected, thus supporting the alternative hypothesis, stating the difference in efficacy of Nitrates and Nicorandil as the p value is <0.05 . So, by considering the reduction in the average pain score, Nitrates has more efficacy in pain reduction over Nicorandil. In contrast, the statistical analysis by paired t test generated a p value that was >0.05 in case of incidence of SGPT variations in Nitrates and Nicorandil treatment groups. Thus, in the respective case, the null hypothesis, stating the equal probability of developing SGPT variations in both the Nicorandil and Nitrates treatment group is accepted. This shows that both the Nitrate and Nicorandil treatment groups can equally generate SGPT variations as a side effect. From our study, it is clear that Nitrates are safer and more effective for the treatment of anginal pain when compared to Nicorandil.

DISCUSSION

Majority of study population was distributed in the age groups 60 above and 50-60. Male gender constituted majority in both the treatment group incidence more common in males. A study conducted by Udaykumar P, *et al.*, reported that 60% study population was males and 40% was females, which coincides with our study results^[13]. Zhu WL, *et al.*, in their study conducted in China reported the incidence of adverse reactions were similar in ISMN and Nicorandil groups. Headache was the most common side effect in both treatment groups. In our study, Nitrates treatment group (24%) showed few occurrences of side-effects compared to Nicorandil treatment group (26%). Headache was the most common side effect (12% in Nicorandil Group and 18% in Nitrates group). Giddiness was found in 12.7% patients in the Nicorandil group. SGPT Variations were similar in both groups (5.4%). Nitrates treatment group (33.82182) showed a significant reduction in the BP and pain compared to Nicorandil (30.89636). The study revealed that significant pulse reduction and maintenance is associated with Nitrates study group. Both the Nitrate and Nicorandil treatment groups can equally generate SGPT variations as a side effect^[16]. A study conducted by Zhu WL,

et al., concluded that Nicorandil was well tolerated and there was no difference with ISMN in its safety profile. On the contrary, another study conducted by Renzo Ciampricotti, *et al.*, concluded that ISMN is superior to nicorandil for the symptomatic treatment of daily angina in the elderly patient population. This study coincides with our study result that Nitrates are comparatively safe and effective for the treatment of anginal pain than Nicorandil^[12]. The main limitation of the study was the number of patients was limited. Potentially large sample size was required for the study so as to get more significant results, Study is based on a tertiary centre, and thus the results may not be generalizable to all patients in the community and ECHO data were unable to be collected due to the Covid-19 pandemic situation.

CONCLUSION

Safety, efficacy and incidence of side effects, were compared among Nitrates and Nicorandil for a duration of 6-month in this study. Study results concludes that Nitrates has more safety and efficacy compared to Nicorandil as number of side-effects are less in Nitrates treatment group compared to Nicorandil treatment group. Also, severity of pain has significant reduction in Nitrates treatment group compared to that of Nicorandil. Nitrates treatment group had significant maintenance of BP and pulse compared to Nicorandil. Thus, this study supports the use of Nitrates for angina pain, compared to Nicorandil.

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