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Improvement in Qualitative Indices with Novel Therapy of Nicorandil in Patients with Peripheral Vascular Disease: A Pilot Study

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Abstract

Introduction: Peripheral vascular disease (PVD) is a chronic condition which affects >20% of people over 70 years. Patients with PVD are symptomatic in 40% cases. Nicorandil, a potassium channel opener that allows the vascular smooth muscle to relax, effectively dilates the microvasculature and has shown improvement in myocardial perfusion. It also prevents endothelial dysfunction and cause significant reduction in peripheral vascular resistance. This effect has the potential in improvement of symptoms in peripheral artery disease. In this study, we studied the effect of Nicorandil on claudication distance and quality of life by measuring change in Peripheral Arterial Questionnaire (PAQ) Score and Claudication distance from baseline after 4 weeks of Nicorandil therapy along with standard of care therapy.

Aim: To find the effect of nicorandil on subjective claudication distance and peripheral arterial questionnaire (PAQ) in patients of peripheral arterial disease.

Methods: In this pilot study done on 18 individuals with peripheral artery disease, tablet Nicorandil 10 mg twice a day was given along with Tab. Clopidogrel 75mg once a day and Tab. Atorvastatin 40mg once a day for 4 weeks and change in subjective claudication distance and quality of life was compared with the baseline data of the same parameters.

Results: Out of 18, 15 (83.3%) were male, 3 (16.6%) were diabetic, 4 (22.3%) were hypertensive and 17 (94.40%) were smokers. Mean age of individuals in study was 57.6 years and mean body mass index was w19.47. There was asignificant increase in the mean subjective claudication distance after 4 weeks of nicorandil from 189.72 meters to 389.44 meters. Symptom scale improved from a mean value of 21.11 to 75.55, treatment satisfaction scale improved from 70.37 to 81.94, quality of life from 25.46 to 69.07, social function improved from 18.40 to 46.64 and mean summary score of quality of life indicators (PAQ) increased from 35.03 to 64.51.

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Conclusion: Our study findings have shown a significant improvement in both claudication distance as well as quality of life of patients with peripheral artery disease with nicorandil therapy. Further study on measurable parameters along with a comparator arm should be done in a larger population for establishing the role of nicorandil in PVD.

Keywords: Peripheral arterial disease; Intermittent claudication; Nicorandil; Amputation.

INTRODUCTION

Peripheral vascular disease (PVD) is common disorder in patients with atherosclerosis. It affects > 20% of people over 70 years. Patients with PVD are symptomatic in 40% cases.[1] PVD can present in a wide array of clinical features ranging from asymptomatic, intermittent claudication to rest pain. Revascularisation, by both endovascular techniques and open surgery, is the mainstay of treatment. However, some of these patients are not amenable to either due to significant co-morbidities and diffused disease. Medical management goals as of now are more towards reducing cardiovascular mortality risk. There has not been any significant breakthrough in medical management in terms of reducing limb complications and improving quality of life. The role of medical therapy is gaining momentum in patients of coronary artery disease. However, no such agents have shown a promising role in patients of PVD. Rheological agents, vasodilators, antiplatelet agents, anticoagulants, prostaglandins and prostaglandin analogue have all been tried in the management.[3] Statin & Antiplatelet agents have been shown to reduce the risk of major adverse cardiovascular events (MACE) but they don't confer much of limb protective effects. Cilostazole does offer symptomatic relief in patients with intermittent claudication but haven't shown any promising results in patients withchronic limb threatened ischemia (CLTI).[4] It is also associated with unwanted adverse drug reactions viz. headache, which can lead to discontinuation of therapy.[5] Treatment for symptoms is a combination of preventive measures such as modification of risk factors, antiplatelet therapy and active exercise. Pharmacotherapy has a significant role in the management. It may be given for symptomatic relief by improving pain-free and overall walking distances. Other drugs like Vitamin K antagonists, Pentoxifylline etc have shown no benefits. Nicorandil is a non-selective adenosine-sensitive potassium channel opener that allows the vascular smooth muscle to relax, effectively dilate the microvasculature and to improve myocardial perfusion. It has shown to have cardio protective effects in ischemic heart disease.[6] It causes a dose dependent reduction of peripheral arterial resistance by reducing the mean aortic pressure. It causes peripheral arterial dilatation (reducing afterload) and microvascular dilatation (reduce microvascular resistance).[7] Protective effect on endothelial function is also seen. Studies have shown that significant reduction in peripheral vascular resistance is seen in doses used for cardio protection.[8] No Study has been done yet exploring its role in Peripheral Arterial Disease. In this study, we measured change in Peripheral Arterial Questionnaire (PAQ) Score and Claudication distance from baseline after 4 weeks of Nicorandil therapy along with standard of care therapy.

METHODOLOGY

Study site: Tertiary care hospital in northern India

Inclusion criteria – All symptomatic patients visiting the vascular clinic with proven peripheral arterial disease were included in the study

Exclusion criteria – Active smoker, Acute Limb ischemia, and connective tissue disorders e.g. vasculitis, other neurological condition which might interfere with assessment of pain e.g. peripheral neuropathy, lumbar disc herniation etc. were excluded from the study. Any patient requiring surgical or endovascular intervention e.g. revascularisation or amputation, during the study period were excluded from the study.

Study duration: 4 weeks

All patients included in study were provided with Patient Information Sheet and written informed consent was taken. Sociodemographic parameters and detailed clinical history of all included patients were recorded. All patients included in study were advised the following prescription for a duration of

4 weeks - Tab. Nicorandil 10mg twice a day, Tab. Clopidogrel 75mg once a day and Tab. Atorvastatin 40mg once a day, Opioid based analgesic was given as an SOS prescription. Patient with adverse reactions were dropped-out from the study and their adverse reactions recorded. ADR were reported according to CTCAE version 4 guidelines. Peripheral arterial questionnaire (PAQ) and Subjective Claudication Distance (SCD) was noted before initiation of treatment and after 4 weeks of treatment. It was ensured that all patients had stopped smoking at least 6 weeks before starting therapy. Any other drugs previously advised to the patient, which might act as a confounder, was stopped during this period.

Statistical analysis: Results are expressed as medians or mean ± SD for continuous variables, and qualitative data are presented as numbers or percentages. Student t-test (paired) was used for comparing pre & post intervention values. ANOVA table compared Δclaudication distance with other parameters. Statistical analysis was done using SPSS v26.

Ethical considerations: Study was conducted after approval of ethics committee AIIMS Rishikesh. Patients were recruited after written informed consent. Principles of Good Clinical Practice was followed at all stages of the study.

RESULTS

A total of 20 patients were enrolled for the study. Two patients were dropped-out mid-way due to adverse drug reactions. One patient had episodes of postural hypotension and another had macular rash over his neck. The study was completed with 18 patients. The baseline characteristics of the study population is summarised in table no. 1. Male to Female ratio of enrolled patients was 5: 1. Mean age was 57.6 years.Mean Body Mass Index was 19.47. The results of pre and post intervention in terms of the various components of peripheral arterialquestionnaire (PAQ) viz. functioning domain, symptom stability, symptom scale, treatment satisfaction, quality of life & social function along with summary score and subjective claudication distance is given in table no. 2. Comparison of change in claudication distance with change in functioning domain, symptom stability, symptom scale, treatment satisfaction, quality of life, social function, and summary score is given in table no. 3.

Table 1. Baseline characteristics of study population

Sociodemographic parameters	n (%)
Male	15 (83.3)
Female	3 (16.6)
Diabetic	3 (16.6)
Hypertensive	4 (22.3)
Smoker	17 (94.4)
Mean age	57.6 yr
Mean BMI	19.47

Table 2: Peripheral Arterial Questionnaire (PAQ) & Subjective claudication distance (SCD) values in pre and post nicorandil therapy

PAQ domains	Baseline score mean	Post-intervention score mean	Correlation	P-value
Functioning Domain	21.52	52.31	0.667	0.003
Symptom stability	51.11	75.55	0.668	0.002
Symptom scale	23.33	61.57	0.678	0.002
Treatment satisfaction scale	70.37	81.94	0.318	0.198
Quality of life	25.46	69.07	0.643	0.004
Social function	18.40	46.64	0.722	0.001
Summary score	35.03	64.51	0.832	0.000
Subjective claudication distance (SCD) in metres	189.72	389.44	0.661	0.003

Both PAQ and SCD showed significant improvement post nicorandil therapy. Mean summary scores of PAQ showed statistically significant change from baseline ($p < 0.05$). Subjective claudication distance was also significantly improved at the end of the study period ($p < 0.05$).

Significant positive correlation was associated with post-test quality of life with post-test summary scores ($r=0.67$, $p=0.02$). A significant positive correlation was present with difference in summary score and difference in subjective claudication distance ($r=0.58$, $p=0.01$). (Fig. 1) All the patients showed subjective improvement in quality of life, more pain-free period and less requirements of analgesics.

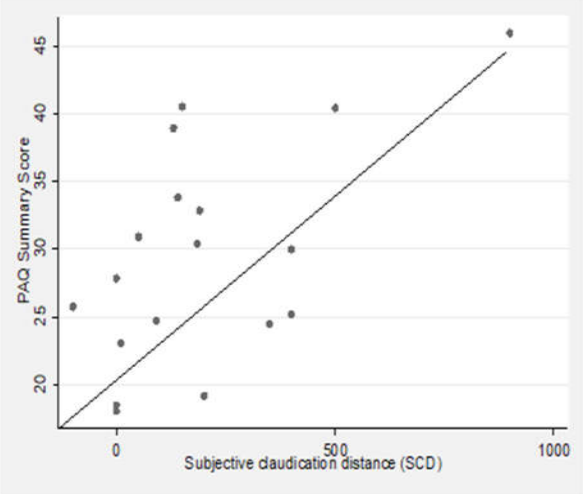

Fig. 1: Correlation between SCD and PAQ summary score

Two adverse drug reactions were noted in the study. One patient had reported postural hypotension (Grade-2) and other had maculopapular rash (Grade-1) in the neck region. None of the ADR were serious in nature. Drug discontinuation had resulted in completed resolution of ADR.

DISCUSSION

Incidence of peripheral artery disease is increasing day by day with 220 million people affected globally.[9] PVD shares the common pathophysiological mechanism, as coronary artery disease and cerebrovascular disease. Atherosclerosis involves gradual accumulation of fatty deposits within arterial walls leading to narrowing of vessels. Inflammatory process, endothelial dysfunction and oxidative stress play pivotal roles in progression of atherosclerosis in PVD. Risk factors of PVD are advanced age, smoking, sedentary life style, diabetes mellitus, dyslipidemia, obesity, race and ethnicity, homocysteinemia and alcohol consumption.[9] PVD is often underappreciated compared to coronary artery disease and cerebrovascular disease. There are various classifications of clinical presentation of PVD. American college of cardiology/American heart association practice guidelines defines the presentation of PVD as asymptomatic, intermittent claudication, critical limb ischemia and acute limb ischemia.[4] Fontaine classification and Rutherford classification are other clinical classifications in practice. Bollinger angiographic classification was proposed by Vogelberg in 1975 based on angiographic finding.

Asymptomatic patients have no claudication pain. Intermittent claudication is the most classical symptom where patient experiences fatigue, discomfort or pain on extremities reproducibly brought on exercise and relieves on rest. Many questionnaires have been developed to identify intermittent claudication e.g. ROSE questionnaire, San Diego questionnaire etc.[10] Ankle brachial index (ABI) is a sensitive and noninvasive useful investigation for diagnosing PAD. Normal values range from 0.9-1.1. It is also a generalized atherosclerotic predictor.[11] CLTI is a component of PVD defined as evidence of atherosclerotic peripheral arterial disease in combination with ischemic rest pain, gangrene or limb ulceration > 2 weeks duration with Ankle pressure <50 mmHg, ABI <0.4 or absent peripheral pulses. Revascularization in CLTI is based on Evidence based revascularization (EBR) and patient risk, limb severity, and anatomic complexity (PLAN) concept. Limb staging like WIfI (wound, ischemia, and foot infection) is used to assess limb severity. Duplex ultrasound, Computed tomography angiography, Catheter angiography, and Magnetic resonance angiography help in delineating anatomic complexity.[12]

Not all individuals are candidates for revascularization. In patients not suitable for revascularization, medical management plays a pivotal role. Medical management for symptoms is a combination of preventive measures such as modification of risk factors, antiplatelet therapy and active exercise. Medical management of diabetes, hypertension, and hyperlipidemia may retard the atherosclerosis progression although they have not been shown to improve symptoms or cause regression of established PVD.[4] Non-pharmacological management of PVD like smoking cessation, exercise, weight loss can improve walking performance.[13] Rheological

agents, vasodilators, antiplatelet agents[14], anticoagulants, prostaglandins and prostaglandin analogue have been tried in the management. Single antiplatelet[15] and statins with hypertension control and glycaemic control is recommended as per AHA guideline 2016.[4] Cilostazol, a phosphodiesterase-3 inhibitor is commonly used and approved for medical management of intermittent claudication but is ineffective in CLTI[16] as they steal blood flow from ischemic area and provide to nonischemic area and worsen ischemia. Vitamin K antagonist, Pentoxifylline etc have shown no benefits.[17]

Nicorandil is a non-selective adenosine-sensitive potassium channel opener that allows the vascular smooth muscle to relax, effectively dilate the microvasculature and to improve myocardial perfusion. It works as a NO donor (NO acts via cGMP signaling pathways within vascular smooth muscle cells causing peripheral and coronary vasodilatation) and a K+ ATP channel opener (vascular smooth cell hyperpolarization and closure of L-type voltage gated calcium channels which acts to dilate both coronary micro vessels and peripheral resistance arteries.[18] It causes a dose dependent reduction of peripheral arterial resistance by reducing the mean aortic pressure. It causes peripheral arterial dilatation (reducing afterload) and microvascular dilatation (reduce microvascular resistance). It protects endothelial function via normalisation of NADPH oxidase and nitric oxide synthase.[19]

Apart from coronary artery disease nicorandil can be used in various diseases like myocardial fibrosis, pulmonary fibrosis, renal injury glomerulonephritis due the effect on potassium ATP opening effect and on male impotency and inflammatory bowel disease through NO donation pathway.[20]

Apart from vasoactive agents, therapeutic angiogenesis is being tried in CLTI. It is the growth of new blood vessels with the use of growthfactor stimulation. Vascular endothelial growth factor (VEGF), Fibroblast growth factor (FGF) and hepatocyte growth factor (HGF) has shown angiogenesis in animal models.[21]

In our study, Nicorandil has shown promise in improvement of symptoms in patients of PAD. As a secondary benefit, it also provides cardioprotective effects. The dose used in this study was the same as used in patients with coronary artery disease.

CONCLUSION

Nicorandil has been used in management of coronary artery disease since long time. But effect of nicorandil on peripheral artery disease has not been established till date. Our study findings have shown a significant improvement in both claudication distance as well as quality of life in patients with peripheral artery disease on nicorandil therapy. Further studies with objective parameters and a comparator arm should be done in larger population for establishing the role of nicorandil in PAD.

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