International Journal of Research in Medical Sciences
Patel D et al. Int J Res Med Sci. 2024 Dec;12(12):4518-4521
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20243699

Original Research Article

In practice usage of extended-release nitrates in patients with angina in the real-world setting: a clinician's perspective

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Received: 06 October 2024
Revised: 20 October 2024
Accepted: 21 October 2024

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ABSTRACT

Background: Nitrates are highly effective in terminating acute angina pectoris attacks and preventing symptomatic and asymptomatic myocardial ischemia.
Methods: This was an observational survey-based study conducted in cardiologists and physicians with clinical expertise in the management of ischemic heart disease from January 2024 to March 2024. Data entry and statistical analysis were done for completed questionnaires and results are expressed in terms of percentages based on the number of responses obtained.
Results: A total of 47 clinicians participated in this survey. Nitrates were preferred as first-line agents by 59.5% of respondents, while 40.5% favoured beta blockers. Headache (51.0%) was the most common reason for shifting from nitro-glycerine to other anti-anginal. Most clinicians (76.5%) co-prescribed beta blockers with nitrates, while 6.3% co-prescribed calcium channel blockers.
Conclusions: The present survey concluded that nitrates continue to be the preferred anti-angina drugs in the real-world setting in India.

Keywords: Beta-blockers, Headache, Myocardial ischemia

INTRODUCTION

Stable angina pectoris is the common clinical manifestation of coronary heart disease. In many, patients, inadequate symptom control adversely affects the quality of life of these patients.[1,2] The current treatments for angina include a variety of drugs such as nitrates, calcium channel blockers, beta-blockers and nicorandil. Although calcium-channel antagonists are the drugs of choice for the treatment of angina due to coronary artery spasm, vasospastic angina can also be successfully treated with nitrates.[3] Clinical trial data showing the superiority of any one anti-anginal drug over another is lacking.[4] All available anti-angina drugs are equally effective in relieving angina symptoms.[1] Nitrates have been used to treat symptoms of chronic stable angina for more than 135 years.[1] Nitrates are highly effective in both terminating acute angina pectoris attacks and preventing symptomatic and asymptomatic myocardial ischemia.[5] Nitrates act by activating the endogenous nitric oxide-current good manufacturing practice (NO-cGMP) signalling pathways and result in reduction of intracellular free Ca2+ and

desensitization of vascular smooth muscle cell vasoconstrictor elements to Ca^{2+}, and thus causing vasorelaxation. The action of nitrates may compensate for deranged endothelial function.[1] Like other anti-anginal drugs, long-acting nitrates improve exercise tolerance, time to symptom onset and time to ST-segment depression during exercise testing in patients with stable effort-induced angina. In a meta-analysis of 51 clinical trials (n=3,595 patients), nitrate therapy decreased the number of angina episodes by about 2.45 episodes per week.[1] More recently, the RANGER study also showed that among patients suffering from stable angina who had recently initiated ranolazine (long-acting nitrate) was well tolerated and associated with fewer angina attacks and improved quality of life.[6]

One drawback of nitrates is the development of tolerance to the antianginal effects if they are used continuously. The only practical way to avoid the development of tolerance is to use intermittent daily therapy with nitrates or eccentric dosing wherein the first dose is administered in the morning and the second dose 7 hours later. This increases exercise duration for at least 12 hours without the development of tolerance to either the morning or afternoon dose. This dosing regimen avoids a rebound phenomenon at night and early hours of the morning in the nitrate-free period.[7] The rationale for this eccentric dosing was the observation that angina attacks in stable effort angina pectoris frequently occur during the daytime and occur less at rest or during sleep. For this reason, it is recommended that plasma nitrate concentrations should be increased during the daytime and reduced at night.

Myocardial ischemia has a marked circadian rhythm. All ischaemic events (total ischaemic burden, myocardial infarction, and sudden cardiac death) are most frequent in the hours immediately after waking. Oral anti-ischaemic prophylaxis should ideally provide protection during this critical period, in order to minimize symptoms, maximize exercise capacity and perhaps also to reduce the risk of clinical events.

The ideal long-acting nitrate formulation should therefore provide a rapid rise in plasma nitrate concentration as well as maintaining prolonged efficacy throughout the dosing interval.[8] Hence the development of novel sustained-release formulations of nitrates has ensured rapid release of nitrates in the first hour and up to 90% release of the drug by 8 hours followed by a nitrate low period. This prevents the rebound angina seen with conventional formulations of nitrates.

Another concern with nitrates is the headache experienced by patients. When the headache occurs within the first hour of nitrate administration, it is usually attributed to vasodilation and can often be avoided by starting with a low dosage. Occurrence of headache usually dissipates after several weeks of therapy, and co-administration of nitrates with aspirin, prescribed for secondary prevention, can also help to reduce this side-effect. Approximately 10 % of patients are unable to tolerate nitrates due to headaches.[1] The use of the extended-release formulation of nitrates reduces the incidence of headaches and improves patient compliance. The present study aimed to solicit the opinion of Indian physicians and cardiologists regarding the use of extended-release nitrates in their patients with angina in a real-world setting.

METHODS

Study design

This was an observational survey-based study conducted in cardiologists and physicians with clinical expertise in the management of ischemic heart disease from January 2024 to March 2024. A structured questionnaire was prepared to solicit the opinion of the experts regarding their practice and preference of drugs for the management of angina in the real-world setting (Table 1). The survey questionnaire consisted of 6 questions. The key questions covered in the survey include epidemiology, treatment, and clinical management of angina. The study-related documents, including the survey questionnaire, were reviewed by experienced cardiologists.

Participant's recruitment

The participants for this survey were selected based on their clinical expertise in the management of ischemic heart disease. Cardiologists and physicians actively involved in treating patients with ischemic heart conditions were invited to participate. There were no specific exclusion criteria for this study. The survey questionnaire was given to clinicians and a duration was allocated for completing the survey questionnaire. Although most questions required a single response, multiple responses were allowed for specific questions (Table 1).

Prior to participation, participants received an overview of the study's objectives and methodologies. It was emphasized that participation was entirely voluntary. This approach was adopted to minimize the potential risk of participation bias and guarantee the authenticity of individual perspectives.

In order to uphold participant confidentiality, all collected data were anonymized. Access to the survey responses was restricted to only research team, ensuring that individual responses remained confidential. All clinicians participated in the survey voluntarily, and no incentives were provided to the clinicians for their participation.

Statistical analysis

Data entry and statistical analysis were performed for completed questionnaires. Data were presented as percentages for categorical measurements. Graphical representations of the data were presented for visual impression.

RESULTS

Of the total 60 clinicians invited, 47 clinicians participated in this survey. A total of 55.3% of clinicians reported that angina most commonly occurred in the 50-60 years of age group, while 27.6% and 17.02% of clinicians responded that it occurred in 40-50 years and >60 years of age group, respectively (Figure 1).

Table 1: Survey questionnaire.

S.no.	Questionnaire
1.	In which age group does angina occur most frequently?
2.	Which of the medications do you consider as a first-line therapy for angina management?
3.	In which patient profile you do not prefer to use nitrates?
4.	Which is the most common reason to shift from nitro-glycerine to other anti-anginal
5.	Along with nitroglycerin which is the most commonly co-prescribed anti-anginal drug?
6.	Are nitrate spray or patches being useful?

Regarding angina management, 59.5% of respondents preferred nitrates as the first-line agent (Figure 2). Total 68.0% of clinicians stated they did not use nitrates in patients with low blood pressure while 32.0% of clinicians responded that they use nitrates for these patients. The majority of clinicians reported headache (51.0%) as the most common reason to shift from nitro-glycerine to other anti-anginal. Most clinicians (76.5%) responded that they co-prescribed beta blockers with nitrates, while 6.3% co-prescribed calcium channel blockers (CCBs) with nitrates. A total of 53.1% of clinicians opined that spray or patches are not useful while 34.0% of clinicians opined that spray or patches are less useful than capsules/tablets.

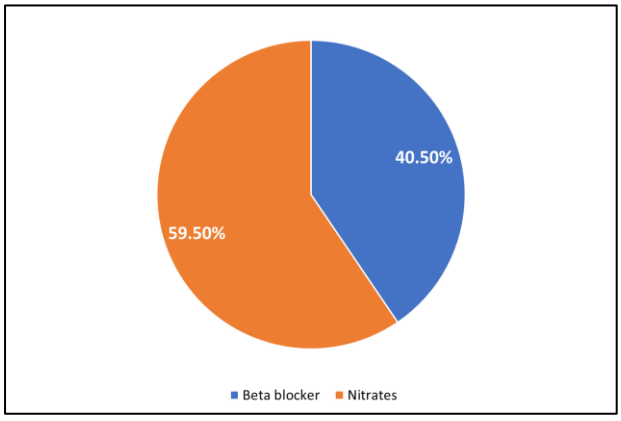

Figure 1: Preferred first line therapy for patients with angina.

DISCUSSION

Nitrates are used extensively for the treatment of angina pectoris. Long-acting nitrate vasodilators, including isosorbide mononitrate (ISMN) and isosorbide dinitrate (ISDN), belong to a group of organic nitrate esters with a nitrooxy (-O-NO2) moiety, which act as NO donors.

At therapeutic doses, nitrates predominantly affect venous capacitance vessels, but they can also dilate large and medium-sized coronary arteries and arterioles of >100 µm. Nitrates cause peripheral venous dilatation resulting in a decrease in venous return, lowering left ventricular end-diastolic filling pressure (preload) and volume, thereby decrease the myocardial work and oxygen demands, and indirectly increase the sub-endocardial blood flow. At higher doses, nitrates cause arterial vasodilatation, reducing systemic vascular resistance (afterload) and blood pressure.[1] Nitrates dilate coronary arteries in pre- and post-stenotic vessels, and in eccentric lesions.[5]

However, continuous therapy with either oral nitrates or nitro-glycerine patches leads to rapid development of tolerance, with loss or diminution of antianginal and anti-ischemic effects. It is recommended to use extended-release nitrate formulations with an eccentric dosing regimen that includes a nitrate-free interval of 8-10 hours to effectively prevent nitrate tolerance.[9] The nitrate low interval facilitated by extended-release formulations of nitrates also decreases the risk of rebound angina. The extended-release formulation of nitrates increases exercise tolerance.[10]

Headache is the most common side-effect of nitrates and has an adverse effect on patient compliance to therapy. However, extended-release nitrate formulations reduce the occurrence of headaches and improve patient compliance.[11]

In the current in practice survey, 59.5% of respondents stated that they preferred nitrates as first-line agents for angina management while 40% preferred beta blockers. 76.5% of respondents co-prescribed beta blockers with nitrates. 6.3% of respondents co-prescribed calcium channel blockers (CCBs) with nitrates. This trend indicates the response observed by Indian physicians in their patients with ischemic heart disease. Secondly, the safety of co-prescription of nitrates with beta blockers and calcium channel blockers was also ratified by their response.

The study has some limitations, including a small sample size of 47 clinicians, which may affect the generalizability of the results. The use of self-reported data in an observational survey could introduce response bias, and the focus on a specific group of cardiologists and physicians may limit the diversity of perspectives. Additionally, the study was conducted in India, so the findings may not be applicable to other regions.

CONCLUSION

The present survey concluded that nitrates continue to be the preferred anti-angina drugs in the real-world setting in

India. Long-acting nitrates improve exercise tolerance, time to symptom onset and time to ST-segment depression during exercise testing in patients with stable effort-induced angina. The extended-release formulation of nitrates offers a nitrate-low period which extends and improves the period of protection from angina. Secondly, a low incidence of headaches with this formulation and the development of tolerance to the headache improve patient compliance. The Expended release formulation of nitrates continues to be a part of the treatment armamentarium for angina in Indian patients.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Patel D, Guthe A, Vishwakarma P, Pradhan A, Ali M, Gupta A, et al. In practice usage of extended-release nitrates in patients with angina in the real-world setting: a clinician's perspective. Int J Res Med Sci 2024;12:4518-21.