

## Tolerability and Compliance Among Patients using Long Acting Organic Nitrates

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### ABSTRACT

**Purpose:** The aim of this project is to examine the tolerability of patients to the various possible side effects of organic nitrate and how that would affect their compliance. **Methods:** A PubMed search of the literature was conducted using the terms nitrates tolerability, nitrates side effects, nitrate compliance. Data for this study was collected from a questionnaire that was distributed to 75 patients. **Results:** The results showed that 69% of patients have experienced side effects when they started using organic nitrates. After continued use, the incidence of side effects decreased to 19 %. The most common side effect was reported to be headache which occurred in the first eight hours of using medication almost as one headache attack daily. **Conclusion:** Organic nitrates have a good tolerability and compliance among patients, it is clear that the incidence of nitrate side effects especially headache decrease with continued use which might be attributed to the tolerance that might develop with the use of nitrates. Starting nitrates in low doses and leaving a daily free interval have been reported to be associated with reduced frequency and severity of headache, and enhanced their clinical efficacy.

**Keywords:** Nitrates, Tolerance, Compliance.

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### INTRODUCTION

Organic nitrates are potent vasodilators capable of lowering blood pressure and cardiac filling pressures<sup>10,11</sup>. Organic nitrates are very effective anti-ischemic agents believed to act by relaxation of vascular smooth muscles via the release of nitric oxide (NO) from nitrites resulting in direct dilation of the blood vessels<sup>2,7,17</sup>. This has made them commonly used in the management of angina pectoris, myocardial infarction, and congestive heart failure<sup>1,21,22</sup>. Other uses for nitrates include preeclampsia and pulmonary hypertension<sup>8,16</sup>. Nitrates can be divided into long acting agents such as isosorbide mononitrate (ISMN), and short acting agents such as glyceryl trinitrate (GTN)<sup>9</sup>. Routes of administration of the nitrates are sublingual, oral, injectable and transdermal<sup>14</sup>. Short acting nitrates are associated with a rapid onset of action making them vital for the relief of acute anginal attacks, while long acting nitrates are primarily used for prevention of ischemic episodes<sup>3</sup>. Despite the wide use of nitrates and long history of use, their exact mechanism of action and mechanism of tolerance development in addition to their long-term efficacy are still debatable<sup>10</sup>. The most common side effects that arises from the use of short and long-acting nitrates are headache, hypotension, dizziness, nausea and skin flushing or irritation<sup>3,22</sup>. These side effects have a major impact on the patient's tolerability and might negatively affects his / her compliance<sup>3</sup>. Additionally, nitrate tolerance is one of the major issues reported with the continued use of nitrates and could be prevented by allowing a daily nitrate-free interval<sup>9,12,18</sup>. These effects make patients' education an important step in the treatment

process since the patient tolerability to the adverse effects and reduction of the drugs' tolerance would improve efficacy of the drugs in controlling the disease and consequently the patients' quality of life. Tolerability to long acting nitrates could be improved by decreasing the incidence of adverse effect occurrence among patients and increasing their awareness of these effects. The aim of this study is to examine the tolerability of patients to the various possible side effects of organic nitrate and how that would affect compliance. This study is the first of its kind in Bahrain since the tolerability of organic nitrates was not studied previously despite its wide use.

### METHOD

A systematic search of literature using several search engines including the National Library of Medicine's PubMed database and Google Search was conducted. The terms used in search were: organic nitrates, nitrates side effects, nitrates tolerability, nitrates tolerance and nitrate compliance. The search profile included comprehensive lists of various clinical studies that were performed in different world areas for statistically relevant information about nitrates tolerance. Data for this study was collected from a questionnaire that was distributed to 75 male and female patients of various nationalities and age groups visiting government hospitals pharmacies. The survey included questions about different aspects of nitrate tolerance, tolerability and compliance. A summary score of percentage correct answers was finally created. The data was analyzed using Microsoft Excel program for statistical analysis.

Table 1: Demographical data of patients

Gander	Female	Male	
	30 %	70 %	
Age Groups	30 - 40	40 - 50	More than 50
	4 %	17 %	79 %
Education	illiterate	School	University
	35 %	29 %	31 %
			Postgraduate
			5 %

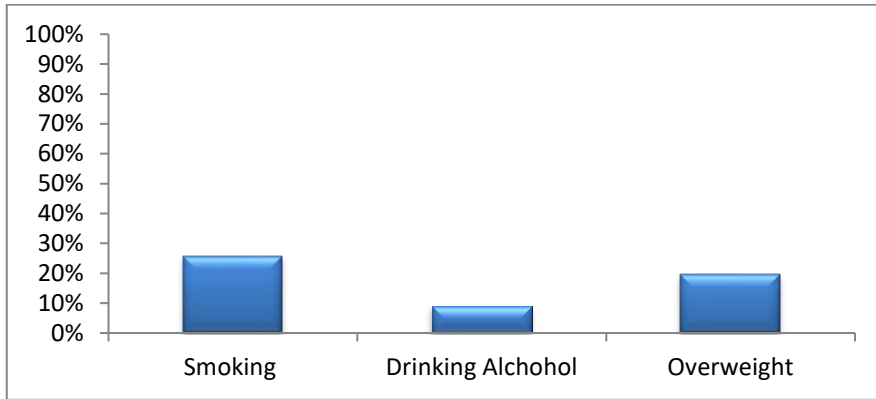


Figure 1: Life-style habits of the patients.

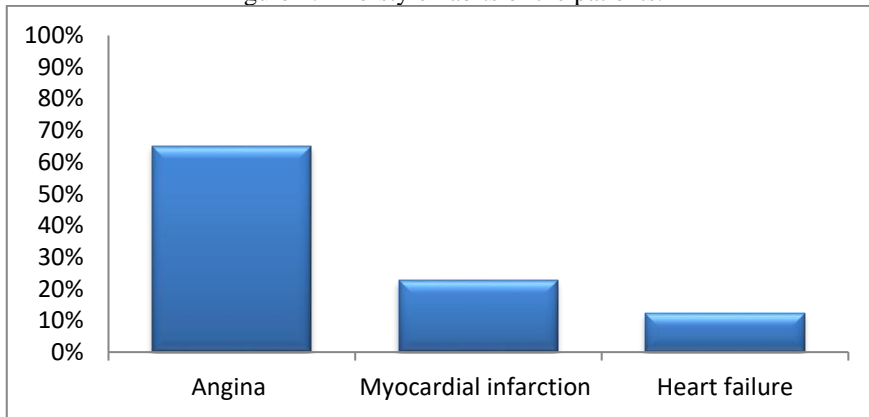


Figure 2: Patients' purposes of the use of organic nitrates.

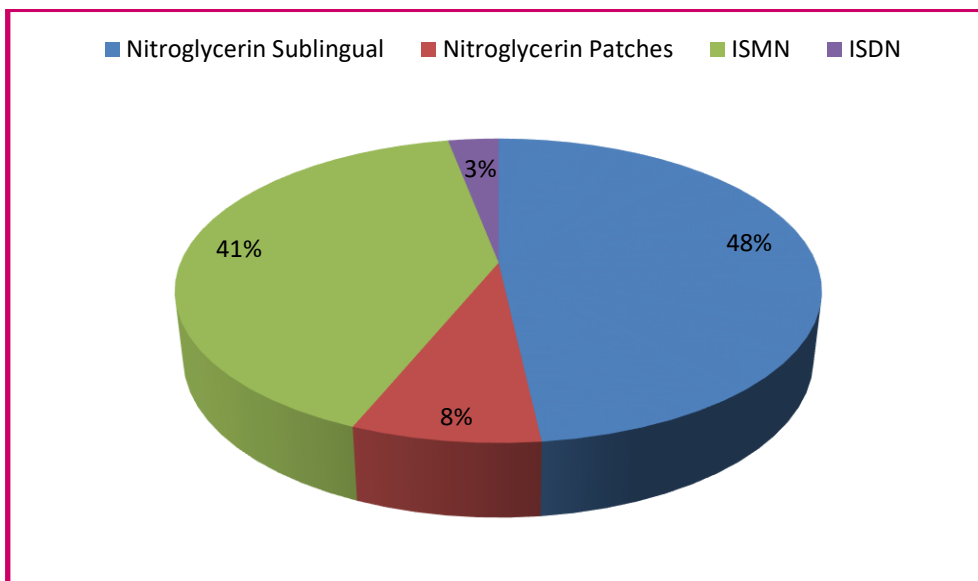


Figure 3: The most common organic nitrates used. ISMN: Iso-Sorbide MonoNitrate , ISDN: Iso-Sorbide Di Nitrates.

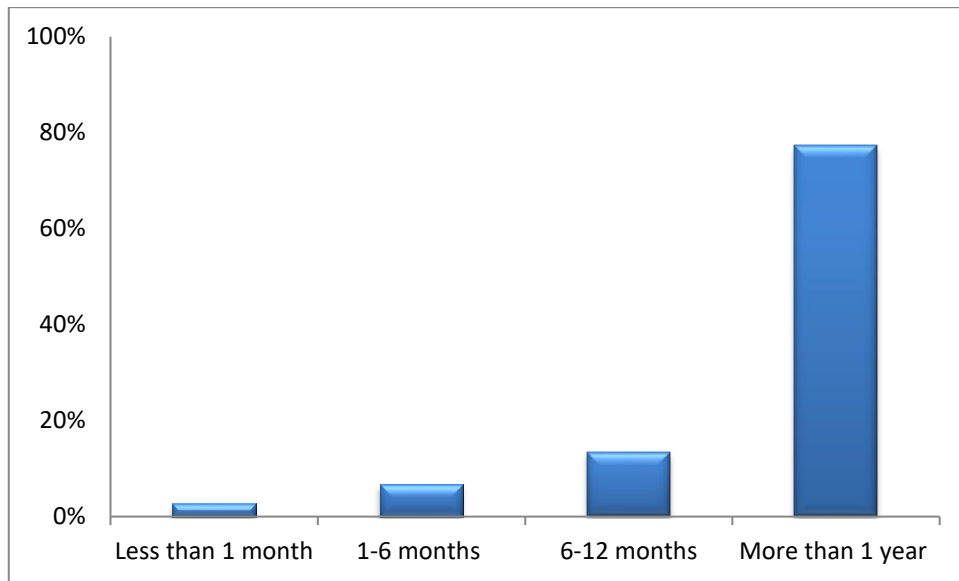


Figure 4: Duration of using organic nitrate.

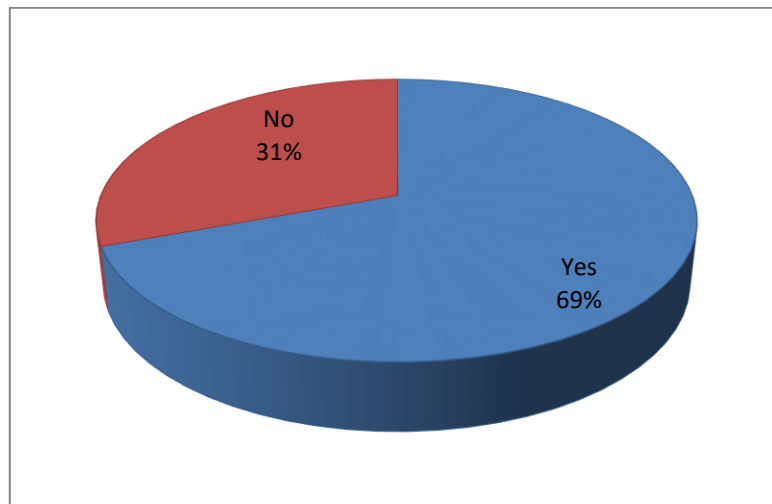


Figure 5: Percentage of patients who experienced side effects when they started using nitrates.

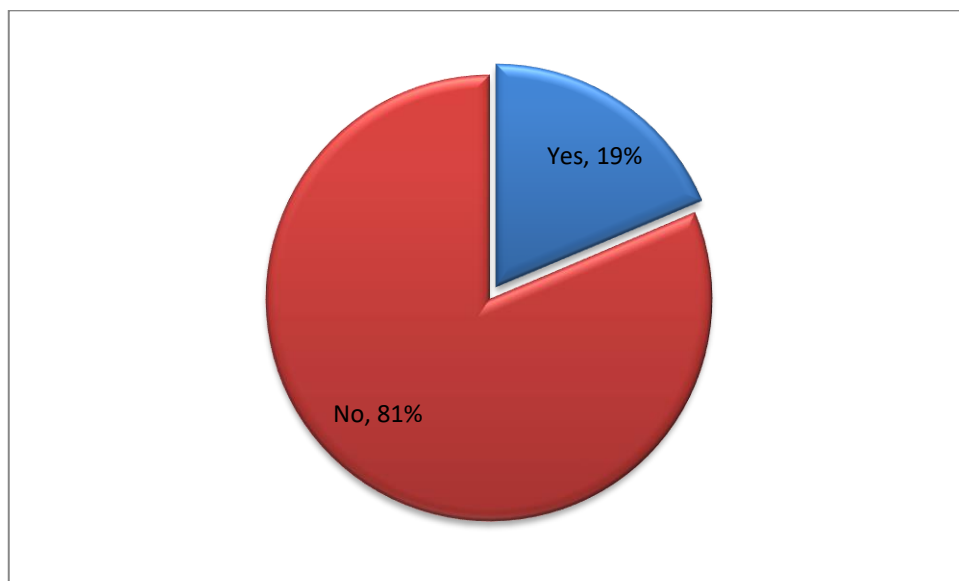


Figure 6: Percentage of patients who suffer from nitrates side effects currently.

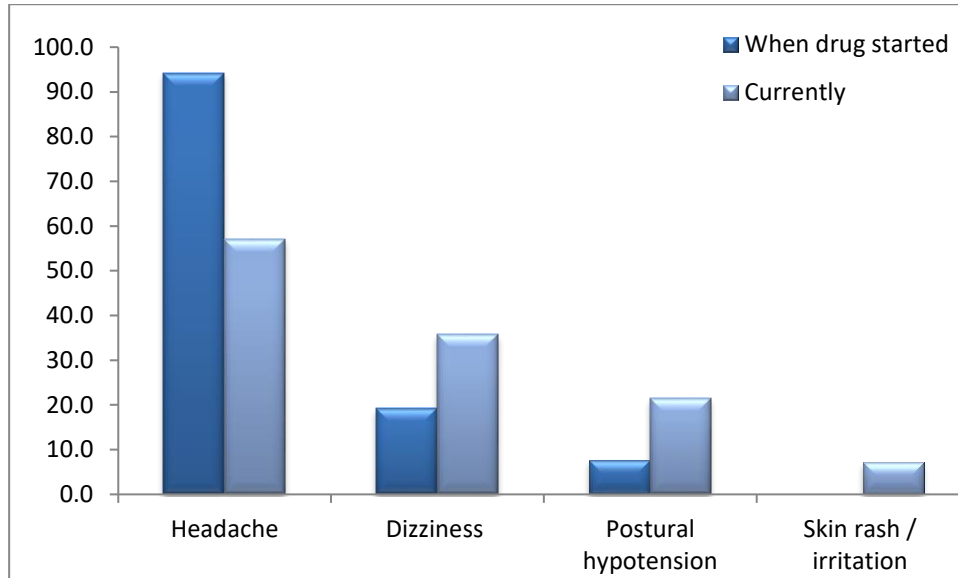


Figure 7: Side effects experienced by patients when nitrate therapy started and currently.

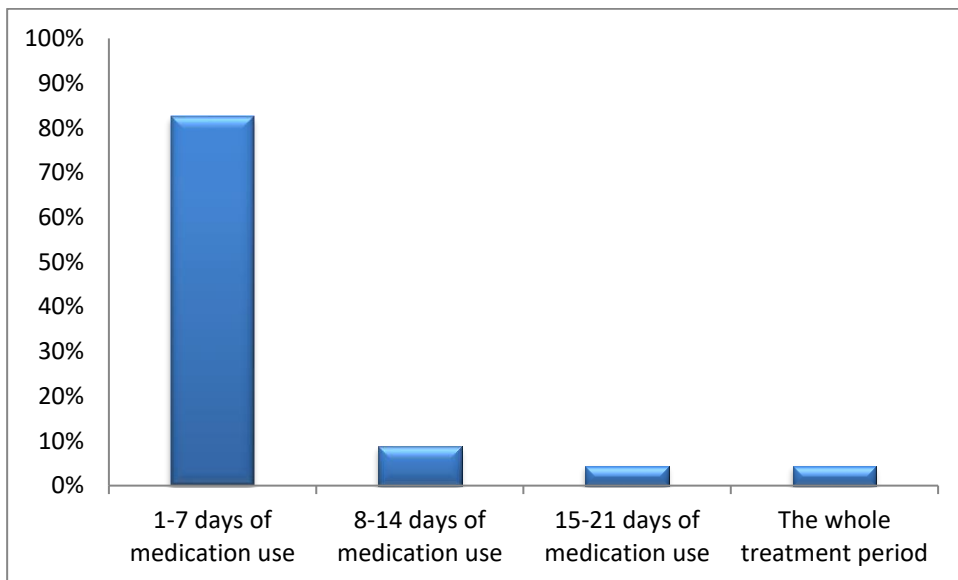


Figure 8: Period during which nitrate side effects were experienced.

**RESULTS**

Demographical data of participants is shown in Table 1. The male patients were 70 %, while the rest were female. The majority (79 %) of patients were more than 50 years age, 17 % were 40 – 50 years and the rest (4 %) were 30 – 40 years. Patients with normal weight were found to be only 42 %, while 46 % were overweight and 12 % were obese. Life-style habits of the patients are shown in figure 1. Smoker patients were found to be 26 %, alcoholics were 9 %, while the overweight were 20 %. Patients use of nitrates was found to be for different purposes as 65 % of patients have angina, 23 % have previous myocardial infarction and 12 % have heart failure (Figure 2). The most common organic nitrates used were sublingual nitroglycerin (GTN, 48 %), transdermal nitroglycerin(8 %), isosorbide mononitrate (ISMN, 41 %) and isosorbide dinitrate (ISDN, 3%) (Figure 3). The duration of use of the organic nitrates was found to be more than a year for most

patients (77 %), while 11 % have used the nitrates for 6 months or less (Figure 4). The results showed that 69% of patients have experienced side effects when they started using organic nitrates (Figure 5). After continued use, the incidences of side effects decreased to 19 % (Figure 6). The most common side effect was reported to be headache (94 %) followed by dizziness (19 %) and postural hypotension (8 %) (Figure 7 ). However, these percentages changed with continued use. Patients who experienced nitrate side effects almost had it at the first week of using medication as reported by 85 %, while 8 % had these side effects at the second week, and a few number of patients had these side effects at the third week or for the whole treatment period (Figure 8). The majority (83 %) of the patients who experienced headache as a side effect of the organic nitrate mentioned that the severe headache attack occurred in the first eight hours of using their medication, while the rest said that it was experienced

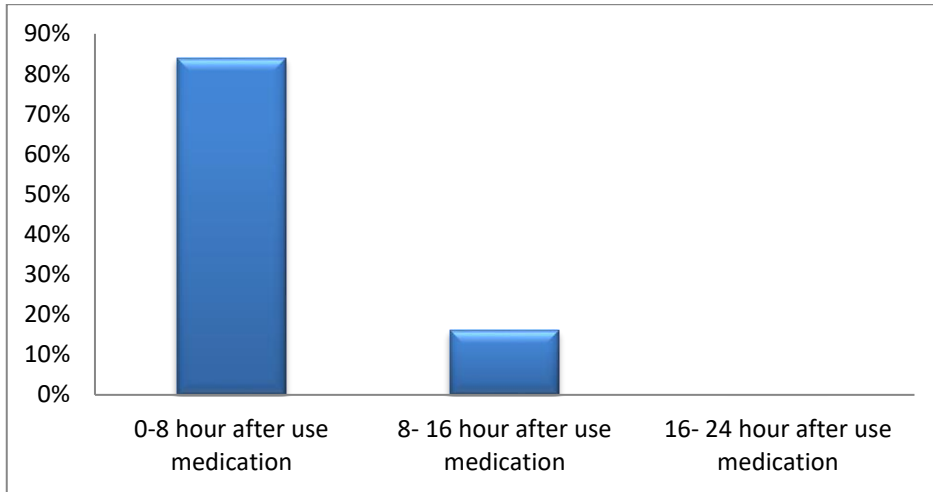


Figure 9: Time of occurrence of the headache attack.

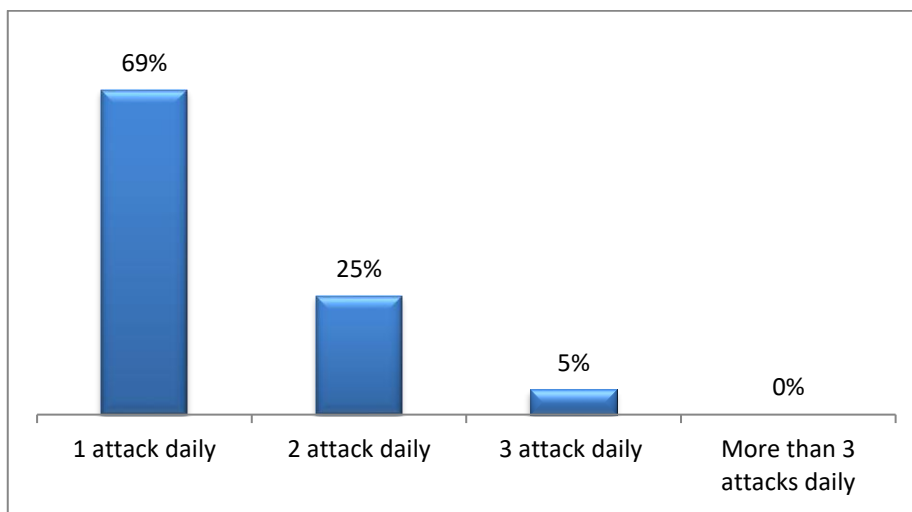


Figure 10: Number of daily headache attacks experienced.

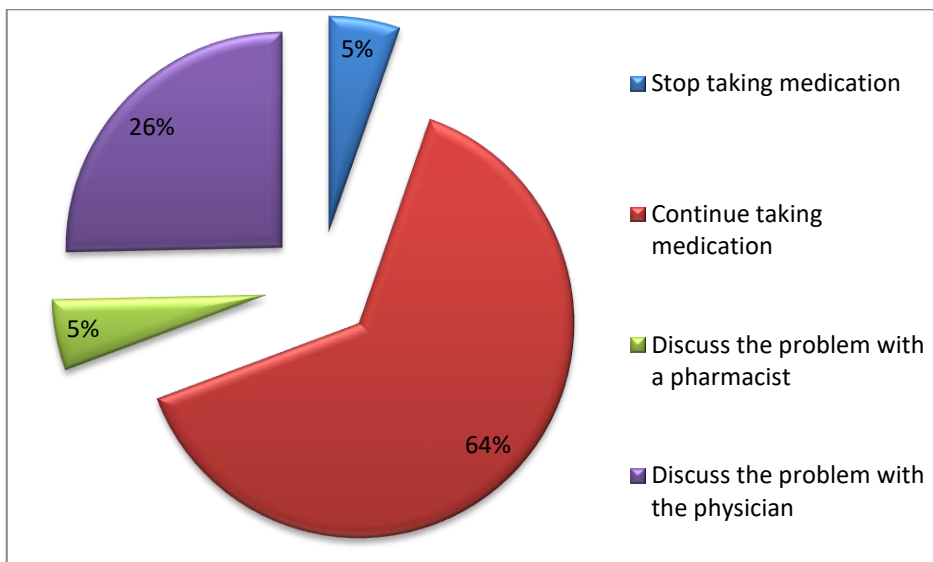


Figure 11: Actions taken by patients when nitrate side effect appeared.

8-16 hours later (Figure 9). 69 % of patients reported that they experienced one headache attack daily, while those who experienced three attacks daily were only minority

(Figure 10). The results showed that 63 % of patients continued taking medication when nitrate side effect appeared, 25% discussed the problem with their physician,

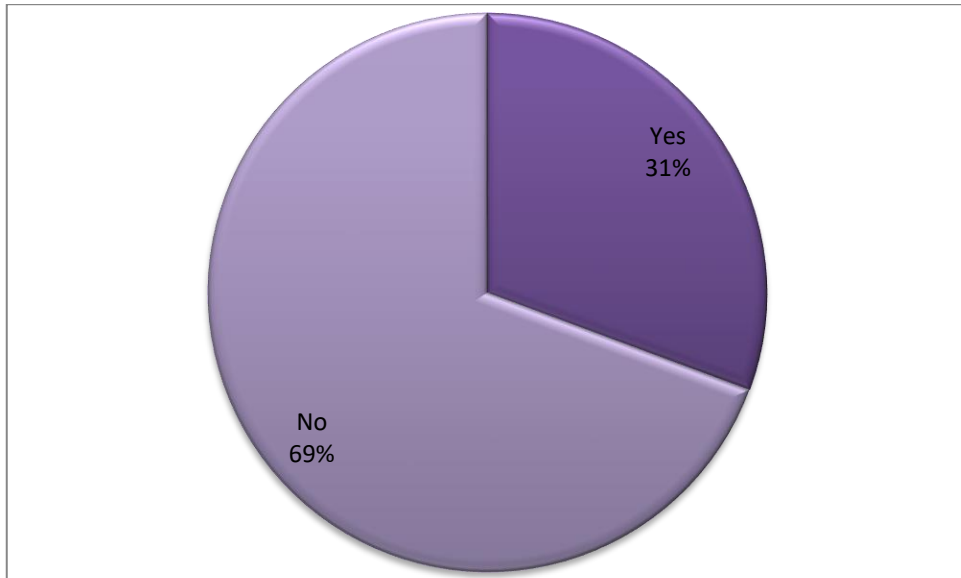


Figure 12: Percentage of patients who used paracetamol to control headache secondary to nitrate use.

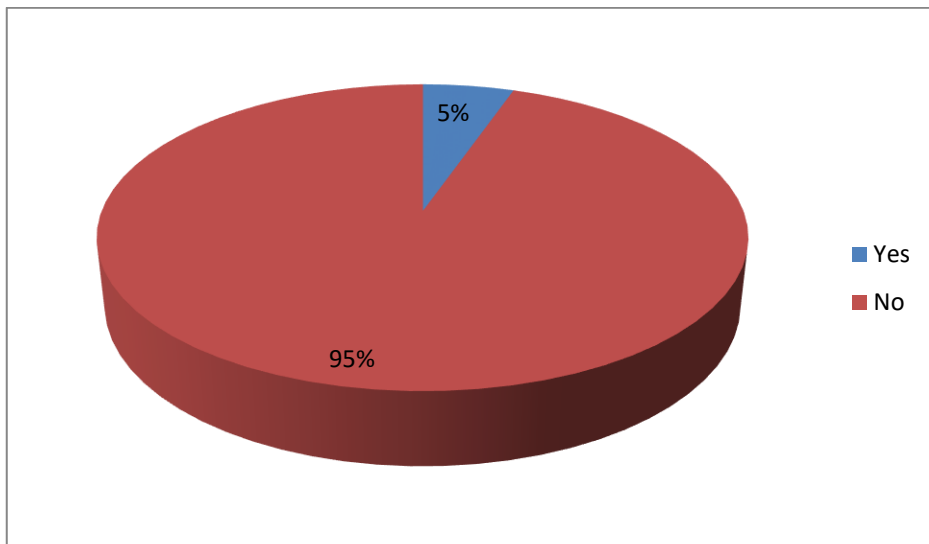


Figure 13: Percentage of patients who developed nitrate tolerance.

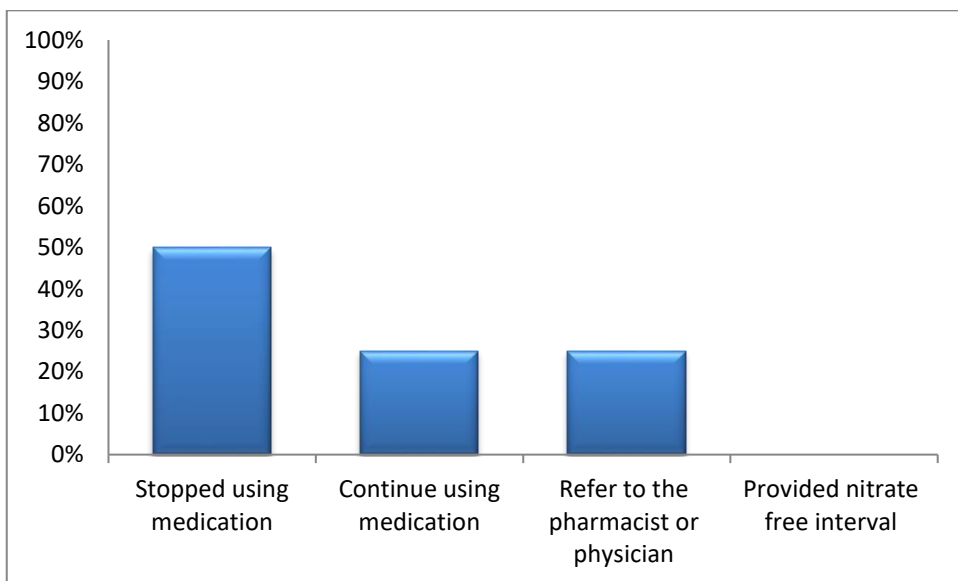


Figure 14: Actions taken by patients when nitrate tolerance developed.

while the rest had either discussed the problem with their pharmacist or stopped taking medication completely (Figure 11). It was found that 31% of patients who experienced headache as a side effect secondary to nitrate use, had used paracetamol to control it (Figure 12). Only few patients noticed that organic nitrates lost their effect after continued use (Figure 13). Many of the patients who developed nitrate tolerance stopped using their medication (Figure 14).

## DISCUSSION

This study has shown that the majority of patients use the nitrates for the management of angina pectoris, and that the most commonly used long acting agent is the isosorbide mononitrate. The patients' experience with nitrates side effects especially headache was found to be similar to that reported in literature, though their incidence was found to decrease with continued use. This could probably be attributed to the tolerance action of nitrates<sup>20</sup>. Nitrates tolerance occurs when nitrates start losing their vasodilatory effect<sup>12</sup>. This would make the drugs unable to exert their desired therapeutic action and adverse effects<sup>12</sup>. Nitrate tolerance was found to occur fast (within 1-3 days of continuous use) when plasma nitrate levels are fixed. Nitrate tolerance is associated with some complications that include increased oxidative stress, endothelial dysfunction, and sympathetic activation<sup>12,14,16</sup>. The mechanism hypothesized for the nitrates tolerance is related to the production of superoxide anion<sup>12,15</sup>. Other studies suggested impaired nitrates bioactivation as a mechanism for the nitrates tolerance<sup>13,15</sup>. Some scientists started using the terms GTN, ISMN and ISDN-tolerance rather than nitrates tolerance based on the belief that the nitrates are not just nitrous oxide donors, but heterogeneous group of compounds in regard to their underlying vasodilatory mechanism<sup>15</sup>. However, nitrate tolerance could be prevented by keeping a daily "nitrate-free period" where the nitrate plasma level is at its minimum<sup>5,6,22</sup>. Conversely, the incidence of dizziness and postural hypotension was found to increase with the continued use, which may be due to patients' routine physical activities or their life style habits like drinking alcohol or smoking. Another reason could be that patients who experience dizziness and postural hypotension are using the short-acting glyceryl tri-nitrate (GTN) which has rapid onset of action. Moreover, the skin rash reported with nitroglycerin patches may be due to lack of following proper application instruction. Despite all that, organic nitrates have a good tolerability and compliance among patients as reflected from the number of the patients who stopped using them. Most patients continue taking their medication when nitrate side effect appeared without referring to their doctor or pharmacist as they are not aware that headache is a side effect of the drug used. Most of the educated patients continue their therapy without taking any medication after discussing their problem with the specialist and finding that these side effects are temporary and tend to subside with continued use of drug. Additionally, most of the patients did not experience nitrate tolerance which may be due to good counseling

given in regard to leaving nitrate free interval. However, patients who experience nitrate tolerance stop using their medication as they believed that drug is useless. Starting nitrates in low doses and leaving a daily free interval was reported to be associated with reduced frequency and severity of headache, and enhance clinical efficacy of the drugs<sup>4,19</sup>. Additionally, research is focusing on development of new organic nitrates effective though does not seem to induce tolerance<sup>8</sup>.

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