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Nitrate Utilization Study in CVD Patients at Tertiary Care Teaching Hospital



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ABSTRACT

The study's aim was to analyze side effects of nitrates in CVD patients as well as utilization & adherence of patients taking nitrates. Cardiovascular disease is a set of conditions that include congestive heart failure (CHF) and ischemic heart disease, and they quickly become the world's leading cause of illness and death. Nitrates are powerful anti-ischemic and venous dilators. They are commonly used to treat chest discomfort and pulmonary congestion in people with heart failure and acute coronary syndromes. Even at very low dosages, organic nitrates are effective venous dilators. However, side effects during nitrate therapy are common. A six-month prospective observational study was done in the cardiology department in a tertiary care teaching hospital. The research ethical committee gave their approval to the study. A total of 60 CVD patients were studied during the period of 6 months in the tertiary care teaching hospital. In these 60 CVD patients there were 51 Males and 09 Females. In our study, patients belonged to 41-60 years age group were most. Our study shows that in CVD patients, they were more in male than female suffering from CVD and study shows headache and dizziness is the most common side effect of nitrates, nearly 25.4% having headache and 27.1% of dizziness and in some cases, minor side effects have been reported hypotension- 6.8%, syncope- 5.1%, constipation- 5.1%, and 1 rare case of bleeding is also found.



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INTRODUCTION

Cardiovascular Disease

Cardiovascular disease (CVD) causes a higher rate of death compared to disease (diabetes, cancer, and stroke). Worldwide deaths from heart disease (CVD) will increase from 171 lakhs in 2004 to 234 lakhs by 2030, according to the World Health Statistics 2008 report, making CVD is the main reason of illness and death all over world. This is true of both industrialized and developing countries, such as India, where the prevalence of cardiovascular disease is predicted to rise dramatically in the near future. Indians are three or four times more likely than white Americans, six times as large in Chinese, and twenty times as large in Japanese ⁽¹⁾. Importantly, the currently confirmed risk factors like hypertension and hypercholesterolemia can only be blamed on approximately 50-75 percent of all CVDs; however, the dangerous CVD material of the novel Cadmium (Cd) has been found to have the potential to be a new risk factor for atherosclerosis⁽²⁾. Atherosclerosis is the most common cause of CVD. It is now more accurately described as inflammation of the lower arterial wall, rather than lipid retention. As a result of the endothelial damage response, it is characterized by lipid insertion and subsequent formation of Tcells and macrophages. Functional oxygen forms play an important role in these processes because they can induce lipids like LDL and polyunsaturated fatty acids to be released. Fats embedded in the artery wall, damaging cell components directly, and promoting inflammation by opening several pro-atherogenic cells⁽³⁾. The most primary trigger of CAD and consequently a major contribution to cardiovascular disease is atherosclerosis. Arterial disorder is a chronic illness that develops before or shortly after one or more known risk factors manifest, and is usually preceded by hypercholesterolemia, hyperglycemia and that is why diabetes has been diagnosed for decades. Many factors are involves in etiology of coronary artery disease, and many of these are exacerbated or triggered by diabetes ⁽⁴⁾.

For many years, pathologists have recognized the importance of thrombotic processes in coronary artery disease. Recently, post-mortem arteriography techniques have shown an important role for thrombotic lesions in sudden cardiac death, often accompanied by rupture of atherosclerotic plaque. Physicians have used a variety of antiplatelet, anticoagulant, and thrombolytic drugs, as well as thrombolytic and antiplatelet therapies, in particular, developed as a standard treatment for acute myocardial infarction, based on a recent review of clinical studies⁽⁵⁾. CVD pathogenesis is affected by a variety of risks that can be described

as curable or consistent. Advanced age, gender (men at greater risk than premenstrual women; postmenopausal women at higher risk than men), race, and family history of CVD are consistent risk factors that cannot be reduced by intervention. On the other hand, variable risk factors are those that can be controlled, treated, or remedied by intervention. Hypertension, nicotine consumption, hyperglycemia, lifestyle factors, non-nutritious diet, lipids, and obesity and obesity are all known evolving characteristics of CVD⁽⁶⁾.

Types of CVD

Angina

Angina pectoris is the most prevalent clinical presentation of IHD is the most significant cause of morbidity and mortality in Western lands. Angina pectoris (also known as angina) is a symptom of myocardial ischemia. The mismatch among cardiac oxygen supply and delivery causes myocardial ischemia. Myocardial oxygen demand is influenced by four main factors: systolic BP, HR, cardiac wall stiffness, and myocardial contractility⁽⁷⁾. Atypical symptoms, such as pain in unusual areas, dyspnoea rather than pain, symptoms closely related to food, or emotional disturbances, can lead to a misdiagnosis of angina pectoris. Days to weeks after the onset of symptoms, the patient will report⁽⁸⁾.

Myocardial Infarction

Acute myocardial infarction or myocardial infarction are known for heart attacks. It comes from the Latin word [infarctus myocardi], literally meaning "cardiac arrest." MI occurs when blood flow to a part of the heart is limited, leading to malnutrition and damage to the cardiac muscles. Some of the arteries that circulate blood to the heart become blocked due to the accumulation of plaque, white blood cells, cholesterol, and fats. When myocardial infarction becomes severe, it is called AMI. Breathing, chest discomfort resulting from left arm or neck, difficulty breathing, sweating, vomiting, nausea, irregular heartbeat, anxiety, fatigue, and other MI symptoms include heart palpitations resulting from left arm or neck, sweating, nausea, vomiting, irregular heartbeat, anxiety, fatigue, and other symptoms. The term "silent" MI refers to the fact that approximately 64% of people with MI do not see chest symptoms. Tobacco use, high blood pressure, low density lipoprotein (LDL) levels, high cholesterol and fats, diabetes, physical inactivity, obesity, CKD, alcohol abuse, and the use of drugs such as cocaine and marijuana are all factors contributing to MI⁽⁹⁾.

Coronary Artery Disease

Coronary artery disease (CAD) is a kind of cardiovascular disease that is becoming a leading cause of death in both developed and developing countries. Coronary artery disease symptoms include stable angina, unstable angina, myocardial infarction (MI), and sudden cardiac death. It is caused by atherosclerosis or atherosclerotic blockage in the coronary arteries causing coronary artery disease (CAD). Atherosclerosis begins when endothelial function in the artery wall is disrupted, leading to the formation of plaque in the coronary spine⁽¹⁰⁾. In CAD nitrates re-open eccentric coronary artery stenosis prevents abnormal heartbeat during exercise, and dilates the coronary arteries, boosting blood supply to myocardium's ischemic zones. As a result of a decrease in diastolic pressure caused by diastolic pressure of the lower left ventricular vein, subendocardial blood flow increases even more⁽¹¹⁾.

Role of nitrate in CVD

Release NO, which further triggers mechanical vasodilation so that its use is justified by a unique combination of cardiovascular actions that have a positive effect on cardiac pre- and post-load, as well as imbalance between myocardial infarction provision and use, in patients with myocardial ischemia or heart failure. Antiplatelet potency is also found in experimental data, which may be helpful in cases of ischemia⁽¹²⁾. When NO couple with soluble guanylate cyclase (sGC), the intracellular level of cGMP increases. Since the discovery of NTG as a therapeutic agent for the treatment of angina pectoris a century ago, other nitro compounds with similar chemical characteristics have been created, especially isosorbide dinitrate (ISDN), isosorbide-5-mononitrate (IS-5-MN), and pentaerythritol tetranitrate⁽¹³⁾. To live nitrates therefore, activating protein kinase-dependent -cGMP (PKG) specific.). PKG increases the phosphorylation of a variety of substrates, including myosin light chain kinase (MLCK), sarco / endoplasmic reticulum Ca²⁺ + -ATPase (SERCA), plasma membrane Ca²⁺ + -ATPase, and Na + / Ca²⁺ + exchanger, once activated. All of these processes cause peripheral vascular resistance to decrease and vasorelaxation. Many researcher have provided proof that NO-induced vasorelaxation can be reversed in the absence of cGMP, similar to the direct activation of the K + channel⁽¹⁴⁾. With prolonged use, total loss efficiency reduced the volume and duration of outcomes, or the requirement for higher doses to get the same impact. In contrast, hemodynamic effects and antianginal efficacy weaken within 8 hrs and are completely eliminated within 24 hrs after administration

of nitroglycerin. Some researchers suggest that variable nitrate tolerance in the arteries and veins is to blame for the loss of nitrate's therapeutic advantages following long-term administration. Some researchers suggest that variable nitrate tolerance in the arteries and veins is to blame for the loss of nitrate's therapeutic advantages following long-term administration. However, literature on the effects of venous nitrate effects is not universal⁽¹⁵⁾. Therapeutic side effects associated with long-term use of oral nitrate, such as drug tolerance, abdominal symptoms, and, more commonly, headache, may adversely affect quality of life (QoL) and consequently adherence to treatment⁽¹⁶⁾.

Aim & Objectives

Aim:

Nitrate utilization study in CVD patients at tertiary care teaching hospital

Objective:

- To assess the utilization of nitrate in CVD patients.
- To assess the adherence of nitrate in CVD patients.
- To assess the patient quality of life using nitrate in CVD patients.
- To assess the side effects related to nitrate in CVD patients.

MATERIALS AND METHODS

A six-month prospective observational study was done in the cardiology department of a tertiary care teaching hospital. A systematic approach was followed for getting authorization from the IEC by presenting a complete Performa of study that included a data collecting form, patient information and consent form, as well as reviewed biomedical literature or papers. The research ethical committee gave their approval to the study.

Selection Criteria of Patients:

Inclusion Criteria

1. Both Gender
2. Patients with age 18 years and above suggestive of cardiovascular diseases.

3. Willing to take part in the research.

Exclusion Criteria

1. Patients under eighteen year of age
2. Mentally ill patients
3. Cancer & HIV positive patients
4. Pregnant females
5. Patient with do not match with inclusive criteria

Sampling Technique:

The 200 patients diagnosed with CVD. Calculation of sample size using the sample size equation with a confidence range of 95% and an error of 5%.

The formula for calculating sample size was used,

$$\begin{aligned}n &= z^2 * p * (100-p) / e^2 \\ &= 3.86 * 4.1 * (100-4.1) / 25 \\ &= 60 \text{ with CVD}\end{aligned}$$



Statistical Analysis

Analysis was done using SPSS 22.0, version (1) to find out the association between study groups with different parameters. The level of significance used was 0.05 for the corresponding degree of freedom. A P value below 0.05 was considered significant and above 0.05 was considered non-significant.

Procedure

The patients with CVD were identified using the angiography, echocardiography and electrocardiography. The utilization of nitrates used was determined by analyzing the prescription of patients included in the study. Adherence of nitrates was studied using the medication adherence rating scale (MARS). It is a self-assessment scale to track the adherence of the nitrates in CVD patients.

Informed Consent Process

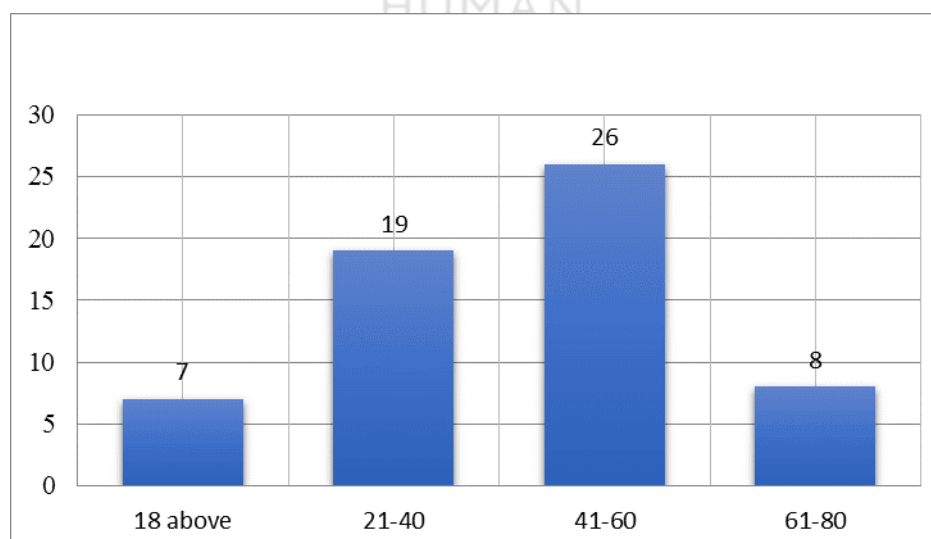
The patients who are enrolled in our study, they given freely concern.

Observation & Results

A total of 60 CVD patients were studied during the period of 06 months in the tertiary care teaching hospital. In these 60 CVD patients there were 51 Males and 09 Females. In our study, patients belonged to 41-60 years age group were most. Our study shows that in CVD patients they were more in male than female suffering from CVD.

Table no. 1 Distribution of Age Group

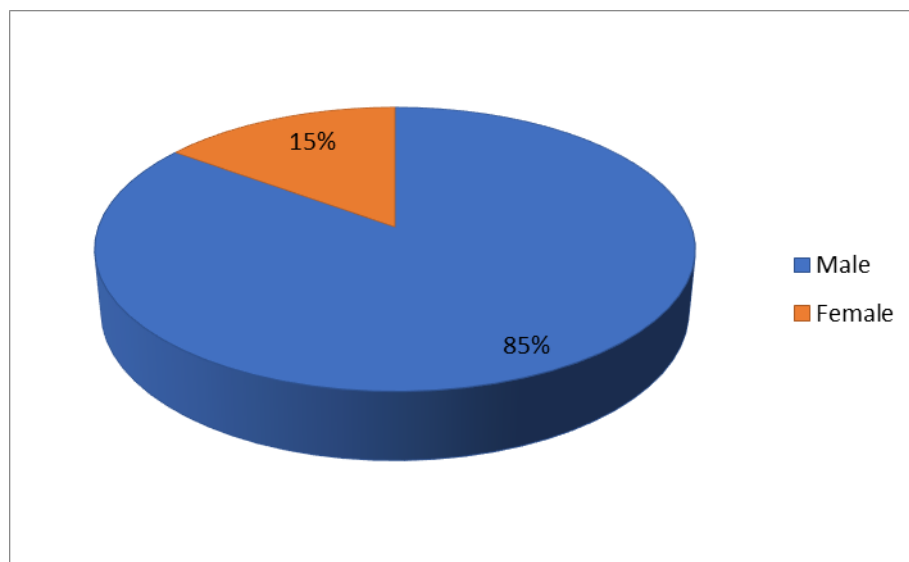
S.N	Age Group	Number	Percentage (%)
1.	18 above	07	11.66
2.	21-40	19	31.66
3.	41-60	26	43.33
4.	61-80	08	13.33
	Total	60	99.98



Our study shows that most of the patients (43.33%) were in the age group between 41 and 60 years.

Table no. 2 Distribution according to Gender

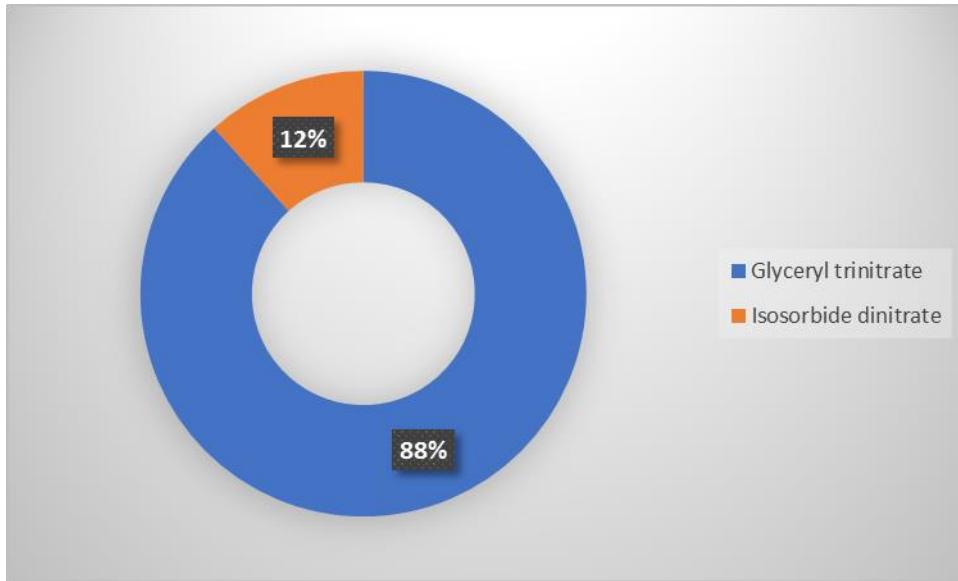
Gender	Number	Percentage (%)
Male	51	85.00
Female	09	15.00



Above table shows distribution of study group as per sex. CVD is of more common seen in male patients (85%) as compare to female population.

Table no. 3 Distribution of Study Group

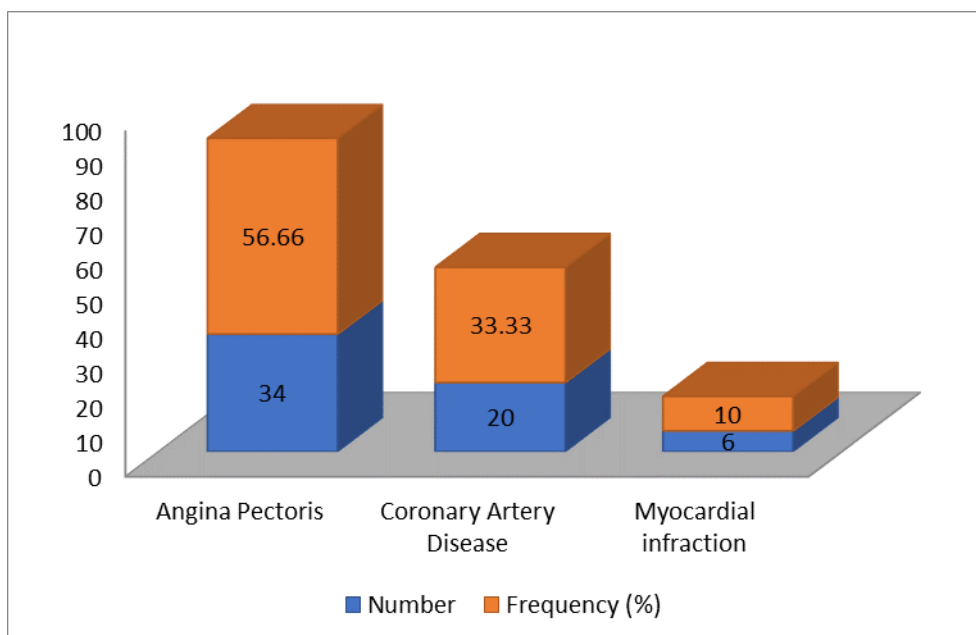
Study Group	Number	Percentage (%)
Glyceryl trinitrate	53	88.33
Isosorbide dinitrate	07	11.66



Out of 60 patients; (53) 88.33% of CVD patients prescribed with GTN and (07) 11.66% patients were prescribed with isosorbide dinitrate.

Table no. 4 Distribution according to Diagnosis

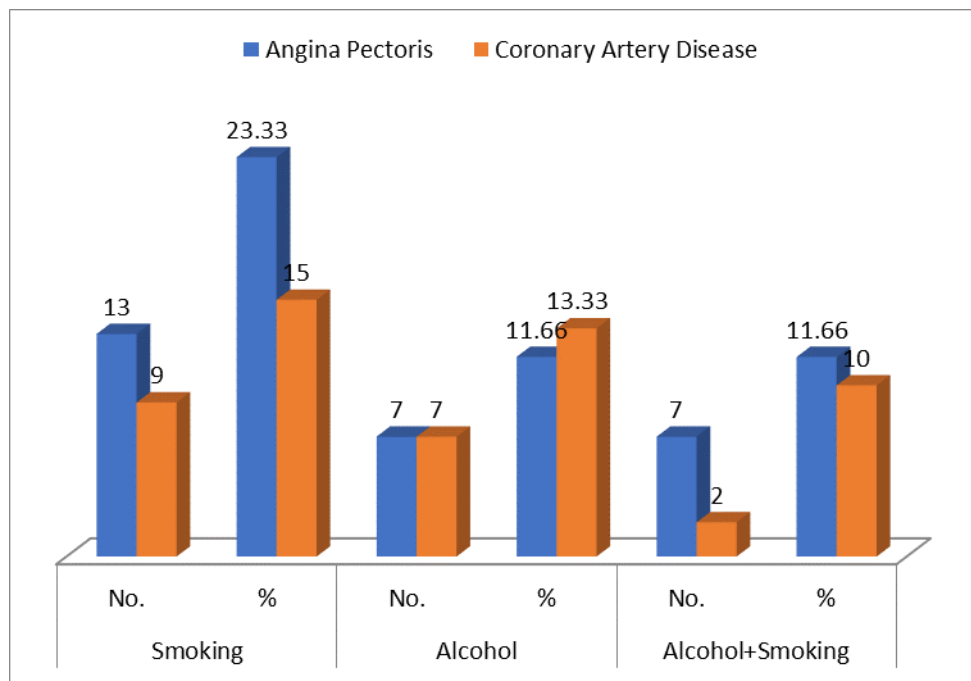
Diagnosis	Number	Percentage (%)
Angina Pectoris	34	56.66
Coronary Artery Disease	20	33.33
Myocardial infraction	06	10.00
Total	60	99.99



Out of the 60 patients in the study, 34 (56.66%) had angina pectoris, 20 (33.33%) had coronary artery disease, and 06 (10%) had myocardial infarction.

Table no. 5 Association of Clinical outcome with social factor

Social Factor		Angina Pectoris	Coronary Artery Disease	SD	p-value
Smoking	No.	13	9	7.90	0.012
	%	23.33	15.00		
Alcohol	No.	7	7	2.88	0.045
	%	11.66	13.33		
Alcohol+Smoking	No.	7	2	3.87	0.003
	%	11.66	10.00		



Above table shows distribution of clinical outcome with social factor. Angina pectoris & coronary artery disease is of more common seen in patients although this distribution is found to be statistically significant.

Table no. 6 Association of Nitrates Utilization with Gender

Class		Rational	Non-Rational	p-value	Association
Male(n=51)	No.	43	8	0.001	Significant
	%	71.66	13.33		
Female (n=9)	No.	6	3	0.014	Significant
	%	10.00	5.00		

Above table shows relation between uses of nitrates with gender. Correlation is found to be statistically significant.

Table no. 7 Assessment of medication adherence according to MARs

Items	Number (60)	Percentage (%)
Change dosages	8	13.33
Forget to take	4	6.66
Stop taking	3	5.00
Skip one of the dosage	4	6.66
Take less then prescribe	6	10.00

The MARs had satisfactory item qualities, according to the study's findings. We are optimistic that the MARs can effectively assess CVD patients' medication adherence.

Table no. 8 Assessment of patient QoL

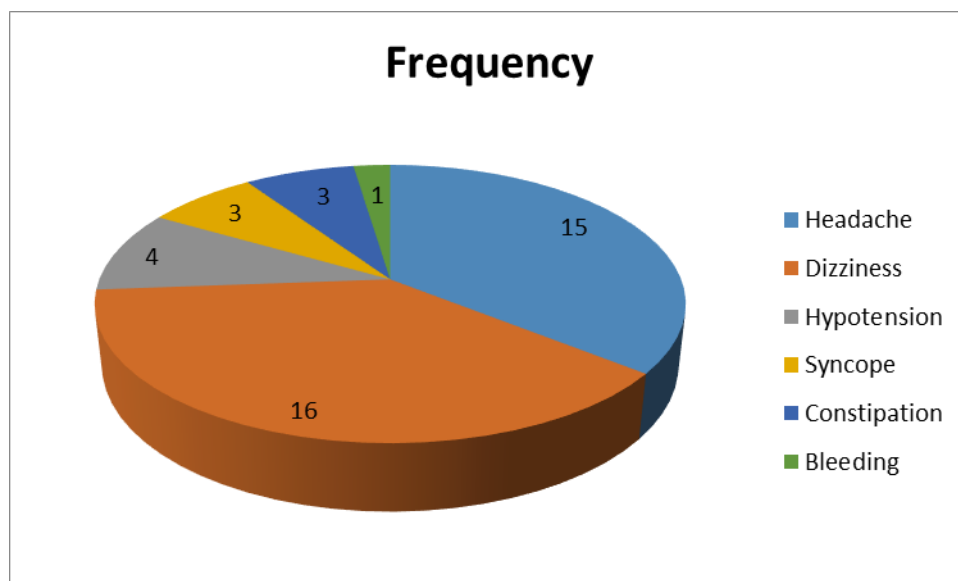
Categories		Pre-Treatment	Post-Treatment
NO	No.	3	47
	%	5.00	78.33
Very little	No.	12	10
	%	20.00	16.66
Very Much	No.	45	3
	%	75.00	5.00

Categories		Mean	SD	p-Value	Association
NO	Pre	2 ±1.132	0.57	0.011	Significant
	Post	30.07 ±17.839	18.20		
Very little	Pre	7.5 ±3.796	3.87	0.013	Significant
	Post	6.25 ±3.163	3.22		
Very Much	Pre	27.5 ±8.487	12.24	0.003	Significant
	Post	2 ±1.132	0.57		

Above table shows comparison between pre & post treatment. Comparison is found to be statistically significant.

Table no. 9 Assessment of side effects related to Nitrates

Side effects related to nitrate	Frequency	Percentage
Headache	15	25.4
Dizziness	16	27.1
Hypotension	4	6.8
Syncope	3	5.1
Constipation	3	5.1
Bleeding	1	1.7



Headache & Dizziness had recorded in majority of the patients (Headache (25.4%) & Dizziness (27.1)). In some circumstances, minor side effects have been reported (Hypotension- 6.8%, Syncope- 5.1%, Constipation- 5.1%, Bleeding-1.7%). The treatment was generally well received by the patients.

DISCUSSION

This study shows that most of the patient (43.33%) were in the age group between 41 & 60 years of age and in previous study stated that cardiovascular disease is a major health concern in the aging population and CVD is of mostly seen in male patients (85%) as compare to female population and in previous study women make up the most significant percentage of CVD diagnosis,. Jennifer L. Rodgers et.,al,⁽¹⁷⁾.

Study shows 88.33% of CVD patients prescribed with GTN and (07) 11.66% patients were prescribed with Isosorbide Dinitrate and in other study also stated that glyceryl trinitrate (nitroglycerin) is the most widely used drug, Uri Elkayam & Wilbert S. Aronow et.,al⁽¹⁸⁾.

Study stated that out of the 60, 34 (56.66%) had angina pectoris, 20 (33.33%) had coronary artery disease, and 06 (10%) had myocardial infarction and in previous study seen that death rate associated with Asian Indians have a 20-50 percent greater rate of coronary artery disease than any other ethnicity, Kumar A. Sreenivas & Sinha Nakul et.,al⁽¹⁹⁾

In our study, angina pectoris & coronary artery disease is most common seen in patients with social factors and in other studies stated that CVD is primarily caused by smoking and its increase the risk factors for CVD, Takahisa Konda, Yoshihisa Nakano, Shiro Adachi, Toyoaki Murohara, et.,al⁽²⁰⁾

We are optimistic that the MARs can effectively assess CVD patients' medication adherence and previous study stated that the both doctors and researchers may find MARs to be a valuable tool for assessing drug adherence, Chung-YingLing ⁽²¹⁾

This study summarized that side effects- Headache & Dizziness had recorded in majority of the patients (headache (25.4%) & dizziness (27.1)). In some circumstances, minor side effects have been reported hypotension- 6.8%, syncope- 5.1%, constipation- 5.1%, and 1 rare case of bleeding is also found. The treatment was generally well received by the patients and in previous study stated that despite a paucity of evidence of efficacy on hard clinical endpoints,

nitrites continue to play a key role in current therapeutic practice for relieving symptoms, Divakaran Sanjay, MD, Loscalzo Joseph, MD, PHD et.,al⁽²²⁾

CONCLUSION

The study indicated that patients between the age group 41-60 have high risk of CVD and the study conclude that CVD is more common in male population as compare to female population and GTN is widely used drug as compare to Isosorbide Dinitrate and on the basis of distribution of diagnosis, seen that angina and coronary artery disease are more common as compare to other cardiovascular disease. And on the basis of association of clinical outcome with social factor angina pectoris & coronary artery disease is of more common seen in patients and also distribution is found to be statistically significant and also shows that males are more compliance towards their medication as compares to females. The study analysis showed that the MARs had satisfactory items properties, we are optimistic that the MARs can effectively assess CVD patient's medication adherence. The most of the patients seemed to have common side effects headache (25.4%) & dizziness (27.1) and in some cases, minor side effects have been reported hypotension- 6.8%, syncope- 5.1%, constipation- 5.1%, and 1 rare case of bleeding is also found. The treatment was generally well received by the patients.

Need of Study

- To gain a better understanding of the role of nitrates in CVD patients.
- To assess the usage of nitrates for purposes other than angina.
- The purpose of this study was to look into the adherence of nitrates in patients with CVD.
- To assess the side effects related to nitrate in CVD patients.

Limitations of study

- This is hospital based study for a shorter period of time, so may not be applicable for general population.
- Only cardiology department patients are included in the study.

List of Abbreviations

1. WHO - World Health Organization
2. CVD - Cardiovascular Disease
3. CAD - Coronary Artery Disease
4. IHD - Ischemic Heart Disease
5. CHF - Congestive Heart Failure
6. HF - Heart Failure
7. AHF - Acute Heart Failure
8. MI - Myocardial Infarction
9. ACS - Acute Coronary Syndrome
10. GTN - Glyceryl Trinitrate
11. ISDN - Isosorbide Dinitrate
12. IS5MN - Isosorbide-5-mononitrate
13. NTG - Nitroglycerine
14. NO - Nitric Oxide
15. cGMP - Cyclic Guanosine Monophosphate
16. ALDH₂ - Aldehyde Dehydrogenase
17. PDE₅ - Phosphodiesterase type-5-inhibitor
18. LV - Left Ventricles
19. BP - Blood Pressure

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