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A SYSTEMATIC REVIEW ON ANGINA - FOCUSING NITRATES AND NEED OF NEWER AGENTS

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ABSTRACT

Angina is a known symptom for a complicated cardiovascular disease i.e, Ischemic Heart disease. It occurs when there is a mismatch of oxygen demand and supply to myocardium. To cater it, drugs from β blockers, Calcium Channel Blockers, organic nitrates and few newer agents are used. For more than a century, the drug of choice has been nitroglycerin. By the end of 19th century, a phenomenon Nitrate tolerance was observed in individuals consuming nitrate sustain therapy or as a prophylactic agent. Various mechanisms have been proposed in different articles for nitrate tolerance which include compromised biotransformation and also increased oxidative stress. It is one of the reason which limited the clinical efficacy of nitrates in angina. Nowadays newer agents with different mechanism of action are introduced like Ivabradine, Ranolazine, Trimetazidineand Nicorandil which will be discussed in this review in detail in terms of their efficacy in improving individual's health and quality of life.

KEYWORDS: Angina, Ischemic Heart Disease, myocardium, nitrate tolerance,Quality of Life.

1. INTRODUCTION

Angina or angina pectoris is a condition or symptom. It is not itself a disease but is of equal significance since it is an alarming situation which an individual experience prior to myocardial infarction. This symptom is an early manifestationof Ischemic Heart disease (IHD) in which there is a decrease in the blood flow and increase in the demand of oxygen by coronary muscles.[1] This etiology of this reduced blood flow can be an atherosclerotic

plaque, sever constriction of coronary arteries, improper functioning of coronary microvasculature or any other pathological condition involving blood circulation like hypertension, or anemia.[2]

The pain of angina initiate from the front o chest and depending on the severity radiates towards the other body parts (i.e, arms, jaw, neck or shoulder). The stimulating factor can be exercise, any enhance physical movement or any stressful mental condition or thought that can aggravate the condition of angina.

In some patients gastrointestinal discomfort with nausea and breathlessness is also observed. All these condition have their negative impact on the quality of life.[3]

2. ANGINA PECTORIS – A GLOBAL BURDEN

About 7 million death are attributed to Ischemic Heart Disease (IHD), according to World Health Organization (WHO).[5] In 2009, American health Association (AHA), published the data concluding that only Chronic Heart Disease (CHD) is the reason of one death among every six deaths in United States of America (USA).

A three year survey initiated in 2007 lead to conclusion that in US population prevalence of CHD is 6.4%.[4]

Also in Australia, Cardiovascular diseases are considered as prime cause of deaths. Almost 72,000 individuals are admitted in hospitals affected by angina Pectoris.[6]

In population of Lebanon, (with age $\geq$ 40 years), prevalence of CHD is found to be 13.4%.[7]

In another review, 62 studies published in between 1990-2014, were evaluated according to which CHD was found to be 5.5% prevalent in Saudi Arabia.[8]

3. TYPES OF ANGINA

3.1 Stable Angina

This type of angina is known to occur if there is excess in physical exertion since the blood is flow to heart is reduce and demand is increased which leads to chest pain. However it is manageable by nitroglycerin administered through sublingual route.[9]Nitroglycerin may take 1-2 minutes. Also this type of angina is released by rest.

If the symptoms persist for more than two months the stable angina then becomes chronic stable angina.[10]

3.2 Unstable Angina

This type of angina occurs even in rest. Alsothe frequency and duration of pain in the chest may vary. In patients having stable angina previously, the precipitating factor varies as well. The formation of small platelet clots surrounding the atherosclerotic plaque or increased tone of coronary artery are defined as etiological factors of unstable angina. The reduction of blood may occur due to the moving non occlusive thrombi in surroundings of an ulcerated plaque. For patients with severe unstable angina, invasive procedures are preferred as compared to the other therapeutic agents which may include Aspirin, heparin, β blockers and statins.

The unstable angina when exaggerated becomes a medical emergency which may lead to death since myocardial infarction is highly associated with this type of angina.[11, 12]

3.3 Variant Angina

Variant angina, also known and Prinzmetal angina, is clinically characterized by chest pain and variation in ST segment of electrocardiogram. It is also known to be caused by spasm in the coronary arteries and based on this mechanism, another name for variant angina is Vasospastic angina.[13]

It was described by Prinzmetal in 1959 after observing 32 patient of angina that variant angina does not occur due to aggressive physical exertion. Also stress is not the triggering factor to this type of angina.[14]

3.4 Microvascular Angina

Coronary reserve flow is defined as the ratio of maximum myocardial flow to the myocardial flow in the resting state. It is determined by microvascular resistance of coronary artery. Microvascular angina (or effort induced angina) is caused when vasodilatory response to coronary microvasculature becomes abnormal.[10]

4. PATHOPHYSIOLOGY OF ANGINA

As mentioned earlier, angina occurs when there is a gap in demand and supply of blood to the myocardium. Arterioles present in myocardium are dilated as a response of increased demand

of blood in the myocadium. This dilation is due to release of some chemicals like nitric oxide, prostaglandins, carbon dioxide, hydrogen ions and adenosine.[2]

The factors on which myocardial oxygen demand depends are listed below

1. Wall stress of myocardium (determinant of preload)
2. Contractility of heart
3. Systolic Blood Pressure (determinant of afterload)
4. Heart rate

4.1 Mechanism Involved In Chest or Neck Pain

The ischemic condition leads to acidosis and also loss of ATP Na/K pump along with membrane integrity. Chemo-sensitive receptors are stimulated due to release of chemicals like Adenosinem Lactate, Serotonin, Bradykinin, Histamine and reactive oxygen species as well. The pathway is given in figure 1.[2]

Thoracic S.T	Cervical S.T
Stimulation ↓ Afferent sympathetic fibers ↓ Chest and arm pain	Stimulation ↓ Vagal efferent pathway ↓ Neck and jaw pain

Fig. 1 Pathways involved for chest and arm pain and neck and jaw pain.

Key: S.T-Spinothalamic Tract.

5. NON PHARMACOLOGICAL MEASURES FOR ANGINA

Two ways are considered to manage angina including either reduction of myocardial oxygen demand or increase in blood supply to coronary arteries. Managing of angina through lifestyle modification cannot be overlooked even after the advancement of its pharmacological therapy.

Increase in daily physical activity of angina patients is still advised by healthcare practitioner as it suppress the mechanism involved in the formation of atherosclerotic plaque. Following are the desired lifestyle changes which can improve the cardiac health.

5.1 Exercise

Any regular activity like slow walking for up to an hour.

5.2 Weight Reduction

The BMI should be maintained within the range of 18.5-24.9 kg/m^2

5.3 Smoking

Quit unhealthy habits like smoking as it aggravate atherosclerotic plaque.

5.4 Blood Pressure

Since increased blood pressure is an important factor that play it role favorably in the formation of plaque, therefore it is required to maintain the systolic BP less than 120 mmHg.

5.5 Cholesterol Level

Consuming a healthy diet with low levels of fats have its own importance since Low Density Lipoprotein is a major component of atherosclerotic plaque.

6. ANTIANGINALS PHARMACOTHERAPY

To rectify the mismatch of blood supply and demand in angina, conventional and advanced drugs are prescribed which vary from individual to individual. The drugs considered as first line therapy for angina includes β blockers, Calcium Channel Blockers (CCB) and Nitrates. In this review β blocker and CCB will be discussed briefly.

6.1 Beta Blockers

β blockers are known to reduce the risk of re-infarction and sudden cardiac death and thereby considered as first line of therapy in treating angina. This class of drugs is vital owing to presence of β1 receptors in heart. When β blockers are administered myocardium oxygen demand is decreased since heart rate and contractility is reduced along with the reduction in blood pressure.[2]

Propranolol

In a study Propranolol when compared with placebo caused reduction in angina episodes by more than 50%.[2]

Carvedilol

It acts on both β receptors and inhibits them non-selectively and also block α1 to some extent as well. Although the use of Carvedilol in angina is not approved but still use commonly in angina. [2]

Atenolol and Metoprolol

Both Atenolol and Metoprolol are β1 selective blockers i.e., cardio selective β blockers and hence are known to improve exercise tolerance and increase quality of life in angina patients.

When compare with non-selective β blockers less side effects occurs with the use of these cardio selective β blockers.

Nebivolol

It selectively inhibits β1 and is involved in nitric oxide production ultimately perform vasodilation. Similar to Carvedilol, Nebivolol is also not approved for therapy of angina.[2]

6.1.1 Side effects from β blockers

Below mentioned are some side dose dependent side effects observed in angina patient upon administration of β blockers.

- Depression
- Sexual dysfunction
- Increase in hypoglycemia
- Increase in weight

It was observed in one study that lower incidents of revascularization and hospitalization due to atherosclerotic plaque occurred when β blockers are administered in patient with recent myocardial infarction (≤ 1 year).[2]

6.2 Calcium Channel Blockers (CCBs)

The contraction of myocardium occurs due to the inward movement of Ca^+ ions into the cardiomyocytes. CCBs as depicted by the class name block this movement of Ca^+ ions into the cells and thus reduce myocardium contractility and heart rate. Through same mechanism, CCBs lead to vasodilation in smooth muscle and reduces the blood pressure.

CCBs are classified as Dihydropyridines and non dihydropyridines. Dihydropyridines (nifedipine, amlodipine and nicardipine) have relatively less effect on myocardium and more effect on vascular smooth muscles.

In contrast, monodihydropyridine (i.e., verapamil and diltiazem) block cardiac Ca channels preferentially and lead to coronary vasodilation and decreases heart rate and contractility.[2]

As per the trial conducted by International multicenter angina exercise, it was concluded that both nifedipine and Metoprolol (β1 selective blocker) equally improve exercise tolerance and decrease frequency of angina.[2]

6.2.1 Side effects from Calcium Channel Blocker

Dihydropyridines causes more side effects as compared to non dihydropyridines. In terms of efficacy the combination of non dihydropyridine with β blockers is more appreciable. Although some adverse effects may occur including bradycardia, palpitation, gastrointestinal disturbances and intolerance. In some patients syncope may occur.

In cases of variant angina, CCBs are the preferred choice of drugs.[2] In this review article we will discuss the nitrates and nitrites in detail.

7. NITRATES AND NITRITES

If define in structural grounds nitrates are nitric acid or nitrous acid esters of polyalcohols. Nitrates cause vasodilation of the coronary and peripheral arteries which in turn reduces preload by decreasing demand of myocardial oxygen. The pathway of initiate from the formation of nitric oxide (NO) free radical that act on smooth muscle and activate guanylate cyclase causing myosin dephosphorylation, the end result of this cascade is vasodilation.[2]

The drugs included in this class are amyl nitrite, isosorbide dinitrite (IDN), Isosorbide mononitrite (IMN) and nitroglycerin.

7.1 Different Types of Nitrates

7.1.1 Amyl Nitrate

It leads to vasodilation in coronary artery and thus indicated in angina pectoris. However after the introduction of newer agents like isosorbide and nitroglycerin, the use of amyl nitrite in angina patients became less frequent. The more frequent use of amyl nitrite in clinical practice is in cyanide poisoning but this use of amyl nitrite is an off label use.[2]

7.1.1 Isosorbides

The isosorbides are available as isosorbide mononitrate (IMN) and isosorbide dinitrate (IDN). The later one is convertible to its active form i.e., mononitrate. The metabolism of IDN occurs in live where it is converted to mononitrate form having a half-life of 4-6 hours. The excretion occurs through renal route if orally administered and low plasma levels are observed due to extensive first pass hepatic metabolism. In contrast to IDN when IMN are administered complete bioavailability with half-life 4-6 hours is obtained. The reason being they donot undergo hepatic first pass metabolism. Because of their sustain plasma concentration in higher levels, they are indicated in long term prophylaxis. Also this

indication is owing to the increased half-life of their metabolite. The half-lives of isosorbide 2 mononitrate and isosorbide 5 mononitrate are 2 to 4 hours and around 5 hours respectively.[15, 16]

7.1.3 Nitroglycerin

In 1879, Murrel described nitroglycerin or glyceryl trinitrate as the first drug for angina treatment. Since then many advancement has been made in this category nevertheless angina is still used as first line for some patients today.[17,18] FDA first approved nitroglycerin in 2000 and Pfizer was the first pharmaceutical company to market the drug under the brand name of Nitrostat.

7.2 Mechanism of Action Of Nitroglycerin

Nitroglycerin is known to cause vasodilation in both arteries and vein. However the effect on arteries is not significant as compare to venodilation. Through this venous pooling nitroglycerin reduces the preload to heart as it causes blood to pool in venous system. The working mechanism of nitroglycerin is no different than other nitrates.[19]

In biotransformation of nitroglycerin Aldehyde dehydrogenase (ALDH2) indolent is observed. ALDH2– a tetrameric enzyme composed of 17 isoenzymes is located in mitochondria and has dehydrogenase, esterase and reductase activity as well.

The reaction of nitroglycerin with ALDH2 produces S-nitrosothiol which is reduced to produce nitrate causing vasodilation by activation of guanylate cyclase.[5]

7.2.1 Influence on endothelial function

A healthy and unbroken endothelium (the innermost layer of endothelial cell) is highly responsive to the mediators that are known to perform contraction or relaxation. One of the function of undisrupted endothelium is to maintain the vascular tone by producing such mediators.

Nitric Oxide (NO) is an endothelium derived relaxing factor (EDRF) which when releases from endothelium activates guanylate cyclase and increases the levels of cyclic Guanosine Monophosphate (cGMP). Upon dysfunctioning of endothelium, production of NO is decreased accordingly.

In order to bring the NO level up to the required mark, organic nitrates administration is suggested in patients suffering from Coronary Artery Diseases (CAD). Although these exogenous nitrates donot execute same physiological effect. The reason being its circulation in a systemic manner. In contrast endogenous NO which is locally produced hormone which is not circulated systemically. The administered (exogenous) nitrate are independent of the endothelial disruption i.e., they donot require intact endothelium for their vasodilatory effect.

7.2.2 Influence on coronary artery and peripheral circulation

Nitrates are known to cause both arterial dilation and venodilation. By dilating coronary artery greater than 100 mcm they enhance the blood flow and so symptom of angina are relieved. Through venodilation nitrates increases the peripheral pooling of blood and venous capacitance. This mechanism allows nitrates to reduce the preload on health.

7.2.3 Influence on thrombocytes

Binding of the fibrinogen to glycoprotein IIb/IIIa receptor is a crucial pre-requisite to platelet aggregation. NO activates platelet guanylate cyclase and hence increase cGMP levels in turn reducing the fibrinogen binding,[16,18] platelet aggregation (Acute coronary syndrome causing factor). This can be considered as an additional mechanism through which NO enhance perfusion to coronary arteries.[2]

7.3 Short Acting Nitrates

This class includes sublingual tablets and spray. For the management of acute angina and angina in emergency, sublingual route of nitrate administration is the choice. It is beneficial in almost all the condition of acute angina. The cause of chest pain can be detected through sublingual administration of nitrates i.e. if intensity of chest pain is reduces or it is fully eliminated in less than 10 minutes, myocardial ischemia is considered as the cause. In below mentioned conditions, the chest pain persists for more than 10 minutes.

- Cardiac cause without ischemia: Aortic dissection, aneurysms
- Non cardiac cause: Esophagitis, costochondritis

Exercise tolerance improvement along with increase in onset time of angina is observed upon prophylactic administration of sublingual nitroglycerin spray in chronic stable angina patients.[16]

In hypertrophic cardiomyopathy patients, sublingual nitroglycerin can be used for screening out the cause.[18]

In aged population, sublingual spray is more acceptable as its action is very quick and also possess long lasting effect. One more effect of using sublingual spray is that the spray do not required excessive saliva in oral cavity for absorption following dissolution.[16]

7.4 Long Acting Nitrates

They are available as oral tablet, sustain release transdermal patches. The class is indicated in prophylaxis of angina. Unfortunately the administration of long acting nitrates is known to give rise to a phenomenon termed as nitrate tolerance which will be discussed later in this review.

Transdermal patches are applied in pain condition and they are designed to release nitroglycerin content over the period of time.[16]

A brief comparison of short acting and long acting nitroglycerin is given below in figure 2 below.[18]

Short Acting NTG	Long Acting NTG
Provide rapid relief from angina because of their rapid absorption	Main indication is prophylaxis of angina
Can be used for supplementation in addition with long term nitrates in case when acute attacks are experienced by patient	Can be used with short acting nitrates in case when their duration of action is desired to be increased
Other than nitrate tolerance side effects are similar to long acting nitrates	Nitrate tolerance occurs. Other side effect vary but are similar to short acting nitrates

Fig 2.Comparison of short acting and long acting nitrates.

Key: NTG – Nitroglycerin.

7.5 Nitrate Tolerance

The use of organic nitrates have been considered as the main stay of the therapy of angina for more than a century. However a phenomenon observed at the end of 19th century, well known as Nitrate tolerance, limits the therapeutic efficacy of nitrates.[21]

Ranging from hemodynamic effect in congestive heart failure and ending up to loss of hypotensive effect in hypertension, the manifestation of nitrate tolerance varies in different clinical conditions. In individuals of Coronary artery disease, during treadmill loss of nitrate

effects are observed along with the time of onset of angina, which is also captured as a manifestation of nitrate tolerance.

In cardiovascular diseases, efficacy of nitrates is reduced and this issue is termed as Nitrate resistance. One mechanism due to which nitrate tolerance is developed, includes administration of nitrate for prophylaxis. In contrast to this mechanism the nitrate resistance is developed independent to nitrate prophylactic use.

Not only the effects of nitrates are minimized, also a rebound effect is experienced by individual. This effect leads to worsening of symptoms of angina upon the withdrawal of nitrates.

7.5.1 Hypothesized mechanism of nitrate tolerance

When it comes to the mechanism by which nitrate tolerance is developed either the concept of impaired biotransformation involving ALDH2 or increase in oxidative stress is considered.

Both the mechanism are entirely different. The mitochondrial enzyme involved in biotransformation of nitrate is also recognized to have a role in the development of tolerance. ALDH2 contains three catalytic sites which contains three sulfhydryl groups placed alongside. The inactivation of ALDH2 may be due to the formation of intramolecular disulfide bond.

Through this mechanism ALDH2 inactivation occur by nitroglycerin, Nitric Oxide (NO), 4 hydroxynonenal (substrate of NO) and other inhibitors of ALDH2.

Another mechanism for nitrate tolerance is the formation of reactive oxygen species. It was concluded by one study that superoxide produced in result ofnitroglycerin stimulation. Also it was observed that mitochondrial ALDH2 inactivation is associated with blockade of mitochondrial respiration and this blockade mediates the generation of reactive oxygen species. This ROS release causes oxidative inhibition of ALDH2 which leads to nitrate tolerance.[5, 20, 46]

7.6 Approach To Avoid Development Of Nitrate Tolerance

Nitrate tolerance is avoidable by the use of treatment methods or timings that allows an individual's exposure of nitrate with interval of 12 hours per day. This strategy was however not found to be a perfect solution of nitrate tolerance since this administration of nitrate is not

fruitful after every 24 hour, also the morning administration of nitrate is harmful reason being the high incidence of Acute Coronary Syndrome.

Also the withdrawal of nitrate therapy lead to rebound ischemia (association includes: endothelial dysfunction is uncontrolled and hypersensitivity to vasoconstrictor). This phenomena is correlated to the significant increase in ischemic episodes during nitrate free intervals which overcomes the therapeutic efficacy of nitrates.[20, 21]

7.7 Side Effects of Nitrates

The most common side effect include dose dependent headache. In 10% patients disabling headache and dizziness made the nitrate intolerable to them. In other patients continuous therapy resolve the headache and in some patients severity of headaches is mild to moderate.

Other side effects include hypotension, coronary steal, and myocardial ischemia. When intermittent therapy of nitrate is administered as patches, patients experience rebound and angina may occurs at night. The combination of nitrate with phosphodiesterase 5 inhibitors (indicated in erectile dysfunction) is contraindicated as it may lead to death owing to profound hypotension.[22]

8. NOVEL AGENTS – NEED OF NEWER AGENTS AS SECOND LINE TREATMENT

In order to improve the QoL in patients of Coronary disease (CAD), European guidelines recommend to use newer agents such as Ivabradine, Ranolazine, trimetazidine and Nicorandil along with long acting nitrate since the use of newer agents is most beneficial.[23] These drugs possess different mechanism of action.[24]

Use of current pharmacological therapy is limited mainly by the side effect and contraindication of conventional treatment which are experienced individuals upon administration. The summary for these side effects is given below in figure 3.[32]

Drug Class	Reasons that limited patient compliance
β Blockers	Side Effect: Fatigue, Sexual dysfunction, bronchospasm, cold extremities, worsening claudication, light headedness, GI disturbances, bradycardia AV block. Their use may be associated with unfavorable changes in lipid profile and glycemic control. Contraindication: Severe bradycardia, high degree AV block, SSS and unstable HF.
Calcium Channel Blockers	Side Effect: Hypotension, lower extremity edema, constipation. Contraindication (Nondihydropyridine):Bradycardia, AV conduction block, sinus node dysfunction. Short acting CCBs with immediate release profile may increase cardiovascular mortality in angina patients.
Nitrates	Side Effect: Dose related headache leading to discontinuation of treatment, nitrate tolerance. Contraindication: Sever aortic stenosis, hypertrophic obstructive cardiomyopathy.

Fig. 3: Reasons that limited the use of First line agents for Angina.

Key - GI: Gastro Intestinal, AV: Atriovantricular, SSS: Sick Sinus Syndrome, HF: Heart Failure, CCBs: Calcium Channel Blockers.

In this review we have discussed the newer agents briefly.

8.1 Ranolazine

In myocardial ischemia, electrolyte balance is disrupted which leads to increase levels of sodium and calcium. In ischemic condition inward sodium channels (I_{NA}) remains open resulting in high levels of sodium in the cell because of the increased level of sodium, Na/Ca exchanger is activated which increase the Calcium level on the cell. This complete phenomenon lead to diastolic stiffness and ultimately mismatch of oxygen demand-supply occurs.

Ranolazine – a piperazine derivative, by inhibiting I_{NA} is known to hinder this pathway eventually balancing the oxygen demand supply.[25, 26]

For patients of chronic stable angina who are not responsive to conventional anti-anginal drugs, Ranolazine is indicated as an adjunct treatment with first line anti-anginal drugs. One survey based study concluded that when Ranolazine is administered for duration of half year to four years it results in improvement in angina severity, frequency and QoL.[27, 28, 29]

Most common side effect that occurs due to the use of Ranolazine include dizziness, nausea, weakness, constipation and headache.[27] Generally Ranolazine is well tolerated by patients. Major benefit of Ranolazine is that it does not affect blood pressure or heart rate.[30]

8.1.1 Recommended therapeutic indication

Ranolazine is approved by FDA as first line agent in the treatment of chronic stable angina or added to ongoing therapy of β blocker or nitrates.

The initial dose as first line agent is 500mg twice a day which can be increased to 1000 mg twice a day within a time period of 4 week - 6 week. The use of Ranolazine is not recommended for Acute Coronary Syndrome. Due to insufficient data use of Ranolazine in reduced left ventricular systolic function is not recommended.[25]

8.2 Ivabradine

Numerous researches have been done which shows the effectiveness of Ivabradine in stable angina. As per one research conducted to examine the effect of Ivabradine on exercise tolerance concluded that individual may have longer exercise duration when individuals are treated with Ivabradine for 3 months. On the contrary insignificant improvement in exercise tolerance was observed when duration of treatment with Ivabradine was less than 3 months.[31]

Ivabradine - approved in 2005 by European Medicine Agency, [32] works by inhibition I_f channels not only located in sinoatrial node (S.A node) but also found in atrioventricular node (AV node), purkinje fibers and in myocardial sleeves around the veins of respiratory system. In short I_f is located throughout the conduction system.

The pacemaker current produced due to I_f is activated during diastolic hyperpolarization. Ivabradine is the only selective inhibitor of I_f channels which works in a dose dependent manner at certain concentration Ivabradine does not affect other ionic channels.

Different trials conducted for Ivabradine monotherapy in comparison with other conventional therapy (β blocker or Calcium Channel Blocker) ended up in concluding that Ivabradine is equally effective in SCAD (Stable Coronary Artery Disease) patients in either to improve angina symptoms or to make exercise testing parameters better.[33]

8.2.1 Ivabradine – reduction of heart rate (HR)

Improving the QoL and symptoms of myocardial ischemia can be achieved by reducing heart rate. Ivabradine through inhibition of I_f channels in SA node is known to reduce heart rate. Studies conducting with Ivabradine shows that it is an effective anti-anginal and anti-ischemic effect and also the effect of Ivabradine are irrespective patient's age, gender, and severity of angina symptoms or any other concomitant disease of patient.

Ivabradine when administered in patient of left ventricular systolic dysfunction (LVSD) and CHF, it may reduce hospitalization.[35, 36]

In a fixed dose combination with Metoprolol, Ivabradine can reduce HR and symptoms of Angina Pectoris and it can also raise exercise capacity.[36]

Regarding the safety profile of Ivabradine, it is considered as a tolerable drug in impairing angina symptom and its adverse effects include sinus bradycardia and visual disturbances.[32]

8.3 Nicorandil

Nicorandil – a drug that treat symptoms of chronic stable angina, works by two mechanism (1) Nitrate like mechanism i.e. activation of Nitric Oxide GMP signaling pathway (2) ATP sensitive K^+ channel opener. Nicorandil significantly improves clinical outcomes in patient with stable angina.[37, 38, 39]

Nicorandil has shown significant improvement in the result of exercise tolerance test. Also when comparatively studied in angina patients, Nicorandil was found to be equally efficacious to Nitrates, β Blockers (Metoprolol, Atenolol, Propranolol) and Calcium channel blockers (Amlodipine, Diltiazem and Nifedipine) when measured on the basis of exercise tolerance est. During the treatment of angina, the most experience adverse effect s headache, for the minimization of which low dose of Nicorandil is administered in patients prone to headache. Also mouth ulcer is an infrequent adverse effect, which may lead to switching of Nicorandil to any other alternative if it gets severe and persistent.[40]

8.4 Trimetazidine

A known effective orally administered and a well-tolerated anti-ischemic agent which works through maintaining cellular hemostasis.[41]

B Blockers, Calcium channel blockers and nitrates play their roles by different mechanism to decrease anginal attacks and myocardial infarction thereby preventing myocardial death. Recent approach to cater said issue is administration of Trimetazidine which provides its cytoprotective effect. It is effective when given alone or in combination with conventional anti-anginal agents.[42, 43]

Trimetazidine inhibits mitochondrial long chain 3 ketoacyl coenzyme A thiolase and shift energy metabolism from oxidation of fatty acid to oxidation to glucose. In light of this newly observed mechanism of action, Trimetazidine is being regarded as prototype for 3 ketoacyl coenzyme A thiolase inhibitors – a new class of anti-anginal agents.

Because of this shift from fatty acid oxidation to glucose oxidation, there is increase in production of ATP (Adenosine Triphosphate) and less consumption of oxygen.

So in myocardial ischemia it is better to use glucose as substrate rather than fatty acid since due to stimulation of glucose utilization ATPs are produced with less oxygen consumption.[44]

Trimetazidine have no effect on heart rate, blood pressure, coronary flow or contractility. However these effects are observed in other conventional drugs.

In both situations i.e. during rest or exercise trimetazidine do not exhibit vasodilatory effect or negative inotropic effect, due to which it can be used with conventional drug as add-on therapy and can be an alternative approach to intolerant conventional drugs.

It has been shown in clinical studies that trimetazidine is well tolerated and upon discontinuation these mild side effects are reduced as well.[45]

9. CONCLUSION

Angina is a prevalent symptom of coronary disease that affects the quality of life and if not resolved may increase mortality rate. First line of treatment includes β Blockers, Calcium Channel Blockers and Nitrates & Nitrites. All the classes have their specific adverse effects. However nitrates on continuous administration lead to a condition, which limits its efficacy, Nitrate tolerance. The newer agents are becoming a new option for angina patients due to their well tolerability and no such phenomena has yet been demonstrated. While use of longer acting nitrates with newer agent may also be beneficial for angina patients.

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