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PCI Vs Thrombolytic Therapy in Acute Myocardial Infarction-A Review

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ABSTRACT
Aim: *The aim of this article is to provide a review on percutaneous coronary intervention vs thrombolytic therapy in acute myocardial infarction.*
Objective: *To provide a comparison between percutaneous coronary intervention vs thrombolytic therapy in the treatment of acute myocardial infarction.*
Background: *Myocardial infarction (MI) is the irreversible necrosis of heart muscle secondary to prolonged ischemia. Myocardial infarction is considered a part of a spectrum referred to as acute coronary syndrome (ACS). The Acute coronary syndrome consists of unstable angina, non–ST-segment elevation MI (NSTEMI), and ST-segment elevation MI (STEMI). As a general rule, initial therapy for acute myocardial infarction is directed towards restoration of perfusion as soon as possible to salvage as much of the jeopardized myocardium as possible. This may be accomplished through medical, drugs or mechanical means, such as Percutaneous coronary intervention or Coronary artery bypass grafting. Thrombolytic therapy is the use of drugs to break up or dissolve blood clots, which are the main cause of both heart attacks and stroke. They include drugs like alteplase, reteplase, streptokinase, tenecteplase etc. Percutaneous coronary intervention (PCI), commonly known as coronary angioplasty, is a procedure where in stents are kept in the stenotic (narrowed) coronary arteries, thus improving the blood flow to the heart and relieving it from compromised blood supply.*
Reason: *To provide a comprehensive review about indications, advantages and disadvantages of percutaneous coronary intervention and thrombolytic therapy in acute myocardial infarction and find the better off the two.*

INTRODUCTION

Coronary heart disease is the leading cause of death worldwide. Acute coronary syndrome (ACS) which includes unstable angina and acute myocardial infarction, occurs as the result of a partial or total occlusion of myocardial blood flow caused by the disruption of built-up lipid-rich atherosclerotic plaque leading to thrombosis. The exposure of the plaque-lipid core to the blood stream triggers a cascade of molecular and cellular process that promote platelet activation, adhesion, aggregation, and thrombin generation, ultimately leading to thrombus formation.[1]

Pathophysiology

Myocardial injury and myocardial cell death

A condition called myocardial ischemia happens if blood supply to the myocardium does not meet the demands of the body. If this imbalance persists, it triggers a cascade of cellular,

inflammatory and biochemical events, leading eventually to the irreversible death of heart muscle cells, resulting in MI.[2]

Evolution of MI and ventricular remodeling

Persistence of oxygen deprivation to the myocardium through the cessation of blood supply will lead to irreversible myocardial injury within 20 to 40 minutes and up to several hours, depending on several factors including the existing metabolic state of the body and presence of coronary collateral blood flow.[3]

Typical MI initially manifests as coagulation necrosis that is ultimately followed by a healing process characterized by formation of myocardial scarring, known as myocardial fibrosis. This mechanism allows significant architectural changes to the composition, shape and contractile function of the myocardium, especially in the left ventricle, which is the major contributor to the contractile function of the heart. Eventually the left ventricle dilates and changes to a more spherical shape, in a process known as ventricular remodeling.[4]

Stunned and hibernating myocardium

Stunned myocardium is a condition of transient left ventricular dysfunction following an ischemic event to the myocardium. It occurs if coronary blood flow was impaired for a brief period of time (5-15 mins). However, prolonged exposure of the myocardium to an ischemic state, results in an impairment of its contractile function, which can be partial or complete, this is known as myocardial hibernation, and is reversible with revascularization.[5]

Plaque

It starts with the arterial intimal thickening followed by the formation of fibrous cap atheroma which has a lipid-rich necrotic core that is surrounded by fibrous tissue. Eventually, a thin-cap fibroatheroma develops, this is also known as a vulnerable plaque which is composed mainly of a large necrotic core separated from the vascular lumen by a thin fibrous cap that is infiltrated by inflammatory cells and is deficient of smooth muscle cells, making it vulnerable to rupture.[6,7]

Causes

The following factors are thought to contribute to the damage: high blood pressure, elevated LDL cholesterol, an accumulation of homocysteine, smoking, diabetes, inflammation.[8]

Symptoms

Patients with typical MI may have the following prodromal symptoms in the days preceding the event: fatigue, chest discomfort, malaise.

Typical chest pain in acute MI has the following characteristics:

- Intense and unremitting for 30-60 minutes
- Retrosternal and often radiates up to the neck, shoulder, and jaw and down to the ulnar aspect of the left arm
- Usually described as a substernal pressure sensation that also may be characterized as squeezing, aching, burning, or even sharp
- Associated dyspnea or shortness of breath
- In some patients, the symptom is epigastric, with a feeling of indigestion or of fullness and gas.[9]

Diagnosis

- Cardiac biomarkers/enzymes
- Troponin levels: Troponin is a contractile protein that normally is not found in serum; it is released only when myocardial necrosis occurs.
- Creatine kinase (CK) levels: CK-MB levels increase within 3-12 hours of the onset of chest pain, reach peak values within 24 hours, and return to baseline after 48-72 hours
- Myoglobin levels: urine myoglobin levels rise within 1-4 hours from the onset of chest pain
- Complete blood count
- Lipid profile
- C-reactive protein and other inflammation markers
- Electrocardiography
- Cardiac imaging

- Coronary angiography[10]

Types

ACS can be classified into 2 main categories: ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), inclusive also of stable angina and unstable angina.

NSTEMI is an acute process of myocardial ischemia that implies non-transmural infarction, but due to embolization, could result in myocardial necrosis. The initial electrocardiogram in patients with NSTEMI does not show ST-elevation, and the majority that do present do not develop new Q-waves. NSTEMI is distinguished from unstable angina by the detection of cardiac markers indicative of myocardial necrosis (i.e., trooping I). Patients that present with NSTEMI may have prolonged chest pain with fixed ischemic changes other than ST elevation (such as ST depression), are not typically as urgently treated and NSTEMI is usually caused by unstable plaque and/or nonocclusive thrombus that embolizes.

STEMI, albeit a condition that occurs less frequently than NSTEMI,[11] is often more severe and has a higher rate of in-hospital mortality, can lead to more mechanical complications of the heart, and is associated with a higher rate of cardiogenic shock [12]. It is generally associated with complete thrombotic occlusion. Typically, there is refractory chest pain and ST elevation on ECG, and STEMI is treated as a medical emergency.

MANAGEMENT

Initial stabilization of patients with suspected MI and ongoing acute chest pain should include;

- Intravenous access, supplemental oxygen, pulse oximetry
- Immediate administration of aspirin en route
- Nitroglycerin for active chest pain, given sublingually or by spray
- Telemetry and prehospital ECG, if available. [13,14]

Following which, fibrinolytic therapy or mechanical means, such as percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery can be implemented.

These interventions are designed to do the following:

- Limit the extent of MI
- Salvage jeopardized ischemic myocardium
- Recanalize infarct-related arteries.

TREATMENT

Reperfusion therapy

A reduction in cardiac function caused by irreversible necrosis of the myocardium can result from complete occlusion of a cardiac vessel. The resultant ischaemia is reversible if treated within 3–6 hours. Therapy aiding reperfusion of ischaemic cardiac muscle within this critical time period can reduce the extent and severity of damage thereby reducing mortality and morbidity [15,16]. Reperfusion is possible by a variety of procedures including, thrombolysis, percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass graft surgery (CABG).

Primary angioplasty

Percutaneous coronary intervention (PCI), commonly known as coronary angioplasty, is a non-surgical procedure used to open narrow or blocked coronary arteries. This method of reperfusion entails performing emergent coronary angiography, after establishing arterial access, which can be achieved via the radial or femoral artery. After identifying the anatomy of the coronary circulation and determining the culprit vessel, coronary stents are placed to establish reperfusion.[17] During angiography, a small tube called a catheter is inserted into an artery, usually in the groin. The catheter is threaded to the coronary arteries.

Special dye, which is visible on x-ray pictures, is injected through the catheter. The x-ray pictures are taken as the dye flows through the coronary

arteries. The dye shows whether blockages are present and their location and severity.

During PCI, a balloon catheter is inserted in the coronary artery and placed in the blockage. Then, the balloon is expanded. This pushes the plaque against the artery wall, relieving the blockage and improving blood flow. A small mesh tube called a stent usually is placed in the artery during the procedure. The stent is wrapped around the deflated balloon catheter before the catheter is inserted into the artery. When the balloon is inflated to compress the plaque, the stent expands and attaches to the artery wall. The stent supports the inner artery wall and reduces the chance of the artery becoming narrow or blocked again.[18]

Thrombolytic therapy

Thrombolytic therapy is aimed at lysis of the occlusion, removal of the obstruction, and restoration of blood flow to the ischaemic myocardium [19,20,21,22,23]. Thrombolytic agents eliminate the obstruction by activating the enzyme, plasmin, which in turn denatures fibrin, a protein binding the fibrous strands in blood clots. Fibrinolytic agents, sometimes referred to as plasminogen activators, are divided into 2 categories:

- Fibrin-specific agents
- Non–fibrin-specific agents

Fibrin-specific agents, which include alteplase, reteplase (recombinant plasminogen activator [r-PA]), and tenecteplase, produce limited plasminogen conversion in the absence of fibrin.

Non–fibrin-specific agents (eg, streptokinase) catalyze systemic fibrinolysis [24].

Alteplase

Alteplase was the first recombinant tissue-type plasminogen activator (tPA) and is identical to native tPA. A systemic lytic state is seen, with moderate amounts of circulating fibrin degradation products and a substantial risk of systemic bleeding.[25]

Reteplase

Reteplase is a second-generation recombinant tissue-type plasminogen activator. Because reteplase does not bind fibrin as tightly as native tPA does, it can diffuse more freely through the clot rather than bind only to the surface as tPA does. At high concentrations, reteplase does not compete with plasminogen for fibrin-binding sites, allowing plasminogen at the site of the clot to be transformed into clot-dissolving plasmin [26].

Tenecteplase

Its mechanism of action is similar to that of alteplase, and it is currently indicated for the management of AMI.[27]

Urokinase

Urokinase [28] is the fibrinolytic agent that is most familiar to interventional radiologists and that has been used most often for peripheral intravascular thrombus and occluded catheters. Unlike streptokinase, urokinase directly cleaves plasminogen to produce plasmin.

Streptokinase

Streptokinase is produced by beta-hemolytic streptococci. By itself, it is not a plasminogen activator, but it binds with free circulating plasminogen (or with plasmin) to form a complex that can convert additional plasminogen to plasmin. Streptokinase activity is not enhanced in the presence of fibrin[29].

Fibrinolytic agents are given in conjunction with antithrombin and antiplatelet agents, which help to maintain vessel patency once the clot has been dissolved.

Antiplatelet Agents[30]

Aspirin

Early administration of aspirin in patients with acute myocardial infarction has been shown to reduce cardiac mortality rate.

Clopidogrel

Clopidogrel selectively inhibits adenosine diphosphate (ADP) binding to platelet receptors and subsequent ADP-mediated activation of glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation.

Prasugrel

Prasugrel is a prodrug, a thienopyridine that inhibits platelet activation and aggregation.

Ticagrelor

Ticagrelor and its major metabolite reversibly interact with the platelet P2Y12 ADP-receptor to prevent signal transduction and platelet activation.

Antithrombotic Agents

Heparin

Heparin augments the activity of antithrombin III and prevents the conversion of fibrinogen to fibrin.

Bivalirudin

Bivalirudin, a synthetic analogue of recombinant hirudin, inhibits thrombin; it is used for anticoagulation in patients with unstable angina,

Dalteparin and Enoxaparin

Enhances inhibition of factor Xa and thrombin by increasing antithrombin III activity

Glycoprotein IIb/IIIa Inhibitors

Abciximab

It binds to the platelet surface glycoprotein IIb/IIIa (GPIIb/IIIa) receptor with high affinity, preventing the binding of fibrinogen and reducing platelet aggregation.

Tirofiban

Tirofiban is a nonpeptide antagonist of the glycoprotein IIb/IIIa receptor. It is a reversible antagonist of fibrinogen binding.

Eptifibatide

Blocks platelet aggregation and prevents thrombosis.

Surgical Revascularisation

Emergent or urgent coronary artery bypass grafting (CABG) is warranted in the setting of failed PCI in patients with hemodynamic instability and coronary anatomy amenable to surgical grafting [31]. Surgical revascularization is also indicated in the setting of mechanical complications of MI, such as ventricular septal defect, free wall rupture, or acute mitral regurgitation. Restoration of coronary blood flow with emergency CABG can limit myocardial injury and cell death if performed within 2 or 3 hours of symptom onset.

Implantable Cardiac Defibrillators

An implantable cardioverter-defibrillator (ICD) is a specialized device designed to directly treat a cardiac tachydysrhythmia, that provides electrical stimuli, thereby causing cardiac contraction when intrinsic myocardial electrical activity is inappropriately slow or absent.[32]

PCI VERSUS FIBRINOLYSIS

The scientific 'battle' (for the optimal reperfusion therapy in acute myocardial infarction) between pharmaco-oriented and balloon-oriented cardiologists has already lasted for many years.

There are, however, several caveats to be considered [33]:

1) All patient-related factors as well as timelines have to be equal.

2) Adjunct treatment, e.g. secondary prevention measures after primary care have to be equally effective. This is of outstanding importance for long-term outcome.

3) Also, outcomes may depend on the experience of the institution/operator.

Patients with STEMI usually have complete occlusion of an epicardial coronary vessel caused by an acute thrombotic obstruction. The earlier the patient presents, and the earlier the artery can be recanalized, the better. Management of ST-elevation myocardial infarction relies on two essential and key components: rapid recognition and timely reperfusion. The strategy could be transfer for PPCI, immediate start of thrombolysis as a lone standing concept, thrombolysis with secondary transfer to a PCI centre for rescue PCI in case of failing thrombolysis, or "facilitated PCI", i.e. routine PCI as early as possible after thrombolysis.[34]

PCI performed within 90 minutes of a patient's arrival is superior to fibrinolysis with respect to combined endpoints of death, stroke, and reinfarction, but unfortunately, PCI is not widely

available at acute care hospitals [35]. PCI for managing AMI has several attractive features:

1. Nearly all patients are eligible.
2. A complete evaluation of coronaries is possible with confirmation of the acute occlusion.
3. It leads to prompt revascularization under vision with >90% TIMI 3 flow and with stent placement the residual stenosis is eliminated.
4. The reocclusion and stroke rates are very low.
5. Early discharge with full risk stratification. [36]

Although primary PCI is the preferred therapy for STEMI, it has severe logistic restraints:

- treatment is delayed by patient transport
- emergency department delay
- preparation of the catheterization laboratory
- a skilled intervention team must be available 24 hours a day.[37]

Fibrinolysis is an important reperfusion strategy, particularly in settings where primary PCI cannot be offered to STEMI patients within the recommended timelines. The pharmacological action of thrombolytic agents is not limited to the site of the thrombus alone; activity extends throughout the vascular system, reducing thrombus formation and improving cerebral reperfusion [38]. The benefits of fibrinolytic therapy are well established during the initial 12 hours after symptom onset. Fibrinolytic therapy is a proven treatment for the management of acute MI. It is more universally available to patients without contraindications, can be administered by any properly trained health care provider, and can be given in the prehospital setting. Its efficacy declines as the duration of ischemia increases. The goal is a door-to-needle time of less than 30 minutes, and every effort must be made to minimize the time to therapy. Patients older than 75 years derive significant benefit from fibrinolytic therapy, even though their risk of bleeding is higher [39]. The benefit of fibrinolysis is greatest when therapy is given within the first four hours after the onset of symptoms, particularly within the first 70 minutes as the resistance of cross-linked fibrin to fibrinolysis is time-dependent [40]. Any longer delay decreases the amount of myocardial salvage and functional benefit.

Fibrinolysis can be done either alone or followed by PCI as either rescue PCI, facilitated PCI or early (pharmaco-invasive) PCI. The term facilitated PCI is defined as immediate PCI after pharmacological therapy (either full dose fibrinolysis, or a combination of half dose fibrinolysis with platelet glycoprotein IIb/IIIa inhibitor). Early PCI or a pharmaco-invasive approach has been defined in recent trials as fibrinolysis in non-PCI centers followed by transfer to a PCI center for catheterization within 24 hours where primary PCI was not feasible; while rescue PCI is defined as PCI performed after failed fibrinolysis.[41]

Fibrinolytic therapy with its adjuncts has thus reached a plateau and despite its impact on improving the survival in general has been shown to have several limitations. These include inability to use in several situations, as mention below:

- Inability to use in several situations.
- Intra cranial bleeding.
- Inability to achieve TIMI 3 flow in 40 - 45% patients.
- Inability to achieve adequate ST segment resolution (>50% or 70%) within 60 to 180 minutes in a large number of patients and relatively high rates of recurrent ischemia and reocclusion.
- Unfortunately, many patients present to the hospital more than six hours after the onset of symptoms.[42]

Key points in the management of patients with non–ST-elevation acute coronary syndrome (NSTE-ACS) is early evaluation and assessment of hemodynamic and electrical stability, estimatation of the overall risk in these patients, and guidance of therapy.

There are two alternative management strategies, either an early invasive strategy with angiography, with intent for revascularization with percutaneous coronary intervention (PCI) or

coronary artery bypass grafting (CABG), or a conservative strategy with initial medical therapy and noninvasive cardiovascular imaging. Regardless of the strategy, both entail aggressive utility of medications such as anticoagulants, antiplatelet agents, beta blockers, statins, and possible use of angiotensin-converting enzyme (ACE) inhibitors for appropriate patient populations.[43]

When thrombolytic therapy is used as the primary reperfusion strategy in a non–PCI-capable facility, the goal remains administration of such therapy within 30 minutes of hospital arrival. Thrombolytic therapies, such as front-loaded tissue plasminogen activator, reteplase, and tenecteplase , open approximately 80% of infarct-related vessels within 90 minutes, but only 50% of these vessels will have normal (TIMI grade 3) flow. In addition, 10% of vessels opened by thrombolysis either become reoccluded or are the source for recurrent symptoms of angina. Also, patients older than 75 years, who have the most to gain from reperfusion, have unacceptably high rates of intracerebral hemorrhage with thrombolysis. Because of these limitations, several randomized trials have evaluated mechanical revascularization with primary angioplasty in the setting of STEMI. The advantage of this approach is that the artery can be opened more frequently (>95%), and the underlying plaque rupture can be treated [44].

Despite the clear benefits of fibrinolytic therapy compared with no reperfusion and its ease of use, there are issues of both efficacy and safety that limit its use.

Primary percutaneous coronary intervention (PCI), if performed in a timely fashion, is the reperfusion therapy of choice in patients who have had an acute ST elevation myocardial infarction (STEMI) or an MI with new or presumably new left bundle branch block or a true posterior MI.[45]

CONCLUSION

With the conceptual frame work: “time delay equals myocardium lost”, the goal has been to achieve reperfusion as early as possible. Defining the optimal standard of care may not be a choice between thrombolysis or primary PCI, but perhaps a combination of pharmacological and mechanical reperfusion.

Pre-hospital thrombolysis is a very logical method of achieving early patency of the infarct related artery which is very relevant to countries like India. Patients presenting after two hours of onset of chest pain and being considered for primary PCI have been shown to have better results if thrombolysis is started before transferring them to a PCI center.[46] Thrombolysis is less effective as time passes, whereas primary PCI seems to be very effective after four hours and appears to be less time dependent than thrombolytic treatment. In places where patients with acute ST elevation MI and symptoms of < 12 hours duration can be transferred safely within two hours after diagnosis to a tertiary centre with a 24 hour PCI service, a treatment strategy of aspirin, clopidogrel, β blockers, and abciximab, and quick reperfusion therapy with primary PCI including stenting can be recommended. This strategy is superior to conventional in-hospital thrombolysis. Pre-hospital thrombolysis (particularly in patients with symptoms of < 2 hours duration) and facilitated PCI appears to represent another promising treatment option and should be compared to primary PCI in future trials [47].

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