International Journal of Cardiology Research
www.cardiologyjournal.in
E-ISSN: 2663-4112, P-ISSN: 2663-4104
Received: 01-10-2020; Accepted: 15-10-2020; Published: 01-11-2020
Volume 2; Issue 2; 2020; Page No. 36-39

Role of pharmaco-invasive therapy in improving outcomes for patients with ST-Elevation myocardial Infarction (STEMI) in Indian context

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DOI: https://doi.org/10.33545/26634104.2020.v2.i2a.29

Abstract
Background: The ischemic myocardium should be promptly reperfused to reduce morbidity and mortality in patients with ST-segment elevation myocardial infarction (STEMI). Conventionally, 2 approaches are the mainstay of reperfusion treatment: primary percutaneous coronary intervention (PCI) and fibrinolytic therapy which are considered as mutually exclusive therapeutic modalities. Primary PCI is considered as the gold standard for STEMI but in a developing country like India, it is not practically achievable in all the cases because of various challenges. Therefore, thrombolysis followed by either PCI or non-urgent coronary angiography seems to be a more practical approach in not only semi-urban and rural areas but also in metro and tier-1 cities in India.
Aim: To arrive at a consensus on the importance of pharmaco-invasive (PI) strategy for patients of STEMI in Indian scenario when a delay in PCI is anticipated. Leading experts across India reviewed various fibrinolytics with reference to their availability, ease of administration and risk benefit ratios. Their views were captured in advisory meetings. They then discussed and presented their views and shared their experiences on the practicality of PI strategy in the metro and tier-1 cities of India. Their opinion is captured in the present document. The panel opined that STEMI patients should be given PI therapy, wherever possible, using a third-generation fibrinolytic, namely, reteplase or tenecteplase if the delay in primary PCI of more than 120 minutes from the time of chest pain is expected. Immediate reperfusion by thrombolysis helps in preserving the myocardium and it also provides a time window for further PCI and coronary angiography, whichever is required. The experts concluded that when delay in access to primary PCI is expected, PI therapy is the preferred choice for STEMI patients. It should be practiced not only in semi-urban and rural areas but also in metro and tier-1 cities in India.

Keywords: STEMI, pharmaco-invasive, thrombolysis, primary percutaneous coronary intervention, India

Introduction

The WHO data shows that the prevalence of coronary artery disease (CAD) is steadily increasing in India. It is now a major contributor to deaths and disabilities in India. About 3-4% of Indians in rural areas and 8-10% in urban areas have CAD[1]. The occurrence of CAD is now more common among young Indians, causing a significant loss of potentially productive years of life in India. Among working-age adults (35–64 years), approximately 18 million productive years of life are expected to be lost to CAD by 2030, which is nine times larger than expected in the United States [2]. In a study conducted in England to evaluate ethnic differences in patients with myocardial infarction (MI), it was observed that Indians were 10 times more likely to develop MI than the white population. This pattern of disease has substantial implications for India's growing workforce and economy. Another cause for concern is the rise of CAD among poor and middle-class Indians when earlier CAD was considered a disease of the elite [3]. There are several reasons for this, some of them including the possible relationship between fetal or childhood malnutrition and the subsequent development of cardiovascular risk factors; uncomplicated use of tobacco products among the poor and less access to preventive services and medical care compared with wealthier patients [4,5,6]. This suggests that the Indians with lower socioeconomic status are at greater risk of acute presentations of CAD and have worse outcomes following such events.

One of the most serious complication of CAD is ST-elevation myocardial infarction (STEMI). The trends in acute coronary syndrome patients come from CREATE, a large clinical registry from 89 large hospitals in 10 regions and cities across India [7]. The registry revealed that amongst more than 20,000 patients enrolled, more than 60% of patients had STEMI, who were younger and had a lower socioeconomic status than patients with non-STEMI. Further, the median time from onset of symptoms to arrival in the hospital was 300 min in STEMI patients which is more than double the delay reported in developed countries. Additionally, only 8% of patients underwent percutaneous coronary intervention (PCI) during their hospitalization and 60% received fibrinolytic therapy. There was a further delay of 50 min to undergo fibrinolysis in comparison to 32-40 min in developed countries. Most of the patients came to the hospital using private

transportation and only 5% utilized ambulance service. A lot of Cath labs have been installed in different parts of India, since 2008, both in Government & private Sector. Hence, incidence of Primary PCI has really gone up since Create Registry. Pharmaco-invasive strategy is the second-best option. However, it is a practical & viable option considering the Socio-cultural & economic condition of a vast country like India. Therefore, an effective plan for acute reperfusion therapy needs to be developed for the Indian setting. Reperfusion is the key to reduce mortality and major cardiovascular events in STEMI care and it is time-dependent. For the effective restoration of myocardial perfusion, it is imperative that the infarction related artery (IRA) be opened as early as possible, completely and consistently. The shorter the time from symptom onset to recurrence, the greater the benefit to the patient. The current recommendation for door-to-balloon (D2B) time is less than 90 min and that for door-to-needle (D2N) time is less than 30 min [8].

Various factors may result in a delay in reperfusion therapy. They are: people are unaware of the importance of time in STEMI and this prolongs the time of first medical contact (FMC) and the time to obtain procedural consent. Further, many people are also not aware that chest pain could possibly be due to STEMI and may reach the emergency department very late or die during transit. Even if they arrive at the hospital in time, physicians may need more time to communicate the importance of the reperfusion procedure. Second, the ambulance system may not be able to transfer STEMI patients to a primary PCI-capable hospital immediately. Thus, patients can only get conservative therapy because of fibrinolysis contraindications or outside the therapeutic time window. Third, activation of the cath-lab is often late since departments within the hospital lack adequate coordination or ED physicians do not recognize STEMI in time. Patients may experience delay in the ED waiting for electrocardiogram (ECG) examination, cardiac marker results or waiting for the primary PCI team to arrive. In addition, some patients may refuse primary PCI procedure due to economic issues [9]. Considering these hurdles, damage to myocardium can be prevented by instituting fibrinolytic therapy. This prolongs the window of opportunity to 24 hours giving time to relatives of the patient to decide their doctor, arrange finances and complete insurance formalities which is all very important in Indian scenario. Taking these points into consideration it can be said that pharmacoinvasive approach is better especially when a delay in PPCI is anticipated. It may be a more appropriate option not only in rural and semi-urban areas but also in tier-1 and metro cities in India, where PCI facility is readily available.

Pharmaco-invasive (PI) strategy

Reperfusing the infarcted artery promptly by starting fibrinolytic therapy followed by early PCI appears to be an optimal reperfusion strategy for patients with STEMI. The benefits of combining fibrinolytic therapy followed by PCI have been described by Dauerman and Sobel [9]. Many studies have shown that PI strategy is an effective option of reperfusion in STEMI.

In the Transfer AMI study of 1059 patients, fibrinolytic therapy was given with tenecteplase at non-PCI centers and the patients were then randomized either to be immediately transferred to another hospital for PCI or were subject to standard treatment, including clinically related PCI. In the immediate transfer group cardiac catheterization was done in 98.5% at a median time of 2.8 hours after randomization, whereas in the standard treatment group 88.7% patients underwent cardiac catheterization at a median of 32.5 hours after randomization. In the first group there was a significant decrease in combined primary endpoint of death, new or worsening congestive heart failure, cardiogenic shock, reinfarction and recurrent ischemia within 30 days in immediate transfer group. However, no significant differences in rate of major and minor bleeding, intracranial hemorrhage and transfusion was found. Similarly, data from STREAM study and STEPP AMI study have shown that PI is comparable to primary PCI in decreasing overall morbidity and fatality rates and PI approach has been endorsed by European guidelines and the US committees. The Indian consensus on PI approach is use of a fibrinolytic (streptokinase, alteplase, tenecteplase or reteplase) within the recommended time frame and adjunctive medical therapy.

Fibrinolytic Agents

Fibrinolytics are the choice of class of drugs for STEMI, because if they are administered within 12 hours of onset of symptoms of MI, they are effective in restoring reperfusion, however, maximal benefit is achieved if they are administered promptly [10,11]. Fibrinolytics act by conversion of plasminogen to plasmin which causes lysis of fibrin, resulting in dissolution of clot and restoration of blood flow to the tissues. The various fibrinolytic agents available in India include the first generation streptokinase, the second generation alteplase and the third generation, reteplase and tenecteplase. A comparison of the characteristics of the fibrinolytic agents is given in the table (Table 1).

Table 1: Comparison of fibrinolytic agents [12, 13]

	Streptokinase	Alteplase	Tenecteplase	Reteplase
Antigenicity	Yes	No	No	No
Allergic reaction	Yes	No	No	No
Systemic fibrinogen depletion	Marked	Mild	Minimal	Moderate
Approximate 90-Minute Patency (%)	50	75	75	60-70
TIMI Grade 3 Flow (%)	32	54	63	60
Molecular Weight (kD)	48,000	70,000	65,000	39,000
Plasma Half-Life (min)	18–23	5	20–24	13–16
Fibrin Specificity	Low	High	Very high	Moderate
Bolus Dosing	Nosss	No	Yes	Yes
Weight-Based Dosing	No	Yes	Yes	No
Dose and administration	1.5 MU infusion over 60 min	15 mg bolus plus 90-min infusion up to 85 mg	0.53 mg/kg single bolus given over 5 seconds	10 + 10 units double bolus given over 2 min with 30 minutes

Streptokinase is the most widely used fibrinolytic agent since it is easily available and is less costly than other fibrinolytic agents. But, because of lack of fibrinogen specificity, short half- life, tendency to cause anaphylactic reactions and need for IV infusion is not the preferred agent [14]. Alteplase is fibrinogen specific but the main disadvantage is that it has to be given as intravenous infusion and needs a weight-based dosing. Tenecteplase has the advantage that it has highest fibrin specificity and resistance to inactivation by plasminogen activator inhibitor-1 (PAI-1) [15]. It is given as a single bolus over 5 seconds but the main disadvantage is that weight based dosing is required which can be a problem due to emergency situations commonly seen in STEMI [16,17]. Though analyses of tenecteplase clinical trials suggest that the use of weight-optimized dosing may improve safety outcomes in elderly patients of low body weight & that weight-optimized dosing with tenecteplase is associated with a low to moderate incidence of ICH and mortality [18]. Reteplase is a third-generation plasminogen activator and is fibrin specific. It is specifically designed for bolus thrombolysis in patients with STEMI [19].

Reteplase is available as a single use vial containing 10 units (18 mg), currently, in India [17]. It can be given as a double bolus regimen (10 IU + 10 IU) which is the preferred method of administration as it helps to achieve reperfusion within a relatively short time as compared to alteplase, streptokinase. Reteplase has the advantage that no dose adjustment is required based on body weight. Moreover, it is easy to administer since it does not require infusion and therefore dosing errors are reduced. Further, the RAPID 1, RAPID 2 and INJECT studies have shown that risk of bleeding complications and other adverse events are relatively less with reteplase as compared to alteplase [20].

Experts Opinion

- It is important to create awareness and educate health care personnel from remote areas on the advantages of the PI strategy and the use of third generation lytics.
- Timely reperfusion is the key for rapidly restoring coronary blood flow and prevent further damage to myocardium.
- The STEMI patients should be given PI therapy, wherever possible, using a third-generation fibrinolytic, namely, reteplase or tenecteplase if the delay in primary PCI of more than 120 minutes from the time of chest pain is expected.
- The healthcare infrastructure should be strengthened across all states in India based on the Hub and Spoke model, which is economical and will ensure appropriate care of STEMI patients.
- The STEMI system of care should be integrated with government health insurance schemes to ensure sustainability of the program. Importantly, the long term viability of the program can be ensured only if each State government is also a stakeholder and there is a public-private collaboration in delivering quick and appropriate reperfusion therapy.

Conclusion

In India even though there are many PCI capable centers in metro and tier-1 cities, delays in primary PCI are common. Therefore, PI therapy should be considered, wherein thrombolysis preferably using a third-generation fibrinolytic agent and then transfer for PI management should be implemented. This can be a lifesaving option especially where delay in PPCI is anticipated. Further, strengthening the healthcare system by setting up 'STEMI India' model for optimal reperfusion therapy in STEMI patients across the entire country will help in reducing morbidity and mortality of STEMI patients.

Acknowledgement

Writing assistance was provided by Dr Reeti Singhal. We gratefully acknowledge the contribution of experts who gave their expert opinion in conceptualization and finalization of consensus in advisory board meeting.

East: Arup Das Biswas, A B Malpani, Manojit Lodha, Subhadip Pal, Sumit Chatterjee

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Disclosure

The expert meetings were done in association with Abbott Healthcare Pvt. Ltd. The views expressed and discussed in the meetings and stated in this consensus article are the views of the authors and not of Abbott Healthcare Pvt. Ltd.

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