Pre-Hospital Thrombolysis
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Abstract
Coronary heart disease (CHD) is a major cause of mortality in India. Patients in India, who have acute coronary syndromes, have a higher rate of STEMI than do patients in developed countries. Since most of these patients are poor, they are less likely to get evidence-based treatments, and have a greater 30-day mortality. Reduction of delays in access to hospital and provision of affordable treatments could reduce this.

Treatment regimes for AMI should aim to open the artery as soon as possible and as wide as possible. In patients suitable for thrombolytic treatment, time is critical and reperfusion should be initiated as soon as possible. Some adjunctive therapies are also beneficial, in particular, the antiplatelet agent aspirin, which should be given in the prehospital setting when a diagnosis of AMI is suspected.

Despite availability of good treatment, mortality from AMI is showing no further reduction due to the prehospital phase and in-hospital delays. Thrombolysis is almost always delivered to patients after arriving in hospital, losing valuable time (and hence heart muscle). Newer drugs combined with recognition of improved outcomes have prompted attempts to decrease the time from symptom onset to treatment delivery via Pre Hospital Thrombolysis (PHT).

However, PHT is significantly superior to in-hospital thrombolysis (IHT). This is especially important in regions where PCI is not available.

In the RIKS-HIA and NRMI, PHT had better outcomes than IHT, but patients who received PPCI had lower mortality and re-infarction rates. They concluded that within 2 h of symptom onset, patients should receive PHT only if PPCI is not available within 4 h.

In CAPTIM, which compared PPCI and PHT followed by PCI if thrombolysis failed and in GRACIA-1 trial, which tested the role of systematic PCI within 24 h of thrombolysis, the policy of systematic PCI following thrombolysis yielded better results than conservative management.

The American Heart Association (AHA) and the American College of Cardiology (ACC) favour the use of PHT over PCI, placing the emphasis on the time factor rather than on the method of reperfusion. However, if PHT cannot be administered, the patient should be treated with PPCI within 90 min of first medical contact or therapy within 30 min such that the total ischaemic time is 120 min.

The National Institute for Clinical Excellence supports reperfusion with fibrinolytics, recommending PHT using the newer agents, reteplase and tenecteplase, whose bolus application simplifies administration.

PHT constitutes one of the means to shorten delays before the administration of reperfusion therapy. However, it poses several organizational problems that can find different answers according to each regional/national system of care. A number of barriers exist that limit the actual use of PHT. Thus the system of care chosen is likely to have a definite impact on the percentage of STEMI patients in whom PHT can be delivered.

Global Trends in Coronary Artery Disease
Coronary heart disease (CHD) is a major cause of morbidity and mortality in India like the rest of the world. Although rates of coronary heart disease have been decreasing over the past three decades in the western world, this is not true in India where we are seeing a rising trend. This decreasing trend has not been consistent across age groups, gender or socio-economic class. A more rapid reduction has been seen in younger age groups (45-54 years), in men and in higher socio-economic groups. In addition, the rate of decline in the UK has been slower than that in other developed counties (e.g. Denmark, Norway, Australia).1

Indian Scenario
Patients in India, who have acute coronary syndromes, have a higher rate of STEMI than do patients in developed countries. Since most of these patients are poor, they are less likely to get evidence-based treatments, and have a greater 30-day mortality. Reduction of delays in access to hospital and provision of affordable treatments could reduce morbidity and mortality in India.2

Pathophysiology of Acute Myocardial Infarction
Coronary heart disease is usually due to atherosclerotic narrowing of the coronary arteries supplying the muscle of the heart (the myocardium). Its first presentation can be an acute myocardial infarction (AMI). AMI is the result of a thrombus or clot forming on top of a ruptured atherosclerotic plaque, blocking the blood flow through the artery. Unless the blood flow can be quickly restored, the muscle supplied by that artery “infarcts” due to ischaemia. This can result in sudden cardiac death. In fact 50% of the patients with an AMI die before they can reach the hospital. This muscle damage weakens the heart, and may also cause heart failure either early (within a matter or hours) or later (over a period of months or years).

Diagnosis of Acute Myocardial Infarction
According to the World Health Organization, the diagnosis of AMI requires that at least two of the following three criteria be met: 1) a clinical history of ischaemic-type chest discomfort, 2) changes on repeated electro-cardiographic (ECG) tracings usually over two to three days, and 3) a rise and fall in serum cardiac markers (typically over 1-2 days but new sensitive markers may allow a diagnosis within 6-12 hours). However, these criteria may not be suitable for the diagnosis of AMI, within
the first 6 hours when interventions to restore blood flow, such as drugs to dissolve the thrombus, may be of most value to save life.

Changes in ECG readings are useful in the diagnosis of AMI and ST segment elevation is very specific in identifying patients requiring reperfusion therapy. These changes may occur in the “anterior” ECG leads (generally indicating an occlusion in the left coronary artery, the main supply to the myocardium and hence affecting more myocardium, with a worse prognosis) or inferior leads generally implying a smaller infarct with a better outlook, possibly due to obstruction in the right coronary artery or circumflex artery unless there is associated right ventricular infarct. However, as many as 50% of patients with AMI may not exhibit ST elevation in the early stages and assessment of change in ST abnormalities has been proposed as a more sensitive diagnostic marker. Changes in traditional serum cardiac markers also often occur too slowly to be of immediate value. Newer, more rapidly available tests are being evaluated.

Current practice for early identification of patients experiencing an AMI, and who might benefit from reperfusion therapy, therefore includes a combination of clinical symptoms and ECG changes. Serial ECG changes are monitored if initial readings appear normal but clinical symptoms persist or become worse. Serial readings may also be needed if initial readings are abnormal but not diagnostic of AMI.

## Treatment

Medical care for patients experiencing AMI has changed over the past 40 years. Care in the 1960s and 70s focused on the treatment of life-threatening arrhythmias. This included the development of specialist coronary care units to monitor these patients. The 1980s saw the conduct of large clinical trials to assess the effectiveness of drugs that broke down the clot (thrombolysis) followed by trials of primary angioplasty. The 1990s saw the development of specialist coronary care units to monitor life-threatening arrhythmias. This included the development of specialist coronary care units to monitor these patients. The 1980s saw the conduct of large clinical trials to assess the effectiveness of drugs that broke down the clot (thrombolysis) followed by trials of primary angioplasty.

Thrombolysis is almost always delivered to patients after arriving in hospital, possibly losing valuable time (and hence heart muscle). Meta-analysis of trials has shown that early thrombolysis is more effective and that the treatment is of limited value once irreversible myocardial damage has occurred. Advances in the speed of action and ease of administration of newer drugs combined with recognition of improved outcomes with earlier administration have prompted further attempts to decrease the time from symptom onset to treatment delivery.

### This is where Pre Hospital Thrombolysis (PHT) comes in

While it seems logical and very attractive is there any evidence that this would save lives?

#### Randomised Trials of Prehospital Thrombolysis vs. In-Hospital Thrombolysis

Randomized controlled trials (RCTs) have shown PPCI to be more effective than fibrinolysis for STEMI when performed by an experienced team within 90 min of first medical contact. Keeley et al. evaluated 23 trials comparing PPCI with thrombolysis using streptokinase or a fibrin-specific agent. Regardless of the

| Table 1: Differences in 30 day and 1 year mortality between all pre-hospital thrombolysis, ambulance-transported pre-hospital thrombolysis, primary percutaneous coronary intervention, and in-hospital thrombolysis for ST-elevation myocardial infarction patients in the RIKS-HIA registry |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Mean age (years)               | 64                                | 66.3                         | 64.2                         | 68.6 |
| 30 day mortality (%)           | 5.4                               | 7.6                          | 4.9                          | 11.4 |
| 1 year mortality (%)           | 7.2                               | 10.3                         | 7.6                          | 15.9 |

Data from Björklund et al.18 and Stenestrand et al.23.
Table 2: Comparison of outcomes at 30 days and 1 year for ST-elevation myocardial infarction patients treated within and after 2 h of symptom onset with pre-hospital thrombolysis, inhospital thrombolysis, or primary percutaneous coronary intervention

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Data from Stenestrand et al.22

The findings from CAPTIM are consistent with those from PRAGUE-2, which showed that within 3 h of symptom onset, mortality rates were almost identical, but in patients randomized after 3 h, mortality following thrombolysis was much higher.12 The investigators concluded that if STEMI patients can be transferred within 20–30 min, they should receive PPCI. If this cannot be performed within 60 min, thrombolysis can be administered up to 3 h after onset. Beyond 3 h, thrombolysis should not be used, and patients should be transferred for PPCI. Likewise, in the Primary Coronary Angioplasty vs. Thrombolysis (PCAT)-2 Trialists Collaborative Group meta-analysis, 30 day mortality doubled in the fibrinolysis group as the time delay increased from 1 to 6 h. The re-infarction rate was also higher in this group and increased with the time delay (not observed in the PPCI group). Thus, the time delay to reperfusion remains central to the choice of strategy.13

Do registry data also suggest the same conclusions?

In the large RIKS-HIA (Register of Information and Knowledge about Swedish Heart Intensive Care Admissions), PHT had better outcomes than IHT, but patients who received PPCI had lower mortality and re-infarction rates and shorter hospital stays.14 However, only a few months before, the same group reported the results of thrombolysis in the same patients treated in the ambulance before hospital admission. In this latter group, mean age was comparable with the age of patients treated with PPCI. Interestingly, comparing 30 day and 1 year results between the ambulance-managed PHT patients and the primary angioplasty group shows that both reperfusion methods yield very similar mortality figures: 5.4 vs. 4.9% at 30 days and 7.2 vs. 7.6% at 1 year, respectively (Table 1).14,15

Time delay to reperfusion appeared very important in the thrombolysis groups, as mortality increased sharply beyond 2 h. The difference was less dramatic for PPCI (Table 2). Overall, time delay was central to the benefit incurred by any type of reperfusion, but loss of benefit with increasing delay was less pronounced with PPCI. Therefore, the authors concluded that within 2 h of symptom onset, patients should receive PHT only if PPCI is not available within 4 h. This conclusion, however, did not take into account the results of PHT in ambulance-transported patients.

The National Registry of Myocardial Infarction (NRMI) registries studied the impact of the difference in time delays between the administration of thrombolysis and PPCI in 192509 patients. Overall, PPCI yielded more favourable results than thrombolysis, but increasing DB minus DT times were associated with increasing mortality rates (P < 0.001).16 The time point at which PCI lost its survival advantage over fibrinolysis varied considerably among various subgroups: from 40 min in patients 65 years of age with an anterior infarction, presenting within 2 h of symptom onset, to 179 min in patients 65 years of age with a non-anterior infarct, presenting after 2 h of symptom onset (Figure 1). The effect of thrombolysis was greatest in patients presenting with a large infarction, short duration of symptoms, and low bleeding risk. The prolonged time window gained for PCI in the elderly appeared related to the increased risk of intracerebral haemorrhage with fibrinolysis.16,17

Is there a need for PCI after PHT?

Another important point is the role of subsequent PCI after PHT. In CAPTIM, 70% of patients in the thrombolysis group underwent PCI before day 30, with 26% requiring rescue PCI. Therefore, the actual comparison in this trial was between PPCI and PHT followed by PCI if thrombolysis failed. Furthermore, the role of systematic PCI within 24 h of thrombolysis was tested in the Grupo de Analisis de la Cardiopatia Isquemica Aguda (GRACIA-1) trial18 and in the CARESS-in-AMI trial.19 In both instances, the policy of systematic PCI following thrombolysis yielded better results than conservative management. The WEST (Which Early ST-elevation myocardial infarction Therapy) study extended this concept and compared tenecteplase alone with tenecteplase and mandatory PCI within 24 h and PPCI with a loading dose of clopidogrel. The results suggested that rapidly applied pharmacological reperfusion with follow-up (rescue and routine) PCI within 24 h produced equivalent results to PPCI.20

The American Heart Association (AHA) and the American College of Cardiology (ACC) favour the use of PHT over PCI, placing the emphasis on the time factor rather than on the method of reperfusion. AHA/ACC guidelines state that PHT should be performed only following the confirmation of STEMI.
The recent update of the Acc/AHA guidelines insists that the door-to-balloon time (arrival to PCI, db) should be 90 min. DN should be 30 min. If, however, the hospital can offer PCI, the door-to-needle time (arrival to the hospital to the administration of thrombolytic, to a hospital that has no PCI facility, the door-to-needle time be administered and the patient is subsequently transported min of the arrival of the emergency services. If PHT cannot benefit more from PPCI. PHT should be performed within 30 min of hospital presentation unless contraindicated (level of evidence A). In patients presenting to a hospital without PCI capability and who cannot be transferred to a hospital centre and undergo PCI within min of first medical contact (level of evidence A). In patients presenting to a hospital without PCI capability and who cannot be transferred to a hospital centre and undergo PCI within min of first medical contact, therapy should be administered within min of hospital presentation unless contraindicated (level of evidence B). The goal is to organize systems of care such that the total ischaemic time be 120 min. The goals for each management step are the following:
1. time from symptom onset to first call to emergency medical service (EMS): 5 min,
2. with 1 min EMS dispatch;
3. EMS on scene within 8 min,
4. ECG on scene and consider pre-hospital fibrinolytic therapy by EMS if capable and time to lytic therapy, 30 min;
5. if transportation to a hospital without PCI capability, DN time, 30 min;
6. if transportation to a hospital with PCI capability, EMS-to-balloon time, 90 min (if patientself-transport: DB time, 90 min).

The National Institute for Clinical Excellence supports reperfusion with fibrinolytics, recommending PHT using the newer agents, reteplase and tenecteplase, whose bolus application simplifies administration.

“People with symptoms of a possible heart attack should receive help from an individual equipped with and appropriately trained in the use of a defibrillator within eight minutes of calling for help, to maximize the benefits of resuscitation should it be necessary and... People thought to be suffering from heart attack should be assessed professionally and, if indicated, receive aspirin. Thrombolysis should be given within 60 minutes of calling for professional help.”

There has been recognition that a goal of providing thrombolysis within this 60-minute time window may be difficult when transport distances (or times) are long. To address this issue the NSF states:

“...usually hospital will be the best place to give thrombolysis. However, where the ‘call-to-hospital’ time cannot be reduced below 30 minutes, it may be more appropriate to plan to give thrombolysis before admission to hospital.”

Pre-hospital thrombolysis: advantages and limitations

PHT constitutes one of the means to shorten time delays before the administration of reperfusion therapy. However, it poses several organizational problems that can find different answers according to each regional/national system of care. A number of barriers may exist and limit the actual use of PHT.

Finally, there remains a discussion on the optimal system of prehospital care, with the on-site involvement of physicians or with the involvement of paramedics without physicians. A study of 641 consecutive STEMI patients in Finland found that the clinical results achieved with an EMS with on-site involvement of physicians were superior to those of an EMS with only paramedics on site. Obviously, the system of care chosen is likely to have a definite impact on the percentage of STEMI patients in whom PHT can be delivered. In the recent French registry of MI in 2005, PHT was used in 19% of the STEMI patients admitted to intensive care units within 48 h of pain onset, representing two-thirds of those treated with intravenous thrombolysis. From a practical standpoint, emergency ambulances in France are physician-staffed and PHT is administered by physicians who decide on its use after the initial clinical and ECG work-up.

Feasibility of PHT in India

It depends on multiple factors
1. Availability of Emergency medical services
2. Accessibility to EMS
3. Trained paramedics and emergency physicians
4. Thrombolytics- Infusion vs. bolus
5. Role of telemedicine
6. Organized PHT program

It is terms like ‘The Golden Hour’ that typify the importance of Emergency Medical Services (EMS) all over the world. It is a well-accepted fact that a patient who receives PHT from trained professionals and is transported to the nearest healthcare facility in case of PPCI has the greatest chance of survival. However, the state of EMS varies drastically from developed to developing countries like India. In spite of the development in the healthcare sector over the past decade, India is yet to create a single, comprehensive EMS that can be accessed throughout the country.

Scenario in India

As compared to developed countries with proper emergency systems in place, there is no single system which could play a major role in managing emergency medical services in India. There is a fragmented system in place to attend the emergencies in the country. 102 is the emergency telephone number for ambulance in parts of India. There are different emergency numbers in India’s 28 states and seven Union Territories. Hospitals in the country provide different telephone numbers for ambulance services. Clearly, India is in need for proper emergency medical service that can be accessed from anywhere in the country. India requires a better emergency medical service to meet the growing number of emergencies. What exists currently in the form of fragmented services across the country falls way short of meeting the requirement. More recently, NGOs and hospitals have come forward to provide their own EMSs. There have been considerable efforts by states across India to develop emergency services.

In 2007, with the extension of Ambulance Access for All (AAA)’s services, American Association of Physicians of Indian Origin (AAPI) founded Emergency Medical Service (EMS) for Mumbai. AAPI has collaborated with the Confederation of Indian Industries (CII) and signed a MoU to endorse the growth of the healthcare sector in India, especially in rural areas. This agreement is to provide knowledge and technology transfer and provide EMS to develop healthcare facilities in India.

Another such facility, Life Support Ambulance Service (LSAS) operating in Mumbai for three years in association with...
London Ambulance Service, UK, has now made inroads into Kerala and has 500 ambulances that can be reached on a toll free number 1298.

Legislation for emergency services

The demand for legislation for EMS has been rising steadily in India. Supporters of such legislation opine that it would mandate a common access number, formation of an EMS council, trained paramedics, graduation of ambulance and hospitals, network of hospitals and define physical and human resources needed for the service. This could help save lives by making access easy for all the patients. Methods, technology, personal skills need to be standardized with formation of legislation in emergency services to provide protection for the providers.

Recent introduction of bolus form of thrombolytic agents and role of telemedicine in decision making would help to form the organized PHT program in India.

References