

Prehospital Thrombolysis in AMI: a Feasible Alternative to Brazil?

Rodrigo Wainstein, Mariana V. Furtado, Carisi Anne Polanczyk

Postgraduation Program in Medicine: Cardiology and Cardiovascular Sciences of Universidade Federal do Rio Grande do Sul

Coronary artery disease (CAD) remains the main cause of mortality, with Acute Myocardial Infarction (AMI) contributing with approximately one-third of the death cases. In this context, the therapeutic resources used to reduce the unfavorable outcomes related to this disease, mainly in its acute form, have significantly increased. The advent of the thrombolytic therapy, for instance, represented a considerable advance in the treatment of AMI. Large randomized clinical trials published in the 80s such as GISSI and ISIS 2 have consistently demonstrated the decrease in mortality associated to these drugs when used timely after the onset of AMI symptoms, with its effectiveness being time-dependent and exponential, i.e., earlier the start of drug infusion, greater the clinical benefit.

Therefore, current studies have focused on strategies capable of decreasing the time from the symptom onset to the thrombolytic agent infusion. Several approaches such as campaigns directed at the early identification of incipient AMI symptoms, chest pain protocols and bolus thrombolytic infusion have been used with this purpose. However, one of the most promising and least used strategies in clinical practice, mainly in Brazil, is the use of prehospital thrombolytic agent. Currently, the evidence supporting the use of pre-hospital thrombolytic is quite strong and allows a careful evaluation of the effectiveness of this strategy. Such strategy had been extensively tested in randomized clinical trials in which it was compared to other strategies such as inhospital thrombolytic, primary angioplasty, facilitated angioplasty and adjuvant anti-thrombotic therapies, such as low-molecular-weight heparin and glycoprotein IIb/IIIa inhibitors¹.

In this issue of the Brazilian Archives of Cardiology (*Arquivos Brasileiros de Cardiologia*) Araujo et al², once again bring the prehospital thrombolysis to the discussion, by publishing an economical study about this intervention. The decision to incorporate or not the new technology must undergo a detailed and broad discussion, not only focusing on the jigsaw puzzle pieces. When analyzing a health technology, it is mandatory that we question its efficacy, effectiveness and cost-effectiveness. Additionally, it is necessary to consider its effect when applying it to the existing scenario of our Public Health System, to our population and on our budget, comparing it with the current situation and the available alternatives

Key words

Cost-effectiveness evaluation; Thrombolytic Therapy; Myocardial infarction.

Mailing address: Carisi A. Polanczyk •

Hospital de Clínicas de Porto Alegre - Rua Ramiro Barcelos 2350, sala 2060 - 90035-903 - Porto Alegre, RS - Brazil

E-mail: cpolanczyk@hcpa.ufrgs.br

Efficacy of prehospital thrombolysis

A detailed description of the evidence falls out of the scope, but a review on prehospital and inhospital thrombolysis reminds us of studies carried out in the last two decades. Most of these studies were small studies or had important methodological flaws, with best available evidence being the meta-analysis published by Morrison et al in 2003³. This systematic review selected the 6 main randomized clinical trials (MITI, EMIP, GREAT, Roth et al, Schofer et al, Castaigne et al) that compared the strategy of prehospital with inhospital thrombolysis in 6,434 patients. The isolated assessment of the studies showed a tendency towards the decreased mortality among the patients who received the prehospital thrombolytic, although without statistical significance. However, when analyzed jointly, the studies showed a statistically significant decrease of 17% in the mortality outcome due to all causes (chance ratio:0.83; 95%CI: 0.70-0.98; p=0.03). The 2% reduction in the absolute risk associated to the prehospital thrombolysis can be translated into one life saved for every 62 patients submitted to this therapy. Despite this relevant initial benefit, the 1-year and 2-year-mortality did show statistically significant differences between the two strategies. The favorable results can probably be attributed to the 60-minute difference between the diagnosis and the start of the prehospital and inhospital thrombolytic therapy (104 vs 162 min). An important aspect discussed in this study was the benefit of thrombolysis regardless of its administration by doctors in mobile emergency care service (MECS) units.

It is currently acknowledged that the later the clinical presentation, the lower the benefit of the thrombolytic agents will be, especially > 3 hours; in this context, the decision for primary angioplasty is supported⁴. The possible advantage of prehospital thrombolysis makes it rational to compare it with this other therapeutic option. In the CAPTIM clinical trial, Bonnefoy et al⁵ compared the primary angioplasty (n=421) with prehospital thrombolysis with Alteplase (n=419). The primary outcome – death, non-fatal AMI and non-fatal stroke within a 30-day period – occurred in 8.2% of the patients in the thrombolysis group and in 6.2% in the primary angioplasty group, with no statistically significant difference between the two groups. A re-analysis of the CAPTIM study published in 2003⁶ showed that the patients randomized to prehospital thrombolytic in up to 2 hours after symptom onset presented a strong tendency towards the decrease in 30-day mortality in comparison with the group randomized to primary angioplasty (2.2% vs 5.7%; p=0.058). Additionally, the subgroup of patients who received prehospital thrombolytic therapy less than 2 hours after the symptom onset presented a statistically significant decrease in the cardiogenic shock rate when compared to the other group (1.3% versus 5.3%; p=0.032).

From the CAPTIM study on, it was concluded that the time from the symptom onset must be one of the main factors to be considered when choosing a revascularization strategy and that the prehospital thrombolysis might be preferable to primary angioplasty in patients treated early (up to two hours of AMI evolution).

Effectiveness of prehospital thrombolysis

The use of prehospital thrombolysis has been considered the standard in the last two decades in several European centers, where a doctor or a trained nurse will carry out the AMI evaluation, diagnosis, triage and treatment. In the United Kingdom, through the Joint Royal Collage Ambulance Liaison Committee (JRCALC), until January 2006, 28 of the 31 ambulance services were capacitated to perform prehospital thrombolysis; however, only 20% of the patients with AMI who received reperfusion therapy with the thrombolytic agent are treated at the prehospital level⁷. In Andalusia, Spain, the PEFEX (Project to Evaluate Out-of-Hospital Fibrinolysis in Acute Myocardial Infarction) registry with 981 treated patients with acute coronary syndrome, 15.2% received prehospital thrombolysis, with 18% receiving it less than 1 hour and 68% less than 2 hours after the onset of symptoms. It is noteworthy the high concordance (97%) between the diagnosis attained by the paramedics and that received by patients at hospital discharge⁸.

The medical registry data of patients admitted at the French hospital network with an AMI diagnosis in the year 2000, show that only 9% (9180/1,922) were treated with prehospital thrombolysis; 19% received in-hospital thrombolysis; 23% underwent primary angioplasty and 49% did not have an indication for reperfusion therapy. Rescue angioplasty was performed in less than 24 hours in 37% of the patients that received prehospital thrombolysis, compared to only 18% of the patients that received in-hospital thrombolysis and 0.7% of the patients who underwent primary angioplasty⁹. Similar results were described in the Swedish medical registry data of AMI (RIKS-HIA Registry), where, in a total of 26,205 patients, 7,084 underwent primary angioplasty, 3,078 received prehospital thrombolysis and 16,043 received in-hospital thrombolysis¹⁰. The primary angioplasty group, when compared to the other two groups, showed a statistically significant decrease in 30-day and 1-year mortality. When the groups that received thrombolysis were compared, the prehospital use also showed a significant decrease in mortality when compared to the in-hospital use. After two hours of AMI evolution, however, the mortality curves in the groups that used thrombolytic agents tend to join, whereas the primary angioplasty maintains its benefit even when employed later.

It is important to consider, in these international experiences, the necessary structure to implement the programs: capacity to perform a 12-derivation electrocardiogram (ECG) by the entire team of medics and paramedics in the ambulances, ECG transmission by telemetry to a specialized center with a cardiologist, ECG interpretation and thrombolytic therapy indication, clinical assessment for the therapy contraindications and referral to a hospital capable of carrying out the treatment, considering that the risk estimate is 4 hemorrhagic cerebral vascular accidents (CVA) per 1,000 treated patients and 7 major non-cerebral bleedings per 1,000 treated patients¹¹.

Additionally, the impact of the intervention also depends on the mean time it took patients to call the ambulance service, mean time of hospital transference and time from symptom onset to the start of the treatment. Awareness and education programs directed at the general population on the disease manifestation and showing the course of action are essential for the success of this strategy¹¹.

In Brazil, there are few available data on the prehospital treatment¹². The figures presented by the Ministry of Health show that 926 towns and cities have access to the Mobile Emergency Care Service (MECS) units, reaching 47% of the Brazilian population, with 114 regulation centers.

There are no statistics on AMI emergency care. The BUSSOLA (*Buscando soluções para a subutilização da terapia trombolítica no Rio de Janeiro - Searching for solutions in the underuse of thrombolytic therapy in Rio de Janeiro*) study showed it is unlikely that a patient with AMI in the city of Rio de Janeiro will receive any type of reperfusion therapy from the emergency services, with no public institutions that have structured routine invasive procedures¹³.

Cost-effectiveness of prehospital thrombolysis

Some studies have been published on the cost and efficiency of the use of prehospital thrombolysis, with results varying according to the country where the study was carried out, cost of the drug and management of the infarction and its complications, so that the capacity of generalization is very limited.

In the study carried out by Araujo et al², with a Markov decision model, incorporating data from the large clinical trial GREAT to cost estimates in Brazil, the use of prehospital thrombolysis is related to a mean survival gain of 0.16 years at a cost lower than R\$176.00 in comparison to the in-hospital therapy. The study is an economic analysis based on the data of a clinical trial carried out in Scotland between 1988 and 1991, for which methodological considerations must be made in order to attain an adequate analysis of the study. Regarding the different types of therapy, the effectiveness of prehospital thrombolysis has shown a mortality reduction of 44%, much higher than that described in the meta-analysis by Morrison et al³, and only found in this study. Alternatively, the benefits of the in-hospital thrombolysis were lower than that observed in large trials^{1,13}. It is not clear, for instance, why the life expectancy of the individuals who received prehospital thrombolysis is, on average, 2.5 years higher than those who received in-hospital thrombolysis, whereas the gain in life-years with in-hospital thrombolysis is only 0.6 years in comparison to the absence of thrombolytic therapy. Additionally, the inappropriate use of thrombolysis in patients without infarction had no effect on mortality, according to the authors. The reinfarction rate for in-hospital thrombolysis was estimated as being two-fold higher than that for the prehospital thrombolysis (10% vs 5.8%), which are data from the GREAT study². However, the percentage of rescue angioplasty is known to be higher in the first group and this fact does not seem to have been considered by the authors in the model, regarding the additional costs. As for the costs, it is clear that

the indirect costs for setting up the infra-structure and the capacitating of all professionals working inside the system were not included, as well as the acquisition of equipment (ECG) and available online medication, supporting the strategy of inhospital thrombolysis. The data do not allow assertions to be made on the cost-effectiveness of the prehospital thrombolysis in Brazil, but they are an initial assessment phase. Models with effectiveness, cost and economic impact data obtained from Brazilian pilot studies must be sought out in order to achieve a more accurate estimate of the assimilation of the prehospital thrombolytic therapy.

Practical perspectives

In a large country such as Brazil, it is a challenge to establish a single strategy for the management of AMI, which will encompass all the scenarios, cities and towns, states and regions. Certainly, more important than the ideal reperfusion is to ascertain that some type of reperfusion therapy will be administered to the patient with AMI and

that this therapy will be safe, effective and rational. From the public healthcare perspective, it is necessary to organize a system to care for the patient with AMI, as it has been done in other countries¹¹. For instance, it has been suggested that just the acquisition of the prehospital ECG equipment can provide important advantages to expedite treatment. Among the available strategies, prehospital thrombolysis can be a logical alternative in some scenarios, but this decision presupposes an important investment and capacitating of professionals in our public and private Emergency Care Services. This investment, which would not be a large one, must be analyzed cautiously, as the experience in other countries show an actual use of thrombolysis in this phase in less than 20% of the eligible cases. Before that happens, it seems more important to promote a broad discussion on the education of the population, referrals, acute care systems, optimization of the inhospital thrombolysis use and primary angioplasty, with an extended analysis of the risks, time, benefits and availability of the existing and the necessary infra-structure.

References

1. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004; 110 (9): e82-e292.
2. Araujo DV, Tura BR, Brasileiro AL, Luz Neto H, Pavão ALB, Teich V. Custo efetividade da trombólise pré-hospitalar VS. intra-hospitalar no infarto agudo do miocárdio. *Arq Bras Cardiol.* 2008; 90 (2): 100-107.
3. Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: a metaanalysis. *JAMA.* 2000; 283: 2686-92.
4. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet.* 2003; 361: 13–20.
5. Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY, et al. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. *Lancet.* 2002; 360 (9336): 825-9.
6. Steg PG, Bonnefoy E, Chabaud S, Lapostolle F, Dubien PY, Cristofini P, et al. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty. *Circulation.* 2003; 108 (23): 2851-6.
7. Kroese M, Weissberg P, Arch B, Scott J. Prehospital thrombolysis—calculated health benefit for catchment population of one hospital. *J R Soc Med.* 2004; 97: 230-4.
8. Vergel FJM, Bailén MR, on behalf of the PEFEX* group, Out-of-hospital treatment of acute myocardial infarction in Andalusia, Spain. *Rev Esp Cardiol.* 2005; 58: 1287-93.
9. Danchin N, Blanchard D, Steg PG, et al. Impact of prehospital thrombolysis for acute myocardial infarction on 1-year outcome: results from the French Nationwide USIC 2000 Registry. *Circulation.* 2004; 110: 1909-15.
10. Stenestrand U, Lindback J, Wallentin L. Long-term outcome of primary percutaneous coronary intervention vs prehospital and in-hospital thrombolysis for patients with st-elevation myocardial infarction. *JAMA.* 2006; 296: 1749-56.
11. Faxon DP. Current state of ST-elevation myocardial infarction care development of systems of care for ST-elevation myocardial infarction. *Circulation.* 2007; 116: e29-e32.
12. Brasileiro ALDS. Expanding the Use of Reperfusion Therapy. From GISSI to DANAMI. *Arq Bras Cardiol.* 2005; 84 (6): 495-9.
13. Sociedade Brasileira de Cardiologia. III Diretriz Sobre Tratamento do Infarto Agudo do Miocárdio. *Arq Bras Cardiol.* 2004; 83 (supl 4): 3-86.