Fibrinolysis in acute myocardial infarction, a historical revaluation?

Fibrinólisis en el infarto agudo de miocardio, ¿una reivindicación histórica?

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According to main cardiology societies guidelines, both percutaneous coronary intervention (PCI) and fibrinolysis have the highest degree of evidence for the treatment of acute ST-segment elevation myocardial infarction (STEMI)^{1,2}. However, favoring PCI over fibrinolysis is recommended even when this implies a delay of up to 120 minutes^{1,2}. In 2003, a meta-analysis³ of 22 studies and 7,739 participants concluded that PCI reduced 30-day mortality by approximately 28% in comparison with fibrinolysis, with non-fatal reinfarction and hemorrhagic stroke rates also being decreased. These results, universally accepted ever since, should be relativized due to methodological limitations of included trials. First, all were open-label studies, which implies a high risk of bias in endpoints with inconsistent and poorly objective definitions, such as reinfarction. Second, most analyzed studies were small, with the benefit of PCI being concentrated there. There are numerous historical examples of meta-analyses of “small” trials that found benefits that were not subsequently reproduced by large trials⁴; thus did concepts such as “optimal information size” and “fragility” emerge for scrutinizing the results of clinical trials and systematic reviews⁵. Third, in said studies, patients receiving fibrinolytic therapy did not have access to rescue PCI when fibrinolysis failed. Finally, the time difference between PCI and fibrinolysis was very small, which magnifies the benefits of the former; in 20 of the 22 trials, this interval was of less than 60 minutes (in one of them, it

was even as short as 7 minutes). This contrasts with what is observed in clinical practice, where only a minority of patients are reperfused within the recommended times^{1,2}, both in high-income countries and, especially, in those of middle and low-income, as our region^{6,8}. In Mexico, the RENASICA III registry informed that half of STEMI received PCI after more than 100 minutes of admission to a center with hemodynamics unit⁶, while in Peru, PERSTEMI reported a delay between first medical contact (FMC) and reperfusion of 3.6 hours on average⁷ and, in Argentina, according to ARGEN-IAM-ST, only 30% of patients received angioplasty within the first 90 minutes⁸. The problem is even more serious, considering that 20-45% of STEMI did not receive any reperfusion treatment⁶⁻⁸. Despite these delays, the use of fibrinolytic drugs was low: 37.6%⁶, 38%⁷ and 16.5%⁸, respectively.

The reasons for the low utilization of fibrinolytic drugs in our region are diverse, although possibly there is an influence of the fact that they are less recommended in guidelines^{1,2}, a belief in the superiority of PCI³ and delays in pre-hospital and intra-hospital transfers in countries with large dimensions and low number of hemodynamics services outside the main metropolitan areas⁹.

So far, the largest clinical trial that has compared fibrinolytic therapy with PCI is STREAM¹⁰, which randomized patients with STEMI within 3 hours after symptom onset and who were unable to undergo PCI within the

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Date of reception: 11-06-2020

Date of acceptance: 06-08-2020

DOI: 10.24875/ACME.M21000206

Available online: 19-07-2021

Arch Cardiol Mex (Eng). 2021;91(2):226-228

www.archivoscardiologia.com

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Figure 1. Forest Plot. Analysis of the impact of treatment with percutaneous coronary intervention vs. fibrinolysis on cardiovascular mortality in clinical trials with low risk of biases.

Figure 2. Forest Plot. Analysis of the impact of treatment with percutaneous coronary intervention vs. fibrinolysis on non-fatal reinfarction in clinical trials with low risk of biases.

first 60 minutes after FMC. There were no differences in mortality between groups (4.4 and 4.6%) and neither did the remaining analyzed endpoints differ, including intracranial hemorrhage. Median FMC-to-balloon time in the PCI group was 86 minutes. As data of interest, 36% of patients who underwent fibrinolysis required rescue or urgent PCI, which could partially explain the excellent results in the tenecteplase group¹⁰.

In view of the foregoing, we decided to compare the impact of fibrinolytic therapy on STEMI mortality by carrying out a meta-analysis that included clinical trials with low risk of large biases (sample size close to or larger than 1,000 participants), according to the criterion used to assess the usefulness of fibrinolytic therapy. This way, only four trials from the Keeley et al.³ meta-analysis met these criteria, with STREAM being added to these trials. Globally, PCI was associated with a trend towards a reduction in the risk ratio (RR) for death in STEMI, which did not reach statistical significance (RR: 0.87; 95% confidence interval: 0.72-1.06; $p = 0.17$) without heterogeneity, and with a sample size similar to that from Keeley et al.³ ($n = 6,299$) (Fig. 1).

In contrast, PCI was superior in reducing non-fatal reinfarction, but with high heterogeneity ($I^2 = 68\%$), as a result of DANAMI-2 findings (Fig. 2).

These discrepancies with the results obtained by Keeley et al.³ suggest the existence of reporting or publication biases in small studies^{4,5} in favor of trials with positive results and centers with a high volume of procedures⁹.

In conclusion, we consider that our results suggest uncertainty regarding the superiority of PCI for reducing STEMI mortality when fibrinolytic drugs are rapidly administered after FMC, especially within a plan that includes a rescue PCI strategy when fibrinolysis fails. While PCI has additional benefits, the reality of our region does not allow for it to be STEMI's main reperfusion strategy. "The golden hour" aphorism is probably more current than ever, and implementing programs based on fibrinolysis for patients who cannot receive PCI within the first 60 minutes after FMC will reduce mortality from this pathology, with comparable results to those of angioplasty.

Funding

This research has not received any specific grant from public, commercial or non-profit sector agencies.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments have been performed on humans or animals for this research.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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