Efficiency of fibrinolytic therapy after recommended pain-to-needle time

Eficiencia de la terapia fibrinolítica después del tiempo puerta-aguja recomendando

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Abstract

Pain-to-needle time (PTN) is defined as the time from chest pain onset till the administration of the thrombolytic injection; representing the total time the artery was occluded and the myocardium was in ischemic conditions. However, thrombolytic therapy is only an option when percutaneous coronary intervention (PCI) is not available within the recommended 120 minutes for door-to-device (DTD) procedures. The impossibility of achieving recommended DTD usually happens in rural institutions, which lack the resources to efficiently transport the patient to the nearest PCI center within such a time lapse. Time is the most valuable resource in the management of ST elevation myocardial infarction, and thus, every approach towards the management of this conditions is confined to narrow time windows. Adherence to these time windows provided by international guidelines has proven to give the best possible results in most scenarios. However, real-world data suggests that many patients, especially those from developing countries, get untimely attention. These extemporary patients are excluded from the pharmacologic fibrinolytic option and are at risk of being non-eligible for PCI due to transport delay and protocols. This review aims to analyze the evidence regarding the efficiency and viability of extemporaneous implementation of fibrinolytic therapy in patients outside recommended PTN.

Keywords: Pain-to-needle time, thrombolysis, fibrinolytic therapy, coronary artery disease, myocardial infarction.

Resumen

El tiempo de dolor puerta-aguja se define como el tiempo desde el inicio del dolor en el pecho hasta la administración de la inyección trombolítica; representa el tiempo total durante el cual la arteria estuvo obstruida y el miocardio estuvo en condiciones isquémicas. Sin embargo, la terapia trombolítica solo es una opción cuando la intervención coronaria percutánea no está disponible dentro de los 120 minutos recomendados para los procedimientos de puerta a dispositivo. La imposibilidad de lograr el tiempo recomendado generalmente ocurre en instituciones rurales, que carecen de los recursos para transportar eficientemente al paciente al centro de PCI más cercano dentro de ese lapso de tiempo. El tiempo es el recurso más valioso en el manejo del infarto agudo de miocardio con elevación del segmento ST, y por lo tanto, cada enfoque hacia el manejo de estas condiciones está limitado a ventanas de tiempo estrechas. La adherencia a estos intervalos de tiempo proporcionados por las pautas internacionales ha demostrado brindar los mejores resultados posibles en la mayoría de los escenarios. Sin embargo, los datos del mundo real sugieren que muchos pacientes, especialmente aquellos de países en desarrollo, reciben atención fuera de tiempo. Estos pacientes excepcionales quedan excluidos de la opción farmacológica fibrinolítica y corren el riesgo de no ser elegibles para la PCI debido a retrasos en el transporte y protocolos. Esta revisión tiene como objetivo analizar la evidencia sobre la eficiencia y viabilidad de la

implementación excepcional de la terapia fibrinolítica en pacientes fuera del tiempo puerta-aguja recomendado.

Palabras clave: Tiempo de dolor a aguja, trombolisis, terapia fibrinolítica, enfermedad coronaria, infarto de miocardio.

Introduction

Cardiovascular disease (CVD) is responsible for one-third of all deaths worldwide and is considered one of the most relevant public health issues nowadays[1]. While CVD encompasses several conditions, coronary artery disease (CAD) ranks as the most prevalent[2]. Typically, CAD manifests clinically as acute myocardial infarction (AMI) and ischemic cardiomyopathy. Although AMI mortality rates have decreased within the past few years, the absolute number of cases has increased nonetheless[3]. Moreover, given the increased survivability rates, there is an increasing number of individuals with non-fatal CAD living with chronic disabilities and impaired quality of life[4]. It is presumed that the increasing incidence will continue to rise, not only due to the increasing prevalence of obesity, diabetes mellitus (DM), and metabolic syndrome, but also because of the increased life expectancy of the general population[5].

The financial impact of CAD from hospitalizations, treatments, and revascularization therapy is considerable, but posterior clinic visits, prescribed drug treatments, and management of complications represent the more significant burden. According to the World Heart Federation, the global burden of CVD in 2010 was US$863 billion, which is predicted to rise to US$1 trillion by 2030[6]. To minimize the impact of CAD, prevention-focused strategies guided by cardiovascular risk management have been developed[7]. Likewise, international protocols for AMI have evolved according to evidence-based medicine and aim to significantly decrease the prevalence of chronic complications associated with AMI through early pharmacologic or surgical revascularization therapy (SRT)[8]. However, the therapeutic window suggested by these protocols is challenging to follow in developed countries and even more in developing countries[9].

During AMI, the patient is expected to go to an emergency department immediately; nonetheless, delay in the pain-to-hospital (PTH) time is still a significant problem in developing countries[10]. Some studies suggest that the mean pre-hospital delay in developing countries is between 4 and 5 hours[11]. This period of time alone excludes the patient as a candidate for fibrinolytic therapy according to international protocols; moreover, according to the same standards, the patient is expected to receive SRT within the next 90 minutes[8]. Nevertheless, adherence to these time lapses is especially difficult for rural healthcare institutions that only have ground transportation. Given these arguments, several questions emerge, such as what to do with a patient outside the window for pharmacological revascularization and SRT. This review aims to analyze the evidence regarding the efficiency and viability of extemporaneous implementation of fibrinolytic therapy in patients outside recommended pain-to-needle time (PTN).

RECOMMENDATIONS REGARDING PAIN-TO-NEEDLE TIME: IS THREE HOURS AN ABSOLUTE DEADLINE?

PTN time is defined as the time from chest pain onset till the administration of the thrombolytic injection; representing the total time the artery was occluded and the myocardium was in ischemic conditions[12]. However, thrombolytic therapy is only an option when percutaneous coronary intervention (PCI) is not available within the recommended 120 minutes for door-to-device (DTD) procedures[8]. The impossibility of achieving recommended DTD usually happens in rural institutions, which lack the resources to efficiently transport the patient to the nearest PCI center within such a timelapse[13]. In these selected cases, pharmacological thrombolysis replaces PCI as the therapeutic strategy, if PTN does not exceed 180 minutes. The latter recommendation is based on several studies showing that thrombolytic therapy retains up to 50% efficiency in mortality reduction within the first 3 hours of symptom onset[14].

Several strategies have been proposed to optimize PTN time, including pre-hospital thrombolysis; but developing countries may lack the resources to perform these recommendations[15]. Furthermore, extensive studies have demonstrated that up to 40% of patients with AMI tend to present late and end up missing the recommended time window for thrombolytic therapy in developed countries[16,17]. In developing countries, this percentage tends to increase significantly, reporting a prevalence of consult delay as high as 80%[18]. When a patient is not a candidate for thrombolytic therapy due to untimely consultation and PCI is not possible because the nearest PCI institution is over 120 minutes away, therapeutic alternatives are severely limited.

In order to address this consultation delay problem, some authors have recommended increasing public awareness of the disease and developing a better transportation system. However, these strategies are not dependent on the healthcare system, making their effectiveness questionable[19]. Most investigations are focused on improving the door-to-needle time (DTN); however, a considerable amount of evidence reports that DTN is almost always within international recommendations, meaning that most of the problem relies

upon timely consultation by the patient[20]. Neither untimely patient consultation nor the distance between the rural institution and PCI centers are modifiable. Hence, it is worth studying the possibility of extending the PTN, in exceptional cases, to define up to which point this therapy can increase patients' survivability, and if other procedures are needed to improve mortality rates in this population further.

International guidelines state that fibrinolytic therapy is recommended within the first 12 hours of symptom onset if primary PCI cannot be performed within the recommended timelapse after diagnosis of ST-elevation myocardial infarction (STEMI)[8]. However, as stated before, the later the patient presents (after 3 hours), the more likely it is for the treatment to not provide its full benefits. Indeed, the longer the consultation delay, the more consideration should be given to transfer the patient to a PCI center, because at that point PCI benefits considerably outweigh the benefits of pharmacological thrombolysis[21]. However, STEMI patients with such time delay are more prompt to develop mechanical and electrical cardiac complications, which can compromise their transportation to the PCI center, primarily when basic vehicles are used instead of specialized ones[22].

A 5-year study analyzed the Portuguese Registry on Acute Coronary Syndrome to identify the relationship between treatment delay and type of reperfusion with post STEMI complications. It was concluded that the time delay was an independent risk factor for developing mechanical complications, especially in patients with more than 6 hours from symptom onset (OR 2.44, CI 95%: 1.37-4.33). However, reperfusion therapy conferred protection against mechanical complications in these patients, and no significant difference was identified between primary PCI and fibrinolytic therapy. The latter suggests that fibrinolytic therapy can be a viable option even at 6 hours after symptom onset, despite being outside the recommended therapeutic window[23].

Furthermore, the LATE study analyzed the efficacy of alteplase administration in STEMI outside the recommended therapeutic window, specifically between 6 and 24 hours from symptom onset. The study demonstrated that the subgroup treated with alteplase between 12 to 24 hours showed no significant differences in mortality compared to the control group. However, the subgroup under 12 hours showed a significant reduction in mortality of over 25% compared to the placebo group (p=0.02, CI 95%). However, patients treated with alteplase had a higher rate of hemorrhagic stroke, which was considered non-significant due to the control group pairing up in incidence after six months. The authors concluded that the time window for thrombolysis should be extended to at least 12 hours after symptom onset[24].

On the other hand, thrombolysis failure is a possible outcome, which becomes more likely when PTN is over 3 hours. One study demonstrated that thrombolysis failure rates between 3-12 hours are over 50%, emphasizing the need for early treatment[25]. Nonetheless, when PCI is not possible and the optimal therapeutic window for thrombolysis is overdue, the delay between patient admission and the therapeutic decision must be minimal. It has been extensively demonstrated that shorter DTN, even in patients with PTN over 3 hours, has a significant impact on in-hospital complications[14]. Likewise, other investigations have demonstrated that the essential factor associated with treatment delay in patients with STEMI is decision time, which may be as long as 60 minutes, making it responsible for up to 80% of the entire treatment delay[26].

Treatment delay after first medical contact significantly increases mortality, complications, and disability rates[27]. Moreover, evidence shows that the longer the patient with STEMI is untreated, the larger the extent of myocardial damage. Every 30 minutes after symptom onset was associated with a 1% increment in infarction size[28]. Sigmundsson et al.[29] demonstrated that the median transportation time of STEMI patients to a PCI center in southern Iceland was over 150 minutes. In light of the above, it was recommended that patients outside the urban area should receive fibrinolysis as the first-line treatment to minimize mortality rates and decision time.

Following thrombolytic therapy, transferring the patient to a PCI center is recommended. D'Souza et al.[30] have demonstrated that routine early referral for PCI after thrombolysis (known as post-thrombolysis PCI) leads to a significant reduction in mortality, re-infarction, and complications during the first year after STEMI in contrast to the watchful waiting strategy[31]. These results suggest that the current conservative approach after thrombolysis is not as beneficial as post-thrombolytic PCI. Moreover, the GRACIA-2 trial demonstrated that early routine post-thrombolysis PCI showed similar benefits compared to primary PCI[32]. The advent of early routine post-thrombolysis PCI is thought to render the extemporary fibrinolytic therapy less reckless, since the risk of thrombolysis failure will be overlapped with the early surgical intervention. Moreover, large trials have demonstrated that a rapidly delivered pharmacologic approach coupled with routine coronary intervention within 24 hours of the initial treatment shows no significant difference from primary PCI[33].

Conclusions

Time is the most valuable resource in the management of STEMI, and thus, every approach towards the management of this conditions is confined to narrow time windows. Adherence to these time windows provided by international guidelines has proven to give the best possible results in most scenarios. However, real-world data suggests that many patients, especially those from developing countries, get untimely attention. These extemporary patients are excluded from the pharmacologic fibrinolytic option and are at risk of being non-eligible for PCI due to transport delay and protocols. In these selected cases, evidence shows that fibrinolytic therapy can be implemented even at 12 hours from symptom onset, accepting the higher risk of therapy failure. However, this extemporary decision, which should not be delayed, opens a new window for the patient to receive an intervention that has shown to be at least as effective as primary PCI.

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