Clinical outcomes of patients after using prehospital fibrinolytic therapy: a systematic review

Desfechos clínicos de pacientes após uso de terapia fibrinolítica pré-hospitalar: revisão sistemática

Resultados clínicos de pacientes después del uso de terapia fibrinolítica prehospitalaria: revisión sistemática

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Abstract

Objective: To compare clinical outcomes of death, reinfarction, and stroke in primary studies assessing Fibrinolytic Therapy (FT) use in relation to Primary Percutaneous Coronary Intervention (PPCI) for myocardial reperfusion in patients with ST-Elevation Myocardial Infarction (STEMI) in prehospital care.

Method: A systematic literature review conducted in the CINAHL, MEDLINE, PUBMED, Science Direct, SCOPUS, and Web of Science databases from October to December 2017. Randomized Clinical Trials, available in full, in any language, without temporal clipping were included. The eligibility assessment was carried out in two stages and applied to the Jadad Scale for methodological assessment of the studies found.

Results: Five Randomized Clinical Trials were included. Prehospital FT presented mortality rates at 30 days after the intervention similar to PPCI, while in five years lower values were found for FT. The treatment instituted in a period of less than two hours of the initial symptoms was associated with the decrease in mortality when FT was used. Non-fatal reinfarction, stroke and intracranial hemorrhage were higher when FT was used, while cardiogenic shock showed lower frequency.

Conclusion: FT was more effective in prehospital treatment to reduce deaths after five years, however, reinfarction and stroke occurred similarly in the sample analyzed. The time factor reduced clinical outcomes, especially when the implemented therapy occurred within two hours after the occurrence of STEMI. Thus, although the interventions presented similar outcomes. However, FT may represent a viable treatment in places where PPCI cannot be achieved in a timely manner.

Resumo

Objetivo: Comparar desfechos clínicos de óbito, reinfarto e Acidente Vascular Encefálico (AVE) em estudos primários que avaliaram o uso da Terapia Fibrinolítica (TF) em relação à Intervenção Coronariana Percutânea Primária (ICPP) para reperfusão miocárdica em pacientes com Infarto Agudo do Miocárdio com supradesnivelamento do segmento ST (IAMCST) no atendimento pré-hospitalar.

Método: Revisão sistemática de literatura com busca realizada nas bases de dados CINAHL, MEDLINE, PUBMED, *Science Direct*, SCOPUS e *Web of Science* no período de outubro a dezembro de 2017. Foram incluídos Ensaios Clínicos Randomizados, disponíveis na íntegra, em qualquer idioma, sem recorte temporal. A avaliação da elegibilidade foi realizada em duas etapas e aplicada a Escala de *Jadad* para avaliação metodológica dos estudos encontrados.

Resultados: Foram incluídos cinco Ensaios Clínicos Randomizados. A TF pré-hospitalar apresentou taxas de mortalidade em 30 dias após a intervenção semelhantes à ICPP, enquanto que em cinco anos foram encontrados valores menores para a TF. O tratamento instituído em um período menor que duas horas dos

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sintomas iniciais apresentou associação com a diminuição da mortalidade quando foi utilizada a TF. O reinfarto não-fatal, acidente vascular encefálico e a hemorragia intracraniana foram maiores quando utilizada a TF, enquanto que o choque cardiogênico apresentou menor frequência.

Conclusão: A TF foi mais eficaz no tratamento pré-hospitalar para a redução dos óbitos após cinco anos, entretanto, o reinfarto e o AVE ocorreram de forma semelhante na amostra analisada. O fator tempo reduziu os desfechos clínicos, principalmente quando a terapia implementada ocorreu em até duas horas após a ocorrência do IAMCST. Assim, apesar das intervenções terem apresentado desfechos semelhantes, entretanto, a TF pode representar um tratamento viável em locais onde a ICPP não pode ser alcançada em tempo hábil.

Resumen

Objetivo: Comparar resultados clínicos de fallecimiento, reinfarto y accidente vascular encefálico (AVE) en estudios primarios que analizaron el uso de la terapia fibrinolítica (TF) respecto a la intervención coronaria percutánea primaria (ICPP) para reperfusión miocárdica en pacientes con infarto agudo de miocardio con supradesnivel del segmento ST (IAMCST) en la atención prehospitalaria.

Método: Revisión sistemática de literatura con búsqueda realizada en las bases de datos CINAHL, MEDLINE, PUBMED, *Science Direct*, SCOPUS y *Web of Science* en el período de octubre a diciembre de 2017. Se incluyeron ensayos clínicos aleatorizados, con texto completo disponible, en cualquier idioma, sin recorte temporal. El análisis de elegibilidad se realizó en dos etapas y se aplicó la escala de *Jadad* para una evaluación metodológica de los estudios encontrados.

Resultados: Se incluyeron cinco ensayos clínicos aleatorizados. La TF prehospitalaria presentó índices de mortalidad 30 días después de la intervención semejantes a la ICPP, mientras que en cinco años se encontraron valores menores en la TF. El tratamiento aplicado en un período menor a dos horas desde los síntomas iniciales presentó una relación con la reducción de la mortalidad cuando se utilizó la TF. Los reinfartos no fatales, los accidentes vasculares encefálicos y las hemorragias intracerebrales fueron mayores cuando se utilizó la TF, mientras que los choques cardiogénicos presentaron menor frecuencia.

Conclusión: La TF fue más eficaz en el tratamiento prehospitalario para reducir los fallecimientos después de cinco años, sin embargo, los reinfartos y los AVE ocurrieron de forma semejante en la muestra analizada. El factor tiempo redujo los resultados clínicos, principalmente cuando la terapia implementada ocurrió hasta dos horas después del episodio del IAMCST. De esta forma, a pesar de que las intervenciones presentaron resultados semejantes, la TF puede representar un tratamiento viable en lugares donde la ICPP no puede realizarse a tiempo.

Introduction

Cardiovascular diseases, especially coronary diseases, represent the main cause of morbidity and mortality and disabilities in the global context.[1] Similarly, it is responsible for the death of about 20% of the Brazilian population over thirty years of age, when acute myocardial infarction represents most of these cases.[2,3] Due to the large part of the case in the extra-hospital environment, prehospital care services should be prepared for rapid and accurate diagnosis of cases of patients with ST-Elevation Myocardial Infarction (STEMI), as well as for deciding which reperfusion therapy will be instituted in due course, whether Primary Percutaneous Coronary Intervention (PPCI) or fibrinolytic therapy (FT). Delays in this diagnostic assessment and therapeutic institution have direct relationships with higher mortality rates.[4-6]

It is known that PPCI deals with the preferred method for reperfusion of STEMI, however, due to the few services that offer such a procedure, FT is often the only therapeutic option, especially in underdeveloped countries or in development. Current guidelines point to FT use in cases of non-existence or non-access to the PPCI service. However, FT should be understood as an initial procedure that does not rule out PPCI use.[7]

Logistical and resource constraints often make it impossible to access the PPCI in an appropriate time, offered in a limited way in various regions of the world.[8] The increase in time spent in the decision for therapeutic institution can cause increased myocardial injury and consequently morbidity and mortality.[9,10] Therefore, the proper use of any form of therapy to reperfuse the cardiac musculature is more important than the choice of therapy itself. Delays for effective treatment can be reduced through prehospital FT use.[4-6]

FT is the most easily accessible therapy and its administration can be initiated earlier than PPCI.[4-6] The relative benefit of PPCI on FT is time-dependent and administration in the prehospital context is still scientifically discussed. The ideal reperfusion therapy has stimulated controversy and aroused interests on the part of the scientific community.[11]

In order to elucidate the relevance of FT as an alternative modality to PPCI to attend cases of STEMI, this study aimed to compare the clinical outcomes of death, reinfarction, and stroke in primary studies that assessed FT use in regarding PPCI for myocardial reperfusion in patients with PPCI in prehospital care.

Methods

It deals with a Systematic Literature Review (SLR), conducted and reported in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[12]

Only Randomized Clinical Trials (RCTs), available in full, in any language, that addressed FT use in prehospital care compared to PPCI use as a treatment for myocardial reperfusion in patients with STEMI were included. Editorials, letters to the editor, abstracts, expert opinions, reviews, reviews, books, book chapters, theses, dissertations, monographs and course completion papers that were not available in the article format were excluded published in scientific journals in the databases adopted for search.

The guiding question to achieve the proposed objective was structured through the strategy of the acronym PICO, when they meant: P: patient with PPCI attended by the prehospital service and treated with reperfusion therapy; I: FT; C: Primary Percutaneous Coronary Intervention; O: death, reinfarction, and stroke.[13] The guiding question was: does FT use in prehospital care compared to PPCI use for myocardial reperfusion in patients with STEMI reduce cases of death, reinfarction, and stroke?

An instrument for data collection was elaborated. Article search was carried out from October to December 2017 in the following electronic bibliographic databases accessed by the proxy of the *Universidade Federal do Rio Grande do Norte*: Cumulative Index to Nursing and Allied Heath Literature, (CINAHL). Medical Literature Analysis and Retrieval System Online (MEDLINE), National Library of Medicine (PubMed), Science Direct, SCOPUS, and Web of Science.

Only controlled descriptors and their respective entry terms identified in Medical Subject Headings were used, according to Chart 1.

To perform the searches in the databases, the descriptors of Chart 1 were combined and systematized in two major intersections, namely **#1** A *and* B *and* C *and* E and **#2** A *and* B *and* D *and* E.

Chart 1. Descriptors and respective entry terms of Medical Subject Headings used in crosses to conduct the search for studies

Controlled descriptor	Entry terms
A. Myocardial infarction	infarction, myocardial; myocardial infarctions; heart attack; myocardial infarct; infarct, myocardial.
B. Myocardial reperfusion	reperfusion, myocardial; myocardial reperfusions; coronary reperfusions; reperfusion, coronary.
C. Fibrinolytic agents	thrombolytic agents; thrombolytic drugs; fibrinolytic drugs; antithrombotic agents; antithrombic drugs.
D. Thrombolytic therapy	therapeutic thrombolyses; thrombolyses, therapeutic; therapy, fibrinolytic; fibrinolytic therapies; therapy, thrombolytic; therapies, thrombolytic.
E. Emergency medical services	emergency services, medical; medical emergency service.

Article eligibility was assessed in two stages after search. The first through a screening by reading the titles and abstracts carried out by a pair of independent reviewers. When in doubt, the articles were selected for the next phase. The second stage was eligibility assessment by reading the full manuscript. It was carried out as a way to guarantee the inclusion of the maximum number of studies, the search in the references of the articles previously selected in this phase, as well as in the gray literature on the theme, without including new works that met the pre-established criteria.

Data were extracted and organized using the clinical records and organized in tables and tables. Of the total of 5,207 articles in the initial sample, five were selected for composition of the final sample (Figure 1).

The Jadad Scale was used to assess the methodological quality of RCTs and as a way to minimize the possibilities of bias, composed of three items with dichotomous responses and two sub-items that assess the presence and adequacy randomization and double blinding, in addition to the description of losses and exclusions.[13] The maximum value to be obtained is five points and the study was considered methodological quality from three points. Therefore, all studies in this review scored three and were considered of good methodological quality.

Results

Of the five articles included, one refers to study Strategic Reperfusion Early After Myocardial
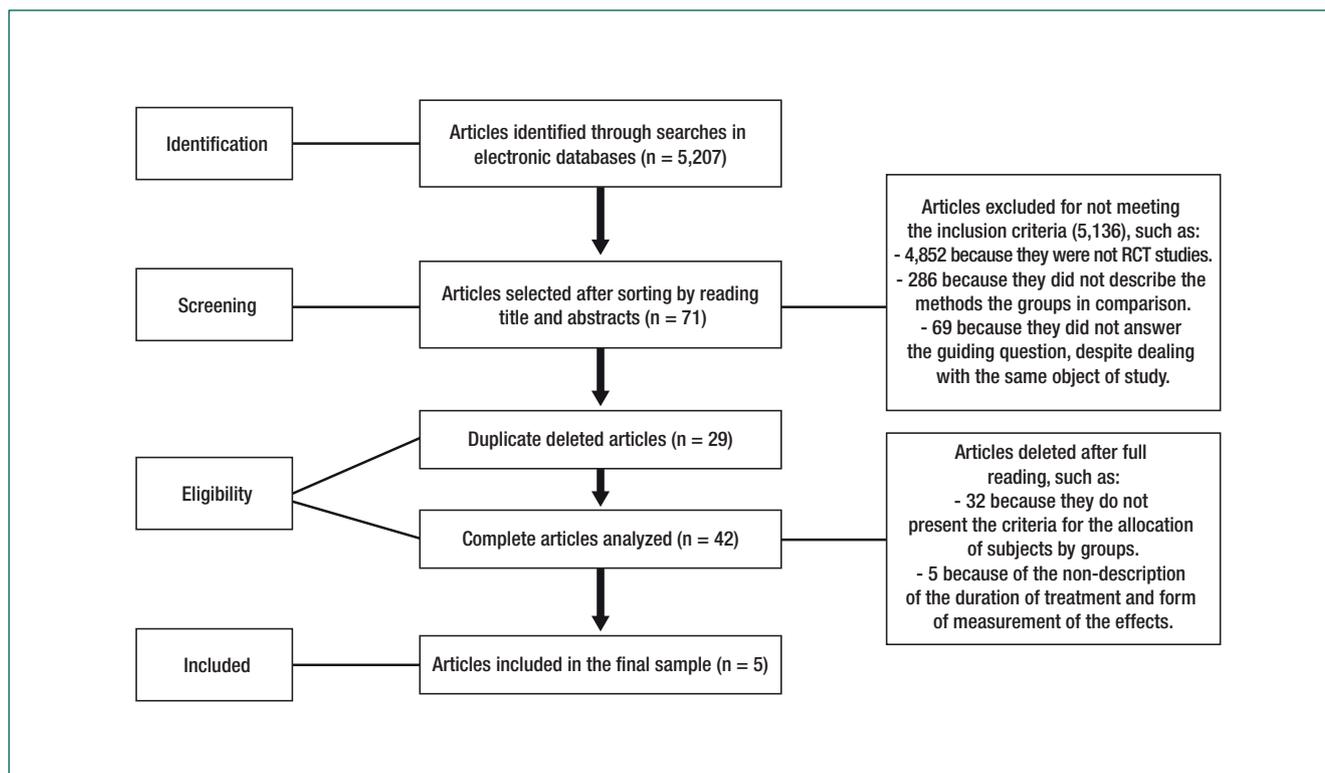
Figure 1. Flowchart of the final sample article selection process

Infarction (STREAM), conducted in Belgium with 30 days of follow-up after treatment. Four referred to the study Comparison of Primary Angioplasty and Prehospital fibrinolysis In acute Myocardial infarction (CAPTIM), performed in France with 30 days follow-up after treatment, except for one with 5 years of follow-up.[14-18] From CAPTIM studies, one was performed with short-term follow-up, another with long-term and two with specific populations by clinical or temporal characteristics.[15-18]

Chart 2 presents the methodological characteristics of the articles, with the respective objectives, main results found and conclusion obtained. The most recent study was the STREAM that used tenecteplase, while in CAPTIM alteplase was administered.

Table 1 shows the clinical outcomes of death, reinfarction, and stroke, which were considered by four of the RCTs within 30 days of therapy. It was observed that death was similar between groups in one year, but in five years the number of deaths was lower in patients undergoing FT, especially when treated in the first two hours.

When patients underwent therapy within two hours of symptom onset, the FT group had fewer deaths, but when treated two hours after the onset of symptoms they presented mortality in five similar years, regardless of the treatment.

As complementary data found by this study, the main adverse effects after reperfusion therapy use adopted by the RCTs analyzed were grouped and described in Table 2 below. Such information allows to complement the implications of the adoption of the modalities compared by treatment modality. Among these adverse effects, hemorrhages were classified differently between studies, when intracranial hemorrhage had a higher incidence in the prehospital FT group, while with cardiogenic shock it occurred in a greater number in the PPCI.

Discussion

Several studies have been found on the therapeutic modalities of myocardial reperfusion to be adopted in cases of STEMI. However, only two large studies, conducted by means of RCTs, were conducted

Chart 2. Characteristics of RCTs and methodological quality of the studies included in the final sample (n=5)

Article	Interventions	Sample/participants per arm	Fibrinolytic therapy used	Time between symptom onset and therapy	Jadad Scale	Objective	Main results obtained	Conclusion
A1[14]	Prehospital FT and PPCI	Sample: 1892 Prehosp FT: 944 PPCI: 948	Tenecteplase	< 3 hours	3	To verify whether prehospital FT is more effective compared to PPCI in patients with early symptoms.	The outcomes of death, shock, CHF or reinfarction at 30 days were slightly lower in those who received prehospital FT (12.4%) when compared to those who used PPCI (14.3%). More intracranial hemorrhages were found in the prehospital FT group than in the PPCI group and the other hemorrhages occurred without difference between the groups.	Prehospital FT resulted in effective reperfusion in patients with STEMI who could not receive primary PCI within one hour after the first contact. Prehospital FT was associated with a slightly higher risk of intracranial bleeding.
A2[15]	Prehospital FT, rescue PCI and PPCI	Sample: 840 Prehosp FT: 419 PPCI: 421	Alteplase	≥ 30 minutes and <6 hours.	3	Check if the PPCI is higher than prehospital FT followed by rescue PCI.	The rate of primary outcomes was 8.2% in the prehospital FT group and 6.2% in the PPCI group. Rescue PCI was performed in 26% of patients who used prehospital FT. There were 16 deaths among patients receiving prehospital FT and 20 among those receiving PPCI.	The PPCI did not present better results of the outcomes death, reinfarction, and stroke when compared to prehospital FT with transfer to an intervention unit for possible rescue PCI.
A3[16]	Prehospital FT, rescue PCI and PPCI	Sample: 840* D: 103 Prehosp FT: 46 PPCI: 57 ND: 731 Prehosp FT: 370 PPCI: 361	Alteplase	≥ 30 minutes and <6 hours.	3	To assess the impact of diabetic status on the relative benefits of reperfusion strategies.	Diabetics had a higher risk, with a higher rate of outcomes death, reinfarction, and stroke (14.6 versus 5.6%) and a high mortality (8.7 versus 3.1%) related to hospital FT use in relation to PPCI, when compared to non-diabetics.	Diabetic patients seen within 6 h after STEMI can benefit from PPCI.
A4[17]	Prehospital FT, rescue PCI and PPCI	Sample: 840 Prehosp FT: 419 PPCI: 421	Alteplase	≥ 30 minutes and <6 hours.	3	To investigate the long-term mortality (5 years) of patients included in the study.	All-cause mortality at 5 years was 9.7% in the prehospital FT group, compared to 12.6% in the PPCI group. For patients seen within two hours, mortality was 5.8% in the prehospital FT group, compared with 11.1% in the PPCI group. In those treated after two hours, the values were 14.5 and 14.4%, respectively.	For patients treated within two hours after the onset of STEMI, five-year mortality was lower than those treated using prehospital FT in general.
A5[18]	Prehospital FT, rescue PCI and PPCI	Sample: 840 Prehosp FT: 419 PPCI: 421 <2 h: 460 ≥ 2 h: 374	Alteplase	≥ 30 minutes and <6 hours.	3	To analyze the effect of treatment instituted with prehospital FT or PPCI due to the time elapsed since the onset of symptoms.	Patients treated up to two hours after symptom onset had lower mortality when treated with fibrinolytic FT compared to those who received PPCI up to 30 days after the event. Those treated after two hours showed no differences for the outcomes of death, reinfarction or stroke by therapeutic modality.	Prehospital FT may be preferable over PPCI for patients treated within the first two hours after the onset of symptoms.

*The clinical picture of six patients was unknown in relation to diabetes; FT - Fibrinolytic Therapy; PCI - Percutaneous Coronary Intervention; PPCI - Primary Percutaneous Coronary Intervention; D - Diabetics; ND - Non-diabetics; CHF - Congestive Heart Failure; STEMI - ST-Elevation Myocardial Infarction.

Table 1. Primary outcomes and median time between the onset of symptoms and therapeutic institution of the studies included in the final sample.

	Death				Reinfarction		Stroke		Median time for treatment (minutes)	
	Prehospital FT		PPCI		Prehospital FT	PPCI	Prehospital FT	PPCI	Prehospital FT	PPCI
A1[14]	Any cause 43/939 (4.6%)	Cardiovascular 31/939 (3.3%)	Any cause 42/946 (4.4%)	Cardiovascular 32/946 (3.4%)	23/938 (2.5%)	21/944 (2.2%)	15/939 (1.6%)	5/946 (0.5%)	100 (75-143)	178 (135-230)
A2[15]	16/419 (3.8%)		20/421 (4.8%)		15/419 (3.7%)	7/421 (1.7%)	4/419 (1.0%)	00 -	130 (95-180)	190 (149-255)
A3[16]	D 6/46 (13%)	ND 9/370 (2.4%)	D 3/57 (5.3%)	ND 14/361 (3.9%)	D 3/40 (7.5%) ND 12/361 (3.3%)	D 3/55 (5.5%) ND 4/346 (1.2%)	D 1/46 (2.5%) ND 3/370 (0.9%)	D 00 - ND 00 -	D: 160 (117.5-225) ND: 155 (115-220)	
A4[17]	1 year 23/419 (5.5%)	5 years 40/419 (9.7%)	1 year 30/421 (7.1%)	5 years 52/421 (12.6%)	N/A	N/A	N/A	N/A	130 (95-180)	190 (149-22)
	5 years < 2 h[1] (5.8%)	5 years > 2 h[2] (14.5%)	5 years < 2 h[1] (11.1%)	5 years > 2 h[2] (14.4%)						
A5[18]	<2h[1] 5/460 (2.2%)	>2h[2] 11/374 (5.9%)	<2h[1] 13/460 (5.7%)	>2h[2] 7/374 (3.7%)	<2h[1] 9/460 (4.0%) >2h[2] 6/374 (3.4%)	<2h[1] 3/460 (1.4%) >2h[2] 4/374 (2.2%)	<2h[1] 3/460 (1.3%) >2h[2] 1/374 (0.6%)	<2h[1] 00 - >2h[2] 00 -	<2 h: 120 (40-260) ≥ 2 h: 225 (120-1275)	

FT - Fibrinolytic Therapy; PCI - Percutaneous Coronary Intervention; PPCI - Primary Percutaneous Coronary Intervention; D - Diabetics; ND - Non-diabetics; 1 - Patients treated within two hours after the onset of symptoms; 2 - Patients treated 2 to 6 hours after the onset of symptoms; N/A - Not Applicable

Table 2. Main adverse events after the institution of reperfusion therapy of the studies included in the final sample (n=5)

Article	Intracranial hemorrhage		Non-intracranial hemorrhage		Severe bleeding		Cardiogenic shock	
	Prehospital FT	PPCI	Prehospital FT	PPCI	Prehospital FT		PPCI	
A1[14]	09/939 (1.0%)	02/946 (0.2%)	266/939 (28.3%)	236/944 (25.0%)	-			
	04/747 (0.5%)[1]	02/758 (0.3%)[1]						
A2[15]	02 (0.5%)	00 -	-	-	02/419 (0.5%)		8/421 (2.0%)	
A3[16]	-	-	-	-	D 00	ND 2/370 (0.6%)	D 00	ND 00
					-		-	-
A4[17]	N/A	N/A	N/A	N/A	N/A			
A5[18]	-	-	-	-	<2h[2] 1/460 (0.4%)	>2h[3] 1/374 (0.6%)	<2h[2] 00	>2h[3] 8/374 (4.4%)

Article	Cardiogenic shock Prehospital FT		Cardiogenic shock PPCI	
A1[14]	41/939 (4.4%)		56/944 (5.9%)	
A2[15]	10/419 (2.5%)		29/421 (7.0%)	
A3[16]	D 3/46 (7.1%)	ND 7/370 (1.9%)	D 6/57 (10.7%)	ND 21/361 (5.9%)
A4[17]	N/A			
A5[18]	<2h[2] 3/460 (1.3%)	>2h[3] 7/374 (3.9%)	<2h[2] 20/460 (8.9%)	>2h[3] 9/374 (4.9%)

FT - Fibrinolytic Therapy; PCI - Percutaneous Coronary Intervention; PPCI - Primary Percutaneous Coronary Intervention; D - Diabetics; ND - Non-diabetics; N/A - Not Applicable; 1 - Adjustment of the dose of fibrinolytics to half in patients over 75 years of age; 2 - Patients treated within two hours after the onset of symptoms; 3 - Patients treated 2 to 6 hours after the onset of symptoms

in a controlled manner to assess the modalities of prehospital FT compared to PPCI, which is why only five publications were included in this review. As a way of didactically organizing the discussion session, it was subdivided into topics that address the discussion of the results related to the therapeutic conduct of reperfusion, the choice of FT, the time to institution of reperfusion therapy, the coronary intervention after prehospital FT, primary outcomes and adverse events after reperfusion therapy use.

Therapeutic approach to myocardial reperfusion

In patients with STEMRI, PPCI is the recommended standard reperfusion strategy, when preferably performed in the first 90 minutes after medical contact.[1] However, most patients do not have access to PPCI, even because of the structure of specific health services available, so this strategy is a major challenge for many countries.[19]

Many regions of the United States of America have access to PPCI, while in Europe prehospital fibrinolytic use is the fastest growing strategy due to its possibility of access in adequate time. In Brazil, services are concentrated in large centers, often in insufficient quantity to serve the entire population and far from the coverage areas.[4] However, there is consensus that emphasis should be placed on timely therapeutic administration of reperfusion therapy rather than the treatment mode itself. [20]

FT presented outcomes similar to PPCI or even higher when administered up to two hours after symptom onset.[18] A great advantage of FT is the possibility of reducing the time for administration through prehospital services, especially in countries where there are few centers capable of performing PPCI, as is the case in Brazil.[4,21,22]

The STREAM study reported the effectiveness of prehospital FT when compared to PPCI, while the CAPTIM study states that it did not find superiority of PPCI.[14] From the CAPTIM advance, similar mortality was found in the period of 30 days after the initial event, but for patients treated within the first two hours of symptom onset, five-year mortality was lower with prehospital FT.[15-17] Early establishment of reperfusion therapy means shorter time of myocardial ischemia, with less extensive lesions, systemic damage of lower repercussion, and cumulative probabilities of increased survival, which confirms that effectiveness of the modality adopted will be time-dependent to reduce negative outcomes and better prognoses.[14-18]

Choose of fibrinolytic drug

FT can be administered in the prehospital or hospital environment when it is most effective if administered within the first few minutes after the onset of STEMI symptoms.[23]

Alteplase consists of a fibrinolytic with high efficacy and safety with a short half-life, which requires complex administration. Tenecteplase is a third-generation fibrinolytic with a longer half-life and higher specificity to fibrin, so it can be administered in single bolus, which makes prehospital administration more safe and agile, in addition to facilitating the reperfusion therapy in prehospital care.[24-26]

The CAPTIM study used alteplase and identified that the time to administer the drug delayed drug reperfusion therapy.[15] Thus, tenecteplase use facilitates administration and optimizes time.

Time to establish reperfusion therapy

The absolute goal of treatment of patients with STEMI is to achieve reperfusion as early as possible, since these treatments are time-dependent.[20] Studies[14-18] showed that the time spent between the onset of symptoms and the institution of reperfusion therapy was shorter when prehospital FT was adopted compared to PPCI. It was also noticed a decrease in the median time when the study showed the population with symptoms up to two hours.

Coronary intervention after prehospital FT

North American and European guidelines indicate that patients undergoing prehospital FT should be referred for angiography within the next six to 24 hours.[4,27] Clinical trials with patients who have been treated with fibrinolytic have shown that angiography routinely performed after drug reperfusion with PCI, if necessary, is associated with a significantly complications with reduced rates of reinfarction.[28-30] In the CAPTIM and STREAM studies, after prehospital FT, patients were referred to centers capable of angiography. Of the population studied, 70.4% and 80.4% of the patients underwent PCI, respectively, which resulted in a high number of patients who required mechanical reperfusion after FT.[14,17] PCI after FT failure due to failure of this therapy was necessary in 40% of diabetic patients, twice as much as in non-diabetic patients, which may indicate a lower efficacy of FT in these patients. This is justified by the fact that they present increased platelet activity and high levels of procoagulants, and consequently a process of compromised fibrinolysis.[16]

Early referral to PCI angiography should be the standard of care after FT in the so-called "pharmacoinvasive" strategy, when necessary. Thus, FT, with subsequent referral to a center capable of performing PCI, can achieve results similar to or higher than the PPCI.[27]

Primary outcomes

For this study, death, reinfarction, and stroke were considered as primary outcomes. Several RCTs presented safety in prehospital FT administration, with time optimization to start reperfusion therapy.[14,15,18,21,31,32] A meta-analysis with RCT pointed out that prehospital administration decreases the risk of death by up to 17% when compared to hospital FT.[33] In a meta-analysis study conducted with 23 RCT, it was found that patients undergoing PPCI had lower rates of nonfatal reinfarction and short-term stroke when compared to patients undergoing FT.[34] Stroke is one of the complications that can happen due to FT use. Independent predictors for stroke when given FT are advanced age, low birth weight, female gender, history of cerebrovascular disease, and both systolic and diastolic hypertension at admission.[35,36] The time between the onset of symptoms and the intervention for myocardial reperfusion also influenced mortality, but not in the occurrence of non-fatal reinfarction and stroke. A higher risk of reinfarction was observed for diabetic patients due to the coronary pathophysiological process.[16]

Adverse events after reperfusion therapy

In relation to prehospital FT, there is a lower risk of cardiogenic shock, however, it is associated with an increased risk for Intracerebral Hemorrhage (HI). This increased risk of HI halved the dose of tenecteplase in patients older than 75 years, which significantly decreased the rate of bleeding in the FT group and led to similar rates between groups.[14] A lower number of non-cerebral hemorrhagic complications and lower blood transfusion were found with tenecteplase use, which has a higher affinity for fibrin and thus lower risk of hemorrhages.[24,27] Cardiogenic shock presents as a complication caused by the STEMI itself in cases of extensive ischemia or mechanical complications and usually occurs in the first 24 hours.[27] A lower number of cardiogenic shock was observed in the population submitted to prehospital FT and time was a protective factor for the occurrence of this condition in the FT group.[14-16]

Conclusion

Prehospital FT administration for patients with STEMI was timely or even superior to PPCI with similar results in benefits, mainly related to mortality. In patients who have received any reperfusion therapy up to two hours after the onset of symptoms, immediate prehospital FT with referral to a center capable of performing PCI may be even more advantageous. Non-fatal reinfarction and HI were more frequent when FT was performed, however, cardiogenic shock occurred in a smaller number. Diabetes patients can benefit from PCI. Prehospital FT is a viable treatment opportunity for regions where PPCI cannot be achieved in a timely manner. It is important that further studies assess and compare the use of these therapies for better understanding and more patients may benefit from their proper and timely use.

Acknowledgments

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