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CLINICAL OUTCOMES OF FIBRINOLYTIC THERAPY FOR PREHOSPITAL TREATMENT OF ACUTE MYOCARDIAL INFARCTION

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Abstract

Fibrinolytic Therapy (FT) is an important form of treatment for cases of Acute Myocardial Infarction (AMI), especially in those places where Primary Percutaneous Coronary Intervention (PPCI) is not available, which is the main form of treatment and can be used even in the prehospital care. Aimed to describe the clinical outcomes of the use of FT in prehospital care for treating patients with AMI. This research covered a total of 53 patients and was carried out from march to october 2017, referring to the care provided from january 2015 to december 2016 in two stages, in which the first occurred with the Mobile Emergency Service (*SAMU*) and Walk-in Emergency Care Units (*UPA*), and the second in the referenced hospital services as gateways to those units. Data were collected from secondary sources. The clinical outcomes of FT considered in the form of absolute and relative frequencies and measures of central tendency were considered. The main signs and symptoms at admission were chest pain (84.62%), sweating (36.54%), dyspnea (26.92%), hypertension (19.23%), nausea (17.31%), malaise (17.31%) and emesis (13.46%). The main characteristic of chest discomfort was chest pain (70.45%). The FT drug administered in all patients was tenecteplase. The median time from symptom-to-door was 180 minutes, while symptom-reperfusion was 300 minutes and door-to-needle 160 minutes. Regarding the outcome, 74.47% had clinical improvement, 19.15% died, 4.25% had refractory AMI and 2.13% had reinfarction. The main characteristic of clinical improvement was the reversal of chest pain (68.57%), characterized as myocardial reperfusion criteria. The present study presented the main outcomes of FT use with improvement of those patients who were treated with it, and shorter times related to chest discomfort and the administration of FT were responsible for increasing the outcomes of clinical improvement and decreasing the outcome of death.

Keywords: Emergency Medical Services. Fibrinolytics. Myocardial infarction. Thrombolytic therapy.

1. Introduction

The treatment of ST-segment elevation acute myocardial infarction (STEAMI) aims at restoring myocardial perfusion that may occur through two interventions: primary Percutaneous Coronary Intervention (PCI) and Fibrinolytic Therapy (FT) (Thygesen et al. 2019).

The therapeutic modality of myocardial reperfusion should be defined according to the patient's clinical conditions and in the shortest time possible so that the morbidity and mortality rates of this population can be reduced (Westerhout et al. 2011; Reddy et al. 2015).

When performed in an ideal working time of up to 90 minutes, primary PCI represents the treatment of choice; however, this strategy is not universally available, since certain regions and even some countries present difficulties of access and to transfer patients to centers capable of performing primary PCI (Westerhout et al. 2011). Thus, FT represents an alternative therapeutic option for acute STEMI treatment indicated for patients who are far from centers that perform primary PCI and do not have imminent risks of bleeding (Widimsky et al. 2010). The principle of early FT use is to approximate the therapy of the patient and to shorten the myocardial ischemia time, with consequent reduction of mortality and of the early and late complications (Reddy et al. 2015).

When used in the prehospital service, FT enables approximating reperfusion therapy with the patient and this pre-hospital phase is the most critical moment, since the time factor is inversely proportional to the size of recovered myocardial area and the number of saved lives (Tubaro et al. 2012).

When considering the possibility of access to prehospital FT and the importance of this treatment in reducing mortality associated with cardiovascular diseases (CVD), this study was carried out with the purpose of describing the clinical outcomes of using prehospital FT for the treatment of patients with acute myocardial infarction.

2. Material and Methods

Study characterization and locations

This work constitutes an epidemiological study implementing a quantitative, observational, descriptive, analytical, individuated approach performed through a sectional design. It was carried out together with a mobile pre-hospital service, called the Emergency Mobile Service (*SAMU*) and fixed services, represented by three Walk-in Emergency Care Units (*UPA*) in northeast Brazil. These are also the hospital services referenced as entrances for the studied units to the amount of eight hospital institutions.

The hospital services received patients referred by the prehospital services for continuity of treatment. All hospitals are located in the city of Natal, capital of the state of Rio Grande do Norte, a large municipality with an estimated population of 884.122 inhabitants (IBGE 2020). Hospital Memorial, Hospital do Coração and Natal Hospital Center are services that assist both privately and to patients affiliated with the National Unified Health System (NUHS). All other services serve exclusively NUHS-affiliated patients. The Hospital Universitário Onofre Lopes is part of the federal assistance network, Dr. Ruy Pereira State Hospital, Monsenhor Walfredo Gurgel Hospital and Dr. José Pedro Bezerra Hospital are part of the state health network in Rio Grande do Norte, while the Hospital Municipal de Natal is part of the municipal care network.

Population and sample

The population of this study was constituted by all medical records of the patients attended by the fixed and mobile prehospital services listed for this study and with a medical diagnosis of STEAMI. The sample was extracted from this population in a census form, composed of all the medical records of the patients with STEAMI who were treated with FT.

The medical records of the treated patients of both genders, of all ages and who were treated with FT were included and non-located patients or those with incomplete, illegible, and inconclusive records for STEAMI diagnosis were excluded.

Clinical outcomes considered for this study were: clinical improvement, reinfarction, refractory AMI and death. Clinical improvement was considered when there was a description of improvement in the clinical picture and/or reversal of the signs and symptoms presented at admission before using FT. AMI which occurred within 28 days after the infarction incident was considered reinfarction, and refractory AMI after 28 days (Piegas et al. 2015). Death was considered when registered by the medical and/or nursing staff.

Data collection

The data collection took place between the months of March and October of 2017 regarding the services performed between January 2015 and December 2016, using an instrument designed specifically for this study, composed of the variables of interest for investigation.

The following sociodemographic variables were considered: age, sex, race, place of residence, educational level, marital status, and occupation. The clinical variables included were: length of stay, the reason for discharge, diagnosis of STEMI, comorbidities, personal history, medications used by the patient, signs and symptoms before FT, drug treatment performed by the pre-hospital service, time of discomfort on admission, characteristics of discomfort, myocardial reperfusion conducts and justification for the choice, time between pain and FT, time between activation of the service and FT, complications after using FT, clinical outcome (clinical conditions after FT) and flow.

Data were collected from secondary sources. The collection was performed in two stages: initially with information being extracted from the records or medical records of the patients served by situated and/or mobile prehospital services (*SAMU* or *UPA*); and then by direct collection in the patient records at the gateway unit(s).

The first stage of the collection was carried out at SAMU and UPA. For all patients who used FT, there was a record in the Pharmacy sector of the respective dispensing services that contained data referring to the identification of each patient, date of care and occurrence, which provided the location of medical or care records. Thus, initially, the patients who used FT were identified by lifting the control of pharmacies and then their respective medical records. At SAMU, the identification of the medical records was carried out by searching the computerized system of the Central Medical Regulation of Urgencies, while in the UPA the medical records were located in the file of each unit. Data collection at the units was carried out through prior contact with the professionals responsible for the sectors and schedule. The medical records were selected based on the inclusion and exclusion criteria adopted and specific instruments were used for each stage.

The second stage of the collection was carried out in hospitals that received patients referred by pre-hospital services (SAMU and UPA) for continuity of treatment. Data were collected from medical records with records from the admission of patients to the outcome at the unit, whether it was discharge, transfer or death. If the patient was transferred to more than one health service, data collection was performed on all those until the outcome was obtained. Data collection was carried out through prior contact with the professionals responsible for the file sector of the medical records of each unit with scheduling and by using a specific form for this stage.

Data analysis and ethical review

Data were organized using Microsoft Excel® 2010. Statistical analysis was performed by Statistics Package for Social Sciences - SPSS® version 20.0. Frequencies and measures of central tendency were used to describe the variables and their distribution patterns.

The Research Protocol of this study was approved in its ethical and methodological aspects by the Research Ethics Committee under opinion number 1,762,797 and CAAE number 59963416.5.0000.5537, according to Resolution no. 466/12 of the National Health Council (*CNS*) of the Health Ministry of Brazil.

3. Results

Ninety-six (96) patient records with STEAMI and use of FT were initially identified, which resulted in a final sample of 53 records being obtained after locating the records in the files and applying the inclusion and exclusion criteria, as shown in Figure 1.

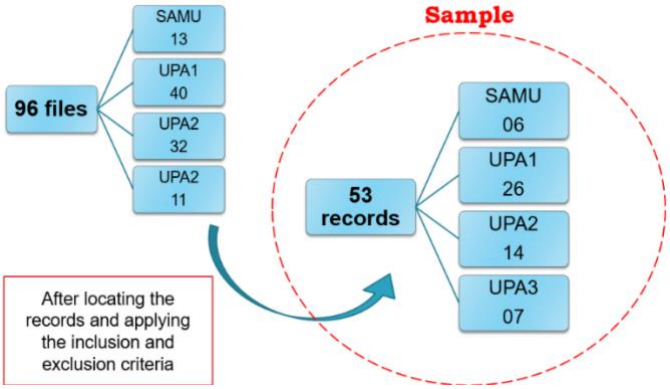

Figure 1. Flowchart of the survey of cases for the final sample.

Several *UPA* medical records were not located due to limitations in the filing system. The reduced number of visits performed by *UPA* 3 is justified by the fact that its operation began in March 2016. Table 1 shows the flow of the patients treated by the prehospital services studied.

Table 1. Flow of patients with STEAMI attended by the prehospital service and transfers by way of the referral service. Natal/RN, Brazil, 2020 (n=53).

Variables	n	%
Flow of patients in the prehospital service		
Discharge	22	41.51
Transfer	20	37.73
Death	07	13.21
No response	04	7.55
Flow of transferred patients (n=20)		
State public hospitals	08	40.00
SUS private hospitals	07	35.00
Federal public hospital	03	15.00
Municipal health services	02	10.00

STEAMI: ST-segment elevation Acute Myocardial Infarction. *SUS*: Brazilian Unified Health System.

Table 2 describes the clinical and demographic characterization of the studied sample and Table 3 shows the therapeutic-care management and clinical outcome of STEAMI cases attended by prehospital health services.

Table 2. Clinical and demographic characteristics of patients with STEAMI treated with FT by emergency pre-hospital services. Natal/RN, Brazil, 2020 (n=53).

Variables	n	%
Gender		
Male	38	71.70
Female	15	28.30
Age		
Up to 58 years	29	54.72
Over 58 years	24	45.28
Comorbidities/Life habits/Personal background*		
Systemic Arterial Hypertension	36	73.47
Diabetes Mellitus	21	42.86
Smoker	20	40.82
Sedentary	17	34.69
Alcohol drinker	10	20.41
Coronary artery disease	10	20.41
Dyslipidemia	08	16.33

Others	21	42.86
Signs and symptoms at admission*		
Chest pain	44	84.62
Sweating	19	36.54
Dyspnea	15	28.85
Arterial hypertension	10	19.23
Nausea	09	17.31
Malaise	09	17.31
Emesis	07	13.46
Others	55	90.38
Characteristics of thoracic discomfort*		
Precordial pain	31	70.45
Irradiation to the upper left limb	10	22.72
Chest pain	09	20.45
Epigastric pain	08	18.18
Burning	04	9.09
Cervical	03	6.81
Insertion	02	4.54
Back	02	4.54
Right chest pain	01	2.27

*Some records did not present data records. Item supports more than one response. STEAMI: ST-segment elevation Acute Myocardial Infarction.

Table 3. Therapeutic-care management and clinical outcome of STEAMI cases attended by prehospital health services. Natal/RN, Brazil, 2020 (n=53).

Variables	n	%
Fibrinolytic therapy		
Tenecteplase	53	100
First-line pharmacological treatment*		
Aspirin	51	96.23
Clopidogrel	47	88.68
Low-molecular-weight heparin	37	69.81
Morphine	32	60.38
Isordil	27	50.94
Oxygen	25	47.17
Captopril	13	24.53
Metoprolol	8	15.09
Propanolol	7	13.21
Others**	39	73.58
Symptom-door time (hours)		
<2 h	9	25
2-6 h	19	52.77
>6 h	8	22.23
Symptom-reperfusion time (hours)		
<3 h	4	13.33
3-6 h	11	36.67
>6 h	15	50
Door-to-needle time		
≤ 30 minutes	4	10
> 30 minutes	36	90
Justification for choosing fibrinolytic therapy		
No vacancy in the hemodynamic service	6	28.57

No vacancy in Intensive Care Unit	6	28.57
Hemodynamics sector was without a doctor	4	19.05
No contact with hemodynamics	2	9.52
Insufficient time for hemodynamics	1	4.76
Recommended fibrinolytic therapy	1	4.76
Hemodynamic care delay	1	4.76
Outcomes	n	%
Clinical improvement	35	74.47
Death	9	19.15
Refractory acute myocardial infarction	2	4.25
Reinfarction	1	2.13

Legend: STEAMI: ST-segment elevation Acute Myocardial Infarction. * Item supports more than one response. **Some charts did not present data records.

The median symptom-to-door time was 180 minutes, while the symptom-reperfusion time was 300 minutes and door-reperfusion were 160 minutes.

Prescription and drug administration records were found that are not established in protocols for patients with STEAMI such as: ranitina, dipyrone, tramal, omeprazole, ceftriaxone, scopolamine, clonazepam, diazepam, insulin, and simethicone, which hypothetically occurred in administering effective drugs for STEAMI.

4. Discussion

The use of FT should be mainly associated with the pharmacological triad - antiplatelet double and heparin, as well as the use of other drugs, according to the patient's clinical condition (Piegas et al. 2015).

In almost all cases, administration occurred with emphasis on the antiplatelet double, as constituted in this study by the use of aspirin and clopidogrel. In the *Clopidogrel in Unstable Angina to Prevent Recurrent Events* (CURE) study, it was reported that clopidogrel is able to reduce outcomes in the STEAMI and randomized clinical trials using clopidogrel and aspirin demonstrated benefits of dual antiplatelet therapy in patients who used FT (Fox et al. 2004).

Similarly, the *Clopidogrel and Metoprolol in Myocardial Infarction Trial* (COMMIT/CCS-2) study, conducted with more than 40,000 randomized patients, was also successful in using the antiplatelet double and treatment with clopidogrel reduced the primary outcome by 9% combination of death, AMI, or Stroke, without increasing bleeding rates (Chen et al. 2005).

The *Assessment of the Safety and Efficacy of a New Thrombolytic Regimen* (ASSENT-3) study was the first large randomized study of more than 6,000 patients comparing the use of Low-molecular-weight-heparin (LMWH) with unfractionated heparin (UFH), and showed that the use of LMWH associated to FT with tenecteplase significantly reduced the relative risk of death, reinfarction or refractory ischemia by 26% in 30 days (ASSENT 2001).

It is important that administration of the antiplatelet double and heparin associated with FT is started as soon as possible, even in the prehospital environment and even before FT (Chen et al. 2005; Steinhubl et al. 2009; Hong 2012).

Most of the patients in the study sample also used adjuvant pharmacology guided by national and international guidelines for treatment of STEAMI, when there is indication depending on the patient's clinical condition, namely: morphine, isosorbide, oxygen, metoprolol, and propranolol (O'Gara et al. 2013; Piegas et al. 2015).

Ischemic time is an important determinant of the size of well-recognized infarct and modulator area in clinical outcomes in patients with STEAMI. This time can be subdivided into symptom-door, symptom-reperfusion, and door-reperfusion times, which is considered as the needle time for FT (Afilalo et al. 2008).

The lack of knowledge by the general population about the signs and symptoms of AMI and the relevance of early treatment is associated with delayed diagnosis and administration of effective AMI therapy, which contributes to the increased morbidity and mortality of the disease (Dracup et al. 2008).

The Strategic Reperfusion Early After Myocardial Infarction (STREAM) is an important multicenter study which compared the strategy of chemical reperfusion with mechanics and presented a median symptom-to-door time of 62 minutes for the FT group, being much lower than that found in this study (Armstrong et al. 2013).

A study that correlated the symptom-to-door time with the left ventricular ejection fraction showed a median time in the patients of 120 minutes and observed a decrease in left ventricular ejection fraction post-infarction, independent of the reperfusion method. It concluded that the reduced symptom-to-door time decreases the risk of left ventricular dysfunction and suggests work in health education for patients at high risk for STEAMI as a strategy to avoid delays in the search for care (Afilalo et al. 2008).

A study carried out to identify the knowledge level about AMI and the attitude towards an emergency situation of a Brazilian population group observed worrisome results related to the lack of knowledge of the signs and symptoms of AMI and the number of the national emergency service and thus the delay in seeking them (Cascaldi et al. 2014).

A study conducted in France also showed a reduction in the time in the same time period from 120 minutes to 90 minutes, and that patients with STEAMI were seeking the service with a time of less than 74 minutes compared to patients who were diagnosed with non-elevated AMI at 105 minutes (Hanssen et al. 2012).

It is important to highlight that the majority of AMI deaths occur in the first hours of disease manifestation, with 40 to 65% in the first hour and approximately 80% in the first 24 hours (Piegas et al. 2015).

Prehospital care aims to reduce the time between the onset of the ischemic event and the effective treatment of myocardial reperfusion, so this service is presented as a facilitating strategy within the care network for patients with AMI.

FT is more effective with shorter ischemia time. Patients who present themselves to the health service within the first hour of symptoms are the ones that most benefit from fibrinolytic therapy, with the possibility of effective reperfusion (Ting et al. 2006).

The STREAM study concluded that when Tenecteplase was administered within the first three hours of symptoms, followed by transfer to a center capable of performing PCI between six and 24 hours, there were higher rates of early reperfusion and minimal elevation of markers of myocardial necrosis when compared to the group which performed primary PCI (Armstrong et al. 2013).

A systematic review with meta-analysis showed that the benefit of prehospital FT may be even more important in the first two hours after the onset of symptoms associated with an improved survival of one year compared to PCI and low rates of intracranial hemorrhage (Roule et al. 2016).

The absolute benefit of primary PCI in relation to FT is reduced in patients with less than two to four hours of discomfort, because FT is more effective the shorter the ischemia time. Thus, the transfer to primary PCI should only be performed at less than 3 hours after the onset of symptoms if the delay time is less than 60 minutes. For patients with more than 3 hours of symptoms, the transfer should be performed if the delay time for primary PCI is below 90 to 120 minutes (Brant et al. 2012).

It is important to note that four patients in the study sample were treated with FT with pain time greater than 12 hours. and two with more than 24 hours. Complications were observed in these patients, such as ventricular tachycardia, massive hemoptysis, death and there was clinical improvement in one of them, but with a 60% diagnosis of coronary obstruction at hospital discharge.

The door-to-needle time has increasingly been shortened and new guidelines present the ideal ten-minute time (Ibanez et al. 2018). The use of Tenecteplase already decreases the onset time of FT due to its single bolus administration.

Door-to-needle time can vary in different regions depending on the health system within the units themselves and flow established in municipalities and states. Understanding which factors directly and indirectly interfere at this time is of fundamental importance for the quality of patient care, as well as for reducing the morbimortality of the population, since time is a greatly important prognosis predictor in the STEAMI.

Factors that explain significant delay in door-to-needle time involve inadequate screening, incorrect initial interpretation of the ECG, accidental discovery of STEAMI, need to investigate the clinical case to rule

out contraindications and delayed preparation of medications, as well as shortage of human resources and service bureaucracy (Loch et al. 2013).

The fibrinolytic therapy used by all patients in this study was Tenecteplase. It is characterized as high biotechnology, with several advantages in effectiveness, safety, and convenience of use. It is more pharmacologically specific and selective to fibrin, it has faster action onset and longer life, which enables single bolus administration (Antman et al. 2008).

Use of bolus fibrinolytic therapy may aid in faster STEAMI treatment due to a reduction in door-to-needle time. There is an advantage of Tenecteplase over other fibrinolytics (Ali et al. 2014).

The use of prehospital FT was associated with a higher clinical improvement rate in the final outcome of patients with effectiveness in its use, and its early administration could still optimize the clinical improvement outcome when performed in up to 3 hours. The STREAM study performed with patients with STEAMI within 3 hours compared the use of FT (Tenecteplase) with primary PCI and the observed results indicated that the groups did not present a statistically significant difference in relation to the primary outcome. A higher rate of early reperfusion was also observed in this study and absence or minimal elevation of necrosis markers in the group that was administered FT (Armstrong et al. 2013).

The CAPTIM study described a greater efficacy of pre-hospital FT (alteplase) associated with shorter STEAMI time, observing that the benefit of fibrinolysis is maximal in the first 2 hours after the onset of symptoms. It demonstrated a 30-day lower mortality with prehospital FT compared to those randomized to primary PCI (2.2% *versus* 5.7%, p=0.05) (Steg et al. 2003).

The myocardial reperfusion criteria after FT administration should be observed with reversal and/or a reduction of at least 50% of ST-segment elevation within 90 minutes (Feldman et al. 2014). Chest pain reversal was observed in 68.57% of patients with clinical improvement, but there was only a reversal of ST-segment elevation in 14.28%, however without detailing the percentage of this reversal, when reperfusion confirmation was confirmed, it gave at least 50% reversal of elevation up to 90 minutes after FT (O'Gara et al. 2013; Piegas et al. 2015).

An outcome of death was higher in women, and this can be attributed to a higher proportion of diabetics and hypertensives in this subgroup. This scenario has also been observed in other studies when identifying that although the STEAMI incidence was lower in women, mortality is approximately twice as high (Iyengar et al. 2013). It is also observed that the TIMI risk score for STEAMI is higher in women (Bagai et al. 2014).

It was found that there were insufficient records of important data such as sociodemographic data related to the clinical picture of the patient, the time in relation to the symptoms, as well as the FT, the diagnosis, the conduct decision to be adopted, the signs and symptoms of myocardial reperfusion and details regarding the clinical picture in the outcome in the unit more clearly in the mobile prehospital service. Another limitation refers to the information bias related to the retrospective study.

5. Conclusions

This study presented the main outcomes of FT use with improvement in the clinical outcomes of the patients who were treated with it. Tenecteplase was the fibrinolytic used by all patients, which generated greater effectiveness in its results since this FT has more specific characteristics to fibrin and greater clinical benefits, in addition to being the medicine established by the National Health Surveillance Agency in Brazil for treating STEAMI in the prehospital environment.

There was an insufficiency of important records, such as sociodemographic data, the patient's clinical condition, the times related to the symptoms, as well as the FT, diagnosis, the decision of the conduct to be adopted, signs and symptoms of myocardial reperfusion and details of clinical condition in outcome in the unit, even more, evident in the mobile prehospital unit. Another limitation refers to the memory bias related to the retrospective study. One must consider the criticality of the study method itself when it was not possible to isolate the variables to demonstrate certain causal relationships.

The shorter times related to chest discomfort and to the FT administration may have been responsible for the increase in the results of clinical improvement and the decrease in the result of death, however, it is necessary to further studies that punctually investigate such an association.

Authors' Contributions: CÂMARA, P.F.M.: conception and design, acquisition of data, analysis and interpretation of data, and drafting the article; FERREIRA JÚNIOR, M.A.: conception and design, analysis and interpretation of data, and drafting the article; VITOR, A.F.: critical review of important intellectual content; SANTOS, V.E.P.: critical review of important intellectual content; FROTA, O.P.: critical review of important intellectual content; CRUZ, G.K.P.: critical review of important intellectual content. All authors have read and approved the final version of the manuscript.

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