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Immediate, mediate and late invasive strategy in non-ST segment elevation acute coronary syndrome

Liliete Caraballoso García[1]✉, MD; Victor J. Caraballoso García[2], MD; Idanis Orea Cordero[2], MD; and Dayma Solís de la Paz[3], MD

[1] Cardiology Department, Hospital Militar Docente Dr. Mario Muñoz Monroy. Matanzas, Cuba.
[2] Surgical Specialties, Hospital Pediátrico Eliseo Noel Caamaño. Matanzas, Cuba.
[3] Rehabilitation and Physics Medicine Department, Hospital Militar Docente Mario Muñoz Monroy. Matanzas, Cuba.

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Acronyms
AMI: acute myocardial infarction
HBP: high blood pressure
NSTE-ACS: non-ST segment elevation acute coronary syndrome

✉ *L Caraballoso García*
Hospital Militar Dr. Mario Muñoz Monroy. Carretera Central km 109, Rpto. 2 de diciembre, CP 40100. Matanzas, Cuba. E-mail address: revista.corsalud@gmail.com

ABSTRACT

Introduction: Non-ST segment elevation acute coronary syndrome (NSTE-ACS) is responsible for 2 to 2.5 million deaths worldwide. The percutaneous coronary intervention is related to better evolution in patients of moderate and high risk; however, there are still doubts about the optimal time to carry out the procedure.
Objectives: To identify the optimal time for the coronary angiography and percutaneous coronary intervention in patients with NSTE-ACS of moderate-high risk.
Method: An observational, longitudinal and prospective study was conducted with 74 patients who were admitted with a diagnosis of NSTE-ACS at the «Instituto de Cardiología y Cirugía Cardiovascular», from January 1, 2011 to December 31, 2013.
Results: A total of 74 patients were analyzed, with a mean age of 69.7±9.56 and a predominance of males (55.4%). There were no discrepancies between the risk factors in each group (p>0.05). The TIMI average was 4.8. Most of patients presented two-vessel disease. The infarct-related artery was mostly the left anterior descending artery. Major events occurred in 8 patients (10.8%), the largest number was observed in the late intervention group. The most frequent minor event was angina, (7 patients), most frequently in the late intervention group. The group with the lowest probability of survival was that of late treatment.
Conclusions: The patients in the intermediate intervention group (between 12 and 24 hours, group B) showed the greatest benefits of the coronary angiography and reperfusion strategy.
Keywords: Acute coronary syndrome, Invasive strategy, Percutaneous coronary intervention

Estrategia invasiva, inmediata, mediata y tardía en el síndrome coronario agudo sin elevación del segmento ST

RESUMEN

Introducción: El síndrome coronario agudo sin elevación del segmento ST (SCASEST) es responsable de 2 a 2.5 millones de muertes en el mundo. El intervencionismo coronario percutáneo se relaciona con la mejor evolución en pacientes de moderado y alto riesgo; sin embargo, aún existe duda sobre el tiempo óptimo de realización del procedimiento.
Objetivo: Identificar el tiempo óptimo para coronariografía e intervencionismo coronario en pacientes con SCASEST de moderado-alto riesgo.

Método: Se realizó un estudio observacional, longitudinal y prospectivo con 74 pacientes que ingresaron con diagnóstico de SCASEST en el Instituto de Cardiología y Cirugía Cardiovascular, desde el 1 de enero de 2011 hasta el 31 de diciembre de 2013.

Resultados: Se analizaron 74 pacientes con una edad media de 69,7±9,56 y predominio del sexo masculino (55,4%). No existieron discrepancias entre los factores de riesgo en cada grupo (p>0,05). El promedio TIMI fue 4,8. La mayoría de los pacientes presentaron enfermedad de dos vasos. El vaso responsable fue mayormente la arteria descendente anterior. Las complicaciones graves se presentaron en 8 pacientes (10,8%), en el grupo de intervención tardía se observó la mayor cantidad. La complicación menor más frecuente fue la angina (7 pacientes), con mayor frecuencia en el grupo de intervención tardía. El grupo con menor probabilidad de supervivencia fue el de tratamiento tardío.

Conclusiones: Los pacientes del grupo de intervención mediata (entre 12 y 24 horas, grupo B) mostraron los mayores beneficios de la estrategia de coronariografía y reperfusión.

Palabras clave: Síndrome coronario agudo, Estrategia invasiva, Intervencionismo coronario percutáneo

INTRODUCTION

The World Health Organization (WHO) predicts that, by 2020, cardiovascular diseases will be responsible for 11.1 million deaths worldwide; among them, the coronary artery disease is the most common manifestation and has a high morbidity and mortality[1,2].

Identifying patients who have an acute coronary syndrome, including many with suspected cardiac pain, poses a diagnostic challenge, especially in cases where there are no clear symptoms or electrocardiographic findings. Despite modern treatments, the rates of death, acute myocardial infarction (AMI) and re-admissions continue to be high[3,4].

Pathological, angioscopic and biological observations have shown that the breakdown or erosion of the atherosclerotic plaque, with varying degrees of thrombotic complications and distal embolization, leading to a myocardial hypoperfusion, are the basic initial mechanism in most patients[4]. The average age of those who present this clinical picture is 65.8 years in men and 70.4 in women, and 43% belong to the female sex.

The term "acute coronary syndrome" is an operational and useful name to refer to a group of symptoms and signs that are compatible with the acute myocardial ischemia and includes the ST segment elevation acute coronary syndrome (STE-ACS) and the binomial, AMI without ST segment elevation and unstable angina; these last two components, with the name: non-ST segment elevation acute coronary syndrome (NSTE-ACS)[5-7].

The NSTE-ACS represents a set of symptoms and signs, usually produced by the atherosclerotic disease and associated with an increased risk of death or AMI. Its spectrum is defined by consistent electrocardiographic changes in the ST segment depression or prominent or inverted T waves, or positive necrosis biomarkers in the absence of ST segment elevation and with an appropriate clinical picture (typical chest pain or ischemic equivalents)[8].

The NSTE-ACS is responsible for 3.5 to 4 million hospital admissions worldwide annually[8,9]. In Cuba, it occupies the third position in the direct causes of death due to ischemic heart diseases[6].

Since the NSTE-ACS is a clinical syndrome rather than a specific disease, an etiological approach has been proposed. There are five pathophysiological processes that contribute to its development: 1) rupture or erosion of an atherosclerotic plaque with superposition of a non-occlusive thrombus (the most frequent cause); 2) dynamic obstruction or spasm of an epicardial coronary artery; 3) progressive mechanical obstruction, 4) inflammation, infection or both; 5) secondary unstable angina, due to the increased myocardial oxygen demand or decreased of oxygen supply to the myocardium (e.g., anemia). Patients may present one, or simultaneously, several of these processes as the cause of their event[10,11].

The immediate objectives of the treatment of these patients, even nowadays, are aimed at pain relief, prevention of AMI and death, by stabilizing the thrombotic process and coronary lesion, treating residual ischemia and applying preventive secondary measures. The antithrombotic therapy is used to prevent a new thrombosis, for facilitating endoge-

nous thrombosis and decrease the degree of stenosis, and it should be continued long term to reduce the occurrence of future complications and progression to complete occlusion. The coronary revascularization should be performed when there is significant stenosis (>70%) of the responsible artery[8]. Therefore, the current debate would focus on when to perform cardiac catheterization y revascularization to the patient[11-15].

Early coronary intervention relates to improved outcomes in patients with moderate and high risk NSTE-ACS[5]; however, there still remains the question about the optimal time for performing this procedure. On one hand, the realization of early intervention and will prevent the ischemic events that may develop while the patient is treated with drugs and waits for late procedure; secondly, maintaining intensive medical treatment, delaying the intervention days can decrease complications related to the procedure, by allowing to act on a plate and a stable patient[5].

For these reasons, it was decided to conduct this research in order to identify the optimal time for coronary angiography and coronary intervention in patients with NSTE-ACS of moderate-high risk.

METHOD

An observational, longitudinal and prospective study was conducted with 74 patients, who were admitted with a diagnosis of NSTE-ACS at the *Instituto de Cardiología y Cirugía Cardiovascular,* from January 1, 2011 to December 31, 2013.

The study population consisted of all patients of both sexes and over 18 years of age, who came with precordial pain to the Emergency Department of the *Instituto de Cardiología y Cirugía Cardiovascular* of Havana, Cuba, consecutively. Those who were diagnosed with NSTE-ACS (population), defined according to the clinical practice guidelines[4,5], were applied the TIMI risk score [10,11] by medical researchers.

The variables studied were: age ≥ 65 years, three or more risk factors, aspirin use in the previous seven days, known coronary artery disease (stenosis ≥ 50%), recent angina (in the last 24 hours), elevated cardiac markers and ST segment deviation ≥ 0.5 mm.

Definition of risk

Patients with a score of 0 to 2 points were considered low risk; of 3 or 4 points at risk, and 5 to 7 points high risk.

Definition of the study sample

The sample consisted of 74 patients with 3 or more points on the TIMI risk score or presence of hemodynamic or electrical instability, although the application of the TIMI risk score was lower than 3 points.

The presence of hemodynamic instability was considered to the finding of sustained arterial hypotension and of difficult control, with systolic pressure less than 90 mmHg or the need for pharmacological support to maintain the pressure or the cardiac output. Moreover, the occurrence of rhythm disturbances in the electrocardiogram, that might endanger the patient's life, was taken into account as electrical instability: supraventricular tachycardia, sustained ventricular tachycardia or not, and ventricular fibrillation.

A randomization was performed through a computer program, which divided the patients into three groups. A first group (A, comprised of 23 patients) received the interventionist strategy as soon as possible upon arrival at the emergency department and the onset of symptoms (immediate strategy) and before 12 hours of the onset. A second group (B, 26 patients) was assigned to receive the interventional strategy in a time window between 12 and 24 hours from the onset of symptoms (mediate strategy). The group assigned to late interventional treatment (C, 25 patients) underwent diagnostic coronary angiography after 24 hours of the onset of symptoms and no time limit (late strategy).

The follow-up was maintained by external consultation for six months.

Processing of information

The instrument for collecting the information was a survey, specially prepared for the research, to be filled out by the medical researcher. The data obtained by quantitative techniques were captured from the collection documents and transferred to a database programmed in Microsoft Excel 2010. The processing was developed using the statistical package SPSS version 19.0 for Windows. This included the calculation of absolute, relative frequencies and other summary measures. The statistical significance was defined by a bilateral value of $p < 0.05$.

The resources of the inferential statistics to be used depended on the type and number of variables. The information was presented in tables and graphs, as applicable. The quantitative variables were presented as mean ± standard deviation and were analyzed by the variance analysis technique. The categorical variables were compared using the

Chi squared and the Fisher's exact test.

The multivariate analysis was performed trough the logistic regression method. Cumulative survival curves, through the Kaplan-Meier methods, were developed and the groups were compared using the log-rank tests and the Breslow's.

Ethics

The study was carried out in accordance with existing regulations and ethical principles for human research and clinical studies. No ethical principle was infringed. Informed consent was requested from all patients and when this was not possible due to their clinical state, it was confirmed by a family member, always explaining to him/her the benefits and risks of the research, as well as its purposes; data confidentiality is guaranteed. Patients were able to ask all the questions they considered necessary and all their doubts were clarified. They, in turn, had the right not to sign the consent, in which case it did not influence in any way the selection of the most appropriate therapeutic strategy.

RESULTS

The study included a total of 74 patients, randomized to 23 in the immediate treatment group, 26 in the medium treatment group and 25 in the late treatment group. The mean age was 69.7±9.56 years. There was a predominance of males (55.4%) and the distribution of sex between the mediate, immediate and late groups was proportional, with a greater representation of men in the immediate and mediate groups, and superiority of women in the late group, although the difference was not significant (**Table 1**).

The most frequently risk factors found (**Table 2**) were high blood pressure (89.2%), which reached 100% in the late treatment group, followed by smoking (64.9%) and hyperlipidemia (51.4%). It is important to note that 31.1% of these researched patients had diabetes mellitus.

The average TIMI score, through which patients were distributed into each of the treatment groups, was 4.8±1.27 in the immediate group; 4.8±1.13 in the mediate group and 4.8±1.16 in the late group, with a total average of 4.8±1.17, similar for all groups (**Table 3**).

There was a predominance of type C coronary lesions (43.5%) and the immediate and mediate (38.5%) groups, while the B1 predominated in the late treatment group (40.0%) (**Table 4**). Type C lesions were predominant in all groups (35.1%), without finding statistically significant differences.

Regarding major adverse events throughout the follow-up and in general, the combination of death, NSTE-ACS and stroke occurred in eight patients (10.8% of the total), throughout the evolution of the study (**Figure 1**). The late intervention group was the one with most complications (20%), while they were lower in the immediate (8.6%) and mediate (3.8%)intervention groups, with statistically significant difference (p=0.049).

The minor events (combined angina, new NSTE-ACS and bleeding) took place in 6.1% of patients in the study (**Figure 2**) and they were represented mainly by the late intervention group, where 14% presented some of the events considered minor during the 6 months of follow-up (p<0.05).

Table 1. Distribution of patients according to age, sex and intervention time.

Demography	Intervention time						Total (n=74)	
	Immediate (n=23)		Mediate (n=26)		Late (n=25)			
	Nº	%	Nº	%	Nº	%	Nº	%
Male	14	60.9	16	61.5	11	44.0	41	55.4
Female	9	39.1	10	38.5	14	56.0	33	44.6
Age (years, $\bar{\chi}$ ± SD)	70.7±9.81		68.7±9.56		69.9±9.57		69.7±9.56	
IC 95%	66.50; 74.98		64.85; 72.61		65.93; 73.83		67.53; 71.96	

F=0.268; p=0.766
SD, standard deviation

Table 2. Distribution of patients according to type of risk factors, history and intervention time.

Risk factor/PPB	Intervention time						Total (n=74)		p
	Immediate(n=23)		Mediate (n=26)		Late (n=25)				
	Nº	%	Nº	%	Nº	%	Nº	%	
Ischemic heart disease	9	39.1	14	53.8	13	52.0	36	48.6	0.541
High blood pressure	19	82.6	22	84.6	25	100	66	89.2	0.099
Smoking	16	69.6	18	69.2	14	56.0	48	64.9	0.521
Hyperlipidemia	11	47.8	12	46.2	15	60.0	38	51.4	0.564
Diabetes mellitus	6	26.1	8	30.8	9	36.0	23	31.1	0.759
Obesity	14	60.9	14	53.8	7	28.0	35	47.3	0.053
CHF	1	4.3	3	11.5	1	4.0	5	6.8	0.483
Previous PTCA	3	13.0	5	19.2	6	24.0	14	18.9	0.617
Previous coronary surgery	0	0	3	11.5	2	8.0	5	6.8	0.131

CHF, congestive heart failure; PPB, personal pathological background; PTCA, percutaneous transluminal coronary angioplasty

Table 3. Distribution of patients according to TIMI score and intervention time.

TIMI	Intervention time						Total	
	Immediate		Mediate		Late			
	Nº	%	Nº	%	Nº	%	Nº	%
Medium risk	11	47.8	10	38.5	13	52.0	34	45.9
High risk	12	52.2	16	61.5	12	48.0	40	54.1
Total	23	100	26	100	25	100	74	100
$\bar{\chi}$ ± standard deviation	4.8±1.27		4.8±1.13		4.8±1.16		4.8±1.17	
IC 95%	4.28; 5.37		4.35; 5.26		4.32; 5.28		5.54; 5.08	

F=0.003; p=0.997
CI, confidence interval

Table 4. Distribution of patients according to type of lesion and intervention time.

Type of lesion	Intervention time						Total	
	Immediate		Mediate		Late			
	Nº	%	Nº	%	Nº	%	Nº	%
A	6	26.1	3	11.5	6	24.0	15	20.3
B1	3	13.0	5	19.2	10	40.0	18	24.3
B2	4	17.4	8	30.8	3	12.0	15	20.3
C	10	43.5	10	38.5	6	24.0	26	35.1
Total	23	100	26	100	25	100	74	100

$\bar{\chi}$ = 9.311; p=0.157

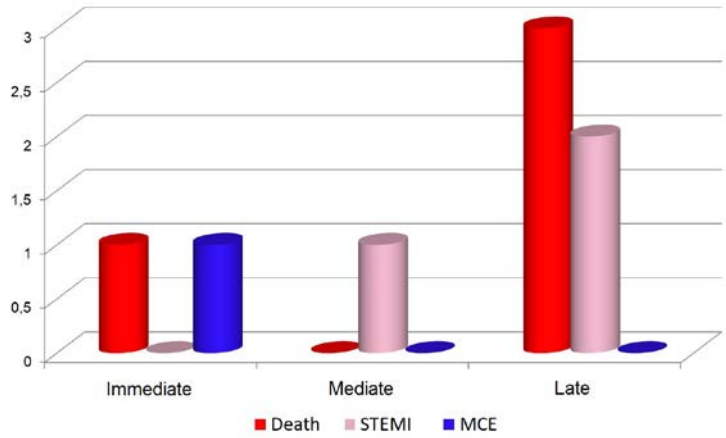

Figure 1. Distribution of patients by occurrence of major adverse events and intervention time (p=0,049). MCE, major cerebrovascular event; STEMI, ST segment elevation myocardial infarction.

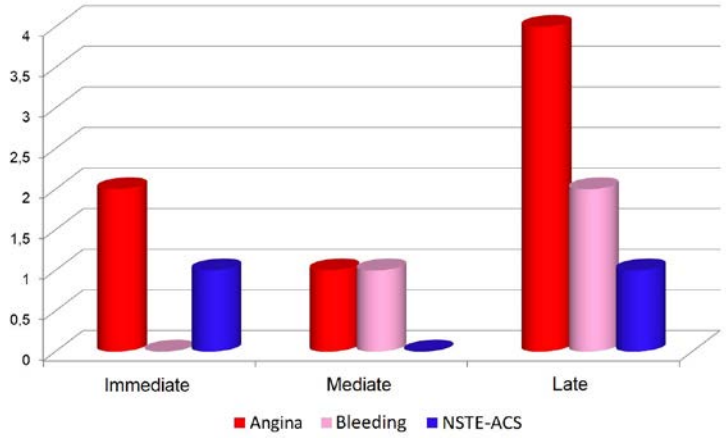

Figure 2. Distribution of patients according to the occurrence of minor events and intervention time. NSTE-ACS, Non-ST segment elevation acute coronary syndrome.

When analyzing the survival of the study in the Kaplan-Meier curve, a higher probability of survival of the patients was obtained in the group of mediate treatment (group B). The group with the lowest probability of survival in the evolution was the one of late treatment, where an abrupt drop in the survival curve was observed at the time of admission and after a month, with a tendency to flatten the curve later in the evolution (**Figure 3**).

DISCUSSION

The study of acute coronary syndromes has generated multiple research that have led to a heterogeneity of results, especially in terms of the way to approach it and the appropriate therapy. However, the incidence, clinical and demographic characteristics of the patients and the principal laboratory findings are quite similar[16].

Age is one of the most important factors for assessing the risk of both hospital mortality and follow-up, which is why it is included in the most significant risk prediction models published and endorsed, such as GRACE (Global Registry or Acute Coronary Events) and the TIMI (Thrombolysis in Myocardial Infarction)[10,11]. The risk of coronary heart disease increases exponentially with the years of life in both sexes.

According to Williams *et al*[8], and in the CURE study, was observed an average age of 64 years and 38.7% of patients were women, similar to the RITA 3[9] study, where the average age was 63 years. In more recent studies that researched treatment strategies in NSTE-ACS, the average age has varied in the range from 60 to 65 years and in all, the male sex predominated, the same result as in this research. In the ISAR-COOL[12] study, men also predominated (66.9%) with an average age of the research subjects of 70 years, similar to the sample of this study.

In men, the occurrence of manifest heart disease takes place early, when compared to women, although in later ages they are equated, and even women can overcome the incidence of cardiovascular diseases after the seventh decade of life[17]. It has been demonstrated that in this sex, there is a diagnostic approach and a less aggressive therapeutic management[18-20].

Regarding the age of presentation and the distribution of sex, the data found are similar to the present research.

The high blood pressure represents, by itself, a vascular risk factor, a contributor to the appearance of ischemic heart disease as a form of coronary heart disease. As the blood pressure levels increase, the vasodilator capacity is lost and the vasoconstrictor is activated. Thus, a normal endothelium becomes a dysfunctional one, which above having abnormal muscle tone will show a series of structur-

al changes that lead to high blood pressure and atherosclerosis[21,22]. In our study, it was observed as the risk factor with the highest prevalence. Other studies have evidenced variable percentages, in one of them was found that 60% of patients with NSTE-ACS suffered from high blood pressure (HBP)[21]; while other studies have found prevalence ranging between 60% and 65%, another research found a prevalence of 70% among their patients[22].

The data of the present research show a somewhat higher prevalence of HBP than most of the referred studies; it is only comparable with one of them, this could be related, first of all, to the fact that the patients of this sample present a picture of cardiovascular disease of high risk and represent a population with a very high level of possibility of presenting it; and secondly, that the HBP in our country is in a high prevalence up to 208 per 1 000 inhabitants[6], hence, it occupies one of the first places worldwide.

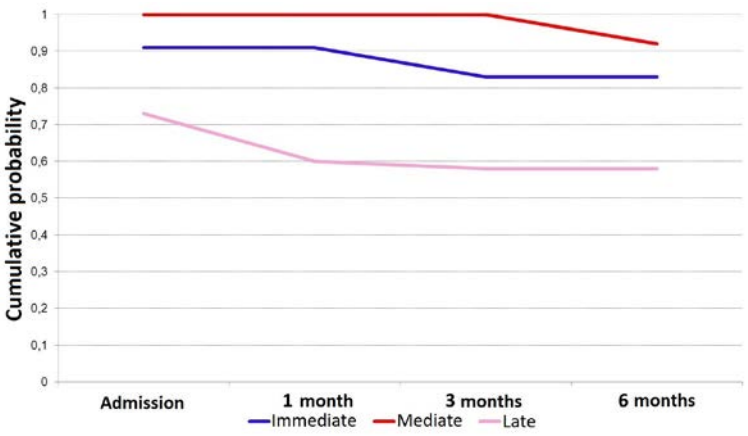

Figura 3. Probability of survival free of major adverse events up to six months, depending on the moment of follow-up and time of percutaneous coronary intervention.

Smoking is one of the most important risk factors in cardiovascular disease, it is considered a progressive multisystem damage syndrome and it has been defined as a chronic disease, with a tendency to relapse[23]. Carbon monoxide and nicotine components are the most studied and both have deleterious effect on systolic pressure and heart rate by sympathetic effects of nicotine, which increases the oxygen demand and, on the other hand, it decreases transport due to increased carboxyhemoglobin[23].

The carbon monoxide has a direct atherogenic effect, reduces tissue oxygenation, triggers platelet activation, increases the adhesion and causes damage to the vascular endothelium, which promotes atherogenesis[23,24]. In this study, a high percentage of smokers was found in the sample, which coincides with the bibliography consulted[23-25].

The coronary atherosclerosis is the most frequent underlying element of the clinical manifestations of ischemic heart disease. The etiology of this process is multifactorial, it is the result of the interaction of a predisposing genetic load and environmental factors, and it is intimately related to lifestyle[1-3].

Among diabetics, macrovascular complications, which include ischemic heart disease, stroke and peripheral vascular disease are major causes of morbidity and mortality [25,26]. The type 2 diabetes produces a series of metabolic disorders supporting an imbalance in the coagulation/fibrinolysis system causing the formation of clots and their stability[24,27]. Diabetic patients have high levels of fibrinogen[27] and the plasminogen activator inhibitor-type 1, both in plasma and in skin lesions; they also have an abnormal platelet function. These anomalies can contribute to giving more weight to the risk of complications caused by atherosclerosis[24,28].

Two studies showed a similar result of up to 22% of the presence of diabetes mellitus in their results[25,26]. In other studies, this risk factor has been found between 23% and 25%[29]. The Euro Heart Survey[30] has revealed that 37% of patients with NSTE-ACS had known or recently diagnosed diabetes. As can be observed, the findings of this research are not in disagreement with the literature reviewed.

The GRACE[10] model is the one that provides the greatest fidelity in the prediction of events at the time of evaluating cardiovascular risk to indicate treatment, but its use is more complex since it requires the implementation of a computer, while the TIMI[10,11] can be easily used at the bedside of the patient. This was derived from the multivariate analysis in TIMI 11B. Besides the risk stratification of these patients, it predicts the benefit of early use of therapeutic measures such as: low molecular weight heparin, blockers IIb/IIIa and performing invasive approach in those at high risk[31]. In this study, the average of the TIMI score was similar for all groups, that is, there was homogeneity among them, which is relevant when analyzing the results achieved; however, the TIMI 18[31,32] study showed that 60% of patients were in a scale according to this intermediate risk of this score.

The analysis of the variables considered as seri-

ous complications in the research conducted found a net mortality of 2.7% (4 patients). The TRUCS[14] study distributed patients to receive an interventional strategy within the first 24 hours or to medical treatment and coronary angiography and coronary intervention after six days. The difference in results between the two groups was significant in favor of early interventionism. The events of the termination variable in the groups at twelve months of follow-up were 7.9% for early interventionism and 16.7% for late interventionism. This research showed that the performance of relatively early coronary interventionism offers important advantages to patients.

It is interesting to show that the benefit of the invasive strategy is more evident in patients at higher risk. On the other hand, those with low risk showed no benefit with this type of strategy. These data are consistent with the research conducted, where a benefit of early invasive strategy in patients at high risk was observed, but the completion time of early procedure does not match the TACTICS-TIMI[11] study.

In our study, which coincides with the above results, severe and minor complications take place more often in group C, followed by group A; it is thought that this could happen because the patients in this study were all considered at high and moderate risk, with a TIMI score, on average, high. There were no low risk patients, unlike the rest of the research analyzed[11,22]; therefore, they were patients with a high probability of ischemic complications. In group C, patients were expecting more than 24 hours for conducting the interventional procedure, that although it is within the times discussed in much of the bibliography reviewed, it is still considered long and gave the possibility of increasing the observation of adverse events.

Although severe complications are left on the edge of the possibility of statistical significance, it was considered that there is a trend towards significant difference. Moreover, the authors reflect about that, although the statistical significance is important, the clinical significance could be taken into account in this case, because it shows the occurrence of more severe complications in the late group, although the number of patients in this study is considered small and perhaps this difference is more visible with an increase in the number of patients.

Likewise, the combination of minor events showed great statistical significance, with most events found in group C, followed by group A, which strengthens the idea that in group C, the waiting time for the realization of angiographic and revascularization procedure was harmful.

According to several studies[22], the benefit of early intervention in NSTE-ACS is directly related to the risk assessment and the magnitude of the clinical benefit, with difference in catheterization times in the different strategies. The early interventionism is not better than late one in preventing death, it has a small effect in the reduction of infarction and a modest reduction in episodes of ischemia[22,31]; but the urgent intervention appears to be preferable in patients at very high risk, while in other situations, it must be evaluated individually for each case.

These data coincide with the research carried out, where the delay in the application of the interventionist treatment brought with it the presence of complications, while a very rapid intervention, although it was better than a delayed one, did not show significant differences with the application of the interventional therapy in an intermediate period.

CONCLUSIONS

The patients of the intermediate intervention group (between 12 and 24 hours, group B) showed the greatest benefits of the coronary angiography and reperfusion strategy.

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