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Original Article

Dual antiplatelet therapy in patients with ST-segment elevation acute myocardial infarction and thrombolytic treatment

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Acronyms
ACS: acute coronary syndrome
AMI: acute myocardial infarction
STEMI: ST-segment elevation acute myocardial infarction

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ABSTRACT

Introduction: Acute coronary syndromes are usually due to plaque rupture, platelet activation, and thrombus formation leading to coronary occlusion and myocardial injury. The use of acetylsalicylic acid, clopidogrel and low molecular weight heparin have reduced the risk of death, myocardial infarction and ischemia recurrence

Objective: To describe the clinical course and benefits of dual antiplatelet therapy associated with thrombolytic therapy in patients with ST-segment elevation acute myocardial infarction (STEMI).

Method: A descriptive, cross-sectional, non-randomized, multicenter study was performed between October 2012 and December 2014 at the Intensive Care Units from Arnaldo Milián Castro, Celestino Hernández Robau and Placetas University Hospitals in Villa Clara, Cuba. The study population consisted of 86 patients divided into study and control groups, who met the inclusion criteria.

Results: STEMI was more frequent in males and between 70-75 years. Most frequent risk factors were smoking and hypertension in 57.0% of patients in both groups. The anterior wall location presented more complications; patients with inferior location of the infarction were the most benefited with dual antiplatelet therapy. It was found in the study group that the earlier the treatment, the better the evolution and the lower the in-hospital mortality.

Conclusions: Dual antiplatelet therapy in patients with STEMI, receiving thrombolytic therapy, decreased ischemic complications frequency.

Key words: Platelet aggregation inhibitors, Fibrinolytic Agents, Myocardial Infarction, Clinical evolution

Doble antiagregación plaquetaria en pacientes con infarto agudo de miocardio con elevación del segmento ST y tratamiento trombolítico

RESUMEN

Introducción: Los síndromes coronarios agudos suelen deberse a la rotura de una placa, la activación plaquetaria y la formación de un trombo que conducen a oclu-

sión coronaria y lesión miocárdica; el uso del ácido acetilsalicílico, clopidogrel y heparina de bajo peso molecular han reducido el riesgo de muerte, infarto de miocardio y recurrencia de la isquemia.

Objetivo: Describir la evolución clínica y los beneficios de la doble antiagregación plaquetaria asociada al tratamiento trombolítico en pacientes con infarto agudo de miocardio con elevación del segmento ST (IAMCEST).

Método: Se realizó un estudio descriptivo, transversal, contrastado, no aleatorizado, multicéntrico, en el período de octubre de 2012 a diciembre de 2014, en las Unidades de Cuidados Intensivos de los Hospitales Universitarios Arnaldo Milián Castro, Celestino Hernández Robau y Placetas, en Villa Clara, Cuba. La población de estudio estuvo conformada por 86 pacientes divididos en grupo estudio y control, que cumplieron con los criterios de inclusión.

Resultados: El IAMCEST fue más frecuente en los pacientes del sexo masculino y entre los 70-75 años. Los factores de riesgo más frecuentes fueron el hábito de fumar y la hipertensión arterial en el 57,0% de los pacientes de ambos grupos. La localización de cara anterior presentó más complicaciones, los pacientes con localización inferior del infarto fueron los más beneficiados con la terapia antiplaquetaria dual, y en el grupo estudio se constató que a mayor precocidad del tratamiento mejor evolución y menor letalidad intrahospitalaria.

Conclusiones: La doble terapia antiplaquetaria en pacientes con IAMCEST que reciben tratamiento trombolítico disminuyó la frecuencia de complicaciones isquémicas.

Palabras clave: Inhibidores de agregación plaquetaria, Fibrinolíticos, Infarto de miocardio, Evolución clínica

INTRODUCTION

Acute coronary syndromes (ACS) are usually due to plaque rupture, platelet activation, and thrombus formation leading to coronary occlusion and myocardial injury. Knowing its pathophysiology has led to the development of highly effective antithrombotic strategies which have reduced the risk of death, infarction and recurrent ischemia[1]. Antithrombotic therapy in ACS context includes 3 components: 1) antiplatelet therapy for reducing platelets activation/aggregation and thrombus formation after plaque rupture, including drugs such as: aspirin, clopidogrel, prasugrel, ticagrelor and glycoprotein (GP) IIb/IIIa inhibitors; 2) anticoagulant therapy including unfractionated heparin and low molecular weight heparin, and 3) fibrinolytic substances used for thrombus lysis including streptokinase and tissue plasminogen activator, among others.

It is important considering that the benefits obtained with fibrinolytic therapy are often limited by inadequate reperfusion or reocclusions that occur later in these patients, hence the important role of both antiplatelet agents and anticoagulants for acute myocardial infarction (AMI) treatment, which have a more proactive influence in preventing complications and death derived from these[3].

Aspirin acts on cyclooxygenase 1, inhibits thromboxane A_2 formation and induces permanent inhibition of platelets function, so it is not only useful for primary prevention of vascular events, but is also effective throughout ACS spectrum and is part of the initial treatment strategy in ST segment elevation acute myocardial infarction (STEMI) suspected patients[4]. Platelet adenosine diphosphate (ADP) inhibitors, clopidogrel, prasugrel and ticagrelor, have a strong synergistic effect with aspirin. Clopidogrel selectively inhibits ADP platelet receptor binding and subsequent GP IIb-IIIa complex activation, mediated by ADP, thereby inhibiting platelet aggregation. This drug irreversibly modifies ADP platelet receptor and thus, exposed platelets are affected throughout their lifespan[5].

STEMI lethality varies between 6-14% and is influenced by many factors, including: age, Killip class, delayed treatment, type of treatment, previous history of AMI, diabetes mellitus, kidney disease, as well as the number of coronary arteries affected and ventricular ejection fraction[6]. Several studies have

found a lethality decrease associated with myocardial infarction when using dual antiplatelet therapy[6,7], so there are strong reasons to support the routine use of clopidogrel added to aspirin as an adjunct to lytic treatment.

Ischemic heart disease is the second cause of death in Villa Clara, only preceded by malignant neoplasias, so it was decided to carry out this research to describe the behavior of dual antiplatelet therapy as adjunctive therapy to thrombolytic treatment in STEMI patients admitted to Intensive Care Units.

METHOD

A descriptive, comparative, cross-sectional, non-randomized, multicenter study was performed from October 2012 to December 2014 at the Intensive Care Units of *Arnaldo Milián Castro*, *Celestino Hernández Robau* and *Placetas* Hospitals, in the province of Villa Clara, Cuba.

Study population

All patients admitted to the hospital's Intensive Care Units, with a STEMI diagnosis, who received thrombolytic treatment, regardless of the place where it was applied, were studied.

Inclusion and exclusion criteria

All patients younger than 75 years, with a (clinical, electrocardiographic and enzymatic) unequivocal diagnosis of STEMI, with antiplatelet therapy were included.

Those at risk for major bleeding, with chronic liver disease, histories of bleeding diathesis, pregnancy and puerperium, and who had received thrombolytic treatment more than 12 hours in advance were excluded.

Groups

Patients were divided into two groups. The study consisted of 43 patients, who were given, after thrombolysis, an initial dose of 300 mg clopidogrel, associated with 250 mg of aspirin; followed by daily doses of 75 mg and 125 mg, respectively, during their hospital stay, and received electrocardiographic, clinical, enzymatic and echocardiographic follow-up until hospital discharge.

The control group consisted of 43 patients, who received thrombolytic treatment, who were given an initial dose of 250 mg aspirin, followed by a daily dose of 125 mg, as the only antiplatelet agent.

Variables

The following variables were studied: age, sex, risk factors, location of infarction (anterior and inferior), interval between onset of symptoms and application of thrombolytic treatment (early [1-3 hours], moderately early [3-6 hours] and late [6-12 hours]), evolution, complications, and in-hospital mortality.

Statistical processing

The information obtained by reviewing clinical records, emphasizing on clinical, enzymatic, electrocardiographic and echocardiographic evolution until hospital discharge was processed through a database and using SPSS statistical software, version 21.0, for Windows. This information was organized into frequency and contingency tables, using it in the description of the same absolute frequencies (number of cases) and percentages. Data was graphically represented according to the type of information.

Chi Square Independence test was used to assess the possible association between qualitative variables. A multivariate binary logistic regression analysis was performed to identify the association between AMI location and treatment application interval with the presence of complications.

In all cases a 95% confidence interval was set, and statistical significance was interpreted according to the following criterion: if $p > 0.05$ there were no significant differences, if $p \leq 0.05$ difference was significant.

RESULTS

Table 1 shows the distribution of patients by groups according to sex and age groups, where it was verified that there were no significant differences between the two. In both groups, male predomi-

Table 1. Distribution of patients according to sex and age by groups.

Age groups	Sex								Total	
	Study (n=43)				Control (n=43)					
	Female		Male		Female		Male			
	N°	%	N°	%	N°	%	N°	%	N°	%
Under 50	2	4,6	1	2,3	0	0,0	8	18,6	11	12,8
50 - 59	2	4,6	6	14,0	3	7,0	3	7,0	14	16,3
60 - 69	1	2,3	11	25,6	3	7,0	10	23,3	25	29,1
70 - 75	8	18,6	12	27,9	8	18,6	8	18,6	36	41,9
Total	13	30,2	30	69,8	14	32,6	29	67,4	86	100,0

χ^2=3,130; p=0,372

Table 2. Distribution of patients according to factors by study groups.

Risk Factors	Study Groups				Total		Statistics	
	Study (n=43)		Control (n=43)					
	N°	%	N°	%	N°	%	χ^2	p
Smoking	26	60,5	23	53,5	49	57,0	0,426	0,514
High blood pressure	24	55,8	25	58,1	49	57,0	0,047	0,827
Ischemic heart disease	20	46,5	13	30,2	33	15,1	2,409	0,183
Diabetes mellitus	7	16,3	15	34,9	22	25,6	3,909	0,048
Sedentary lifestyle	8	18,6	5	11,6	13	15,1	0,816	0,366
Obesity	5	11,6	6	14,0	11	12,8	0,104	0,747
Alcoholism	5	11,6	5	11,6	10	11,6	0,000	1,000
Hypercholesterolemia	4	9,3	5	11,6	9	10,5	0,124	0,725
Stress	7	16,3	1	2,3	8	9,3	4,962	0,026
High salt-fat diet	4	9,3	3	7,0	7	8,1	0,156	0,693

nated, about 70% of the cases, and ages between 70-75 years (41.9%), followed by those between 60-69 years (29.1%).

Risk factors behaved similarly in both groups (**Table 2**); there were only significant differences in the presence of diabetes mellitus, which was predominant in the control group (34.9 vs. 16.3%; p= 0.048). There were also significant differences in the presence of stress, which predominated in the study group (16.3%) compared to the control group (2.3%) (p=0.026). Predominant risk factors were smoking (57%) and arterial hypertension (57%), followed by history of ischemic heart disease (38.3%) and diabetes mellitus (25.6%).

Regarding to the infarction location and its relation to the appearance of complications (**Figure 1**), a significant association was observed, more frequent in the anterior wall AMI, which was manifested in 32.6% of the patients in the study group; against a 7% who did not complicate and had the same infarction location. However, in this same group, 27.9% of patients with inferior wall AMI had complications, compared to 32.6% who had none.

As for the particular treatment interval and clinical evolution (**Table 3**) for both groups there were no significant differences, hence they behaved similarly, due to the predominance of unfavorable evolution as the time interval between the onset of

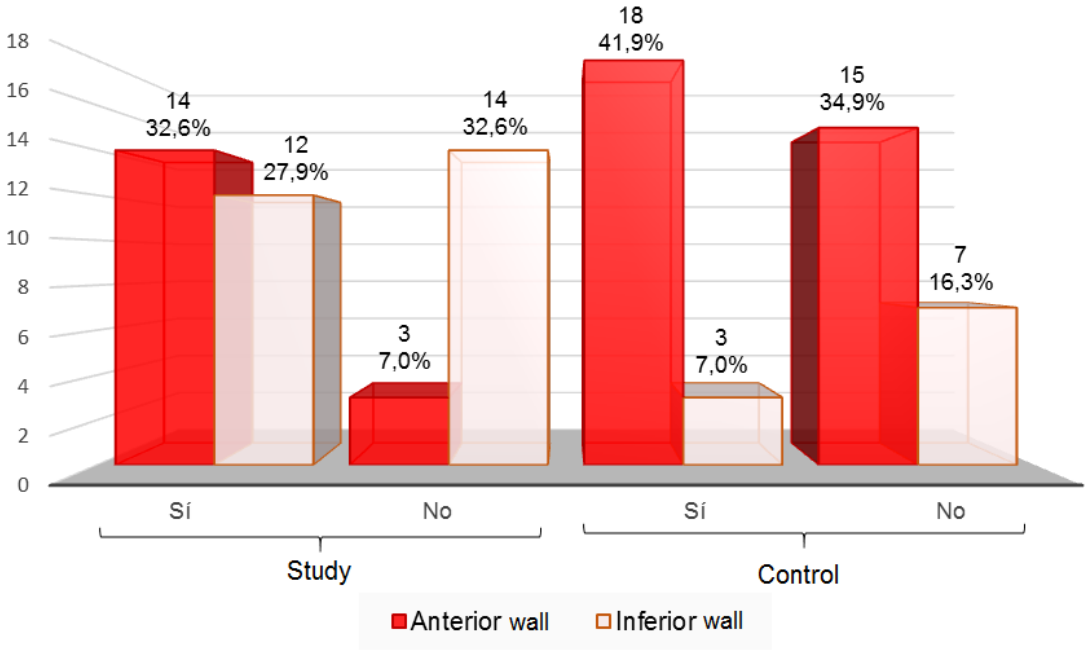

Figure 1. Distribution of patients according to the infarction location and presence of complications by study groups.
AMI location, between groups: χ^2=0,754; p=0,385
AMI location, study group: χ^2=5,635; p=0,0176
AMI location, control group: χ^2=1,850; p=0,1737

symptoms and the application of treatment increased; however, when the interval was related to the patients' evolution by groups, a significant association was observed in the study group (p=0.029), where 37.2% presented a favorable evolution, with a slight difference of the only 25.6% of the control group.

On the other hand, no significant differences were observed in the control group related to the time of treatment, since only 7% of early treated

Table 3. Distribution of patients according to their evolution and the interval between onset of symptoms and treatment application.

Intervalo	Evolution								Total	
	Study group (n=43)				Control group (n=43)					
	Favorable		Unfavorable		Favorable		Unfavorable			
	N°	%	N°	%	N°	%	N°	%	N°	%
Early	12	27,9	9	20,9	3	7,0	10	23,3	34	39,5
Moderately early	3	7,0	12	27,9	6	14,0	14	32,6	35	40,7
Late	1	2,3	6	14,0	2	4,7	8	18,6	17	19,8
Total	16	37,2	27	62,8	11	25,6	32	74,4	86	100,0

Treatment interval (Study): χ^2=7,047; p=0,029
Treatment interval (Control): χ^2=0,412; p=0,814
Treatment interval (between groups): χ^2=3,126; p=0,210
Evolution (between groups): χ^2=1,350; p=0,245

Table 4. Distribution of patients, according to complications by study groups and infarction location.

Complications	Infarction location				Total	Estadígrafos	
	Study (n=43)		Control (n=43)				
	Anterior	Inferior	Anterior	Inferior		χ^2	p
Electrical Complications							
Bradiarthymia	3 (7,0)	6 (14,0)	4 (9,3)	9 (20,9)	22 (25,6)	0,977	0,323
RVR	6 (14,0)	1 (2,3)	4 (9,3)	2 (4,7)	13 (15,1)	0,090	0,763
CPA in VF	4 (9,3)	1 (2,3)	1 (2,3)	1 (2,3)	7 (8,1)	1,400	0,237
Ventricular tachycardia	3 (7,0)	0 (0,0)	0 (0,0)	1 (2,3)	4 (4,7)	1,049	0,306
Ischemia	10 (23,3)	2 (4,7)	9 (20,9)	10 (23,3)	31 (36,0)	2,472	0,116
Mechanical Complications							
Pump failure	2 (4,7)	7 (16,3)	4 (9,3)	4 (9,3)	17 (19,8)	0,073	0,787
Cardiogenic shock	6 (14,0)	3 (7,0)	3 (7,0)	2 (4,7)	14 (16,3)	1,365	0,243
Ventricular aneurysm	0 (0,0)	0 (0,0)	2 (4,7)	1 (2,3)	3 (3,5)	3,108	0,078
Other	1 (2,3)	1 (2,3)	4 (9,3)	2 (4,7)	8 (9,3)	2,205	0,138

CPA: cardiorespiratory arrest, RVR: rapid ventricular response atrial fibrillation, VF: ventricular fibrillation.
Data express n (%)

Table 4-A. Global statistical analysis of complications.

Complications	Study		Control	
	χ^2	p	χ^2	p
Bradiarithmia	1,117	0,291	2,266	0,132
RVR	3,888	0,049	0,717	0,392
CPA in VF	1,911	0,167	0,000	1,000
Ventricular tachycardia	3,108	0,078	1,012	0,315
Ischemia	6,198	0,013	0,068	0,795
Pump failure	3,103	0,078	0,000	1,000
Cardiogenic Shock	1,117	0,291	0,212	0,645
Ventricular aneurysm	-	-	0,345	0,557
Other	0,000	1,000	0,717	0,392

FA: fibrilación auricular con respuesta ventricular rápida,
FV: fibrilación ventricular, PCR: parada cardiorrespiratoria

patients had a favorable outcome; 14% from those treated moderately early, and 4.7% from those treated late.

When the infarction location and complications were related (**Table 4**), both groups behaved similarly, without observing significant differences between them. Ischemic complications were the most frequent for both (36%), followed by bradyarrhythmias (25.6%) and pump failure (19.8%).

When each group was independently related (**Tabla 4-A**), it was observed that in the study group, atrial fibrillation with rapid ventricular response was more frequent in anterior and inferior AMI (14.0 vs. 2.3%, p=0.049), as well as ischemic complications (23.3 *vs.* 4.7%; p=0.013), which were significant differences in this group. The rest of the complications behaved the same way regardless of AMI location in both groups.

The association of in-hospital lethality between both groups was not significant. However, when the association between lethality and treatment time interval application was analyzed, the difference was significant in the study group (p=0.03), where the increase in lethality was directly proportional to the thrombolytic treatment delay. Percentage of deaths reached 7% when this therapy was applied late, it was reduced to 2.3% when applied moderately early, and no deaths were recorded in patients who received prompt treatment (**Figure 2**).

There was no significant association between the treatment time interval application and the control group lethality (p=0.68). Overall, a slight decrease 9.3% (4 patients) in in-hospital mortality was ob-

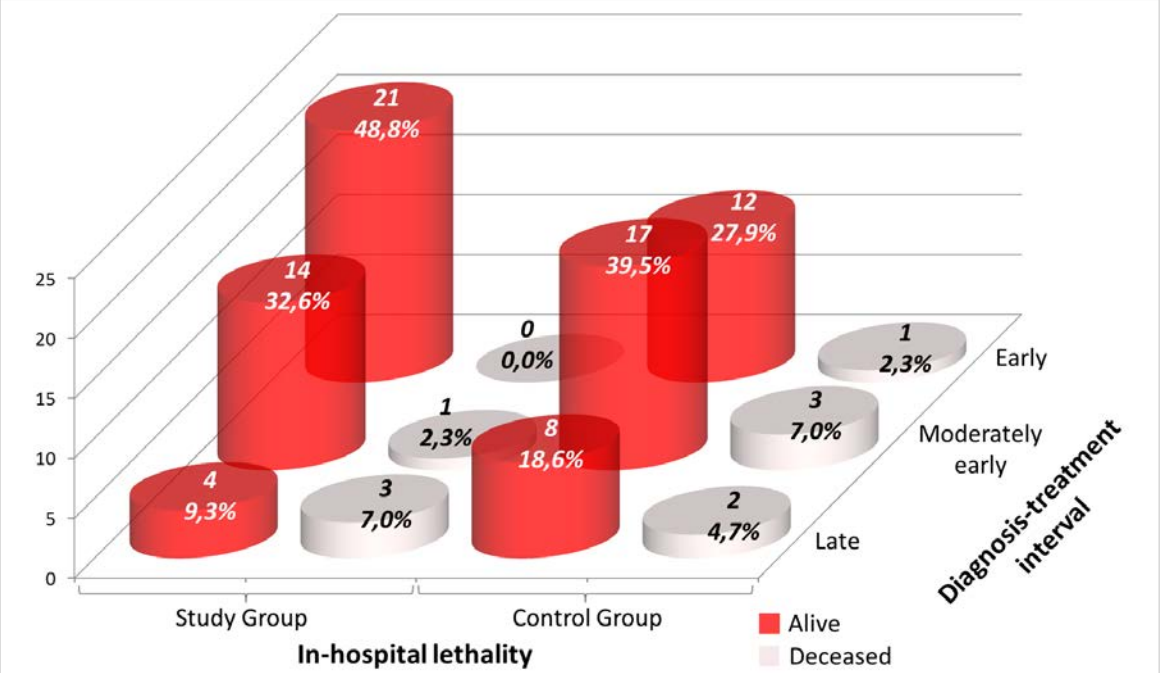

Figure 2. Distribution of patients according to the interval between onset of symptoms, treatment application and in-hospital lethality.
Mortality-treatment, between groups: χ^2=0,453; p=0,501
Mortality-treatment, study group: χ^2=11,61; p=0,03
Mortality-treatment, control group: χ^2=0,747; p=0,68

served in the study group, compared to 14% (6 patients) in the control group.

DISCUSSION

AMI continues to be a public health problem in developed and developing countries, so effective and feasible treatment schemes are needed[8].

There was a male predominance in this study which corresponds to what was reported by Kaul *et al.*[2] in a multicentre study (TRACE) conducted in India, where STEMI was more frequent in 50 years old, and male patients; and with what was found by Correia *et al.*[9] where mean age was 63±13 years and 72% were men. Similar data are collected in a study carried out in South Korea[10], where the mean age of the patients studied was 63.9±9.6 and male sex predominated (69.7%); and also by Rakowski *et al.*[11] where mean age was 62 (56-73) years and 69% were males.

Kaul *et al.*[2] point to previous ischemic heart disease, high blood pressure, diabetes and dyslipidemia as the main risk factors; while Cho *et al.*[10] reported high blood pressure and diabetes mellitus, which coincides with PLATO[7] study findings. Results similar to our research were found by Wang *et al.*[12], since 55% of their patients smoked and 51% had high blood pressure. Other authors also include among the most frequent risk factors the history of previous ischemic heart disease[11].

It has been observed in the United States that the incidence of poor responders to aspirin has been significantly increased in the diabetic population, which results in a platelet hyperactivity and a pro-atherogenic phenotype, which increases the risk for ischemic cardiovascular disease in these patients[13].

Regarding the most frequent localization of AMI, Rakowski *et al.*[11] in Poland reported that 43% of STEMI was on the anterior wall and that these presented more complications, due to a greater affection of the myocardial muscle; similar results to those reported by Wang *et al.*[12] who found this location in 51.9% of the patients, and found that

when AMI is associated with diabetes mellitus and a late start of treatment, there is a higher frequency of pump failure with Killip-Kimball class greater than I.

In addition, the study by Rakowski *et al.*[11] shows that the evolution, including the associated complications and quality of life after ACS, is closely connected to the starting time of reperfusion therapy; the faster the vessel reperfusion associated with AMI, the better outcome, although in this study a better quality of life was observed in those patients who underwent percutaneous coronary intervention. In agreement with this work, no significant differences regarding the treatment evolution and application in the control group were observed, and it had a greater proportion of patients complicated, in spite of the therapeutics time.

In a study carried out in China[12], they refer to factors that significantly influence the outcome of these patients: time elapsed from diagnosis to treatment application, anterior wall location of infarction, history of diabetes mellitus and absence of loading doses of clopidogrel for dual antiplatelet therapy. In the United States, studies have also been conducted highlighting the importance of early treatment in AMI, because in patients who were given a prompt treatment (because the pre-hospital care system was activated), there was a lethality decrease of 6.7% vs. 9.5% of those who were not offered pre-hospital care for reperfusion and dual antiplatelet therapy[14].

Regarding the type of complications presented in the TRACE[2] study, it is suggested that ischemic complications were the most frequent, followed by cardiogenic shock, which coincides with this series results. Similar data are collected in Rakowski *et al.*[11] work performed in Poland, where most frequent complications were pump failure followed by ischemic complications.

In a comparative study carried out in China[12], it is noteworthy that most patients in whom, in addition to reperfusion therapy and aspirin, loading dose of clopidogrel was not given, had a higher incidence of pump failure with a Killip-Kimball class greater than I, than the group that used loading doses followed by 75 mg as maintenance doses on subsequent days. So, it is concluded that its use is important in preventing secondary STEMI complications.

Also, other authors emphasize that dual antiplatelet therapy is very important for secondary prevention in patients who have suffered ACS[15,16].

In the TRACE[2] study, increased ischemic-related complications appeared in patients who received antiplatelet therapy only with aspirin, compared to those in whom clopidogrel and aspirin were used; and it was found that patients who did not receive dual antiplatelet therapy had an increased risk of lethality-related complications; which agrees with the results obtained in this work.

In a study carried out in Canada[17] there was a decrease in reinfarction when clopidogrel was associated with aspirin. However, the superiority of prasugrel and ticagrelor is emphasized, although they recommend making a risk-benefit balance with respect to the risk of bleeding. Sabatine *et al.*[3] in their series that included 3491 STEMI patients concluded that patients younger than 75 years of age who received aspirin, clopidogrel and fibrinolytic therapy had a decreased lethality and recurrence of AMI.

According to the reviewed literature, this protective effect may be affected in some people by the use of lipophilic statins, calcium channel blockers, and smoking, diabetes mellitus and obesity, since they may predispose to platelet function variations. Although resistance to clopidogrel effect is described as the most important factor that interferes with the prevention of complications[18,19]. Such is the importance of the genetic polymorphism and resistance to clopidogrel effect for the prevention of complications after the ischemic event, that studies have been carried out in the United States where it is suggested that the choice of antiplatelet agent can be guided by genotyping as a cost-effective strategy in ACS patients, especially if patients undergo percutaneous coronary intervention[20].

In the TRACE[2] study, higher mortality was reported in the group that only used aspirin as an antiplatelet agent, which coincides with the work done by Husted *et al.*[7] that shows a lethality reduction associated to AMI with the use of dual antiplatelet therapy. In the PLATO study, the use of prasugrel (9.9%) and clopidogrel (12.1%) when associated with aspirin (cardiovascular lethality due to AMI-related complications) is referred to as a lethality decrease. However, the risk of bleeding was higher in patients using prasugrel (2.4 vs. 1.8%). Oliver *et al.*[21] also report that ticagrelor has shown superior efficacy compared to clopidogrel in reducing lethality (9.0 vs. 10.7%, respectively), due to ticagrelor's pharmacodynamic characteristics, that in these studies has been shown to be a more rapid and potent platelet aggregation inhibitor than clopi-

dogrel, because it alters the uptake of adenosine by red blood cells, which may influence its efficacy and safety[22].

There are other factors that influence lethality risk, as it increases in patients with previous infarction due to poor secondary prevention, non-lifestyle modification, or treatment withdrawal[15].

Other complications associated with the use of antiplatelet agents, such as spontaneous subcapsular renal bleeding or hematoma, were not found in this study, which coincides with the findings reported in the CONMIT study[6].

Study limitations

Among the study limitations was the impossibility of follow-up for 6-12 months after the STEMI in the study group, which would have given a more complete idea about long-term treatment benefits, as well as the late mortality in these patients.

CONCLUSIONS

The clinical application of dual antiplatelet therapy reflected a decrease in the incidence of ischemic complications following ST segment elevation acute myocardial infarction in patients receiving thrombolytic therapy. Those who had an inferior infarct location were more benefited. In addition, the in-hospital mortality associated with infarction-related complications was reduced in the study group, mainly influenced by early treatment.

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