A randomized pilot study of the Amicath® II microcatheter use for the intralesional infusion of drugs in patients with STEMI to improve microcirculation and ventricular function. AMIway study

Estudio piloto aleatorizado del uso del microcatéter Amicath® II para la infusión intralesional de fármacos en pacientes con STEMI para mejorar la microcirculación y la función ventricular. Estudio AMIway

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ABSTRACT

Background. ST-elevation acute myocardial infarction and its reperfusion continues to be a topic of debate in clinical practice, without a doubt the method of choice is primary percutaneous coronary intervention, although it is still not clear how to improve microcirculation. Intralesional drug treatment has been used to improve results.
Purpose. Two objectives were established in the study, firstly, to evaluate the feasibility of using a microcatheter assessed for its ability to cross the lesion, show the distal territory and allow the injection of drugs, and the second objective was to assess the improvement in LVEF between 3 and 6 months of evolution analyzed by baseline echocardiography and follow-up.
Methods. The AMIway is a randomized pilot study of two arms with patients with STEMI with a high thrombotic burden such as TIMI Thrombus ≥ 3 to be treated with primary PCI with intralesional Adenosine and Tirofiban infusion through the Amicath® II Catheter, IHT, Barcelona, Spain, compared with patients treated with primary PCI with placebo infusion through the same microcatheter within 12 hours of STEMI, in both groups treated with stents. Amicath® II is a rapid exchange micro perfusion catheter for intracoronary use, combines a single lumen in its proximal section (Teflon-coated stainless steel hypo tube). The outer lumen of the distal section ("Dotter" tube, made of flexible polymeric material, Pebax), has a progressive diameter, to obtain a cross ability effect and presents four distal holes, to measure distal perfusion pressure and infuse drugs. The other fast exchange lumen is for the 0.014" wire. It also presents 5 radiopaque marks with a distance of 10 mm between them.
Results. In three centers in Buenos Aires, Argentina, between October 2019 and March 2022, 50 patients were included, who were randomized into two groups with 25 patients in each. There were no significant differences between the two groups in baseline clinical and angiographic characteristics, the majority of patients were male, and diabetes was present in one third of both groups. The vessels treated were the Anterior Descending and Right Coronary Arteries, most were by radial approach. In all patients the microcatheter could be used without difficulties or complications; the lesions were crossed without difficulty and the distal vessel to the occlusions were observed and the infusion of drugs (adenosine and tirofiban) was carried out ultra-selective in the active group and placebo in the control group, it was possible to measure the length lesion in the culprit vessel compared with angiographic quantification. Seven patients in the placebo group underwent a crossover to the active treatment. LVEF improved at 223 days of follow-up±195 days from a baseline of 50.6±8.8 and increased to 59.5±9 at follow-up with a p=0.02, while in the control group it improved from 50.7±10 to 56.6±9.7 with a p=0.07. Three patients died of non-cardiac death associated with the SARS-CoV-2 virus, two patients in the control group.TIMI 3 flow was similar and myocardial Blush was better in the active group.
Conclusions. In this pilot study it was possible to observe that the Amicath® II catheter was able to cross the lesion in all the patients that was attempted, being able to observe the vessel of the involved territory and infuse the study drugs without complications. LVEF improvement was observed in the medium term in patients where microcirculation was treated ultra-selective in patients with a high thrombotic burden.

Keywords: *Amicath, STEMI, LVEF, primary PCI, adenosine, tirofiban.*

RESUMEN

Antecedentes. El infarto agudo de miocardio con elevación del ST (IAMST) y su reperfusión continúa siendo un tema de debate en la práctica clínica. Sin duda, el método de elección es la intervención coronaria percutánea primaria (ATC), aunque aún no está claro cómo mejorar la microcirculación. Se ha utilizado tratamiento farmacológico intralesional para mejorar los resultados.
Propósito. En el estudio se establecieron dos objetivos. En primer lugar, evaluar la viabilidad del uso de un microcatéter según su capacidad para atravesar la lesión, mostrar el territorio distal y permitir la inyección de fármacos; y el segundo objetivo fue evaluar la mejora en FEVI entre 3 y 6 meses de evolución analizada mediante ecocardiografía basal y seguimiento.
Métodos. El AMIway es un estudio piloto aleatorizado de dos ramas con pacientes con IAMST con alta carga trombótica como TIMI Thrombus ≥ 3 para ser tratados con PCI primaria con infusión intralesional de adenosina y tirofibán a través del catéter Amicath® II, IHT, Barcelona, España, en comparación con los pacientes tratados con ATC primaria con infusión de placebo a través del mismo microcatéter, dentro de las 12 horas posteriores al IAMST, en ambos grupos tratados con stents. Amicath® II es un catéter de microperfusión de intercambio rápido para uso intracoronario, combina una única luz en su sección proximal (hipotubo de acero inoxidable recubierto de teflón). La luz exterior de la sección distal (tubo "Dotter", de material polimérico flexible, Pebax), tiene un diámetro progresivo, para obtener un efecto de cruzabilidad y presenta cuatro orificios distales, para medir la presión de perfusión distal e infundir fármacos. La otra luz de intercambio rápido es para para la guía coronaria de 0,014". Presenta además 5 marcas radioopacas con una distancia de 10 mm entre ellas.
Resultados. En tres centros de Buenos Aires, Argentina, entre octubre de 2019 y marzo de 2022, se incluyeron 50 pacientes, quienes fueron aleatorizados en dos grupos de 25 pacientes en cada uno. No hubo diferencias significativas entre los dos grupos en las características basales clínicas y angiográficas, la mayoría de los pacientes eran hombres y la diabetes estaba presente en un tercio de ambos grupos. Los vasos tratados fueron la Descendente Anterior y la Coronaria Derecha, la mayoría fue por abordaje radial. En todos los pacientes el microcatéter pudo utilizarse sin dificultades ni complicaciones; las lesiones se atravesaron sin dificultad y se observó el vaso distal a las oclusiones y la infusión de fármacos (adenosina y tirofibán) se realizó ultraselectiva en el grupo activo y placebo en el grupo control, se pudo medir la longitud de la lesión en el vaso culpable en comparación con la cuantificación angiográfica. Siete pacientes del grupo de placebo se sometieron a un "cruzamiento" al tratamiento activo. La FEVI mejoró a los 223 días de seguimiento±195 días desde un valor inicial de 50,6±8,8 y aumentó a 59,5±9 en el seguimiento con una p=0,02, mientras que en el grupo control mejoró de 50,7±10 a 56,6±9,7 con p=0,07. Tres pacientes murieron por muerte no cardíaca asociada con el virus SARS-CoV-2, dos pacientes del grupo de control. El flujo TIMI 3 fue similar y el Blush miocárdico fue mejor en el grupo activo.
Conclusiones. En este estudio piloto se pudo observar que el catéter Amicath® II logró atravesar la lesión en todos los pacientes que se intentó, pudiendo observar el vaso del territorio involucrado e infundir los fármacos del estudio sin complicaciones. Se observó una mejora de la FEVI a mediano plazo en pacientes en quienes la microcirculación se trató de forma ultraselectiva, en pacientes con una alta carga trombótica.

Palabras clave: catéter Amicath, SCACEST (síndrome coronario agudo con elevación del ST), FEVI (fracción de eyección ventricular izquierda), ATC primaria (angioplastia coronaria percutánea), adenosina, tirofibán.

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TABLE 1. Angiographical and clinical basal characteristics.

	Control, % (n=25 patients)	Amicath, % (n=25 patients)	p Value
Age	59.8+/-11.6	58.7+/-9.8	0.71
Sex	88 (22)	72 (18)	0.157
Smoking	68 (17)	68 (17)	1.00
Dyslipidemia	72 (18)	92 (23)	0.066
Diabetes	36 (9)	32 (8)	0.76
HBP	64 (16)	64 (16)	1.00
CKF	8 (2)	0 (0)	0.149
pre PCA	20 (5)	12 (3)	0.44
pre CRM	0 (0)	4 (1)	0.31
Radial access	88 (22)	80 (20)	0.53
DA	48 (12)	40 (10)	0.56
RC	36 (9)	48 (12)	0.39
CX	16 (4)	12 (3)	0.68
Reference diameter	3.21+/-0.43	3.26+/-0.28	0.63
Distal lesions	36 (9)	16 (4)	0.10
Tortuosity	32 (8)	40 (10)	0.55
Severe calcification	32 (8)	24 (6)	0.52
Adenosine infusion	40 (10)	100 (25)	<0.001
Tirofiban infusion	32 (8)	100 (25)	<0.001
Cloridogrel	56 (14)	28 (7)	0.045
Ticagrelor	28 (7)	48 (12)	0.145
Prasugrel	16 (4)	16 (4)	1.00

HBP (high blood pressure), CKF (chronic kidney failure), PCA (percutaneous coronary angioplasty), DA (anterior descending artery), RC (Right Coronary), CX (Circumflex artery).

TABLE 2. Patients grouped in the control group and active treatment with Amicath® II catheter, with their echocardiographic follow-up, in their basal state and in the follow-up.

By intention of treatment (follow-up 223 +/- 195 days)			
N	Basal LVEF	Follow-up LVEF	P
Control group (25)	50.7+/-10	56.6+/-9.7	0.07
Pharmacological group (25)	50.6+/-8.8	59.5+/-9	0.02

LVEF (Left Ventricular Ejection Fraction)

INTRODUCTION

The myocardial reperfusion via catheter is still the treatment chosen by patients with STEMI[1], and LVEF in the long-term follow-up is the most efficient method of evaluating the prognosis in patients[2]. The impact of the microcirculation in these patients and their treatment is a challenge[3]. Prior studies with the treatment with adenosine systematically had promising results[4,5]. We conducted a pilot study, randomized in order to evaluate the feasibility of the use of a micro-catheter of quick interchange, devoted to the infusion of drugs in the invasive treatment of STEMI, the Amicath® II (IHT, Barcelona, Spain), and to evaluate medium-term LVEF, in patients treated with the infusion of adenosine and a Glycoprotein IIb IIIa inhibitor (GPI) ultra selectively in the infarct area.

MATERIAL AND METHODS

STUDY DESIGN

AMIway is a randomized, prospective pilot study where patients with STEMI were included within the 12 hours once the pain began in three centers with cath-labs in the Buenos Aires Metropolitan Area in Argentina. The centers were approved by the Ethics and Research committees. This study evaluated the feasibility of the use of a micro-catheter designed for the infusion of liquids or pharmacological drugs as they contribute to the myocardial mechanical reperfusion to improve the microcirculation and, thus, to achieve a higher recovery of the infarcted area. In order to do so, we designed a strategy of primary revascularization with stents in all the patients according to the standards of each interventional laboratory, where previously an adenosine infusion and an Inhibitor of GPI, the tirofiban (Agrastat, Patheon Manufacturing Service, Greenville, USA), took place directly in the affected area through the Amicath® II catheter in the active group compared with the placebo infusion in the other group with the same catheter. At the same time, in order to evaluate the acute myocardial infarction (AMI) size, LVEF was used, measured by a Doppler echocardiogram immediately post procedure and in the follow-up at three to six months after the primary angioplasty.

SELECTION AND RANDOMIZATION

The patients who underwent a STEMI were chosen to take part in the study. These patients had to be within the criteria of inclusion and they did not have to present any contraindication to enter. The details of the inclusion and exclusion criteria are shown in the Appendix of the study. The randomization was performed in blocks and by sealed envelopes which were pre-established before beginning the study. The researcher had to open those envelopes after including the patient and had to follow their instructions.

All the patients were previously evaluated by a Cardiology staff and the standards of STEMI treatment were followed.

All the events were evaluated by an independent safety committee.

The study was ruled by the good clinical practices and Helsinki principles.

REVASCULARIZACIÓN, PHARMACOLOGICAL TREATMENT AND FOLLOW-UP

All the patients were submitted to a primary coronary angioplasty performed according to the technical standards either by femoral or radial via according to the patient and operator's preferences. All of them received a 600 mg clopidogrel dose, a 60 mg prasugrel dose or 180 mg ticagrelor dose and a 300 mg aspirine dose. Intra- procedure: all of them received 100 U/kg of heparin. After positioned a coronary guide in the index vessel, a microcatheter of rapid exchange with marks of distance, Amicath® II, was passed where contrast was infused which indicated the size of the distal bed, the length of the lesion. After that, in the active group 2000 µg of adenosine and 2.5 mg of tirofiban (Agrastat) were passed slowly, and in the control group two syringes with 10 ml of physiological solution each one. Next, in both groups pharmacological stents were implanted according to the need to cover all the lesion to obtain a final TIMI III (**Figure 1**).

The treatment of the other vessel with severe lesion was left to the operator's criterion, although the treatment by stages was strongly recommended if it was necessary.

Post-procedure: all the patients were submitted to an

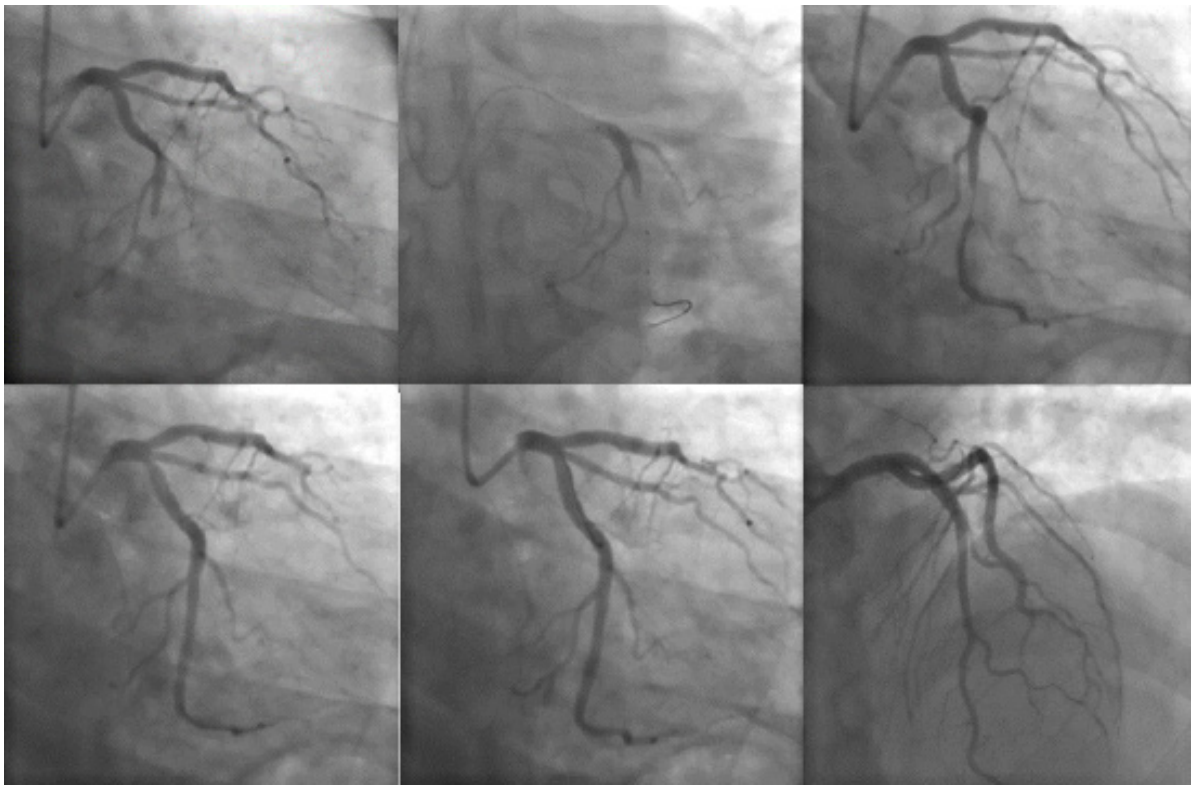

Figure 1. *A) Patient STEMI of lateral territory, with 100% total occlusion TIMI 0 of the circumflex artery. B) The Amicath® II catheter is observed where through its holes the drugs of the study are injected, after that. C) the lesion can be clearly observed and the distal bed can be quantified, D) in this image the immediate post-timplant of the stent which still has the coronary wire can be seen, E) and finally without the coronary wire and F) in the final axial view in front of TIMI III and BLUSH 3.*

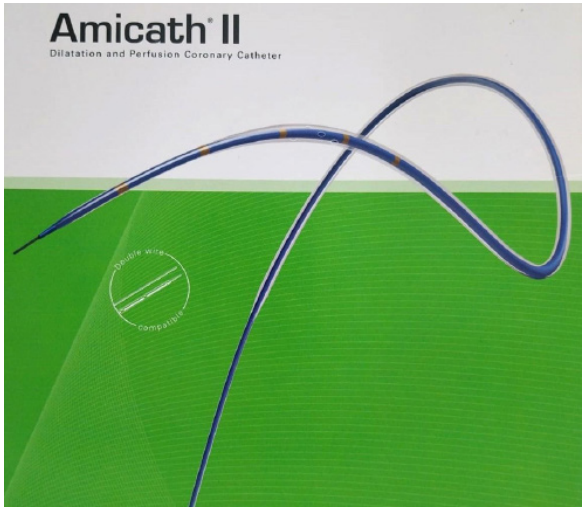

Figure 2. *Amicath® II is a rapid exchange coronary perfusion microcatheter.*

echocardiogram with LVEF measurement with Simpson´s method and at six months of follow-up.
All the data and their analysis obtained were monitored by the CECI (Centro de Estudios en Cardiología Intervencionista)

DESCRIPTION OF AMICATH® II

Amicath® II is a rapid exchange coronary perfusion microcatheter with 5 (five) radiopaque marks at a 10 mm distance among each other used in the intracoronary procedures of angioplasty during acute myocardial infarction.. It combines an only lumen in its proximal section (a stain steel hypo-tube covered by Teflon). The external lumen of the distal section ("Dotter" tube, of flexible polymeric material, Pebax) has a progressive diameter to be able to cross easily through dilatation ("Dotter") and it has four distal holes to measure distal perfusion pressure and pass drugs (saline solution, vessel-dilating drugs, glycoprotein inhibitors, thrombolytic, etc.). The other lumen (double lumen) of rapid exchange allows the passage of a coronary guide of 0.014" to ease and allow the progress of the catheter through the occlusion to be treated **(Figure 2).**

PRIMARY AND SECONDARY OBJECTIVES

The study primary objectives are to evaluate the feasibility of the use of a microcatheter designed for drug infusion in STE-ACS and to test if the adjuvant treatment of adenosine and tirofiban injected ultra selectively in STEMI index vessel improves the microcirculation, which would suppose a LVEF improvement in patients at six months under treatment compared with the post-procedure immediate results.
The secondary objectives are the major cardiovascular events and their components such as death, AMI, stroke and a new intervention of the vessel treated. The stent thrombosis was also analyzed.

STATISTICS

We calculated the sample size according to pilot studies similar to ours and to what García-García et al[6] state on this issue. For pilot studies we used a sample of 25 patients in each group. A level of significance of a $p< 0.05$ and a power of 80% were considered.

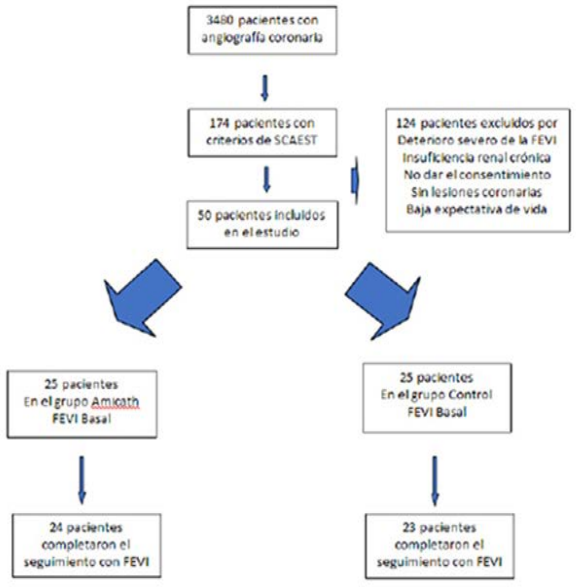

Figure 3. *Study flow diagram*

We calculated the averages and standard deviations (SD) of the continuous variables in both groups and we analyzed them with the test of the t-Student. The binary variables were reported as percentages and they were analyzed with the Chi2 test or the exact Fisher test.

RESULTS

Three centers of the Buenos Aires Metropolitan Area in Argentina which had the capacity of performing primary angioplasty took part in the study. Between October 2019 and March 2022, 3480 patients were admitted for a coronary angiography. Among them, 174 patients had STEMI, of them, 50 patients who qualified for the inclusion were accepted for the study and they were randomized in two groups of 25 patients in each one. **(Figure 3).**

Both groups were similar as regards clinical and angiographic basal characteristics, without significant differences among the analyzed variables **(Table 1).** Between both groups, most of the patients were male and diabetics was present in a third in both groups. The predominant vessels of treatment were the anterior descending and the right coronary. Most of the patients were approached through radial access.

In all the patients the Amicath® II microcatheter could be used without difficulties or complications related to it. The lesion could be passed through and the distal bed to the occlusion could be shown. The infusion of drugs (adenosine and tirofiban) could also be carried out ultra selectively in the active group and the placebo in the control group. Besides, the length of the lesion could be measured in the culprit vessel compared with the online coronary angiographic quantification.

There were 7 (seven) patients in the placebo group who made a crossover to the active treatment.

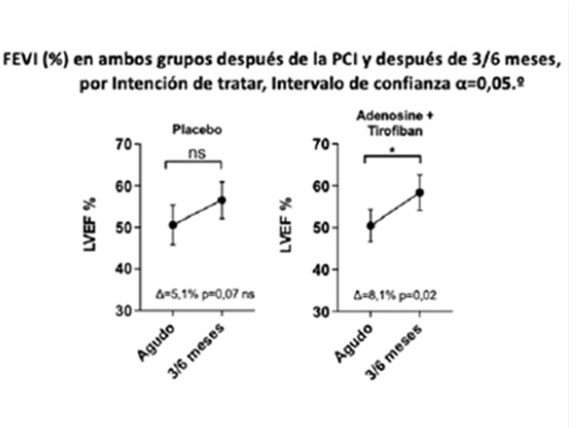

Figure 4. *LVEF improvement between both groups, between basal measurements and in the follow-up.*

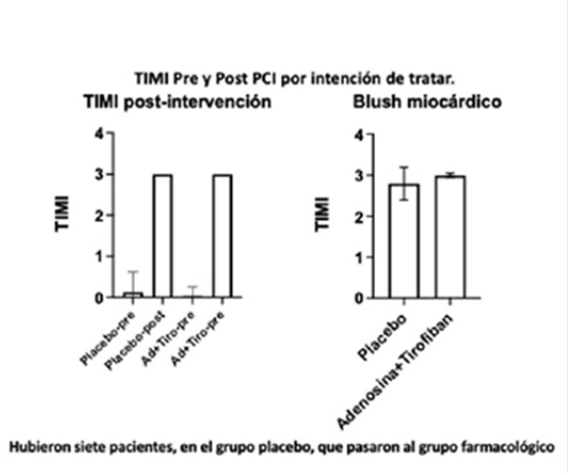

Figura 5. *Evaluación de la perfusión miocárdica a través del flujo TIMI y el blush miocárdico.*

All the patients were analyzed by treatment intention where it was observed that LVEF improved after 223 ± 195 follow-up days: from a basal of 50.6 ± 8.8 it was increased to 59.5 ± 9 during the follow-up with a p=0.02, while in the control group it improved from 50.7 ± 10 to 56.6 ± 9.7 with a p=0.07 **(Figure 4, Table 2).**

During the follow-up, probably due to the pandemic, three patients died due to a non-cardiac death related to the SARS-CoV-2 virus, two patients were in the control group and the other one in the pharmacological group.

As regards the TIMI flow and the myocardial blush, it is observed that there were no differences between the final TIMI between the two groups, but a slight improvement of the myocardial blush was observed in the active group **(Figure 5).**

DISCUSSION

In this pilot study we could see that the Amicath® II microcatheter has an excellent profile because in the 100% of the cases it could pass through the lesion without difficulty in all the patients where the primary TCA was performed, the vessel and its distal bed could be dyed being able to observe the lesion in detail and the adenosine could also be injected at high dose without obser-

ving in the majority of the patients the pauses frequently related to the infusion of the adenosine systematically plus the GPI in the form of intralesional bolus. Besides, in the active group an improvement of LVEF evaluated immediately after AMI could be seen and in the follow-up between 3 and 6 months, improvement that was significant.

The primary TCA has turned into the treatment chosen by the STEMI patients[1], and the evaluation of the ventricular function on the mid-term sets its prognosis[2].

The preliminary studies on the intracoronary adenosine in animal samples of myocardial ischemia indicate that it protected from the vascular injury[7].

The adenosine also present powerful anti-inflammatory effects like the adhesion inhibition of neutrophils to endothelium, the release of cytokines of the mononuclear cells, the release of radicals free from oxygen and the apoptosis of cardiomyocites[8]. Its antiplatelet effect has been also shown, which could limit the thrombus burden and allow the vessel permeability[9].

In the AMISTAD I[4] study where the adenosine infusion was used for three hours in patients with STEMI who received fibrinolytics, a reduction of the infarct size could be seen in the patients who presented infarct of the anterior face and did not present it in the other territories. Next, the AMISTAD II[5] study was performed; the adenosine infusion at 50 and 70 gammas to these same patients with STEMI, but infarcts of the descending anterior territory were only included. Benefits with higher infusion dose could be observed, which suggests that high dose of adenosine are needed in the infarct site as we could infuse our patients with Amicath® II catheter super selectively.

The GPI are very powerful drugs which inhibit the platelet aggregation immediately through the fibrinogen inhibition and von Willebrand factor related to the platelets[10], and they help to quickly reduce the thrombus size which is exaggerated in these patients.

In order to boost the beneficial effects of the adenosine we add to the GPI, that we know they are very good as contributors in the STEMI since the publication of the last meta-analysis of the GPI use in STEMI with 21 trials and more than 8500 patients, 10 trials with tirofiban, 9 trials with abcximab, one with eptifibatide and one mixed of tirofiban plus abcximab, only one trial used ticagrelor or prasugrel; all the cardiovascular events were reduced and the higher and lower bleeding was significantly higher in the GPI group, but not the intracranial[11] . In order to mitigate the latter and its potential danger, the concept of its intracoronary application was born. Small trials were made quickly which are summarized in the first meta-analysis: between the GPI injection by intravenous or intracoronary via there was a reduction of events in favor of the intracoronary strategy, although there was heterogeneity of the trials[12]. More recently, a new meta-analysis was carried out with 14 ttials with more than 3000 patients where LVEF, TIMI and the resolution of the ECG were better in the intralesional treatment than the systemic one, but without differences in the MACCE on the long-term, without differences in bleeding [13].

A recent review has revived this concept of intralesional application especially to patients with a high thrombotic burden creating an algorithm of treatment in these patients [14].

We believe that in these patients undergoing STEMI the aggressive treatment on the thrombus and the microcirculation can generate a better and higher recovery of LVEF at first instance and after the long-term events.

LIMITATIONS AND STRENGHTS

This is a study with a small sample size correlated with the fact that it is a pilot study. It tests strongly the use without complications of a microcatheter designed for drug infusion. Regarding the LVEF recovery, it seems promising, although a high scale trial is missing to be evaluated. Finally, an evaluation of cardiovascular events on the long-term must be carried out.

CONCLUSIONS

First of all, this study showed the feasibility of using accurately the Amicath® II catheter in all the patients to whom it was tried. It did not show complications during its usage and it demonstrated that it is able to indicate the lesion adequately allowing the drug infusion through it.

The administration of drugs, adenosine and intralesional tirofiban, did not show adverse effects and a LVEF mid-term improvement could be observed.

Being a pilot study, it leads to potential hypothesis for greater magnitude studies.

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