

Role of thrombectomy devices during PCI in acute myocardial infarction

Rol de los dispositivos de trombectomía durante la angioplastia en el infarto agudo de miocardio

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RESUMEN

La eliminación del trombo antes de cualquier otra intervención durante la angioplastia en lesiones con contenido trombótico puede disminuir dramáticamente el riesgo del fenómeno de "no-reflow" y tiene el potencial de mejorar la sobrevida. Existen factores angiográficos y clínicos predictores de riesgo elevado de este fenómeno luego de la angioplastia, y es en éstos casos en donde la extracción del trombo estaría indicada, ya que el no reflujo debido a la embolización estuvo asociado a con una tasa de mortalidad muy alta. Existen numerosos tipos de dispositivos de trombectomía actualmente disponibles: desde los catéteres basados en la aspiración del trombo de forma manual, incluyendo aquellos dispositivos de protección antiembólica proximal o distal, a los nuevos dispositivos, avanzados tecnológicamente, que utilizan la energía mecánica para fragmentar y eliminar el trombo. Sin embargo, los resultados de trombectomía antes del implante del stent han producido resultados contradictorios y no existe consenso sobre su uso rutinario en las lesiones que contienen trombo durante la angioplastia coronaria.

Palabras claves: infarto agudo de miocardio, trombo, trombectomía, stent trombosis, angioplastia coronaria.

ABSTRACT

Removal of thrombus before any other intervention in thrombus containing lesions may dramatically decrease the risk of no-flow, and has the potential for improvement in survival. A specific procedural approach to thrombus removal should be considered in the large majority of patients with acute myocardial infarction and in patients with angiographic evidence of thrombus and large area at risk, or a pre-existing severe left ventricular dysfunction, since in these patients a no-reflow due to embolization is associated with a very high mortality rate. Many types of thrombectomy devices are currently available, from low technology catheters based on manual thrombus aspiration, including proximal or distal antiembolic protection devices, to high technology devices using mechanical energy allowing fragmentation and removal of thrombus. Studies on thrombectomy before stenting have produced conflicting results and there is not consensus on their routine use in lesions containing thrombus.

Key words: acute myocardial infarction, thrombus, thrombectomy, stent thrombosis, coronary angioplasty.

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INTRODUCTION

Occlusive or nonocclusive thrombosis triggered by a disrupted or eroded atherosclerotic plaque is the anatomic substrate of most acute coronary syndromes including ST-segment elevation myocardial infarctions (AMI). For this pathological substrate, macro- and microembolization during percutaneous coronary intervention (PCI) in the setting of AMI is frequent and may result in obstruction of the microvessel network, and decreased efficacy of reperfusion and myocardial salvage¹. Thrombus may complicate other complex anatomic conditions associated with an altered flow such as ectatic

or aneurysmatic coronary arteries, degenerated venous grafts, or coronary stents. In this conditions frequently the thrombotic burden is large and the risk of extensive macro- and micro-vessel network disruption and myocardial infarction due to embolization during PCI is very high. Removal of thrombus before any other intervention may dramatically decrease the risk of no-flow, and has the potential for improvement in survival. A specific procedural approach to thrombus removal should be considered in the large majority of patients with AMI and in patients with angiographic evidence of thrombus and large area at risk, or a pre-existing severe left ventricular dysfunction, since in these patients a no-reflow due to embolization is associated with a very high mortality rate².

Many types of thrombectomy devices are currently available, from low technology catheters based on manual thrombus aspiration, including proximal or distal antiembolic protection devices, to high technology devices using mechanical energy allowing fragmentation

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and removal of thrombus. Studies on thrombectomy before stenting have produced conflicting results and there is not consensus on their routine use in lesions containing thrombus.

ANTIEMBOLIC PROTECTION DEVICES

Antiembotic protection devices include distal an proximal occlusive devices and filters. All studies on these devices in the setting of AMI have failed to show any reduction on infarct size and improvement in clinical outcome³⁻⁷. Conversely, their use in the treatment of degenerated venous grafts is supported by the positive results of several trials⁸⁻¹⁰.

MANUAL ASPIRATION CATHETERS

The majority of published studies on thrombectomy in patients with AMI used aspiration catheters¹¹⁻¹⁷. A major advantage of manual aspiration catheters is the easy of use. Two major limitations of these devices are the unpredictability of the efficacy, since in 30% of cases of successful lesion crossing by the catheter the aspiration is completely negative, and the high profile of the catheters that may promote embolization when the occlusion is crossed or prevent their utilization in tortuous, calcified, or small vessels. The routine use of manual aspiration catheters in the setting of AMI was supported by the positive results of some single center studies. In the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction (TAPAS) trial 1,071 patients were randomized to manual aspiration or conventional PCI, and 10% of patients randomized to thrombus aspiration crossed to conventional PCI since the operator considered the target vessel too small or tortuous to allow the use of the aspiration catheter¹⁵. Thus, in this study any traumatic attempt to cross the lesion with the aspiration catheter in patients with a difficult anatomy was avoided. Despite the exclusion from aspiration of patients with difficult anatomy, particles could be retrieved in only 72.9% of cases randomized to aspiration, and manual aspiration was associated with a better myocardial reperfusion as assessed by the surrogate angiographic primary end point of myocardial blush¹⁵. At 1 year follow-up, patients randomized to manual aspiration had a better survival than patients randomized to conventional PCI: the mortality rates were 3.6% and 6.7%, respectively¹⁶. However, it should be outlined that the study was not powered for survival and the differences in survival could be due to chance. The results of the TAPAS trial were not confirmed by TASTE trial, that is the largest trial comparing manual aspiration with conventional angioplasty in patients with AMI and sufficiently powered for clinical outcome^{18,19}. This multicenter study randomized 7,244 patients to manual aspiration or conventional PCI.

Randomization to manual aspiration was not associated with improved survival at 1 month and at 12 months. The 30-day mortality rates were 3.0% in the standard PCI arm and 2.8% in the manual aspiration arm (HR=0.94; 95%CI: 0.72-1.20; p=0.63). At 1 year, there were no difference in the composite of death, myocardial infarction and stent thrombosis between the 2 arms (17.7% in the standard PCI arm, and 16.3% in the manual aspiration arms). Another ongoing trial comparing manual aspiration with standard PCI is enrolling 10,700 patients and will provide a definite answer to the usefulness or futility of routine use of manual aspiration catheter in AMI (TOTAL; ClinicalTrials.gov number, NCT01149044).

MECHANICAL THROMBECTOMY DEVICES

The rheolytic thrombectomy (RT) system (AngioJet, Boston Scientific, Minneapolis, MN) consists of a dual lumen catheter with an external pump providing pressurized saline solution via the effluent lumen to the catheter tip. Multiple saline jets from the distal part of the catheter travel backwards at 390 mph, and create localized negative pressure zone that draws thrombus where the jets fragment it and propel the small particles to the evacuation lumen of the catheter. The first 5 F generation catheter for coronary use was associated with a substantial device failure rate due to the uncrossability of the lesion by the large and poor trackable catheter, embolization, and vessel perforation. In a post-hoc analysis in a series of 70 patients with AMI enrolled in the VEGAS 1 and 2 trials, the device failure rate was 22%^{20,21}. The second generation AngioJet catheter (XMI) and the more recent third generation catheter (Spiroflex) that are available are 4 F in size and have an improved design of the profile and of the opening of the jets allowing easy and nontraumatic navigation also in complex anatomy (tortuous or calcified vessels), and the ability to remove quickly large amount of fresh thrombus. The last generation catheter can cross the lesion without the need for pre-dilation in more than 95% of the cases.

Four randomized trials tested the efficacy and safety of RT in different settings. The efficacy of RT in decreasing procedural embolization and subsequent clinical adverse events was demonstrated by the VeGAS-2 trial that enrolled patients with a very high risk of embolization, such as patients with diseased venous grafts or native vessels with angiographic evidence of large thrombus.²¹ Patients with AMI were excluded. The study, based on a sample of 352 patients compared RT with intravessel infusion of urokinase and showed a more > 50% reduction in 1-month major adverse events in patients randomized to thrombectomy (16% and 33% respectively, P < 0.001). The Florence-AngioJet randomized trial is a mechanistic small study based on a sample of 100 patients with a first AMI and the end points of the

study were early ST-segment resolution, the corrected TIMI frame count, and the infarct size as assessed by technetium-99m sestamibi scintigraphy at 1 month.²² All end points were met. Patients randomized to thrombectomy before direct stenting had a higher incidence of early ST-segment elevation resolution (90% vs 72%, $P = 0.022$), lower corrected TIMI frame counts (18.2 ± 7.7 vs 22.5 ± 11.0 ; $P = 0.032$), and smaller infarcts ($13.0 \pm 11.6\%$ vs $21.2 \pm 18.0\%$; $P = 0.010$) as compared to patients randomized to direct stenting alone. By multivariate analysis, the only variables related to the early ST-segment resolution were randomization to thrombectomy (OR=3.56; 95%CI: 1.11 to 11.42; $P = 0.032$), and diabetes mellitus (OR=0.24; 95%CI: 0.07 to 0.86; $P = 0.029$). At 1 month, no patient died, or had reinfarction, and the 6-month clinical outcomes were identical in the 2 arms: the mortality rate was 2% in both groups, and no patient had reinfarction. The AIMI trial is a multicenter randomized trial that compared RT before stenting of the infarct artery with conventional PCI and is based on a sample of 480 patients²³. The primary end point of the study was infarct size as assessed by sestamibi scintigraphy at 14 to 28 days after the procedure. The study showed larger infarcts in the thrombectomy arm as compared to the control arm ($12.5 \pm 12.13\%$ and $9.8 \pm 10.92\%$ respectively, $P = 0.03$), and more importantly, an unexpected higher mortality in the thrombectomy arm at 1 month (4.6% vs 0.8%; $P = 0.02$) and at 6 months (6.7% vs 1.7%; $P = 0.01$). Final TIMI grade 3 flow was revealed more frequently in the control arm as compared to the thrombectomy arm (97% and 91.8% respectively, $P < 0.02$). Several concerns in study design and in RT technique may explain the negative and harmful results of the study. The enrollment criteria did not include angiographically visible thrombus, and moderate to large thrombus (grade 3 and 4 according to TIMI thrombus score) was present in an unrealistic minority of patients at baseline angiography (21.3% in the thrombectomy arm and 19.6% in the control arm). This figure suggests a selection bias against the enrollment of patients with a large amount of thrombus and who could derive the strongest benefit from thrombectomy before coronary stenting. Unfortunately, the Authors did not provide a screen fail registry, but other characteristics of the study patient cohort strengthen this suspect. More than 1 third of patients (35%) had an already open infarct artery at baseline angiography, and more importantly the infarct size is very small in both arms, with similar normal left ventricular ejection fraction at the time of scintigraphic assessment ($51.3 \pm 11.53\%$ in the thrombectomy arm, and $52.3 \pm 10.89\%$ in the control arm). Another concern of the study design is the exclusion from enrollment of patients with severe left ventricular dysfunction and cardiogenic shock. The exclusion of these high-risk patients is not easily explained considering that just in this type of patients a no-reflow due to PCI embolization may be

immediately fatal. Finally, the nonuniformity of treatment may have introduced confounding effects favoring the control arm. Eight per cent of patients randomized to thrombectomy did not have the treatment, procedural variables that may have a significant impact on the risk of no-reflow, such as predilation, or postdilation, or stent type were left at discretion of the operator, as well as the thrombectomy technique, with a distal-to proximal approach used in 48% of cases. The thrombectomy retrograde technique should be considered as inappropriate since with this technique the activation of the thrombectomy catheter is made only after the positioning of the device across the occlusion favoring embolization before thrombectomy. The JETS-TENT trial is a multicenter trials that enrolled 501 patients with AMI and angiographic evidence of thrombus TIMI grade 3 to 5, and compared RT before direct infarct artery stenting with direct stenting alone²⁴. The co-primary end points of the study were early ST-segment elevation resolution and infarct size as assessed by ^{99m}Tc-sestamibi scintigraphy. The ST-segment resolution was more frequent in the RT arm as compared with the DS alone arm: 85.8% and 78.8%, respectively ($p=0.043$), while no significant differences between groups were revealed in infarct size and the other surrogate angiographic end points. The 6-month major adverse cardiovascular events rate was 11.2% in the thrombectomy arm and 19.4% in the direct stenting alone arm ($p = 0.011$). The 1-year event-free survival rates were 85.2 2.3% for the RT arm, and 75.0 3.1% for the direct stenting alone arm ($p = 0.009$). At multivariable analysis RT was independently related to early ST-segment elevation resolution (OR=1.70; 95%CI: 1.03-2.82; $p = 0.0039$) and to major adverse cardiovascular events at 1 year (HR=0.55; 95%CI: 0.35-0.86; $p = 0.008$). Although the primary efficacy end points were not met, the results of this study support the use of RT before infarct artery stenting in patients with acute myocardial infarction and evidence of coronary thrombus.

A small randomized study including 80 patients with AMI, the SMART trial, compared the efficacy of RT with manual aspiration catheter²⁵. The primary end point of the study was residual thrombus burden after thrombectomy and before direct infarct artery stenting as assessed by optical coherence tomography. The study showed large residual thrombus burden more frequently in the manual aspiration arm as compared to RT (patients with number of quadrants containing thrombus above the median value were 60% in the manual aspiration arm and 37% in the rheolytic thrombectomy arm, $p = 0.039$). All surrogate markers of reperfusion were better in the RT arm, and, at 6 months, the percentage of malapposed stent struts in the manual aspiration arm was higher than the RT arm ($2.7 \pm 4.5\%$, and $0.8 \pm 1.6\%$, respectively, $p=0.019$). More importantly, the study showed that both techniques do not allow the complete removal of thrombus (only 1 out of

80 patients did not have residual thrombus after thrombectomy). It is unknown if the residual more organized thrombus after thrombectomy has a decreased potential for embolization after infarct artery stenting.

CONCLUSIONS

According to the available evidence the following points should be outlined: 1) The routine use of manual aspiration catheters in the setting of AMI is

not recommended due to the complete ineffectiveness of this technique in approximately 40% of cases, and the high rate of high residual thrombotic burden in most cases of positive aspiration of atherothrombotic macrodebris; 2) Rheolytic thrombectomy is more effective than manual aspiration in thrombus removal and can be used also in difficult and complex coronary anatomies but data from randomized studies are insufficient to recommend its routine use in the setting of AMI.

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