

THROMBUS ASPIRATION

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ABSTRACT

ST-segment elevation myocardial infarction results from acute occlusion of a coronary artery. Mortality is high in this acute coronary syndrome. Mechanical reperfusion by primary percutaneous coronary intervention (PCI) is the most effective method to restore coronary circulation. The ultimate goal of primary PCI is successful myocardial reperfusion. Thrombus aspiration (TA) using manual TA catheters has been reported to improve coronary and myocardial circulation. This, however, does not translate into long-term mortality benefit and may be associated with an increased risk of stroke. This article reviews the role of TA as an adjunct to mechanical reperfusion during PCI.

Keywords: Thrombus aspiration (TA), myocardial infarction, thrombectomy, myocardial reperfusion.

INTRODUCTION

Rupture of an atherosclerotic plaque with subsequent thrombus formation and vessel occlusion constitutes the principal mechanism of acute ST-segment elevation myocardial infarction (STEMI). Prompt recognition of symptoms and time-dependent return of the coronary blood flow is associated with greater myocardial salvage. Primary percutaneous coronary intervention (PCI) is the preferred method of revascularisation and is the standard of care in PCI-capable hospitals. Compared with thrombolytic therapy, patients undergoing primary PCI have faster resolution of symptoms and ST elevations, along with improved thrombolysis in myocardial infarction (TIMI) flow and myocardial blush grade (MBG). Better coronary artery patency, as well as lower re-infarction and re-occlusion rates are also seen with mechanical intervention. Thus, the most important therapeutic challenge, and the main objective of primary PCI is successful myocardial reperfusion.¹ This is dependent on restoration of flow in the epicardial vessel as well as in the microvascular circulation.^{2,3}

Mechanical intervention in STEMI patients results in disintegration and distal embolisation of thrombus and plaque fragments. This cellular debris contains platelets, erythrocytes,

fibrin, inflammatory cells, and tissue factors. Downstream, these cellular elements trigger a local inflammatory and vasoconstrictor response causing microvascular plugging. Other postulated theories of microvascular plugging include interstitial and cellular oedema, calcium overload, myocardial necrosis, and reperfusion injury from oxygen free radicals. Irrespective of the aetiology, the resultant microvascular injury causes circulatory stasis at the capillary level, thus precluding nutritive flow to the affected areas of the myocardium. Fortunately, extensive microvascular injury is uncommon, and in most cases is angiographically evident. Rarely, however, microcirculatory occlusion persists despite a patent epicardial vessel. This results in 'slow or no re-flow' phenomena and a low MBG.⁴ Slow or no-reflow is an independent predictor of adverse outcomes and is associated with larger infarct size, contractile dysfunction, heart failure, ventricular arrhythmias, and death.⁵⁻¹¹ Myocardial obstruction and reperfusion can be measured by various angiographic, non-invasive, and clinical criteria. These include TIMI flow and MBG,⁴ ST-segment resolution on echocardiogram, late gadolinium enhancement on cardiac magnetic resonance T1 imaging, and reduction in infarct size and survival free from heart failure.¹²

ANTI-EMBOLIC PROTECTION DEVICES

Myocardial salvage is dependent on reducing micro-embolisation. The presence of intracoronary thrombus at the culprit lesion site increases the risk of downstream embolisation. A large thrombus load at the time of PCI is associated with increased incidence of microvascular stasis and major adverse cardiac events (MACE).¹³ In tackling this challenge, pharmacological agents such as systemic infusion of glycoprotein IIb/IIIa inhibitors, intracoronary infusion of vasodilators, and antithrombotic/thrombolytic agents have been ineffective in most cases. Mechanical devices including mechanical thrombectomy and distal protection devices seem attractive but have failed to show any superiority compared to conventional PCI in meta-analysis and randomised controlled trials.¹⁴

Manual aspiration catheters were developed with the intent to aspirate the clot and reduce the intracoronary thrombus burden. These devices have a simple design, are easy to use, and are an inexpensive adjunct to PCI. The catheters are soft tipped for ease of use, and front and side holes are made for maximal aspiration. They require a 6 Fr guiding catheter. A head-to-head comparison of catheters with different internal lumens did not show any difference in angiographic or electrocardiographic outcomes.¹⁵ Thrombus aspiration (TA) can be performed readily and as expected, the retrieved material shows clot and plaque debris.¹⁶ During PCI, extracting a part of the thrombus out of the vessel, visualising the clot, and establishing TIMI 3 flow is appealing to the interventional cardiologist. Due to the above mentioned advantages there has been a rapidly growing interest in TA, and its use has gained acceptance in everyday clinical practice.

TRIALS AND META-ANALYSIS

Initial studies showed that the use of TA improved the coronary blood flow and helped resolve the ST elevation.¹⁷⁻¹⁹ The EXPIRA trial²⁰ further reinforced these findings and validated a reduction in 24-month MACE. Favourable results with regards to MACE and mortality benefit compared to conventional PCI alone were also reported.^{14,21,22} A meta-analysis revealed that manual aspiration thrombectomy resulted in lower all-cause mortality and fewer MACE in patients who received aspiration thrombectomy compared to conventional PCI.

This meta-analysis, however, was limited by the inclusion of data from non-peer-reviewed trials.²³ Another meta-analysis of randomised controlled trials looking at adjunctive manual TA during STEMI concluded that the use of manual TA devices could improve post-procedure myocardial reperfusion, but had no effect on long-term clinical outcomes.²⁴

In certain selected STEMI patients, TA alone without balloon angioplasty and stenting was found to be safe and effective. These were, however, small and non-randomised studies. Additionally, STEMI in these patients was not due to plaque rupture but likely due to embolism, plaque erosion, hypercoagulable states, and endothelial dysfunction.^{25,26} A recent analysis from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) suggests that TA may be beneficial in reducing the risk of stent thrombosis. This benefit may come without an increased risk of stroke. At 30 days, there was a 2.9% reduction ($p < 0.001$) in the relative risk of stent thrombosis; however, the absolute difference was small. The rates of thrombosis were 0.4% in the aspiration group versus 0.6% in the PCI-only group, while the stroke rates and mortality were similar in both groups.²⁷ Although these findings are encouraging, they need to be interpreted with caution.

The TAPAS trial, a landmark study of 1,071 patients, was performed to assess whether manual aspiration was superior to conventional treatment during primary PCI. Angiographic and electrocardiographic signs of myocardial reperfusion, as well as clinical outcomes were assessed. An MBG of 0 or 1, defined as absent or minimal myocardial reperfusion, occurred in 17.1% of patients in the TA group versus 26.3% in the conventional PCI group. The authors concluded that manual thrombectomy results in better reperfusion and clinical outcomes than conventional PCI. This was irrespective of the baseline clinical and angiographic characteristics of the enrolled patients.¹⁸ One-year follow-up of the TAPAS trial showed that TA was beneficial with respect to mortality even with a longer follow-up period.²⁸ The TAPAS trial was a major breakthrough and changed the practice paradigm; aspiration thrombectomy was adopted as a routine adjunct to primary PCI. Thus between 2011 and 2013 various STEMI guidelines endorsed manual TA as reasonable for patients undergoing primary PCI, placing it in Class IIa with level of evidence B

indication in STEMI patients; this included the guidelines from the following organisations: In 2011, the American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography Interventions (ACCF/AHA/SCAI) for PCI; in 2012 the European Society of Cardiology (ESC) for STEMI; and in the 2013 the ACCF/AHA for STEMI.²⁹

The debate regarding the routine use of aspiration prior to PCI was initiated by the results of the TASTE trial.³⁰ This well designed, multicentre, prospective, randomised, open-label controlled trial evaluated 7,244 patients with STEMI who were randomised to either manual TA followed by PCI or to PCI only. The primary endpoint was all-cause mortality at 30 days. Death occurred in 2.8% of the TA group compared with 3.0% in the PCI only group. There was no significant difference in the rates of stent thrombosis target-lesion revascularisation, rate of stroke, heart failure, or left ventricular dysfunction at the time of discharge. A neutral outcome was seen in all subgroups, irrespective of baseline clinical or angiographic characteristics. The authors concluded that manual TA before PCI did not reduce 30-day mortality among patients with STEMI. One-year follow-up of the TASTE trial showed comparable all-cause mortality of 5.3% in patients belonging to the TA group compared with 5.6% in the PCI only group.³¹ The TASTE trial results were somewhat limited by the fact that angiograms were not reviewed in a blinded fashion. The findings with respect to myocardial salvage, microvascular obstruction, and biochemical variables were not recorded in the registry. Any reasons for deviation from the randomly assigned treatments were not documented. Additionally, the angiographic variables were entered into the registry by the treating physicians and as they were already aware of which group each patient was assigned to, these variables were susceptible to bias.

This set the stage for TOTAL, a large, international, investigator initiated, multicentre, prospective, randomised trial comparing primary PCI with or without upfront routine manual thrombectomy.³² A total of 10,732 patients with STEMI, referred for primary PCI within 12 hours of symptom onset, participated in the trial. These patients were randomly assigned to routine upfront manual thrombectomy with PCI versus PCI alone. Thrombectomy was performed by Export AP® Aspiration Catheter (Medtronic) with a standard

specified technique. PCI was performed either after or without thrombectomy according to the operator's usual technique. Baseline characteristics were well balanced between the two groups, however there were fewer smokers and a longer average time interval from symptom onset to hospital arrival in the thrombectomy group compared with the PCI alone group. There were low crossover rates: 4.6% from thrombectomy to PCI alone group, and 1.4% from PCI alone to thrombectomy group. Bailout thrombectomy was permissible in case of failure in the initial PCI alone strategy.

The primary outcome of composite death from cardiovascular causes, recurrent myocardial infarction, cardiogenic shock, or New York Heart Association (NYHA) Class IV heart failure within 180 days was similar in both groups (6.9% in the thrombectomy group versus 7.0% in the PCI alone group). The incidence of stroke, however, was higher in the thrombectomy group at 0.7% versus 0.3% in the PCI alone group. The authors concluded that for patients undergoing primary PCI for STEMI, the strategy of routine manual thrombectomy did not reduce the risk of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or NYHA Class IV heart failure within 180 days, but was associated with increased rate of stroke within 30 days.

Limited data exist regarding TA in patients receiving bioresorbable vascular scaffolds (BVS). As the use of BVS is expanding, the interest in routine TA is dwindling down. A recent meta-analysis of six randomised controlled trials comparing everolimus-eluting BVS versus everolimus-eluting metallic stents showed an increased incidence of subacute stent thrombosis with the BVS group.³³ Nonetheless, there are not enough data available to properly assess the role of TA in this subset of patients as only a few STEMI patients given BVS were studied.

In the largest registry study of TA so far, 10,929 patients from the British Cardiac Intervention Society (BCIS) dataset had primary PCI performed at UK hospitals. Seven thousand three hundred and fifty-seven (67.3%) patients had conventional PCI while 3,572 (32.7%) underwent TA as an adjunct therapy. TA was performed at the operator's discretion. TA was more often performed in sicker patients who had TIMI 0 flow, were younger, and had poor left

ventricular function. There were fewer in-hospital MACE in the TA group (4.4% versus 5.5%), however there was no difference in the incidence of MACE at 3-year follow-up. This signifies that even in selected patients TA is not advantageous.³⁴

In a recent meta-analysis of 17 trials, which included 20,969 patients, aspiration thrombectomy failed to show improved clinical outcomes compared to conventional PCI. There was no significant reduction in the risk of mortality, re-infarction, or stent thrombosis. Aspiration thrombectomy was, however, associated with a non-significant increase in risk of stroke.³⁵ TA may not be as benign as initially comprehended; complications such as systemic embolisation and a trend towards an increased risk of stroke were also reported with the use of TA devices in other studies.^{36,37} Data reported from Sweden found higher mortality among patients who had TA before PCI compared to PCI alone.³⁸

THE ROLE OF THROMBUS ASPIRATION IN SUBACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION AND NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION PATIENTS

Similarly, in contrast to earlier reports, a recent randomised trial evaluated thrombectomy in subacute STEMI patients. These patients presented between 12 and 48 hours after symptom onset. They underwent cardiac magnetic resonance imaging for assessment of reperfusion success. The study concluded that the routine use of TA in such patients does not have any benefit in angiographic and clinical endpoints.³⁹

TA is ineffective and infrequently used in Non-STEMI (NSTEMI) patients. This may be due to a smaller thrombotic burden and delayed time to PCI compared with STEMI patients. Additionally, NSTEMI patients have a more organised and fibrin-based thrombus.⁴⁰ Subgroup analysis of the ACUITY trial showed a 2% use of TA in NSTEMI patients.⁴¹ In the TATORT-NSTEMI trial, 440 patients with thrombus-containing lesions presenting with NSTEMI were randomised to PCI with aspiration thrombectomy or PCI alone. Adjuvant TA did not improve the TIMI flow or MBG, nor did it reduce the amount of late microvascular obstruction or infarct size. At 6 months there was no significant difference in mortality, target-vessel revascularisation, or

new congestive heart failure benefits between the two groups.⁴²

The most recent focussed update document by the ACCF/AHA/SCAI downgraded routine aspiration thrombectomy to Class III, level of evidence A (no benefit) as a result of the large randomised clinical trials TASTE and TOTAL.⁴³ Thrombectomy was demoted in the ESC/European Association for Cardio-Thoracic Surgery (EACTS) revascularisation guidelines from Class IIa level of evidence B recommendation to Class IIb level of evidence A recommendation.⁴⁴

Different trials have shown varying results and many reasons account for this discrepancy. It is clear that not all STEMI patients are alike and not all vessels behave in the same fashion. STEMI resulting from atherosclerotic plaque rupture may behave differently from that of plaque erosion. TA in a calcified lesion will not respond in a similar way to a non-calcified vessel. Ectatic and aneurysmal arteries are prone to reduced TIMI flow, stasis, and large thrombus burden in acute coronary syndromes; TA in this group of patients is not well studied. Clinically, the time from symptom onset to reperfusion, the degree of thrombus burden, and concomitant pharmacotherapy use all impact the final results and success of PCI and TA. Additionally, trial design, patient selection biases, and other limitations of different trials will affect the outcomes of different trials.

The TAPAS trial had several limitations. It was a single-centre experience, randomisation was performed before PCI, and as a consequence some patients did not undergo PCI or receive alternate therapy. This selection bias may have diluted the positive effects of TA. The effect of pre-dilation of a lesion was not evaluated, while the findings of both TASTE and TOTAL apparently leave little or no role for manual TA as a routine adjunct to PCI in STEMI patients. These trials were also not without limitations. Patients with low thrombus burden, who would be less responsive to thrombectomy, were included in the trials. The treating interventionists were aware of the study group assignments and this could have led to management biases, e.g. concomitant use of different types and doses of antiplatelet and anticoagulant agents. Angiograms were not read in a blinded fashion. TA was reserved as bailout in the PCI alone group and so selective use of thrombectomy versus no thrombectomy was not compared. The reason for

deviation from randomly assigned treatment was not documented, and neither trial excluded the possibility of benefit in high-risk patients. On the contrary, the incidence of stroke associated with TA, one of the more important findings of the TOTAL trial, was noted between 30 and 180 days post-procedure. Certainly this cannot be explained by a periprocedural event, raising the possibility of it occurring by chance. Analysis from the SCAAR suggests that similar stroke rates occur in both groups.

Keeping these aspects in consideration, the door to TA may not be closed to all subsets of patients. STEMI patients that might benefit from this easy adjunct to PCI include those with large thrombus burden, especially in ectatic arteries. STEMI resulting from an embolic aetiology should be considered for TA. Additionally, young patients without much atherosclerotic disease and patients with STEMI resulting from plaque erosion may also have a favourable response. TA may also be valuable in retrieving a large, distally-embolised thrombus distal to the plaque rupture site.

Primary PCI, when available, is the most effective method of reperfusing an occluded artery. Distal embolisation of thrombus and plaque fragments during PCI triggers a local inflammatory and vasoconstrictor response causing microvascular obstruction. Failure to restore flow at the microvascular level results in expansion of the necrotic zone and is associated with adverse clinical outcomes. TA is an easy adjunct step to primary PCI, and initial studies demonstrate improved clinical outcomes. Nonetheless, large randomised clinical trials and recent meta-analysis have failed to show any clinical benefit. Thus, currently all major cardiac societies recommend against its routine use in STEMI revascularisation guidelines. Precisely which subgroups of patients may benefit from this technique, and the genuine concerns about its safety and increased risk of stroke, need to be investigated in future studies.

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