ACTA SCIENTIFIC NEUROLOGY

Volume 2 Issue 9 September 2019

Review Article

Revolution in the Care of Acute Ischemic Stroke; Mechanical Thrombectomy

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Received: July 29, 2019; **Published:** August 30, 2019

Abstract

Early arterial recanalization of the occluded vessel with adequate restoration of blood flow remains the primary objective of acute ischemic stroke and is crucial for achieving favorable functional outcome. Endovascular thrombectomy is a highly effective treatment for acute ischemic stroke due to large arterial occlusion. Endovascular recanalization can be achieved using two main approaches [1] intra-arterial fibrinolysis and [2] endovascular thrombectomy and clot retrieval. Although intravenous fibrinolysis can be provided faster than endovascular interventions, it has a lower recanalization rate than their endovascular counterpart. Early randomized trials that evaluated the role of thrombectomy in comparison to medical therapy failed to demonstrate the superiority of thrombectomy; primarily, because of the later onset of treatment of patients enrolled in the studies and modest recanalization rate. Randomized trials that assessed the use of newer devices including stent retrievers resulted in better recanalization rates, lower incidence of hemorrhage, and better functional outcomes. With the advent of better recanalization tools as well as improved systems that aim to reduce door-to-recanalization time and improved selection of patient that would benefit from intervention (patients with proximal large vessel occlusion associated with penumbra) create a new era in stroke management. More recent randomized controlled trials, dating back to November 2014, that assessed the role of mechanical thrombectomy [1] clearly showed the benefits of this procedure. The efficacy of thrombectomy in the treatment of stroke is very high and has never been met with previous stroke treatment. Thrombectomy has a number needed to treat of less than 3.Without any doubt, the literature elucidates the revolutionary benefits of thrombectomy for stroke patients; however, the key challenges related to access, effectiveness, and safety of this procedure should still be addressed in order to improve stroke care [1].

Keywords: Acute Ischemic Stroke; Mechanical Thrombectomy; Stroke

Introduction

The word carotid is derived from the Greek term karotids or karos, meaning to stupefy or plunge into a deep sleep. The term was applied to the arteries of the neck by Rufus of Epheses (circa 100 A.D.) and compression of these arteries was noted to initiated sleep or drowsiness in a person [2]. In ischemic stroke, an acute arterial occlusion rapidly produces a core of infarcted brain tissue surrounded by hypoxic, but potentially salvageable, tissue, the ischemic penumbra [3-5]. Penumbral tissue is viable due to collateral blood flow and the time to irreversible injury is largely dependent on the degree of collateral flow. The goal of recanalization therapy is rapid restoration of blood flow and preservation of the ischemic penumbra [6,7]. Intravenous (IV) recombinant tissue plasminogen activator (tPA) is a recanalization agent approved by the Food and Drug Administration (FDA) for the treatment of acute ischemic stroke within 3 hours of symptom onset [8]. However, IV tPA achieves reperfusion in only 30–50% of large-artery occlusion, in part because of the low concentration of lytic agent arriving at the target thrombus [7]. The number needed to treat of IV thrombolysis in stroke patient ranges from 5 (if administrated within 90 mins of stroke onset) to 9 (if administrated within 3-4.5 hours of stroke onset) [9]. The main factors that are associated with poor

outcome following IV thrombolysis administration are the location [12,13] and length [10,11] of the thrombus. Given the limitations of systemic thrombolysis for cervicocerebral reperfusion, intense efforts have been directed at developing endovascular reperfusion treatments.

Intra-arterial thrombolysis

Intra-arterial (IA) thrombolysis was first reported by Zeumer et al. in 1983 where five patients with vertebrobasilar occlusion were treated with local IA fibrinolysis [15]. As initially the majority of experience with IA thrombolysis was based on retrospective studies, no definite conclusions could be drawn with respect to efficacy or safety of IA thrombolysis. Three large, multicenter trials have been performed in IA thrombolysis: Prolyse in Acute Cerebral Thromboembolism Trial (PROACT), PROACT II and the Japanese Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT).

PROACT I

PROACT I was designed to evaluate the safety and efficacy of IA administration of pro-urokinase in patients with acute ischemic stroke. The study consisted of a uniform population of stroke patients presenting within 6 hours of symptom onset with middle cerebral artery (MCA) M1 or M2 occlusion. Forty patients were randomized at a median 5.5 hours from symptom onset with 26 receiving pro-urokinase and 14 placebo. Partial or complete recanalization was seen in 15 of 26 (57.7%) patients treated with pro-urokinase and in two of 14 (14.3%) placebo patients. Symptomatic hemorrhage occurred in four of 26 (15.4%) treated patients and in one of 14 (7.1%) placebo patients (P -value non-significant). The number of patients was too small to show statistical significance in clinical outcome. The 90-day mortality was 26.9% in the pro-urokinase group and 42.9% in the placebo group (P -value non-significant) [16].

PROACT II

In the PROACT II trial that compared intra-arterial pro-urokinase with heparin versus heparin alone for the treatment of middle cerebral artery ischemic stroke without hemorrhagic transformation or signs of early infarcts on CT. Results were in favor of the former group: 40% of patient achieved good outcome in treatment arm versus 25% in the control arm that only received heparin [14]. This endovascular approach resulted in the development and advent of mechanical thrombectomy. Despite the increased frequency of early hemorrhage, patients receiving IA pro-urokinase exhibited improved clinical outcome at 90 days. Although PROACT II was a positive trial, it did not lead to regulatory approval of pro-urokinase for acute ischemic stroke, as the FDA typically requires two positive trials for new drug registration and the sponsor did not pursue a confirmatory study.

Intra-arterial thrombolysis in the posterior circulation

Ischemic stroke involving the posterior circulation carry different nuances that differ it from its counterpart in the anterior circulation. The literature addressing bilateral vertebral artery or basilar occlusions indicates a poor prognosis with a mortality rate ranging from 70 to 80% [17-19]. Moreover, the signs and symptoms that results from a posterior circulation stroke differ from those associated with an anterior circulation stroke. In the case of an anterior circulation stroke, the timing of symptoms usually coincide with the abrupt event of vessel occlusion. In posterior circulation strokes, symptoms tend to be more gradual than in anterior circulation strokes [20,21].

This makes it difficult to accurately define the timing of symptoms onset to see whether the patient falls within the safe and effective window for reperfusion. Posterior circulation infarcts are also found to have a high frequency of concomitant severe intracranial large vessel disease [22,23]. *In situ* thrombosis associated with atherosclerosis disease is more common in posterior circulation stroke as compared to anterior circulation ischemic stroke. Fibrinolysis treatment may clear a clot partially, which may be a hazard for re-thrombosis due to the burden of the remaining clot [24,25]. Due to the slower progression of posterior circulation strokes and the lower risk of hemorrhagic sequels (as smaller amount of tissue is at risk), thrombolysis beyond 6 hours in posterior circulation strokes may be more beneficial than in anterior circulation strokes. Multiple series have reported cases that received treatment up to 24 hours following symptom onset.

Mechanical thrombectomy

The advent of mechanical clot retrieval have announced a new dawn for the management of large vessel strokes. Interventions for acute cerebral ischemia have followed, more slowly, the evolution of interventions of acute myocardial ischemia, with the iterative development of mechanical techniques superior in recanalization efficacy to IV or IA thrombolysis alone [26,27]. Attempts of angioplasty with/without stenting have been employed as a substitute treatment [28]. However, a potential disadvantage of this strategy is forcing the clot into the deep penetrating arteries with worsening ischemia and the potential risk of rupturing the blood vessel. Other strategies included delivering energy to fragment the clot

with the utilization of ultrasound and laser devices. MERCI Retriever (Concentric Medical, Mountain View, California) was one of the first devices approved by Food and Drug Administration (FDA) for ischemic stroke treatment [29,30]. the initial design of the Merci retriever was a tapered wire with five helical loops of decreasing diameter from 2.8 mm to 1.1 mm at its distal end. The retriever is placed through the micro catheter and as it exits the micro catheter the helical loops begin to reshape in order to snare the clot in the occluded vessel. The clot is then pulled back to the carotid vessel in the neck and aspirated out through the guide catheter. In August 2004, the FDA approved Merci Retrieval System (MERCI), which is the first endovascular device to be cleared for stroke [31]. The MERCI randomized controlled trial [32] showed a recanalization rate of 47% when MERCI was used alone versus 60.8% when MERCI was used in combination of recombinant TPA. Cerebral hemorrhagic complication rate of 7.8%.

The Multi MERCI trial [33] that evaluated a later-generation MERCI demonstrated a recanalization rate of 69.5% when used following lytic therapy (IV or IA) with favorable clinical outcome in 34% of patients. No control group was involved in the study. In 2009 a new mechanical device, the Penumbra System, was approved by the FDA for clot removal in acute ischemic stroke patients [34]. The Penumbra System (Penumbra, Alameda, California) removes the thrombus primarily by aspiration. The PS entails 3 major components: the reperfusion catheter, separator, and the thrombus removal ring. The initial safety and effectiveness study was carried out enrolling subjects with acute ischemic stroke presenting within 8 hours of symptom onset [34]. A total of 23 patients were enrolled with 21 vessels treated. All 21 vessels (100%) were successfully revascularized.30 days post-treatment, 9 subjects (45%) had an NIHSS score > 5 or mRS =< 2. The overall mortality rate was 45% (9 out 20 patients). Stent retrievers were developed to improve earlier thrombectomy devices by allowing intraluminal flow restoration when deployed with more effective clearance of the thrombus, less risk for fragmentation and embolism of the thrombus, and minimal trauma to the wall of vessels [35,36].

The first FDA approved stent retriever, Solitaire FR Revascularization Device (Coviden Neurovascular, Irvine, California), was approved based on the results of the SWIFT trial [37]. SWIFT depicted the efficacy and safety of the device as compared to the MERCI coil retriever. This was a randomized, controlled trial that involved 21 centers in the United States and France. Ischemic stroke patients with large vessel occlusion who presented within 8 hours of onset of symptoms were randomized to either treatment using Solitaire FR or using the MERCI device. The primary objective of the study was successful revascularization, as evaluated by a core lab and defined as TIMI2 or 3 flow in without symptoms of intracranial hemorrhage. A maximum of 3 passes of the device was allowed to achieve arterial revascularization. In case of failure to retrieve the clot within 3 passes, the thrombectomy procedure would be considered a failure and further rescue therapy using an FDA device would be done. After subject randomization (Solitaire arm: 58, Merci arm: 55) a pre-specified stopping rule was dictated, and if reached, the trial would be terminated. The primary efficacy outcome was achieved more often in Solitaire vs Merci patients, 60.7% vs 24.1% (difference 36.6% [18.5% to 53.4%], OR, 4.87; 95%CI, 2.14 to 11.10; non-inferiority P < 0.0001; superiority P = 0.0001). The rate of good neurologic outcome (mRA =<2, or increase in NIHSS score > 10 points, equal to prestrike mRS if it was >3) at 3 months was higher in Solitaire arm than in the Merci arm (58.2% vs. 33.3% p=0.02) Mortality was reduced with Solitaire, 17.2% vs 38.2% (difference −20.9% [−38.6% to −2.7%], OR, 0.34; 95%CI, 0.14–0.81; non-inferiority P = 0.0001; superiority P = 0.02). In conclusion, the Solitaire FR device was shown to achieve a higher rate of recanalization than the Merci retriever and better follow-up clinical outcome (mortality and neurologic outcome).

Optimism about thrombectomy was diminished when three early randomized controlled trials published in 2013 [38-40] failed to show improved efficacy of endovascular clot retrieval compared with intravenous thrombolysis. However, the study designs were criticized because of the following: limitations in patient selection (in one of the studies,38 documented large vessel occlusion was not required), use of older technology (mainly first generation clot retrieval devices) and a long delay from stroke onset to intervention. Still, a post-hoc subgroup analysis of patients that had large vessel occlusion (on CT angiogram imaging) showed that they benefited from IV-rTPa treatment within 90 mins of onset of symptoms [41].

Everything changed with the publication, in rapid succession, of nine landmark randomized controlled trials [42-49] testing new-generation stent retriever devices (between December 2010 and February 2015), which showed the consistently clear superiority of endovascular clot retrieval over standard medical care alone in reducing disability at 90 days in patients with ischemic stroke due to anterior circulation large vessel occlusion, as measured by the modified Rankin Scale (mRS; the primary outcome measure).The MR CLEAN study (Multicenter Randomised Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke) [42] was ended before completion of patient enrollment due proof of efficacy and/or

loss of equipoise. The early study termination might have resulted in overestimation of effect size in subsequent trials. Unlike previous stroke trials that showed no benefits of devices, these studies only selected patients with proven large vessel occlusion as assessed by CT angiography imaging and for the most part enrolled patients within 6 hours of the stroke onset. The HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) meta-analysis which was a collaboration project that involved all first 5 fives positive studies [50] provided high-level evidence in favor of the efficacy and safety of mechanical thrombectomy. In the pool of 1287 patients collected in the meta-analysis, additional subgroup analyses that were not feasible in individual trial (due to limited group size) were explored. The HERMES meta-analysis showed that a good, independent, functional outcome (mRS of 0 to 2 at 90 days follow-up) was achieved in 46% of patient who received mechanical thrombectomy versus 26.5% in patient who only had best medical treatment. IV-rtPA was administered to 83% of the subjects in the thrombectomy arms and 87% of the subjects in the control arms. In order to achieve a decrease of 1 point on the mRS scale, the number needed to treat to was found to be 2.6. The 90 days mortality as well as the rate of symptomatic ICH was similar in the IV-rTPA and IV-rTPA with thrombectomy arms. The benefit was also appreciated in patients older than 80 years and patients who did not get IV-rTPA treatment. Thrombectomy was beneficial across the different NIHSS scores ranging from mild to severe strokes.

Despite the lack of statistical heterogeneity in regard to the level of ischemia (measured using the ASPECTS score), a clear benefit was appreciated for subjects with ASPECT>5 (limited extent of early ischemia).However, only few patient had an ASPECTS score below 5.The major findings from HERMES have been confirmed by other more recent meta analyses [51-53]. Based on these findings, updated guidelines were published in Canada, USA, Europe, and the UK. They now recommend that mechanical thrombectomy be provided to patients with occlusion of the proximal middle cerebral artery or internal carotid artery who have received treatment with IV r-tPA within 4.5 hours of onset [53] and can undertake the procedure (arterial puncture) within 6 hours of symptom onset. Of the five studies [54-61], improved outcomes were shown when thrombectomy is performed up to 7.3 hours after onset of symptoms in patients that meet imaging criteria of the randomized trials. The greatest benefit is still intervention within the first two hours. Patients with minor infarct core volumes (ASPECTS 9-10) had a greater decline in benefit and longer symptom onset than Those with moderate infarct core volumes (ASPECTS 7-8) Just as with IV r-tPA, the speed of delivery of mechanical thrombectomy is paramount in achieving best possible results. However, the treatment window for smaller, irreversibly damaged ischemic cores could be longer.

Patients selection

It's imperative to have expedient expert assessment for localization, severity, stratification and diagnosis (NIHSS) together with clear brain vascular images. It's also crucially important to have excellent communication and teamwork between neurointerventionist and stroke physician as decisions are time sensitive and complex. To determine the probability of access to the target occlusion its essential to obtain an extracranial vessel image from the CT angiogram.

The selection criteria applied in practice should parallel those of the successful trials, including the following

- Documented large vessel anterior circulation occlusion (middle cerebral artery, M1 or internal carotid artery)
- Significant clinical deficit at the time of treatment (this might be NIHSS>5 or a lower score that is functionally significant for the patient; note that even mild deficit from proven large vessel occlusion has a high risk of clinical deterioration).
- Lack of extensive early ischemic change (those with ASPECTS more than 5 on plain CT clearly benefit).
- Pre-stroke functional status and lack of serious comorbidities indicating potential to benefit from treatment (note that age>80 years alone is NOT a contraindication to treatment).
- Treatment with intravenous thrombolysis within 4.5 hours (although patients ineligible for intravenous thrombolysis due to bleeding risk were also included in some of the trials and might also reasonably be offered treatment).
- Thrombectomy can be performed within 6 hours.
- Good collateral circulation (though benefit in patients with poor collaterals remains uncertain.

Future direction

There are many remaining questions regarding thrombectomy with a little data on thrombectomy for basilar artery thrombosis. Existing data suggests a high percentage of patients (68%) have unsatisfactory outcomes (mRS>3) with no notable variance in the use of mechanical thromectomy [62] and intravenous thrombolysis. As demonstrated in the anterior circulation, recanalization is

a main prognostic in posterior circulation stroke. A meta-analysis of 45 observational studies (n=2056) comparing reperfusion versus no reperfusion in acute basilar stroke demonstrated a number needed to treat to decrease depending or death of 3 [63]. The time window is thought to be longer for basilar thrombosis (up to 12-24 hours) due to the hemodynamics of collateral vasculature in the posterior circulation, clot composition, and tissue properties of supplied parenchyma. The best form of imaging and processing available to delineate the extent of ischemia and potentially salvageable tissue as well as collateral supply requires additional study. Is MRI more optimal than CT? Is perfusion imaging needed or will ASPECTS and collateral assessments suffice? This is a crucial issue fort thrombectomy implementation since imaging triage is likely to become critical in the "drip and ship" model.

Continuous quality improvement is an essential component of any effort to improve the quality of stroke care. It begins with agreement on the outcomes to be measured followed by the structured collection of clinical data in clinical registries. That information is then used to identify gaps in care, followed by education and the implementation of processes designed to improve care.

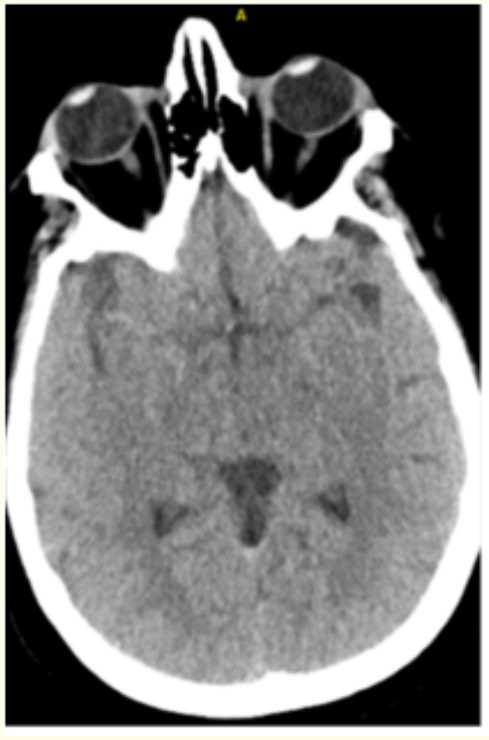

Figure 1: Hyperdense sign in RT MCA.

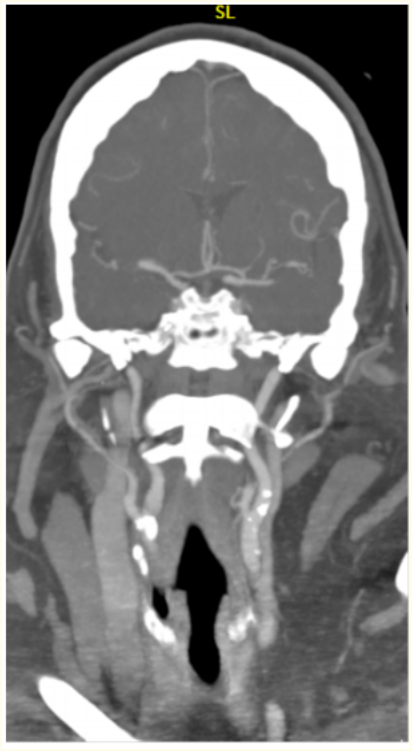

Figure 2: Occlusion of RT MCA.

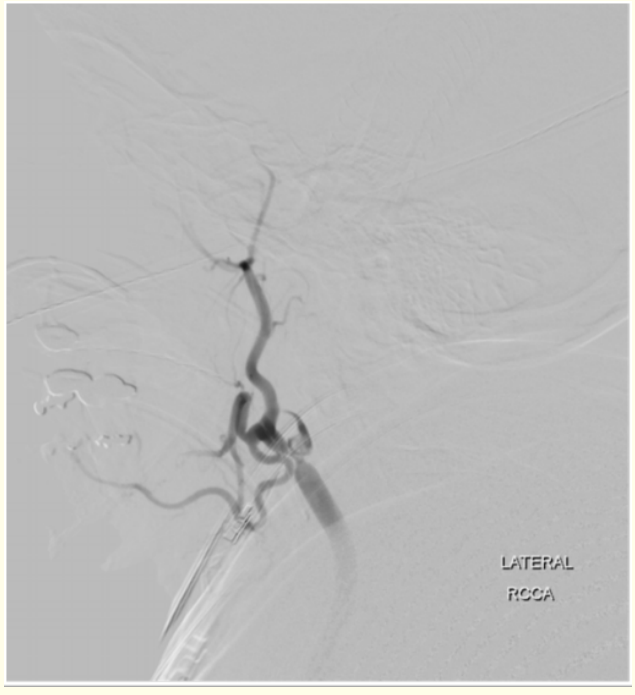

Figure 3: Occlusion of the RT ICA at the origin.

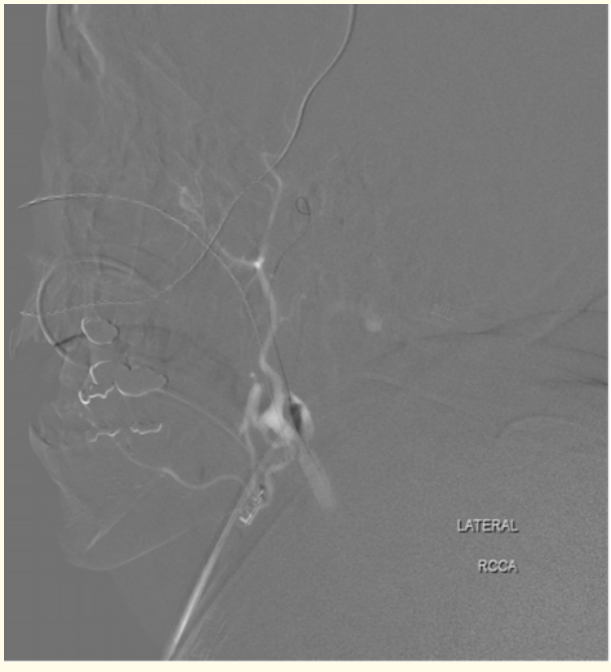

Figure 4: Balloon angioplasty.

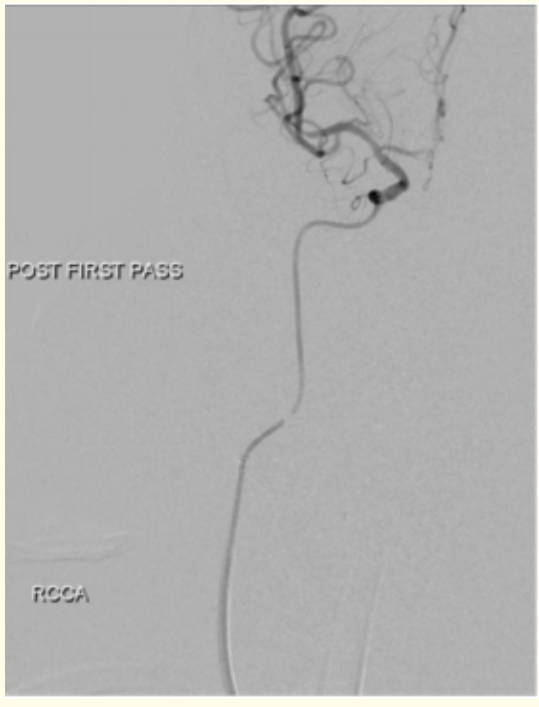

Figure 6: Distal recanalization.

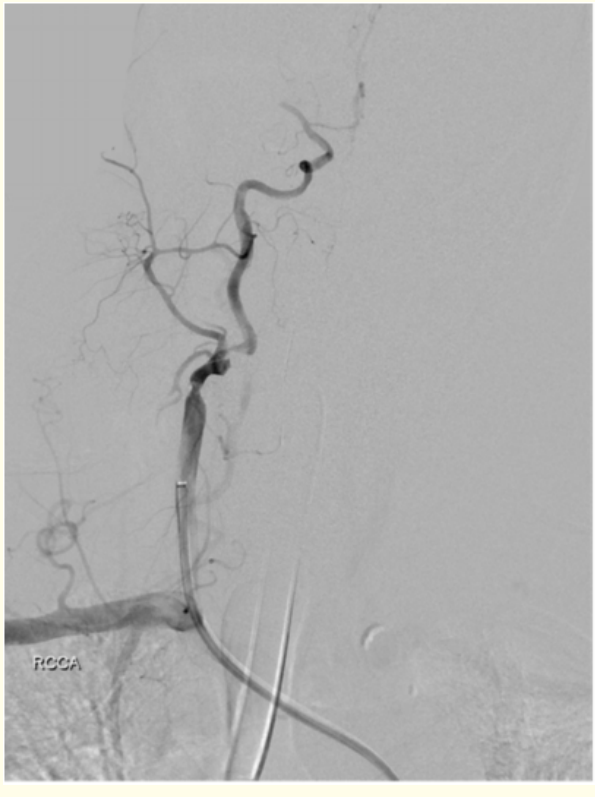

Figure 5: Tandem lesions.

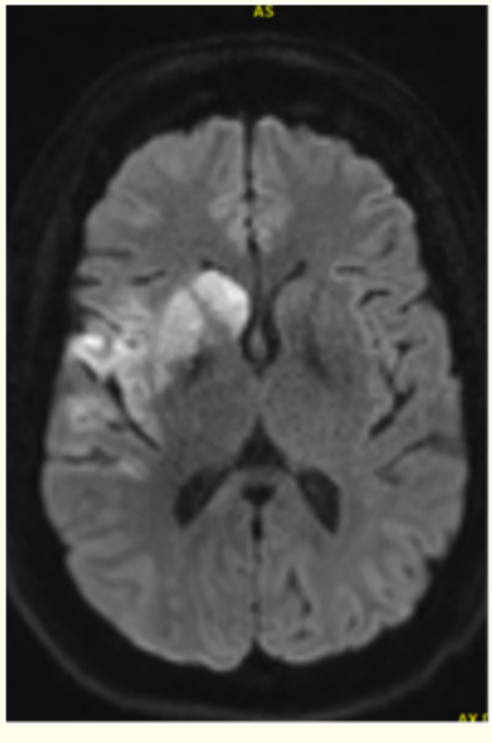

Figure 7: Post OP MRI brain.

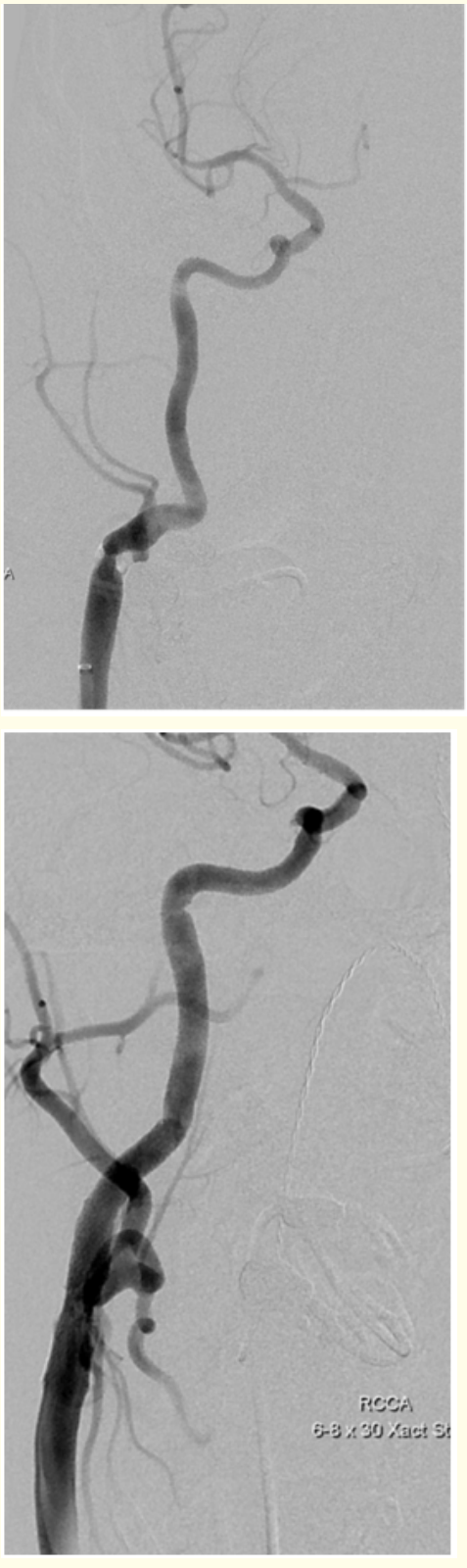

Figure 8: ICA stenosis that addressed in second stage with stent placement.

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