Mechanical Thrombectomy: Answering Unanswered

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Abstract

The stroke physician community witnessed a major "breakthrough" in acute stroke therapeutics when the results of the first of the many positive trials, "MR CLEAN," were published showing a significant absolute benefit in favor of mechanical thrombectomy in patients with large vessel occlusion (LVO). Thereafter, the investigators of ESCAPE, SWIFT PRIME, REVASCAT, THRACE, and PISTE concluded the same. Based on the initial studies, the American Stroke Association amended the 2013 guidelines in 2015 to include mechanical thrombectomy as the standard of care in patients with LVO presenting within six hours. In the past year, the horizon was further expanded when two major landmark trials, DAWN and DEFUSE 3, established the benefit of mechanical thrombectomy in the delayed window period in a select group of patients. It further led to the inclusion of the delayed window period treatment strategies in the 2018 guidelines. However, there are many unanswered questions in scenarios like small deficit with LVO, borderline large core, wake-up stroke (WUS), tandem occlusion, imaging of choice, conscious sedation (CS) versus general anesthesia (GA), and choice of technique. In our review, we aim to answer these questions along with a schematic representation of current techniques used in stroke thrombectomy.

Keywords: ASPECTS, large core, low NIHSS, mechanical thrombectomy

Introduction

In recent years, there has been a mammoth change in the management of acute ischemic stroke (AIS). After a series of failed trials, numerous trials have shown a strong benefit with mechanical thrombectomy. The first of these trials, MR CLEAN, had a broader inclusion criterion; in particular, there was no need for advanced imaging-based core volume estimation. The median final infarct volume in the endovascular intervention arm was the highest amongst all trials at 49 ml, and it is likely to represent a real-life scenario. The trial favored intervention in the first six hours with an absolute benefit of 13.5 percentage points (32.6% vs. 19.1%; odds ratio [OR] –2.16).[1] Another trial, the ESCAPE trial, mandated core and collateral estimation based on computed tomography (CT) angiography and imaging to puncture and reperfusion times of <60 and <90 minutes, respectively. There were more functionally independent patients in the intervention arm with odds of a good outcome in favor of endovascular management being 2.6 fold (43.7% vs. 28.2%). Furthermore, this was the only trial that showed an absolute mortality benefit of 9%.[2] Thereafter, the perfusion imaging-based trial, the EXTEND IA, showed the strongest benefit that was fourfold in favor of the mechanical thrombectomy. The median final core volume was 23 ml, which was less than half of that found in the MR CLEAN trial. Therefore, the main criticism was that stringent imaging inclusion criterion may have resulted in the exclusion of a considerable proportion of patients who may have otherwise benefited from treatment.[3] Overall seven trials, including REVASCAT, SWIFT PRIME, THRACE, and PISTE, showed a benefit in favor of mechanical thrombectomy in large vessel occlusion (LVO).[4–7] Based on the above trials, the American Stroke Association has recommended mechanical thrombectomy with a stent retriever in a functionally independent adult (age > 18 years) presenting with a large clinical deficit (National Institutes of Health Stroke Scale [NIHSS] score of ≥ 6) from an occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA) segment 1 (M1) and a small core (ASPECTS of ≥ 6), provided the treatment can be initiated (groin puncture) within six hours of symptom onset.[8] However, there are many burning unanswered questions and our review aims to address these questions in a systematic fashion.

Delayed window period: How wide is the window?

Globally, less than 10% of stroke patients received thrombolysis making it explicit that the major hurdle was to get in patients within the acceptable time window. To address the question if patients could be treated in the later time windows, two landmark thrombectomy trials, namely DAWN and DEFUSE 3, were conducted. In the DAWN trial, 206 patients were recruited in the 6 to 24 hours window if patients either had a core volume less than 50 ml with a big clinical deficit (NIHSS score of >20) or core volume <30 ml with a less severe deficit (NIHSS score of >10). They noted an absolute benefit in favor of mechanical thrombectomy of 36% (49% vs. 13%); there was no increase

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in rates of symptomatic intracranial hemorrhage (sICH).[9] In the perfusion imaging-based selection trial, DEFUSE 3, the core cutoff limit was 70 ml and the ratio of tissue at risk to core volume was ≥1.8. They randomized 182 patients in the 6- to 16-hour window and noted an absolute benefit of 28% in favor of thrombectomy (45% vs. 17%).[10] Until these two trials, it was relentlessly believed that time was one of the, if not the most, crucial factor in determining the chance of a good outcome following mechanical thrombectomy. Contrary to the above popular belief, the above two randomized trials, which enrolled patients at late time windows, showed a much higher absolute benefit in good outcome when compared with the early time window trials. This paradox can be explained by the rate at which infarct progressed. After stroke onset, it was noted that the patient group who had a target mismatch had a much slower rate of progression in infarct volume as compared with the group with a no target mismatch. The rate at which the infarct progressed is dictated by the extent of collaterals and it can be either slow (2.9 ml/hr) or rapid (43.9 ml/hr) (DEFUSE 2 trial).[11] Of note, the median final core volume was 8 ml in the DAWN trial and 9.4 ml in the DEFUSE 3 trial. Therefore, it is apparent that the late window trials included only those patients who had a small core and were slow progressors. However, it is known that if the slow progressors are not reperfused, the the diffusion-weighted magnetic resonance imaging (DWI-MRI) core volume tends to increase volume tends to increase gradually and reach the maximum at three days. Hence, based on the above two trials, the American Stroke Association recommended mechanical thrombectomy in selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria.[8]

Small clinical deficit: Are minor strokes candidates?

The other area of uncertainty is the therapeutic strategy one should adopt in the set of patients who have a mild deficit (NIHSS score of ≤5) and an LVO, the main concern being early symptomatic neurological deterioration (END). The meta-analysis of individual patient data from five randomized trials (HERMES collaborators) showed a trend toward benefit with thrombectomy in the 177 patients with an NIHSS score of <10; however, the point estimate was not statistically significant and there were very few with NIHSS score of ≤5.[12] Therefore no conclusion could be drawn from these trials. In a prospective cohort, Khatri *et al*. observed that END occurred in approximately 25% of patients with mild stroke. They further noted that the key independent predictor of END was symptomatic vessel occlusion.[13] Later, Kim *et al*. concluded that there was a higher chance of early neurological deterioration in proximal ICA (OR: 7.2; 1.87–78.3) and proximal MCA occlusion (OR: 3.03; 1.01–9.81).[14] To second this, Nogueira *et al*. observed that deterioration occurred in 41% of patients with LVO.[15] As deterioration is not uncommon in this subset with an LVO, one may have to decide whether to intervene straightaway or to intervene when the patient deteriorates. In a prospective study, when mechanical thrombectomy was offered at the time of admission as opposed to when patient deteriorated they noted a favorable NIHSS score shift.[15] However, a larger multicenter cohort study of 340 patients showed no beneficial effect with mechanical thrombectomy (MT) at admission as opposed to when patient deterioration.[16] The jury is still out; however, it is clear that a significant proportion of patients can have early deterioration. For the same reason, some centers may offer therapy at the first point of contact, but we propose a closely observed and advocated MT in case of deterioration.

Large infarct core

Shifting focus from a minor stroke, we discuss the possible benefit of mechanical thrombectomy in patients with a large stroke. The meta-analysis of individual patient data from five randomized trials showed a benefit with thrombectomy in patients with an ASPECTS of 6–8 (OR 2.34); however, no benefit was noted in the patient group with an ASPECTS of 0–5 (OR 1.24).[12] To further analyze this subset of patients, one would have to define the core volume beyond which reperfusion is futile with a higher risk of sICH. Desilles *et al*. after prospectively analyzing 218 patients subjected to mechanical thrombectomy and concluded that there was a definite benefit with mechanical thrombectomy in patients with DWI ASPECTS of 6, a tendency toward a favorable outcome in patients with DWI ASPECTS of 5 and no benefit in patients with DWI ASPECTS of 0–4. Importantly, they observed no increase in siCH in patients with DWI ASPECTS of 0–4.[17] Similarly, Rebello *et al.* noted an appreciable benefit with mechanical reperfusion in patients with infarct core 50–70 ml but no benefit in patients with an infarct core >70 ml.[18] Most studies have at best reported favorable outcome ranging from 12%–22% in patients with a core volume >70 ml. However, they are observational studies, so this remains a key limitation of these studies.[19–20] In our opinion, the subset of patients with a moderate core (50–70 ml or ASPECTS of 5, 6) is likely to benefit from mechanical thrombectomy; whereas, in the patient group with a large core (>70 ml), one needs to be more selective and can consider offering therapy in a select group of patients when clinically eloquent area is not infracted.

Wake-up stroke or Unknown time of onset

Wake-up stroke (WUS) and unknown time of onset (UTS) are again a domain where management strategy is unclear. This subset cannot be ignored and not offering therapy to this group may mean that a substantial proportion, as high as 30% of patients, can be deferred therapy. WUS and UTS are likely to be governed by different pathophysiologic characteristics. Increase in platelet aggregation and blood pressure (BP) surge may be associated with WUS and not UTS. Therefore, WUS may have occurred just prior to awakening. One of the ways to determine the time of onset based on imaging could be the DWI–FLAIR mismatch. A retrospective observational study, PRE-FLAIR, noted that the positive predictive value of DWI–FLAIR mismatch to determine the time of onset to be <4.5 hours to be nearly 90%.[21] The DAWN trial included 114 patients with WUS and 67 patients with UTS.

There was a significant benefit in both groups in favor of MT: 49% vs. 11% in the WUS group and 41% vs. 13% in the UTS group.[9] Similarly, in the DEFUSE 3 trial, there was a significant absolute benefit in favor of mechanical thrombectomy in both groups. The absolute benefit was 35% (42% vs. 7%, n = 91) in the WUS group and 34% (58% vs. 14%, n = 66) in UTS group.[10] Further, Henkes *et al*. analyzed a large cohort of 293 patients treated endovascularly and noted a significant benefit in WUS treated mechanically and not in UTS patients treated endovascularly.[22] However, when imaging (CT perfusion [CTP] or magnetic resonance imaging [MRI]) was used there was a significant benefit in both groups. Based on the randomized trials where a significant proportion of patients were either WUS or UTS, one can offer endovascular therapy in a subset of patients where there is LVO and a small core as defined by the inclusion criterion in the above trials.

Age: Do the elderly benefit?

Systematic review and meta-analysis of data from the HERMES study of patients aged 80 years or older who underwent mechanical thrombectomy for AIS revealed a sizeable benefit with MT in the octogenarian population. Approximately 30% of patients had a good functional outcome with odds of the good outcome being four-fold, the rates of siCH being higher at 8%, and the mortality was 28%. The researchers recommend that the octogenarian population not be excluded from this extremely beneficial therapy.[23]

Choice of imaging during "routine time window" and "beyond window period"

Among the early window period trials, the MR CLEAN trial had no core volume estimation as a part of the inclusion criterion. The ESCAPE and SWIFT PRIME had NCCT ASPECTS of 6–10 in the imaging inclusion criterion. The coronary CT angiography (CTA) collateral scoring with the collateral flow in more than 50% of the occluded territory was included in ESCAPE and CTP core volume estimation with an upper core volume limit of 70 ml and mismatch ratio of >1.2 (TAR/Core volume >1.2) was a part of EXTEND IA trial. A common theme for the early window period trials was using noncontrast CT (NCCT) brain to calculate ASPECTS and CTA to look for LVO. In the late window trials, core estimation was compulsory. In the DAWN trial, core estimation based on either MRI–DWI or CTP imaging was mandatory. The DEFUSE 3 trial mandated assessment of target mismatch profile on CTP or MRI (ischemic core volume is <70 ml, mismatch ratio is >1.8, and mismatch volume is >15 ml).

Based on the above trials, the American Stroke Association has recommended intervention in patients with a core measure on NCCT by ASPECTS of 6 or more with contributory LVO in the early window and core assessment on MRI or core and penumbral volume assessment on CTP or MR perfusion imaging in the delayed window period.[1–10]

Techniques of thrombectomy: Which technique for which patient?

Early reperfusion and the extent of reperfusion determined the outcome in LVO. In keeping with this, Chamorro *et al*. (2017) noted that the odds of a better outcome were 2.7 times more with mTICI 3 reperfusion as compared to TICI2b reperfusion. Therefore, the drive is to achieve first-pass complete reperfusion (i.e., mTICI 3 reperfusion at first attempt). To address the same, the techniques of thrombectomy have evolved over the years. The four main techniques popularly practiced are stentriever thrombectomy with proximal flow arrest using a balloon-guide catheter (SR + BGC) [Figures 1a and 2], aspiration through a large-bore catheter (ADAPT) [Figures 1b and 3], combining aspiration with stentriever thrombectomy (SOLUMBRA) [Figures 1c and 4], and lastly combining the latter technique with proximal flow arrest with a balloon-guide catheter (SOLUMBRA + BGC) [Figure 1d]. The technical aspects are described in the form of a line art [Figure 1a-d]. In the randomized trials that proved the efficacy of mechanical thrombectomy, stent retriever was the predominantly used device. Following this, the technique of aspiration was compared with a stent retriever. The researchers of the ASTER trial concluded that aspiration was noninferior to SR + BGC. However, it is worth noting that there was a tendency toward frequent use of rescue therapy in the aspiration group (32%).

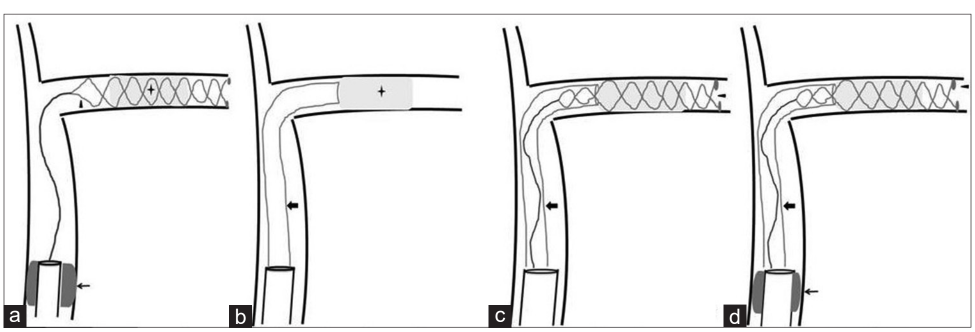

Figure 1: ((original) (a) SR + BGC: Inflated balloon guide parked beyond ICA origin (black arrow), SR (arrow head) deployed across the thrombus in the M1 MCA (black star)—clot retrieval with balloon inflation. (b) ADAPT: Large bore guiding in distal ICA. Aspiration catheter (0.068/0.07') taken to the site of the thrombus (bold arrow) and connected to aspiration pump. (c) SOLUMBRA technique: Combines local aspiration (bold arrow) and SR technique. (d) ARTS: The Aspiration Retriever Technique in Stroke combines SOLUMBRA and balloon-guide catheter; note an inflated balloon at the origin of the ICA (black arrow)

[24] In the more recent COMPASS trial, aspiration again was noninferior to SR-based technique (in many a SOLUMBRA technique rather than SR + BGC was used). In approximately 20% of patients, a second device was used in the aspiration group. The drop in numbers was attributed to the more frequent use of ACE 68 in comparison with ACE 64 catheters.[25] In support of the same, Delgado Almandoz *et al.* (2018) reported that the rate of first-pass reperfusion was better with the ACE 68 (53%) as opposed to the ACE 64 (37%) aspiration catheter.[26] However, a recent multicenter retrospective study of 450 patients showed that reperfusion rate was favorable with the combination of stentriever and aspiration (86%) when compared with aspiration alone (75%) or stentriever alone (66%).[27] However, there was no significant difference in the reperfusion rates between the ADAPT and SR + BGC techniques. Embolism to new territory was the lowest with the combined approach (6.6%) as compared with ADAPT (11.6%) and stentriever alone (9.8%) techniques. In the researchers' opinion, the operator experience shall determine the preference of the technique. As achieving complete reperfusion is the key, in the near future, one may see a trend in favor of a combined approach with proximal flow arrest.

Tandem Occlusion

Tandem lesions are defined as cases in which an extracranial internal carotid occlusive or stenotic lesion accompanied the principal (intracranial) lesion treated. The main issue is that commonly these patients respond less to intravenous thrombolysis as compared with those with isolated M1 occlusion. The meta-analysis of individual patient data from five randomized trials showed an absolute benefit of 18 percentage points (45.9% vs. 27.8%, n = 122) in favor of mechanical thrombectomy.[12] It is clear that this set of patients benefits from thrombectomy, but the main issues are regarding how to technically manage tandem occlusions. In which, the two main dilemmas include, do we go for proximal to distal (treating the extracranial ICA stenosis/occlusion first followed by thrombectomy for the intracranial occlusion) or distal to proximal (reverse; intracranial occlusion first) approach and whether emergency stenting is safe. With regards to the approach, although the proximal to distal approach seemed to be safe and effective with the main argument in favor of better access to the distal site of occlusion, Lockau *et al*. (2015) demonstrated a significantly shorter reperfusion time (mean difference [MD] of 67 minutes) and better outcomes (52% vs. 33%) in favor of the distal to proximal approach. Henceforth, based on the above arguments and the researchers' personal experience, a distal to proximal approach may be a reasonable approach to be taken.[28] The second question to be answered is if emergency stenting is safe. To answer this, one has to determine the risk of a repeat stroke. In persistent severe stenosis, the recurrence risk in the first 24 hours may be as high as 16%. Therefore, the main argument in favor of emergency stenting is the prevention of reocclusion and recurrent embolization. Jadhav *et al.* systematically analyzed 147 tandem occlusion patients and concluded that good outcomes (modified Rankin Scale, 0–2 at 90 days) were higher in the stenting group (68.5% vs. 42.2%; P = 0.003) without an increase in sICH.[29] However, the shortcomings are that it is nonrandomized data and the patients had median ASPECTS of 8. Technically, post stent placement, one is committed to dual antiplatelet and the associated risk of intracranial hemorrhage, particularly in patients with a large core. The middle path is doing an angioplasty alone and with this approach, the risk of repeat stroke drops to approximately 10%. One may have to use a pragmatic approach, and this may be based on if the patient has received intravenous thrombolysis, the infarct core volume, the time from groin puncture to reperfusion, and the extent of residual stenosis.

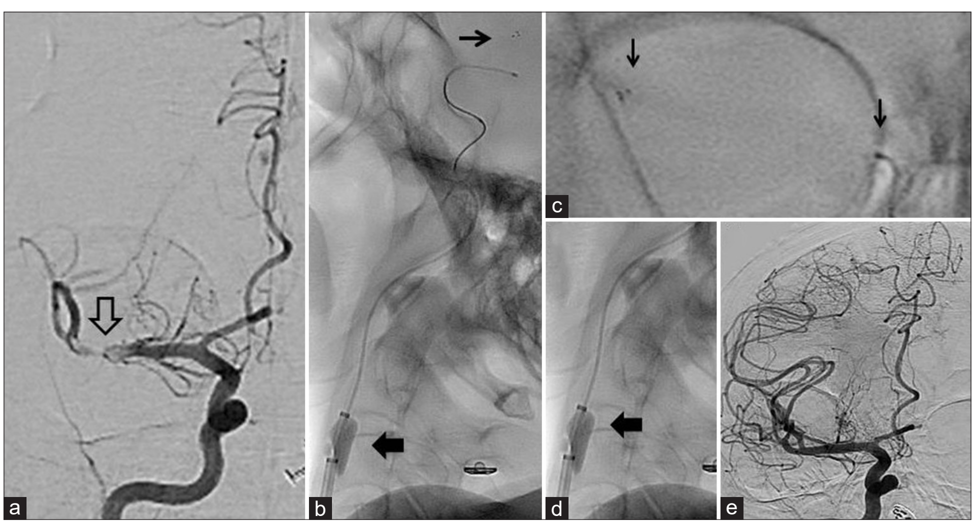

Figure 2: (original) Stentriever and balloon-guide catheter technique; (a) right M1 MCA occlusion. (b) Note inflated balloon beyond ICA origin (bold black arrow) and deployed Solitaire (black arrow). (c) Enhanced view showing the Solitaire deployed across the clot. (d) Enhanced view of the inflated balloon. (e) Reperfused MCA territory

According to the researchers, stenting may be considered for a patient who is presented early with a small infarct, a short groin to reperfusion time, and persistent significant residual stenosis. To the contrary, it would be wise to avoid stenting in a patient who has a borderline infarct core and latter in the time window. In this subset, angioplasty alone will suffice. Our practice is a distal to proximal approach. To avoid untoward macrodissection while navigating a large-bore catheter, we do an angioplasty initially with a small balloon as described in Figures 4 and 5.

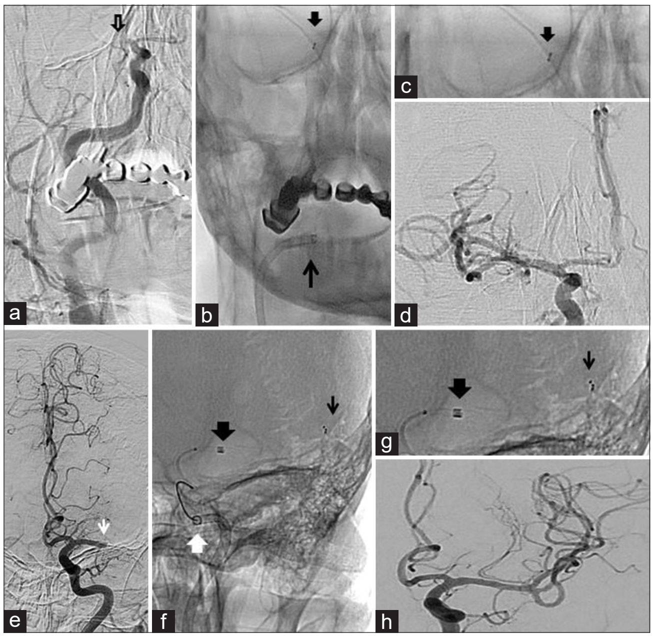

Figure 3: (original) Aspiration technique; (a) Right M1 MCA occlusion (hollow black arrow). (b) Neuron Max at the mid-cervical ICA (black arrow), ACE 68 catheter at the MCA origin ingesting the clot (bold arrow). (c) Enhanced view showing the large bore catheter tip abutting the clot. (d) Complete reperfusion. SOLUMBRA technique; (e) Left M1 MCA occlusion. (f) Neuron Max parked at the petrous ICA (bold white arrow), aspiration catheter proximal to the thrombus (bold black arrow), and SR across the thrombus. (g) Aspiration catheter and the stent deployed across the thrombus. (h) Complete reperfusion

General anesthesia versus conscious sedation: Which one to prefer?

Conscious sedation (CS) was strongly favored over general anesthesia (GA) until two recent large-scale trials concluded otherwise. Schönenberger *et al*. noted that there was no difference in outcomes based on a randomized clinical trial involving 150 patients. They noted a 10-minute delay in the GA arm, but no difference in mean arterial pressures.[30] Similar findings were noted by the researchers of the AnStroke trial. They noted slightly shorter arrival to puncture time (MD of 9 minutes) and longer puncture to reperfusion time (MD of 19 minutes) in the CS group; however, the difference was not statistically significant and can be attributed to smaller numbers.[31] In addition, the mean arterial pressure as a fraction of the baseline was not different between the two groups. However, a recent metaanalysis of 4716 patients has shown higher odds of death and respiratory complications and lower odds of a good outcome with GA. There was no difference in vascular complications. They have listed delay to puncture and drop in BP to be the key factors that contribute to the poor outcome in the GA arm.[32] Brinkikji *et al*. (2017) further highlighted a delay of approximately 30 minutes in the GA arm in the MR CLEAN trial. Therefore, they believe that in a real-life scenario a <10-minute delay to groin puncture, avoiding a significant drop in BP during induction, and maintenance of anesthesia may not be achievable. Based on these arguments, one can restrict to CS where possible and consider GA in patients who are unable to protect the airway or are extremely restless.

Conclusion

Mechanical thrombectomy has emerged as one of the most effective treatments in stroke therapeutics. A strong absolute benefit in favor for thrombectomy over intravenous thrombolysis/standard medical therapy was not only noted in the first 6 hours after stroke onset but also seen in carefully selected patients based on core imaging in the 6- to 24-hour window. Further, WUS and UTS patients were also noted to strongly benefit from therapy when the core volume was

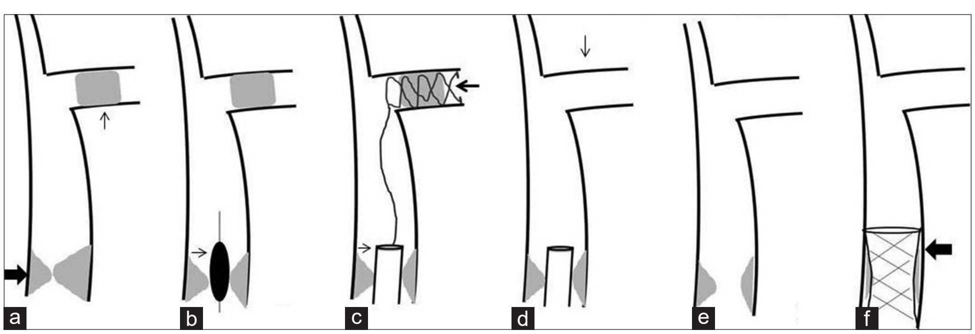

Figure 4: (original) Approach to Tandem occlusion; (a) Note occlusion in the M1 MCA (black arrow) and atherosclerotic tight stenosis at the origin of the ICA (Bold black arrow), (b) Step 1: Balloon angioplasty of the ICA stenosis/occlusion with a 2-mm diameter balloon (c) Step 2: Management of distal occlusion; A large bore 6-F catheter is taken across and parked in the cervical ICA (black arrow), following this the Stentriever is deployed across the clot and thrombectomy performed (bold arrow); aspiration technique can be adopted as well. (d) Note retrieval of the MCA clot. Then the proximal stenosis can be either be managed by angioplasty alone (e) or stenting (f) (bold arrow)

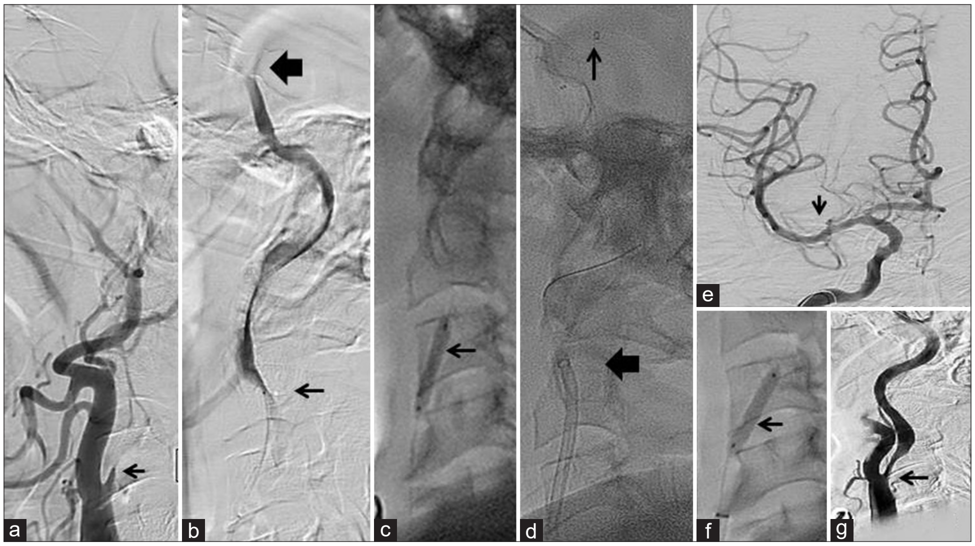

Figure 5: (original) (a) ICA origin occlusion (arrow). (b) Micro catheter taken across and injection taken to confirm true lumen and demonstrate terminal ICA occlusion (bold arrow). (c) Balloon angioplasty prior to taking guiding catheter across to avoid macroplaque dissection (black arrow). (d) Aspiration catheter taken to terminal ICA and Neuron Max taken across stenosis over the aspiration catheter (bold arrow) to support the aspiration catheter and clot aspirated (arrow). (e) Complete re perfusion and (f) balloon angioplasty (4 mm) for the proximal stenosis. (g) Post angioplasty residual stenosis noted

small. Early and complete reperfusion of the occluded territory remains the key for good outcomes.

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Conflicts of interest

There are no conflicts of interest.

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