Mechanical thrombectomy for large vessel occlusion with large ischaemic core


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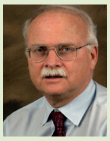
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Abstract

Endovascular therapy in acute ischaemic stroke with large vessel occlusion changed the landscape of stroke treatment. Early randomised trials largely focused on patients with small to moderate ischaemic core defined as ASPECTS 6 or greater. Patients with large ischaemic core are generally defined as those who have ASPECTS 5 or less, or ischaemic core volume greater than 50 ml or 70 ml. Recently, six randomised trials on patients with large ischaemic core and anterior large vessel occlusion have been completed, supporting mechanical thrombectomy in large core patients with a low number needed to treat. In this review, we summarise the rationale, design, and results of these trials.

Endovascular therapy in acute ischaemic stroke with large vessel occlusion changed the landscape of stroke treatment [1–4]. Meta-analyses of clinical trial data from the early and late window trials showed a large treatment effect with a NNT in the range of 2 to 3 [5,6]. However guidelines remained restrictive in their recommendations on eligibility of this treatment [7,8], whereas other guidelines have not been as restrictive [9]. One group in which guidelines have not caught up with clinical data is the subgroup of patients with a large vessel occlusion and large core as patients with predominantly small cores were enrolled to provide proof of concept for a new intervention. Of note, there was evidence in subgroup analysis of the HERMES meta-analysis to suggest that large core patients could benefit [5]. Concerns about reperfusion hemorrhage into a large infarct and futility of intervention tempered this excitement and provided rationale to enrol patients in clinical trials [10]. Given the results of the most recent trials, the data is more clear that select patients in this group can benefit.

The first large core trial published was RESCUE Japan LIMIT in 2022 which randomised 203 patients presenting with NIHSS ≥ 6 who had an ICA or M1 occlusion [11]. The trial enrolled early window patients as judged by a last known well from onset (LKW) of < 6 hours or a DWI FLAIR mismatch (i.e. no FLAIR signal change) on MRI if they presented 6-to-24 hours from symptom onset. Large core was an Alberta Stroke Program Early CT Score (ASPECTS) of 3-5 on CT or MRI. More than 70% of patients in this trial presented in the 0-to-6-hour time window. The primary outcome of independent ambulation was increased in the EVT compared to medical management group (31% vs. 12.7%, RR 2.43; 95% CI 1.35-4.37; P=0.002). Ordinal shift in mRS also favoured the EVT group. Any intracranial hemorrhage (ICH) was significantly

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increased in the EVT group (RR 1.85; 95% CI 1.33 – 2.58; P < .001). Symptomatic ICH (sICH) was numerically higher in the EVT group but not significantly. MRI was the predominant modality of screening patients which raised concerns these patients may not be large core patients as MRI ASPECTS would be more sensitive in picking up areas of infarct and therefore score lower. However, the low rates of good functional outcome in this trial suggests these patients were large core patients.

The next trials to provide data were ANGEL ASPECT and SELECT 2 [12,13]. The ANGEL ASPECT trial was a Chinese study that looked at 456 patients presenting with a NIHSS 6 to 30 who had an intracranial ICA or initial segment of the MCA occlusion. The trial enrolled patients with LKW of up to 24 hours. Large core was defined by an ASPECTS score of 3-5 within 24 hours on HCT. If ASPECTS was less than 3 within 24 hours or ASPECTS greater than 5 within the 6-to-24-hour window, then a CTP with core volume of 70 ml to 100 ml was required. The primary outcome of mRS shift favoured the EVT group (OR 1.37; 95% CI 1.11 to 1.69; p=.004). The proportion of patients achieving functional independence and independent ambulation was also significantly increased in the EVT group. Like RESCUE Japan, any ICH was increased in the EVT group (RR 2.71; 95% CI 1.91 to 3.84; p < .001) with a trend towards more sICH although not significantly. The SELECT 2 trial looked at 352 patients in North America, Europe, New Zealand and Australia with an ICA or MCA occlusion with LKW within 24 hours. Large core was defined as ASPECTS of 3-5 on HCT or MRI/CTP imaging with an infarct core of 50 cc or more. The primary outcome of shift on mRS score favoured the EVT group (generalised OR 1.51; 95% CI 1.20 – 1.89; p < .001). The proportion of patients achieving functional independence and independent ambulation was also significantly increased in the EVT group. sICH did not differ between both groups. The benefit of thrombectomy was maintained at 1 year [14]. Rates of mRS 0-1 and 0-2 were numerically higher at 1 year in the EVT group as compared to 90 days. Since many thrombectomy capable centres receive patients as transfers, SELECT 2 evaluated patients transferred with initial scans showing large core and found a benefit in outcomes without treatment heterogeneity compared to directly presenting patients [15].

The TESLA trial results overall fell in line with the aforementioned trials. The TESLA trial looked at 300 patients in the USA with an ICA terminus or M1 MCA occlusion with LKW of 24 hours. Large core was defined at ASPECTS of 2-5 on HCT [16]. The primary endpoint of 90 day utility weighted mRS score fell short of being significantly better in the EVT group but there remained a strong trend in favour of the EVT group. Additionally, secondary outcomes of mRS of 0 – 3 and early neurologic improvement were significantly better in the EVT group [17]. Notably the TESLA trial was the first trial to show a signal of benefit with selection criteria using CT without advanced imaging. TESLA 1 year results were presented in 2024 which showed thrombectomy was associated with higher rates of functional independence and independent ambulation at 1 year signifying the gap between the thrombectomy arm and medical management arm had widened at 1 year [18].

The TENSION trial looked at 253 patients in Europe and Canada with a distal intracranial ICA or M1 occlusion within 12 hours of LKW [19]. Large core was defined as ASPECTS of 3-5 on CT or DWI MRI. The primary outcome of shift on the 90 day mRS favoured the EVT group (adjusted common OR 2.58; 95% CI 1.60 – 4.15; p = .0001). Secondary outcomes of functional independence and independent ambulation were also significantly improved in the EVT group. sICH did not differ. Mortality and dependency was significantly improved in the EVT group. At one year, the benefit of EVT compared to medical management was also maintained in TENSION [20].

The LASTE trial investigators looked at 333 patients in Europe with an intracranial ICA, M1 or M1/M2 occlusion within 6.5 hours of LKW. Large core was defined as ASPECTS of 0-5 with 58% of patients being enrolled in the 0-2 cohort [21]. The results indicated that the primary outcome of shift on the 90-day mRS scale favoured the EVT group (OR 1.63; 95% CI 1.29 – 2.06; p < .0001). Rates of functional independence and independent ambulation were increased in the EVT group. There was a mortality benefit in the EVT group.

Although the data from the above trials has confirmed that patients with a large vessel occlusion and large core do benefit from EVT, it has also raised other questions now which may guide research efforts in the future. One such question is if core should be a hard stop at all in decisions to treat. The results of LASTE and low NNT of other large core trials suggest possibly ignoring a threshold for core as a requirement of treatment, especially in the early window. In SELECT 2 and ANGEL ASPECT, subgroup analysis also did not reveal heterogeneity of treatment by mismatch profile [22,23]. This is surprising given the core penumbra hypothesis has driven stroke treatment for large vessel occlusions. Although the above data does seem to question the core penumbra hypothesis or the validity of our understanding of it, the data also provides proof that preventing growth of infarcted tissue mediates benefit in the large core population as well.

Subgroup analysis of both ANGEL ASPECT and SELECT 2 were performed based on stratification of core volume [22,24]. In the ANGEL ASPECT analysis, they found that EVT was associated with a higher rate of functional independence when looking at ASPECTS of 3 to 5 with a core volume of less than 70 ml and higher rates of independent ambulation when looking at ASPECTS of 3 to 5 irrespective of core volumes. They did not find benefit for patients enrolled with ASPECTS 0-2 although this was limited by the small sample size. The subgroup analysis of SELECT 2 did not find a significant effect for heterogeneity across different core sizes although numerically odds ratios for improvement with EVT were less for cores greater than 100ml and 150ml. Functional outcomes and rates of functional independence or independent ambulation also worsened for incremental increases in core volume. Additionally, core growth was numerically less in patients receiving EVT in both ANGEL ASPECT and SELECT 2 pointing towards at least part of the benefit being mediated by salvage of tissue. Additionally SELECT 2 and TESLA showed that the benefit of EVT extended to a year and the treatment effect even widened with time which may reflect increasing time needed to recover function after larger volume of tissue damage [14,18].

Another consideration is the grading of core using ASPECTS. Subtle grey white blurring and a well circumscribed infarct are graded the same way on ASPECTS numerically but the fate of this tissue and response to recanalisation may be different. Broocks et al (2013) looked at net water uptake (NWU) which is a measure for the level of hypodensity on a non contrast CT head [25]. They found that the NWU mediated the effect of recanalisation on outcomes. Although they did not look at haemorrhage, it would be interesting to see if markers such as this could find patients that may be harmed by treatment given that some trials did find trends towards higher sICH although no significant increases were seen in the overall population. Other considerations regarding safety may pertain to treatment technique. Given the larger extent of injury in these patients, the endothelium may behave differently, and safety of stent retriever or aspiration may be different. Similarly, the number of passes that can safely be attempted without increasing hemorrhage risk may also be less in this patient population [26]. Even in patients with large core who fail recanalisation, an analysis of ANGEL ASPECT showed that the outcomes of these patients are not worse than medically managed patients. However, infarct growth was larger in patients with EVT failed recanalisation than the medically managed group [27].

In conclusion, there are now 6 randomised trials and observational data supporting mechanical thrombectomy in large core patients with low NNT to benefit patients [28,31]. Although good outcomes occur at a lower rate than the early smaller and moderate core trials and at a lower rate with the inclusion of ultra large cores, mechanical thrombectomy still renders patients a better chance at recovery than no therapy at all. Importantly with core being less of a determining factor in the decision to treat, simpler imaging paradigms as used in some of these trials without the need for advanced imaging can be utilised to save time, costs and improve access to thrombectomy in lower resource settings [32-36]. Although there is optimism in regards to treatment of the largest strokes, outcomes still remain relatively poor and further research into identifying patients that may be harmed and optimising therapy are warranted.

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