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Mini Review Open Access

Thrombectomy for proximal intracranial occlusion beyond 24 hours after time last seen normal: A narrative review

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ABSTRACT

Endovascular thrombectomy (EVT) revolutionized the treatment for acute ischemic stroke due to large vessel occlusion (LVO). Current guidelines published by multiple academic societies recommend EVT for eligible patients who present within 24 hours of the time last seen well. However, more recent data suggests that extending this window past 24 hours produces more favorable outcomes in specific patients presenting with anterior circulation LVO. More specifically, recent observational data indicates a higher probability of functional independence, functional improvement, and long-term survival with EVT when compared to best medical management. Based on the available data, there is unclear equipoise in randomizing all patients with acute ischemic stroke due to LVO to EVT or medical management. However, for those patients with large established infarction, distal occlusions, or well beyond the 24-hour window, randomized clinical trials are called upon to determine whether there is benefit of EVT in these patient groups. In this narrative review, we will summarize the most recent data on EVT in the ultra extended window (>24 hours after time last seen normal) and discuss further considerations of this treatment.

Background

Most patients with acute ischemic stroke from a proximal large vessel occlusion (LVO) present to medical attention within 24 hours; many of which are eligible for endovascular therapy (EVT). However, a considerable minority of patients with an acute LVO present beyond 24 hours or with an unknown time of onset, and thus are not eligible for EVT based on current guidelines from the American Heart Association/ American Stroke Association[1], Society of Vascular and Interventional Neurology[2], and Society of Neurointerventional Surgery[3]. These guidelines were predicated based on rigorously designed randomized clinical trials using second-generation thrombectomy devices and techniques. Due to trial limitations and accepted standards for evidence-based therapy[4,5], EVT was not recommended for patients who did not meet stringent trial criteria, such as patients identified using unenhanced imaging without perfusion imaging[6], more distal occlusions, and pre-existing disability[7]. However, certain patients who present beyond 24 hours from the time they were last seen well (TLSW) may actually benefit from EVT but recommendations in these populations lack support from randomized clinical trials.

In this mini-review, we will summarize the available evidence supporting the use of EVT in select patients with proximal anterior circulation LVO who present in the ultra extended window (>24 hours after TLSW), with particular emphasis on patient selection, risks of treatment, and future directions in stroke care. Manuscripts summarized

in this review were identified through a PubMed and Google Scholar search using the terms "thrombectomy" or "endovascular therapy" and "extended window", "24 hours", and by manual review of the references cited by these studies. These manuscripts were supplemented with any other published manuscripts known to the authors.

Control Comparisons and Best Medical Management

In this review, comparisons between EVT and best medical management are made according to the most recent guidelines,[1] considering infarct volume, risk of hemorrhagic transformation, and natural history. Studies selected for this review article had similar study designs, as the majority were retrospective and nonrandomized (Table 1). In this review, we exclusively considered EVT versus best medical management in proximal LVO of the anterior circulation. More specific clinical features and subgroups are described in the methods of the referenced studies. Among the key covariates in determining thrombectomy eligibility beyond 24 hours among "trial-ineligible" patients[8,9] were baseline National Institutes of Health Stroke Scale (NIHSS) score, location of the intracranial occlusion, Alberta Stroke Program Early Computed Tomography Scale (ASPECTS) score, and perfusion imaging findings.

Of note, CTP/DWI-MRI imaging was utilized in a few studies listed below. There were specific inclusion criteria for infarct core volume sizes, based on age and NIHSS. Not every study included core volumes, however the two studies that did included patients with the following: if age less than or equal to 80, NIHSS ≥10 and infarct core volume <31 mL or NIHSS score ≥20 +infarct core volume <51 mL; if greater than or equal to 80, then NIHSS score ≥10 mL and infarct core volume <21 mL. Specific perfusion and ASPECTS criteria have not been officially validated for use in the ultra extended window and therefore may not be as specific as previously used in the 6-24 window[10], which is likely why most studies did not include this criteria. Notably, there was no significant difference in sICH between most studies, whether perfusion data was used or not. The primary and secondary outcome(s) of included studies are provided in Table 1. Methods for adjusting for measurable confounding are also summarized, where appropriate.

The Importance of Time

A considerable number of patients with acute LVO are not considered for EVT on the basis of delay in arrival and extent of tissue injury[11]. The notion that "time is brain" is an age-old paradigm referring to the progression of irreversible ischemic injury with ongoing failure of cerebral circulation. Estimates from human studies indicate that nearly 2 million neurons die every minute during stroke due to LVO[12]. However, recent data highlights the importance of collateral circulation. Ischemic infarcts are combated by collateral flow, which dictate the size of infarct cores and speed of infarct progression. Some patients may lose brain tissue more quickly (called "fast progressors") whereas others lose brain tissue more slowly (<35000 neurons lost per minute[13]), and have been called "slow progressors"[14]. Fast progressors typically have larger regions of "ischemic core" from poor collaterals; while slow progressors have better collateral flow, therefore slower infarct growth[14]. As many as 55% of patients with anterior occlusions are slow progressors, and many have milder severity at onset, according to their NIHSS[15]. Even though such patients may progress slowly through their irreversible ischemic injury, it is likely that earlier intervention would be beneficial. These patients were likely selected for endovascular therapy in many of the published studies to date–creating a notable selection bias in outcome assessment–as they were the individuals who still retained salvageable brain tissue in the ultra-extended window.

Stroke volume and time of onset are arguably two of the most important factors in determining intervention, and they are strongly interrelated[16,17]. While earlier reperfusion treatment is unequivocally associated with more favorable clinical outcomes than delayed treatment[18,19], the dichotomization of treatment eligibility based on presentation within a specific time window is increasingly arbitrary. The individualized benefit of EVT is driven largely by the extent of irreversible tissue injury rather than any time cutoff.

The Late Window Paradox

Following the publication of the DEFUSE-3 trial, which showed *greater* clinical benefit of EVT in an extended time window of 6-16 hours after TLSW, many stroke providers became perplexed by the paradoxically *better* outcomes for patients treated in a later window. For example, in the pooled analysis of individualized patient data from early window trials (<6 hours) reported by Goyal et al. in 2016, the odds of achieving functional independence was 70% higher with EVT over medical management (rate ratio 1.70, 95% confidence interval [CI] 1.41-2.05)[20]. By comparison, DEFUSE-3 reported a considerably greater treatment effect with EVT (odds ratio 2.77, 95% CI 1.63-4.70)[21]. In his editorial on the topic[22], Dr. Albers highlights the seemingly greater treatment effect (with respect to 90-day mRS shift) with EVT in the late window (vs control) compared to EVT in the early window (vs control). There are multiple reasons for this paradox to exist. Perhaps most importantly, a large percentage of patients with LVO who have favorable initial imaging (with unenhanced and enhanced CT or MRI) are "slow progressors". Therefore, any additional delay from baseline imaging to endovascular reperfusion is unlikely to result in considerably greater ischemic progression. For example, a patient with ⅓ of the middle cerebral artery infarction (ASPECTS score ~7) at 4 hours after TLSW may show more rapid progression as compared to an identical

patient with a similar ASPECTS score who presents at hour 14[23]. In addition, those patients treated in randomized clinical trials in the early time window had a much broader range of inclusion criteria across trials–including adjudicated ASPECTS scores as low as 0-2–for whom the margin of benefit of EVT may be very small/absent[24]. Since these early window trials, more late-window randomized clinical trials have evaluated the efficacy of EVT in patients with larger regions of infarction and still observed a benefit of EVT[25]. This explains the "paradox" from the first late window trials.

Outcomes

To date, only a handful of randomized clinical trials evaluated outcomes for patients with anterior circulation LVO treated with EVT versus best medical management between 6 and 24 hours after TLSW: DEFUSE-3 (up to 16 hours)[21], DAWN[26], RESCUE Japan LIMIT (Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism–Japan Large Ischemic Core Trial)[27], ANGEL-ASPECT (Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core)[28], and SELECT2 (Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke)[29]. The primary outcome of these trials typically involves a favorable shift in the 90-day modified Rankin Scale (mRS), a 7-point assessment of functional status ranging from lack of symptoms (0) to death (6). In addition, a dichotomized outcome using the mRS according to functional independence (score 0-2) or dependence/death (3-6) has also been reported and permits consolidation of data for meta-analyses.

In one of the earliest cohort studies evaluating outcomes for patients treated beyond 24 hours of TLSW, Desai et al. retrospectively analyzed data for 21 patients that underwent EVT for anterior circulation proximal LVO who otherwise met DAWN clinical and imaging criteria[30]. The investigators reported 90-day outcomes were similar to those of the DAWN interventional arm[26]. In a larger, pooled multicenter cohort study (SELECT LATE, n=301) which evaluated outcomes using inverse probability of treatment weighting, Sarraj et al. reported a higher rate of functional independence with EVT over medical management (38% vs. 10%, inverse adjusted OR, 4.56, 95% CI 2.28-9.09) and 51% lower odds of mortality (adjusted OR 0.49, 95% CI 0.27-0.89)[31]. Notably, each hour of delay to thrombectomy beyond 24 hours was associated with no significant decrease in treatment effect with EVT (OR 0.99, 95% CI 0.98-1.00, p= 0.20). Furthermore, better outcomes with EVT were observed in large infarcts (ASPECTS 0-5; 21% for EVT vs. 5% for medical management, p=0.02), and those with large regions of perfusion core estimate ≥50cc using regional cerebral blood flow estimates >30% (17% vs. 0%, p=0.15). In a separate multi-center cohort study which included several overlapping sites with SELECT LATE (n=334 patients), Mohamed et al. corroborated more favorable outcomes associated with EVT, including a higher rate of functional independence (adjusted OR 5.73, 95% CI 1.23-26.70)[32].

The clinical advantage of EVT over medical management in the ultra extended window must be weighed against the risks associated with treatment. Perhaps the most serious risk of emergent reperfusion therapy in patients with LVO is symptomatic intracerebral hemorrhage (sICH). sICH rarely occurred in each study measuring mortality outcomes. Multiple patients experienced post-procedural hemorrhage, however fewer than 10% were symptomatic based on SITS-MOST criteria (neurological deterioration of greater than or equal to four points on the NIHSS from baseline, lowest value between baseline and 24 hours, or death within 24 hours). Among all-comers from the SELECT LATE study, there was no significant increase in sICH with EVT. However, in those with poor ASPECTS, EVT was associated with nearly fivefold higher odds of sICH (OR, 4.58; 95% CI, 1.35-15.51)[31]. Most studies did not specify criteria in those with sICH, therefore it is unknown which key subgroups had poorer outcomes. Nonetheless, there was an absolute benefit of functional independence favoring EVT (16%), which was statistically significant. Mohamed et al. reports the risk of sICH was numerically greater in the EVT arm (5.6% vs. 2.5%), but was not statistically significant[32]. Therefore, the risk of sICH is outweighed by the overall potential benefit in this subgroup.

Additionally, small single-center and multi-center cohort studies analyzing patients with LVO treated in the ultra extended window reported no significant improvement in outcomes associated with EVT. However, these studies are limited by their small sample size[33,34], which often precludes more sophisticated propensity score matching or adjusted multivariable modeling, as described in studies like SELECT LATE. Other studies were only able to report outcomes between those treated in the ultra extended window against those treated within 24 hours of TLSW[35], which are indirect comparisons.

Conclusions and Translational Significance

EVT in the ultra extended window has been consistently associated with similar–if not greater–odds of achieving functional independence among most patients with anterior proximal LVO. Furthermore, there is no greater risk of sICH or procedural complications. Earlier treatment for a symptomatic LVO is always advisable, but there is likely a clinically meaningful treatment effect for patients who reach medical attention >24 hours after TLSW.

While current guidelines recommend EVT in

Table 1: Summary of observational studies.

Investigator/Study Name	Design	Location of Occlusion	Population	Primary Outcome	Results
Desai et al. 2018[30]	Multicenter retrospective cohort study	ICA/MCA (M1)	21 patients presenting >24h after TLSW who met DAWN trial criteria vs. interventional arm of DAWN	mRS 0-2 at 90d Odd of sICH	No significant difference in rate of good outcome, 43% vs. 48%, p=0.68 No significant difference in odds of sICH (5% vs 6% DAWN intervention arm, p=0.87)
Mohamed et al. 2023[32]	Multicenter retrospective cohort study	ICA (cervical and terminus, +M1), ACA, MCA (M1/M2),PCA, VA, BA	334 patients presenting with an LVO > 24 hours TLSW (64% received MT and 36% received SMT only)	mRS 0-2 at 90d, mortality, NIHSS on discharge Odds of sICH	Significant difference in mRS at 90 days (p=0.026), less mortality (34% vs 63%, p<0.001), better discharge NIHSS (p<0.001). No significant difference in odds of sICH (5.6% vs 2.5%, p=0.19)
Pandhi et al. 2023[36]	Retrospective Study	ICA/MCA (M1/M2)	39 patients presenting > 24 hours TLSW	mRS 0-2 at 90d, Favorable Outcome Rate of sICH (no control variable)	Favorable outcomes in 49% of patients. Patients with posterior occlusion had a significant difference in higher mRS (p=0.016). 3 patients with sICH (7.7%)
Shaban et al. 2023[10]	Multicenter retrospective cohort study	ICA, ACA, MCA (M1/ M2/M3), PCA, VA, BA	121 patients presenting >24h TLSW vs 1824 in 6-24hr window	mRS 0-2 at 90d Odds of sICH	No significant different in rate of good outcome; patients were less likely to be independent (18.8% vs 34.9%, p=0.005) Lower number of attempts was associated with good outcomes (OR 0.027, p=0.022) No significant difference in odds of sICH (10.2% in 6-24 hour window vs 7.6% in >24 hour window, p=0.54) Higher odds of mortality at 90 days (OR 2.34, p=0.023)
Ha et al. 2022[37]	Multicenter retrospective cohort study	ICA/MCA (M1/M2), BA, VA	274 patients underwent EVT, in three different windows (early 109, late 104, very late 61)	ENI vs END based on NIHSS >4 after EVT Odds of sICH	Significant difference in ENI in early vs. late vs. very late (60.6% vs 51% vs 29.5%, p=0.001) Rate of END in early vs. late vs. very late (11% vs 13.5% vs 4.9%) No significant difference in odds of sICH (1.8% in <6 hour window vs 1% in 6-24 window vs 4.9% in >24 hour window, p=0.233)

Purrucker et al. 2022[35]	Multicenter retrospective cohort study	ICA (terminus), ACA, MCA (M1/M2/M3), PCA, VA, BA	43 patients presenting >24h underwent EVT (16 after LSW and 27 from first symptom recognition) vs EVT in <24h in both anterior and posterior circulation LVO	mRS 0-2 at 90d or return to prestroke mRS at 90d Rate of sICH (no control variable)	Significant difference in favorable outcome (23.3% vs 39.4%, p=0.04) 1 patients with sICH (2%)
Dhillon et al. 2023[34]	Multicenter retrospective cohort study	ICA/MCA (M1/M2)	19 of 35 patients presenting >24h after TLSW with similar ASPECTS (6-8)	mRS 0-2 at 90d Odds of sICH and mortality	No significant difference in rate of good outcome, No significant difference in sICH (5.3% in EVT vs 0% in MM; p=0.28) No significant difference in mortality (26.3% vs 37.5%, p=0.42)
SELECT-LATE, 2023[31]	Multicenter retrospective cohort study	ICA/MCA (M1/M2)	185 of 301 patients presenting >24h after TLSW based on clinical characteristic, ASPECTS and perfusion parameters	mRS 0-2 at 90d Odds of sICH	Significant difference in rate of good outcome 38% vs. 10%, p<.001 Significant difference in odds of sICH (10.1% in EVT vs 1.5% in MM, p=0.003)

TLSW denotes time since last well, DAWN Diffusion weighted imaging or computed tomography perfusion Assessment with clinical mismatch in the triage of Wake-up and late presenting strokes undergoing Neurointervention with Trevo.
Early neurologic improvement (ENI); Early neurologic deterioration (END); Standard Medical Therapy (SMT); National Institutes of Health Stroke Scale (NIHSS); Modified Rankin Scale (mRS); Alberta Stroke Program Early CT Score (ASPECTS); Symptomatic Intracranial Hemorrhage (sICh); Anterior cerebral artery (ACA); Middle cerebral artery (MCA); Posterior cerebral artery (PCA); Internal carotid artery (ICA); Vertebral artery (VA); Basilar artery (BA)

appropriately selected patients who present with anterior LVO within 24 hours of TLSW, the natural history of LVO is poor and treatment should be individualized. Far more important than any time threshold is imaging evidence illustrating tissue viability and likelihood of successful reperfusion. Therefore, therapy should be tailored to an individual's brain tissue window, not time window. There is growing evidence supporting EVT in patients beyond 24 hours from TLSW, and in patients with substantial degrees of early ischemic damage. Because the non-randomized evidence strongly supports EVT in many of these patients, there is not likely equipoise to randomize all-comers beyond 24 hours from TLSW. Future randomized trials for EVT in the ultra extended window should target (1) patients with large areas of ischemic injury where the benefit of EVT over best medical management is less clear, (2) distal occlusions, or (3) patients who present well beyond 24 hours (e.g., >48 or 72 hours) for whom there may be very limited tissue viability.

Conflict of Interest Disclosure

No competing financial interests exist for all authors. No added funding was provided. No other disclosures were reported.

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