The Challenges of ELVO With Low NIHSS Score

Evaluating available data on the safety, efficacy, and feasibility of treatment for mild acute strokes with associated LVO.

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Available scientific data on the management of patients with mild stroke and associated large vessel occlusion (LVO) are limited. The natural course of the disease is not considered favorable in a significant proportion of cases. Predicting which patients do better or worse with or without acute treatment is challenging. Extrapolating from the available nonrandomized, mostly retrospective data and recent landmark endovascular trials, many experts argue that medical and/or endovascular therapy would likely benefit this patient population. Prospective randomized controlled trials are needed to assess the safety, efficacy, and feasibility of available treatment approaches, but this will require a coordinated multicenter effort.

BACKGROUND

There have been significant advancements in the management of acute stroke over the last 25 years. Almost 2 decades after the approval of recombinant tissue plasminogen activator (tPA), mechanical thrombectomy (MT) became the standard of care for patients with emergent large vessel occlusion (ELVO) and moderate to severe stroke.[1] The recent extension of the therapeutic time window was also quickly incorporated into the guidelines, and it further increased the number of patients who are potentially eligible for MT.[1] A smaller but specific population—acute stroke patients presenting with mild symptoms and associated LVO—has not been well studied and has long presented a difficult diagnostic and therapeutic dilemma. Data suggest that the long-term natural outcome of this population may be less than optimal, but patients are not often considered for acute medical or endovascular therapy due to a lack of severe deficits. Recent landmark, prospective, neurointerventional trials mostly included patients with National Institutes of Health Stroke Scale (NIHSS) scores ≥ 6, thus providing little relevant information about the feasibility of endovascular therapy in this unique patient population. In addition, there is variability in the NIHSS score threshold that is used to define a "mild stroke." Values range anywhere from 3 to 8 in available, mostly retrospective reports. Unfortunately, no high-quality, prospective, randomized controlled studies are currently available that define the efficacy and safety of MT in acute stroke patients with a low NIHSS score and ELVO.

INCIDENCE AND NATURAL HISTORY

The exact number of patients presenting with mild symptoms and concurrent LVO is not known. In the large Get With the Guidelines–Stroke registry, 22.4% of 33,995 patients had an NIHSS score < 6, but vessel status was not specifically studied. Mortality was low at 1.3%, but at discharge, 30.3% of patients could not ambulate independently and 29.4% could not return directly home.[2] In a study analyzing data from the SITS International Stroke Thrombolysis Register, 24.9% of patients with NIHSS scores < 6 had visible arterial occlusion on vascular imaging.[3] The incidence of LVO and low NIHSS score has ranged from 14% to 54% in smaller cohorts, likely due to variability in the definition of a "low" NIHSS score and the vascular territory involved.[4-8]

The natural course of the disease appears to be unfavorable in many studies. Heldner et al showed that without thrombolysis or MT treatment, 22.7% of patients with ELVO and a low NIHSS score deteriorated within 24 hours, 33.3% deteriorated during the hospital stay, and 41.4% deteriorated within 3 months, with a mortality rate of 6.7%.[9] Another analysis demonstrated that 32% of patients with mild ischemic symptoms or rapidly improving symptoms who did not undergo intravenous (IV) thrombolysis remained dependent or

died during admission.[10] Kim et al studied 119 patients with symptomatic LVO and low NIHSS scores and found that 24.5% developed early neurologic deterioration (END). Symptomatic arterial occlusion was an independent predictor of END (odds ratio [OR], 2.206; 95% confidence interval [CI], 1.219–3.994; $P = .009$).[4] Similar findings were demonstrated by Rajajee et al, showing that three out of eight (37.5%) patients with mild symptoms, ELVO, and no treatment developed END with infarct expansion, as opposed to one out of 31 (3.2%) patients without ELVO (OR, 18; 95% CI, 1.6–209; $P = .02$).[11]

Another study reported that 53.8% of patients with ELVO and low NIHSS scores who received no treatment had an unfavorable outcome (modified Rankin Scale [mRS] > 2).[12] However, in another report, only 25% of patients with low NIHSS scores with or without LVO eventually had mRS > 1; the presence of a proximal LVO increased the odds of unfavorable outcome or death by 7.13-fold (95% CI, 1.1–45.5; $P < .038$).[13] Other studies showed that only 66.7% of patients with proven LVO reached mRS 0–2 with conservative management,[9] and only two-thirds of patients with ELVO who were excluded from thrombolysis could walk independently at discharge.[14] A large European observational cohort found that one-third of mild stroke patients with LVO did not have a successful recovery.[15]

TREATMENT OPTIONS

IV Thrombolysis

The use of IV thrombolysis has been rare in this patient population, possibly due to the presumed benign course of the disease. In addition, tPA has been shown to be less effective in treating proximal LVOs.[16] Although they do not specifically mention large vessel status, the most recent American Stroke Association guidelines suggest that IV thrombolysis may be beneficial for patients with mild or improving symptoms.[1] In a retrospective cohort comparing acute stroke therapy with conservative management, the odds of a favorable outcome (mRS 0–2) was 4.5 times higher in patients undergoing acute therapy, mostly in the form of IV thrombolysis (OR, 4.5; 95% CI, 1.26–19.2; $P = .028$).[12] In an Austrian stroke unit registry, there was a shift toward improved outcomes in patients with IV thrombolysis (OR, 1.49; 95% CI, 1.17–1.89; $P < .001$).[17] In another study, where approximately 50% of patients underwent IV thrombolysis, thrombolytic therapy was shown to be a predictor of favorable outcome (mRS 0–2; OR, 3.103; 95% CI, 1.021–9.428; $P = .03$).[9]

In one of the largest observational studies of patients with low NIHSS scores and LVO, there was still a 10-fold END increase in those with internal carotid artery (ICA) terminus and tandem occlusion (ICA and middle cerebral artery) compared with patients without visible occlusion, despite IV thrombolysis. At 3 months, 77% of the patients with deterioration had mRS 3–6. The rate of parenchymal hemorrhage after IV tPA was the same for patients without LVO (3% for both groups) in this large cohort.[3] Of note, the recently published PRISMS study found no difference in 90-day outcomes between tPA and aspirin for patients with NIHSS scores ≤ 5, but the study was terminated early, and determination of large vessel status was not required for enrollment.[18]

Endovascular Therapy

There have been no randomized controlled trials investigating the efficacy of MT for ELVO and low NIHSS scores, only observational studies and case series. The retrospective, nonrandomized nature of these reports, along with differences in methods, NIHSS score threshold, and treatment time windows, limit data interpretation and generalizability.

A North American retrospective multicenter study noted favorable outcomes (mRS 0–2) at 3 to 6 months in patients who underwent MT versus medical management (93% vs 69.2%; $P = .04$), based on a 26-pair matched analysis. Endovascular therapy was statistically associated with a lower NIHSS score at discharge ($P = .04$) and a favorable NIHSS score shift ($P = .03$). Also, independence rates increased at discharge ($P = .03$) and at 3- to 6-month follow-up ($P = .04$). Parenchymal hemorrhage was seen in 7.7% of matched patients.[19]

A retrospective analysis of six international comprehensive stroke center databases investigated immediate or delayed (rescue therapy after neurologic deterioration) MT versus best medical management for patients with mild stroke and LVO. The odds of good outcome were increased with immediate MT (adjusted OR, 3.1; 95% CI, 1.4–6.9). At 90 days, in the matched analysis, there was a 14.4% absolute difference in good outcome favoring immediate MT (84.4% vs 70.1%; $P = .03$). There were no safety concerns in the study.[20]

A smaller study looking at early MT versus late MT (at the time of neurologic deterioration) found excellent outcomes (mRS 0–1) in the early versus late group (75% vs 33%), with no symptomatic intracranial hemorrhage (sICH) in either group.[21] Other small, retrospective, single-arm analyses showed acceptable efficacy and safety profiles, with mRS 0–2 achieved at 90 days in 63% to 75% of patients and a low rate of sICH.[22,23] Limited data presented from a smaller, ongoing, prospective, single-arm registry showed promising early results in the first few patients and a good safety profile.[24]

A meta-analysis of five studies evaluating acute stroke therapy in this population confirmed substantial heterogeneity among the individual studies. The odds of a favorable outcome (mRS 0–2) at 90 days were four times higher with MT and IV tPA compared with no acute stroke therapy (95% CI, 1.82–10.48; *P* = .001). The odds of an excellent outcome (mRS 0–1) were nearly two times higher with acute stroke therapy. There was no significant difference in functional outcome between MT and IV tPA alone. No treatment subgroup was associated with ICH or death.[25]

Other studies did not suggest definite benefits of endovascular intervention. In the HERMES meta-analysis of recent major MT trials, a subgroup of patients presenting with NIHSS scores ≤ 10 favored a trend toward better outcomes with MT; however, this was not statistically significant.[26] In two large observational European studies, there was no significant difference between MT and standard medical therapy in achieving excellent outcomes (mRS 0–1) at 90 days.[15,27] In one of these studies, the rate of successful revascularization was higher in the MT group (91.2% vs 63.4%; *P* = .006), as was the risk of sICH (11.8% vs 0%; *P* = .033).[15] The other large multicenter cohort study, involving four European comprehensive stroke centers, also demonstrated that any ICH occurred more frequently in the endovascular group compared with the medical group (16.5% vs 6.1%; *P* = .008), although there was no difference in all-cause mortality. However, in the same study, 18.3% of patients in the medical arm developed END and underwent MT but were still analyzed in the medical arm.[27]

Another international retrospective cohort of patients with mild stroke and LVO undergoing MT versus medical therapy found no difference in favorable (mRS 0–2) outcomes (63.3% vs 67.8%; adjusted OR, 0.9; 95% CI, 0.43–1.88; *P* = .77), and sICH rates were higher with MT (5.8% vs 0%; *P* = .02).[28]

A smaller study comparing 10 patients treated with MT and 22 patients treated with medical therapy also found no significant difference in 90-day mRS 0–2 (100% vs 77%; *P* = .15), yet multivariable linear regression indicated that MT was independently associated with a beneficial NIHSS score shift (*P* = .04).[29]

CHALLENGES AND FUTURE DIRECTIONS

Current data on the treatment of patients with mild stroke and associated LVO are limited, with no available randomized controlled trials. The natural history of the disease is less benign than previously assumed because of a significant risk of long-term disability. There is a strong demand to better understand this stroke subtype and to identify safe and efficient treatment strategies, but there are a few challenges ahead.

The efficacy and safety of MT have been well established in moderate to severe strokes, but some argue that patients with mild presenting symptoms are different and may have an unfavorable risk/benefit profile with an invasive procedure (ie, primum non nocere). Identification of ELVO is not often made during the first presentation because patients only have mild symptoms, which are not pressing enough for an aggressive and rapid initial workup that includes immediate vessel imaging. In addition, even if an LVO is identified, the question is raised whether the LVO represents a secondary process from an underlying lesion, such as severe atherosclerotic plaque or dissection, or if it is a true ELVO with an acute thrombus.

Potential difficulties when considering a randomized trial may include a low number of patients and slow enrollment; lack of a simple, widely accepted and used clinical grading system to assess for mild deficits not detectable by NIHSS score (ie, cognitive, psychiatric, and/or behavioral issues); and reluctance from patients, families, and physicians to enroll due to the established benefit of MT for ELVO with more severe strokes. On the other hand, advanced imaging techniques and additional research may help with safer patient selection and more efficient, targeted intervention by determining the presence and size of a perfusion deficit and its correlation with the underlying LVO, the patient's collateral flow status and reserve, vessel wall abnormalities and/or underlying lesions, and the consistency, age, and characteristics of the occlusive thrombus. Newer thrombolytic agents and endovascular devices with safer profiles will further decrease the risks of acute treatment, and they will likely tip the balance in favor of early intervention.

Ongoing prospective registries will provide additional important data,[30] but well-coordinated, multicenter, randomized controlled trials will ultimately be necessary to fully validate the utility of acute stroke therapy in this unique population. ■

1. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018;49:e46-110.
2. Romano JG, Smith EE, Liang L, et al. Outcomes in mild acute ischemic stroke treated with intravenous thrombolysis: a retrospective analysis of the Get With the Guidelines-Stroke registry. JAMA Neurol. 2015;72:423–431.
3. Mazya MV, Cooray C, Lees KR, et al. Minor stroke due to large artery occlusion. When is intravenous thrombolysis not enough? Results from the SITS International Stroke Thrombolysis register. Eur Stroke J. 2018;3:29–38.
4. Kim JT, Park MS, Chang J, et al. Proximal arterial occlusion in acute ischemic stroke with low NIHSS scores should not be considered as mild stroke. PLoS One. 2013;8:e70996.
5. Köhrmann M, Nowe T, Huttner HB, et al. Safety and outcome after thrombolysis in stroke patients with mild symptoms. Cerebrovasc Dis. 2009;27:160-166.
6. Zhu W, Churilov L, Campbell BC, et al. Does large vessel occlusion affect clinical outcome in stroke with mild neurologic deficits after intravenous thrombolysis? J Stroke Cerebrovasc Dis. 2014;23:2888-2893.

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7. Laurencin C, Philippeau F, Blanc-Lasserre K, et al. Thrombolysis for acute minor stroke: outcome and barriers to management. Results from the RESUVAL stroke network. Cerebrovasc Dis. 2015;40:3-9.
8. Choi JC, Jang MU, Kang K, et al. Comparative effectiveness of standard care with IV thrombolysis versus without IV thrombolysis for mild ischemic stroke. J Am Heart Assoc. 2015;4:e001306.
9. Heldner MR, Jung S, Zubler C, et al. Outcome of patients with occlusions of the internal carotid artery or the main stem of the middle cerebral artery with NIHSS score of less than 5: comparison between thrombolysed and non-thrombolysed patients. J Neurol Neurosurg Psychiatry. 2015;86:755-760.
10. Barber PA, Zhang J, Demchuk AM, et al. Why are stroke patients excluded from TPA therapy? An analysis of patient eligibility. Neurology. 2001;56:1015-1020.
11. Rajajee V, Kidwell C, Starkman S, et al. Early MRI and outcomes of untreated patients with mild or improving ischemic stroke. Neurology. 2006;67:980-984.
12. Cerejo R, Cheng-Ching E, Hui F, et al. Treatment of patients with mild acute ischemic stroke and associated large vessel occlusion. J Clin Neurosci. 2016;30:60-64.
13. Nedeltchev K, Schwegler B, Haefeli T, et al. Outcome of stroke with mild or rapidly improving symptoms. Stroke. 2007;38:2531-2535.
14. Mokin M, Masud MW, Dumont TM, et al. Outcomes in patients with acute ischemic stroke from proximal intracranial vessel occlusion and NIHSS score below 8. J Neurointerv Surg. 2014;6:413-417.
15. Urra X, San Román L, Gil F, et al. Medical and endovascular treatment of patients with large vessel occlusion presenting with mild symptoms: an observational multicenter study. Cerebrovasc Dis. 2014;38:418-424.
16. Saqqur M, Uchino K, Demchuk AM, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. Stroke. 2007;38:948-954.
17. Greisenegger S, Seyfang L, Kiechl S, et al. Thrombolysis in patients with mild stroke: results from the Austrian Stroke Unit registry. Stroke. 2014;45:765-769.
18. Khatri P, Kleindorfer DO, Devlin T, et al. Effect of alteplase vs aspirin on functional outcome for patients with acute ischemic stroke and minor nondisabling neurologic deficits: the PRISMS randomized clinical trial. JAMA. 2018;320:156-166.
19. Haussen DC, Lima FO, Bouslama M, et al. Thrombectomy versus medical management for large vessel occlusion strokes with minimal symptoms: an analysis from STOPStroke and GESTOR cohorts. J Neurointerv Surg. 2018;10:325-329.
20. Nagel S, Bouslama M, Krause LU, et al. Mechanical thrombectomy in patients with milder strokes and large vessel occlusions. Stroke. 2018;49:2391-2397.
21. Messer MP, Schönenberger S, Möhlenbruch MA, et al. Minor stroke syndromes in large-vessel occlusions: mechanical thrombectomy or thrombolysis only? AJNR Am J Neuroradiol. 2017;38:1177-1179.
22. Pfaff J, Herweh C, Pham M, et al. Mechanical thrombectomy in patients with acute ischemic stroke and lower NIHSS scores: recanalization rates, periprocedural complications, and clinical outcome. AJNR Am J Neuroradiol. 2016;37:2066-2071.
23. Bhogal P, Bücke P, Ganslandt O, et al. Mechanical thrombectomy in patients with M1 occlusion and NIHSS score ≤5: a single-centre experience. Stroke Vasc Neurol. 2016;1:165-171.
24. Toth G, Cerejo R, Tsai J, et al. E-154 A prospective pilot study to assess the safety of endovascular therapy for acute large vessel occlusion with low NIHSS. J Neurointerv Surg. 2018;10(suppl 2):A125.
25. Griessenauer CJ, Medin C, Maingard J, et al. Endovascular mechanical thrombectomy in large-vessel occlusion ischemic stroke presenting with low national institutes of health stroke scale: systematic review and meta-analysis. World Neurosurg. 2018;110:263-269.
26. Goyal M, Menon BK, van Zwam WH, et al; for the HERMES Collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387:1723-1731.
27. Dargazanli C, Arquizan C, Gory B, et al; for the ETIS REGISTRY Investigators. Mechanical thrombectomy for minor and mild stroke patients harboring large vessel occlusion in the anterior circulation: a multicenter cohort study. Stroke. 2017;48:3274-3281.
28. Sarraj A, Hassan A, Savitz SI, et al. Endovascular thrombectomy for mild strokes: how low should we go? Stroke. 2018;49:2398-2405.
29. Haussen DC, Bouslama M, Grossberg JA, et al. Too good to intervene? Thrombectomy for large vessel occlusion strokes with minimal symptoms: an intention-to-treat analysis. J Neurointerv Surg. 2017;9:917-921.
30. Mild acute ischemic stroke with large vessel occlusion (MISTWAVE). Clinicaltrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03731351. Accessed January 9, 2019.

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