Original research

Early neurological improvement as a predictor of outcomes after endovascular thrombectomy for stroke: a systematic review and meta-analysis

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ABSTRACT

Background Early neurological improvement (ENI) is a potential predictor for 90-day outcomes following mechanical thrombectomy for acute ischemic stroke (AIS). We performed a systematic review and meta-analysis to better understand whether ENI can be used as a surrogate for long-term outcomes following mechanical thrombectomy for AIS.

Methods Following the PRISMA guidelines, a systematic literature review of the English language literature was conducted using PubMed, MEDLINE, and Embase. ENI definition, including timing and degree of improvement on the National Institutes of Health Stroke Scale (NIHSS), was catalogued for each included study. Outcomes of interest included 90-day modified Rankin Scale (mRS) 0–2, symptomatic intracranial hemorrhage (sICH), and mortality. We calculated pooled ORs and corresponding 95% confidence intervals (CI) for all definitions of ENI.

Results We included nine studies with 2355 patients in our analysis. ENI definitions included improvement in NIHSS of 8 points, 4 points, 12%, and 30% or greater. There was a significant association between ENI and mRS 0–2 rates (OR 8.62, 95% CI 4.86 to 15.29; p<0.001). Significance of the association was maintained across all definitions (p<0.001). Moreover, achieving ENI was a significant predictor of reduced odds for reported sICH rates (OR 0.11, 95% CI 0.06 to 0.21; p<0.001). There was a significant association between ENI and reduction in mortality rates (OR 0.09, 95% CI 0.05 to 0.15; p<0.001).

Conclusions Broadly defined, ENI is a promising predictor of good functional outcome at 90 days and is associated with lower rates of mortality and sICH.

INTRODUCTION

Stroke is a widespread medical event that impacts patients’ lives, often resulting in reduced independence.1 Assessing outcomes following treatment for acute ischemic stroke (AIS) traditionally includes a multitude of measurements. A good outcome is commonly defined as a modified Rankin Scale (mRS) score of 0–2 at 90 days post-treatment.2 The mRS is typically measured at 90 days after treatment and is used to assess the degree of disability in patients who have suffered a stroke. The National Institutes of Health Stroke Scale (NIHSS) is a parameter which can be measured sooner than 90 days post-treatment, most commonly at admission and after 24 hours as a deficit rating scale, and can be used as a predictor of functional outcome and mortality.3,4

Early neurological improvement (ENI) has been used as a 24-hour measurement to assess a change in NIHSS score.5 ENI has been defined in several different ways, most commonly as an integer improvement in the NIHSS score after 24 hours of 8, but also as a percentage change in NIHSS score.5 ENI has been defined in several different ways, most commonly as an integer improvement in the NIHSS score after 24 hours of 8, but also as a percentage change in NIHSS score.5

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Early neurological improvement has thus far been used to assess the clinical improvement in patients 24 hours after stroke treatment.

WHAT THIS STUDY ADDS

⇒ This study examines the literature on early neurological improvement and its predictive value for long-term outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Our systematic review and meta-analysis indicates that early neurological improvement is a promising predictor for 90-day outcomes following mechanical thrombectomy for acute ischemic stroke.

⇒ Our study also compares different definitions of early neurological improvement and highlights the need for a consistent definition of the term.

METHODS
Search strategy
On 28 January 2022, following the PRISMA guidelines for performing systematic reviews, a systematic literature review of the English language literature was conducted within the Nested Knowledge Autolit software per the drafted protocol from inception, using PubMed, Embase, Web of Science, and Scopus. Based on each database, different combinations of possible keywords and/or MeSH terms were used for that purpose. Keywords and MeSH terms included: “stroke”, “cerebral infarction”, “thrombectomy”, “NIHSS”, “National Institutes of Health Stroke Scale”, “early”, “neurological improvement”, “neurological outcome”, “functional outcome”, “functional independence”, “clinical outcome”, “clinical improvement”. Moreover, we did an extensive manual search through the references of the included articles to retrieve any missed papers.

Screening process
We included all original studies fulfilling our pre-determined PICO: Population was patients with AIS with reported ENI, Intervention was thrombectomy, there was no Control group, the Outcomes of interest were the modified Rankin Scale (mRS) 0–2, mortality, and symptomatic intracerebral hemorrhage (sICH). We excluded papers where the ENI was not described, review articles, duplicate studies including the same patients presented in another included paper, case reports, case series with fewer than five patients, and conference abstracts. We did not pose any limitations regarding sample size, study design, or patients’ characteristics.

Two authors carried out the title and abstract screening against the pre-defined criteria. This was followed by a full text screening of any retained studies of the first screening step. In both stages, the senior author was consulted to resolve any conflicts in the decisions.

Data extraction
Following a pilot extraction, an extraction sheet was built and the extraction was performed by at least two authors. The extracted data included study characteristics, baseline data of the included patients, and the aforementioned outcomes of interest. After performing the extraction, a third author carried out an extensive revision of the extracted data to avoid any prior mistakes.

Risk of bias
We assessed the risk of bias using ROBINS-I, a tool for assessing risk of bias in non-randomised studies of interventions. Ten authors evaluated the quality of each study, which was adjudicated by a third author when needed.

Statistical analysis
Using R software version 4.1.2, we calculated pooled ORs and their corresponding 95% CIs. A random model was adopted to pool all data due to heterogeneity among the included studies in defining ENI. Heterogeneity was assessed using Q statistics and the I² test, where I² > 50% or p < 0.05 were considered significant. Among the performed analysis, the number of studies was <10 so publication bias (Egger’s regression test) and the impact of sample size (meta-regression) were not tested. Since the included studies used different definitions of ENI, we used subgroup analyses to investigate different definitions and test for statistical differences among them.

RESULTS
Search and screening results
Following the removal of 1586 duplicate records, we retrieved 800 papers for further screening. We excluded 776 records at the title and abstract screening stage, thus retaining 24 records for full-text screening. Finally, nine papers were determined to satisfy our inclusion criteria with the appropriate report of outcomes of interest (see online supplemental figure S1).

Study characteristics and risk of bias
Of the nine included studies, six used a retrospective design and five were multicenter studies. The sample size of the included studies ranged from 91 individuals to 568, with reported outcomes at 3 months of follow-up for all studies. The median NIHSS score at baseline and patients’ characteristics/comorbidities are shown in table 1. Five papers included in the meta-analysis defined ENI as a reduction in NIHSS score of 8 or more,11–13 Weyland et al defined ENI as any improvement in the NIHSS score in 24 hours,14 Soize et al defined ENI as a reduction in NIHSS score of 4 or more,15 Pu et al defined ENI as a ≥2% or greater reduction in NIHSS score,16 and Cao et al defined ENI as a 30% or greater improvement in NIHSS score.17 Definitions of both ENI and sICH are shown in online supplemental table S1. All definitions of ENI focused on improvement of score from baseline to 24 hours after baseline.

For all included studies there was no high risk of bias among all assessed domains. However, certain specific bias risk was identified in specific study aspects. A detailed assessment of risk of bias is shown in online supplemental table S2.

Functional independence (mRS 0–2)
Nine studies with 2355 patients reported the functional independence rates in relation to ENI. Overall, there was a significant association between ENI and mRS 0–2 rates (OR 8.62, 95% CI 4.86 to 15.29; p<0.001); however, a significant heterogeneity was observed among the included studies (I²=84%, p<0.001). On further stratification of studies based on their definition of ENI, the significance of the association was maintained across all definitions (p<0.001; figure 1). Moreover, the residual heterogeneity dropped to an insignificant level between studies (I²=37%, p=0.171), confirming the different definition as the main source of the overall heterogeneity. Nevertheless, the odds of achieving functional independence were significantly variable among different ENI subgroups/definitions, as shown by the test for subgroup differences (p<0.001).

Incidence of sICH
Three studies of 1208 patients reported the incidence rates of sICH as associated with ENI. Overall, having ENI was a significant predictor of reduced odds for the reported sICH rates (OR 0.11, 95% CI 0.06 to 0.21; p<0.001), with no heterogeneity among the included studies (I²=0%, p=0.694). This significance was present across different ENI definitions, except for ≥8 NIHSS points18 (OR 0.16, 95% CI 0.01 to 2.99; p=0.220); however, there was no significant variability across different ENI subgroups (p=0.694; figure 2).

Mortality rates
Five studies with 1161 patients reported the association between ENI and subsequent mortality. There was a significant association between ENI and the reduction in mortality rates (OR 0.09, 95% CI 0.05 to 0.15; p<0.001), with no significant heterogeneity among the included studies (I²=18%, p=0.302). This
**DISCUSSION**

In this meta-analysis and systematic review we have shown that ENI of various definitions is correlated with 90-day outcomes following thrombectomy for AIS. These findings are important because it will allow clinicians to inform patients and their families about the likelihood of long-term outcomes without the need to wait the full 90 days. Additionally, we found that patients who achieve ENI had a significantly lower rate of mortality at 90 days and lower rates of sICH compared with those who did not achieve ENI. This association between ENI and good outcomes is likely due to the fact that patients who demonstrate a significant improvement in the NIHSS score at 24 hours are poised to improve further until the clinical course for recovery from their stroke stabilizes at day 4.4 8 22

We found that, although there were multiple definitions of ENI, all definitions were associated with good functional outcomes at 90 days. This holds true for safety outcomes (mortality, sICH), except in the study by Heit et al in which no significant association between sICH and ENI was found.

Using retrospective analyses, previous authors have found that ENI is significantly correlated with 90-day outcomes.6 23–24 These previous studies, however, had small patient cohorts, making it difficult to extrapolate the results to broader patient populations. However, even though previous studies have had small cohorts, the association between ENI and good outcomes has been consistent with the present study.9 Our study adds to the current literature by increasing the power of these studies with a larger cohort of 2355 patients in the form of a systematic review and meta-analysis. With this larger patient population, we achieved results consistent with the smaller studies that were analyzed. Additionally, our study examined the value of using different definitions of ENI, with results showing that all definitions of ENI were significantly correlated with good functional and safety outcomes.

Our meta-analysis has a number of limitations. The major limitation that must be noted is the heterogeneity in the definitions of ENI. Most of the studies analyzed did not agree on a definition of ENI, and definitions ranged from any improvement in NIHSS score at 24 hours to an 8-point improvement in NIHSS score at 24 hours. Other studies used percentage thresholds ranging from 12% to 30% improvement in NIHSS at 24 hours. This means that we were not able to pool together these studies under a single definition of ENI, thereby decreasing the power of our study. Similarly, NIHSS scores trend towards being higher for left hemisphere strokes than for right hemisphere strokes, and this bias must be considered when using the NIHSS score.25

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We were unable to control for these factors since we did not have access to patient-level data. It has been shown that underlying pathologies such as increased blood pressure and increased mean glucose levels, and varying treatment modalities such as pretreatment with intravenous thrombolysis are associated with outcomes.26–28 We were unable to control for these factors since we did not have access to patient-level data. Instead, these studies only reported on the analysis of their data without providing the raw data for our analysis. Despite these limitations, we were able significance persisted among the different definitions of ENI, with no significant variability among the definitions (p=0.296; figure 3).
Ischemic stroke to obtain statistically significant results with low heterogeneity between studies. It is important to note that integer changes in NIHSS scores at 24 hours have their own limitations. For example, a patient who has a 5-point improvement in the NIHSS score from 15 to 10 (33%) may fare worse than a patient who has a 4-point improvement in the NIHSS score from 7 to 3 (57%). Though the former 5-point improvement had a greater absolute change...
There is a need for further validation of the association and to investigate if it is clinically meaningful.

CONCLUSIONS
In this meta-analysis of a systematic review of nine studies, ENI was found to be a promising predictor of long-term functional outcomes in patients treated with mechanical thrombectomy for AIS. Additionally, ENI was found to be significantly associated with lower rates of sICH and mortality. Future prospective studies are needed to further validate the association and to investigate if it is clinically meaningful.

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Supplemental material
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Ischemic stroke


