Early Neurological Deterioration after Recanalization Treatment in Patients with Acute Ischemic Stroke: A Retrospective Study

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Abstract

Background: Early neurological deterioration (END) is a prominent issue after recanalization treatment. However, few studies have reported the characteristics of END after endovascular treatment (EVT) as so far. This study investigated the incidence, composition, and outcomes of END after intravenous recombinant tissue plasminogen activator (IV rt-PA) and EVT of acute ischemic stroke, and identified risk factors for END.

Methods: Medical records of patients who received recanalization treatment between January 1, 2014, and December 31, 2015 were reviewed. Patients were classified into IV rt-PA or EVT group according to the methods of recanalization treatment. The END was defined as an increase in the National Institutes of Health Stroke Scale (NIHSS) ≥4 or an increase in la of NIHSS ≥1 within 72 h after recanalization treatment. Clinical data were compared between the END and non-END subgroups within each recanalization group.

Results: Of the 278 patients included in the study, the incidence of END was 34.2%. The incidence rates of END were 29.8% in the IV rt-PA group and 40.2% in the EVT group. Ischemia progression (68.4%) was the main contributor to END followed by vasogenic cerebral edema (21.1%) and symptomatic intracranial hemorrhage (10.5%). Multivariate logistic regression showed that admission systolic blood pressure (SBP) ≥160 mmHg (odds ratio [OR]: 2.312, 95% confidence interval [CI]: 1.105–4.837) and large artery occlusion after IV rt-PA (OR: 3.628, 95% CI: 1.482–8.881) independently predicted END after IV rt-PA; and admission SBP ≥140 mmHg (OR: 5.183, 95% CI: 1.967–13.661), partial recanalization (OR: 4.791, 95% CI: 1.749–13.121), and nonrecanalization (OR: 5.952, 95% CI: 1.841–19.243) independently predicted END after EVT. The mortality rate and grave outcome rate at discharge of all the END patients (26.3% and 55.8%) were higher than those of all the non-END patients (1.1% and 18.6%; P < 0.01).

Conclusions: END was not an uncommon event and associated with death and grave outcome at discharge. High admission SBP and unsatisfactory recanalization of occluded arteries might predict END.

Key words: Early Neurological Deterioration; Endovascular Treatment; Intravenous Thrombolysis; Ischemia Progression; Symptomatic Intracranial Hemorrhage; Vasogenic Cerebral Edema

Introduction

Approximately 2.2–37.5% of patients with acute ischemic stroke might encounter early neurological deterioration (END). The reported incidence rates of END in patients who received intravenous recombinant tissue plasminogen activator (IV rt-PA) ranged from 8.1% to 28.1%, and the incidence rates for those who did not receive IV rt-PA ranged from 16.3% to 17.6%. The clinical types of END can be classified into several categories, including symptomatic intracranial hemorrhage (sICH), cerebral edema (CE), early recurrent ischemic stroke, and epilepsy, but there is still a large proportion of END cases in which the underlying cause could not be identified and are therefore categorized as unexplained END. In 2016, Kim et al. made a new classification of END that was based on the idea that early recurrent ischemic stroke and unexplained

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END might be regarded as ischemia progression (IS). They also reported that the percentage of END cases could be classified as IS (49.1%), CE (27.3%), and sICH (23.6%). In recent years, intervention techniques have rapidly developed, resulting in increasingly more patients receiving endovascular treatment (EVT) or IV rt-PA bridging EVT. However, few studies have reported the characteristics of END after EVT as so far. Therefore, we conducted a retrospective study on patients who received recanalization treatment (including IV rt-PA and EVT) in Xuan Wu Hospital during 2014–2015, to give insight on the incidence, clinical types, risk factors, and outcomes of END in different kinds of recanalization treatment, especially EVT, and to propose prevention measures on the basis of our findings.

Methods

Ethical approval
The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Xuan Wu Hospital, with a waiver of informed consent due to the retrospective study design.

Patient inclusion
The medical records of patients with acute ischemic stroke who received recanalization treatment in Xuan Wu Hospital between January 1, 2014, and December 31, 2015 were collected. Patients receiving recanalization treatment in other hospitals or admitted with modified Rankin Scale (mRS) >2 before symptom onset were excluded from the study.

Research methods
This study was a retrospective cohort study. Patients were classified into IV rt-PA group or EVT (including IV rt-PA bridging EVT) group according to their recanalization treatment methods, and they were also divided into END or non-END subgroup according to their early neurological status.

Protocols and result identification of recanalization treatment
The protocols of recanalization treatment were determined by neurological physicians according to previously reported guidelines.[10-13] IV rt-PA protocol: rt-PA 0.9 mg/kg was infused over 1 h if symptom onset was within 4.5 h (maximum dose: 90 mg), with 10% of the dose given as a bolus over 1 min. EVT protocol: mechanical thrombectomy (MT) or intra-arterial thrombolysis (IAT), combined with angioplasty or not, was initiated within 6 h of stroke onset in anterior circulation; the treatment time window of posterior circulation infarction could be extended to 24 h after symptom onset. When IV rt-PA was useless, EVT was initiated if appropriate for the patients.

The result of IV rt-PA was determined by transcranial Doppler (TCD) performed within 24 h after IV rt-PA if large arteries were involved. Results of EVT were determined by digital subtraction angiography (DSA) after the operation and classified into complete recanalization (Thrombolysis in Cerebral Ischemia [TICI] 3 and 2b), partial recanalization (TICI 2a), and nonrecanalization (TICI 1 and 0).

Definition and classification of early neurological deterioration
The National Institutes of Health Stroke Scale (NIHSS) was assessed as the following pattern after recanalization treatment: every 15 min for 2 h, then every 30 min for 6 h, then hourly up to 24 h, and then daily. If patients developed severe headache, acute hypertension, nausea, or vomiting, the NIHSS was assessed immediately.

Definition of END: An increase in NIHSS ≥4 or an increase in Ia of NIHSS ≥1 within 72 h after recanalization treatment.[6,7]

Classification of END: deteriorations were categorized into three types according to imaging examinations. sICH: Computed tomography (CT) verified hematoma accompanied by subarachnoid hemorrhage or hemorrhage in lateral ventricle or neither.[83] IS: Progression of initial infarction or new infarctions in other artery territories verified by magnetic resonance imaging (MRI) (diffusion-weighted imaging showed high signal, and apparent diffusion coefficient mapping showed low signal) or consecutive follow-up CT scan (exclude hemorrhage and cerebral edema).[2,9] Vasogenic CE (VCE): Swelling in infarction and its surrounding region verified by MRI (diffusion-weighted imaging showed high signal, while apparent diffusion coefficient mapping showed equal or high signal) or consecutive follow-up CT scan and TCD (CT showed extravasation of contrast medium and TCD showed the velocity of cerebral blood flow was normal or increased).[10-13] CT or MRI scan could be obtained at 24 h after recanalization treatment and when END occurred. TCD monitoring could be obtained within 24 h after recanalization treatment, and neurological imaging could be followed up continuously in END patients if necessary.

Clinical data collection
Patient information included age, gender, comorbidities, history of cerebral vascular disease, antiplatelet condition before symptom onset, responsible lesion, and Trial of Org10172 in Acute Stroke Treatment (TOAST) subtype, admission NIHSS and blood pressure, fasting blood glucose, recanalization treatment method (IV rt-PA or EVT), and recanalization result. The END types and onset time for END occurrence (within 24 h, 24–48 h, and 48–72 h after recanalization treatment) were described. The treatment methods (medical treatment, surgical treatment, and hypothermia) after recanalization treatment were collected. The outcomes measured at discharge were death and grave outcome (mRS ≥5).

Statistical analysis
All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were shown as mean ± standard deviation.
Incidence of early neurological deterioration
A total of 284 patients received recanalization treatment with 4 patients receiving treatment in other hospitals and 2 patients admitted with mRS >2 before symptom onset. Therefore, 278 patients were included in the final analysis [Figure 1]. Among these patients, 161 (57.9%) were treated with IV rt-PA alone and 117 (42.1%) were treated with EVT. In the EVT group, 2 patients received IV rt-PA and IAT, 20 patients received IV rt-PA and MT, 31 patients received IAT alone, 53 patients received MT alone, and 11 patients received both MT and IAT. The incidence rates of END were 34.2% (95 patients) in all patients recruited, 29.8% in the IV rt-PA group, and 40.2% in the EVT group. However, one important thing needed to be clarified was that the admission NIHSS in the EVT group (median: 18 [13, 24]) was much higher than that in the IV rt-PA group (median: 5 [4, 10]; Z = −11.56, P < 0.01). For that reason, there had no value to compare the incidence of END directly between the IV rt-PA and the EVT groups. Among the 95 END patients, 80 patients (84.2%) occurred within 24 h after recanalization treatment. Therefore, the patients who received EVT were more likely to encounter END, and the first 24 h after recanalization treatment was a critical period for END occurrence.

Composition of early neurological deterioration
Among all the END types, IS occupied the highest proportion (65 patients, 68.4%), followed by VCE (20 patients, 21.1%), while sICH was the lowest (10 patients, 10.5%). The proportion of IS in the IV rt-PA group was higher than the EVT group, but the proportion of VCE and sICH was higher conversely [Figure 2]. Further analysis showed EVT might increase the occurrence of VCE [Figure 3]. All sICH (100.0%) and VCE (100.0%) and most of the IS (76.9%) occurred within 24 h after recanalization treatment. This suggested that the composition of END varied according to the different recanalization methods.

Risk factors of early neurological deterioration
In the IV rt-PA group, the proportion of admission NIHSS ≥8, admission systolic blood pressure (SBP) ≥160 mmHg, fasting blood glucose ≥6.1 mmol/L, and large artery occlusion after IV rt-PA in the END subgroup was higher than the non-END subgroup, with significant differences [Table 1]. Multivariate logistic regression analysis (stepwise, backward) showed that admission SBP ≥160 mmHg and large artery occlusion after IV rt-PA independently predicted END [Table 2]. While in the EVT group, admission SBP ≥140 mmHg,
In this study, the overall incidence rate of END after recanalization treatment was 34.2%. The first 24 h after IV rt-PA and EVT independently predicted END [Table 1]. Multivariate logistic regression analysis (stepwise, backward) showed that admission SBP ≥140 mmHg, partial recanalization, and nonrecanalization independently predicted END [Table 2].

Outcomes of early neurological deterioration
There were 21 patients who experienced END that received the following single or combined treatments: partial decompressive craniectomy (8 patients), hematoma evacuation (6 patients), lateral ventricle puncture and drainage (5 patients), and surface hypothermia (13 patients). Of these patients, 12 patients died in hospital and 9 were severely disabled at discharge.

The mortality rate and grave outcome rate of END patients were 10.4% and 27.1% in the IV rt-PA group, and 42.6% and 85.1% in the EVT group, respectively. The mortality rate (26.3% vs. 11.1%; \( \chi^2 = 45.57, P < 0.01 \)) and grave outcome rate (55.8% vs. 18.6%; \( \chi^2 = 40.27, P < 0.01 \)) at discharge of all the END patients were higher than those of all the non-END patients. These indicated that the occurrence of END was associated with adverse outcomes.

DISCUSSION
In this study, the overall incidence rate of END after recanalization treatment was 34.2%. The first 24 h after recanalization treatment was the peak occurrence time for END. IS was the most common type of END, but VCE was found at a higher proportion in the EVT group. Admission SBP ≥160 mmHg and large artery occlusion after IV rt-PA independently predicted END after IV rt-PA. Admission SBP ≥140 mmHg, partial recanalization, and nonrecanalization independently predicted END after EVT. END could increase the mortality and grave outcome rates at discharge. Thus, it is necessary to focus on END after recanalization treatment.

The incidence rate of END in this study was higher in comparison to previous reports because the definition of END and the subjects in this study were different with previous studies.\(^{[1,3]}\) Besides, about 42.0% patients in our study received endovascular treatment. In fact, most patients who received EVT had a plethora of problems including more serious condition on arrival, large artery occlusion, and relatively delayed time for vessel recanalization. These patients also had risks during the procedure of endovascular intervention, and the pathophysiological change of brain tissue was more complicated after treatment. Therefore, we got a higher overall incidence of END, compared with other studies.

Most of the previous studies reported sICH as the main type of END after IV rt-PA at nearly 20% of all END cases.\(^{[1]}\) However, this study found that IS was the highest proportion of END, followed by VCE and sICH in two recanalization treatment groups, which was consistent with the results of Kim et al.\(^{[16]}\) Although IS was the most common type of END, the prevalence of VCE after EVT was prominent. These results suggested that VCE could increase and might even become the main type of END as the development of EVT. When acute ischemic stroke happens, the damage to the blood–brain barrier (BBB) and an increase in BBB permeability in the ischemic area take place before recanalization treatment. These changes could become the pathophysiological basis for VCE and could be aggravated over time.\(^{[14,15]}\) The time for achieving recanalization in the EVT group is usually longer than that in the IV rt-PA group, while the recanalization rate and degree are usually better than the latter.\(^{[16,17]}\) As a result, longer duration of ischemia and better reperfusion result become important reasons to bring about VCE. Taking into all these factors, it is necessary to conduct closely monitoring on patients who receive recanalization treatment at least for 24 h. At the same time, patients who receive IV rt-PA should be focused on the possibility of IS, while patients who receive EVT should be focused on the occurrence of VCE.

The study showed that admission SBP ≥160 mmHg was an independent risk factor for END after IV rt-PA, and admission SBP ≥140 mmHg was an independent risk factor for END after EVT. A few studies have reported that hypertension on admission or acute hypertensive response was related to neurological deterioration after acute ischemic stroke: high SBP could increase the risk of CE and stroke recurrence.\(^{[18]}\) Australian streptokinase trial showed that baseline SBP ≥165 mmHg would increase the risk of cerebral hemorrhage.\(^{[19]}\)

The mechanism of the neurological deterioration caused by high SBP might be explained by the disturbance of cerebral vascular autoregulation: high SBP may cause breakthrough vasodilation of cerebral microvascular in the ischemic area since the autoregulation function in this area is weakened, and then bring about increasing of blood flow which may lead to CE and damage of BBB.\(^{[20]}\) Apart from this, the disfunction of microvascular autoregulation might cause exacerbation...
of ischemia in the penumbra when blood pressure waves or even decreases after recanalization.[21] The cutoff of admission SBP in the IV rt-PA group was higher than that of the EVT group, the reason might be that the ischemic area of the latter was larger and the ischemic degree was severer which caused the dysfunction of microvascular much more extensive and serious. In fact, the management of blood pressure in acute phase after ischemic stroke is controversy. There were few studies regarding the management of blood pressure after recanalization treatment, especially EVT; thus, more comprehensive and detailed researches are needed. Based on our research, patients with elevated admission SBP should be monitored closely before and after receiving recanalization treatment.

This study also found that unsatisfactory recanalization result was independently related to END. Saqqur et al.[22] found that inability to achieve or sustain vessel patency at the end of rt-PA infusion correlates with the likelihood of clinical deterioration and poor long-term outcome. When failing to achieve recanalization, there is no doubt that ischemic damage will further be aggravated. As a result, the risk of IS and hemorrhagic transformation is increased.[23] As for partial recanalization, large artery sclerosis before onset might lead to long-term hypoxemic state in the supplied

### Table 1: Clinical characteristics of all patients with acute ischemic stroke receiving recanalization treatment in this study (n = 278)

| Characteristics                      | IV rt-PA group (n = 161) | EVT group (n = 117) |
|--------------------------------------|--------------------------|---------------------|
|                                      | Non-END subgroup (n = 113) | END subgroup (n = 48) | Statistical values | P |
| Age (years), mean ± SD               | 60.3 ± 11.8              | 59.5 ± 12.1          | 0.41*            | 0.68 |
| Male, n (%)                          | 80 (70.8)                | 35 (72.9)            | 0.07             | 0.85 |
| Comorbidities, n (%)                 |                          |                     |                  |     |
| Hypertension                         | 73 (64.6)                | 31 (64.6)            | 0.00             | 1.00 |
| Diabetes mellitus                    | 40 (35.4)                | 18 (37.5)            | 0.06             | 0.85 |
| Hyperlipidemia                       | 53 (46.9)                | 22 (45.8)            | 0.01             | 1.00 |
| CVD history, n (%)                   | 29 (25.7)                | 8 (16.7)             | 1.54             | 0.22 |
| Antiplatelet treatment, n (%)        | 17 (15.0)                | 2 (4.2)              | 3.83             | 0.06 |
| TOAST subtypes, n (%)                |                          |                     |                  |     |
| Large-artery atherosclerosis         | 52 (46.0)                | 22 (45.8)            | 0.00             | 1.00 |
| Cardiac embolism                     | 14 (12.4)                | 8 (16.7)             | 0.52             | 0.61 |
| Small artery occlusion               | 47 (41.6)                | 16 (33.3)            | 0.96             | 0.37 |
| Others                               | 4 (3.5)                  | 2 (4.2)              | –                | 1.00 |
| Responsible lesion, n (%)            |                          |                     |                  |     |
| Anterior circulation                 | 96 (85.0)                | 39 (81.2)            | 0.34             | 0.64 |
| Admission examination*, n (%)        |                          |                     |                  |     |
| NIHSS ≥8                             | 34 (30.1)                | 24 (50.0)            | 5.79             | 0.02 |
| SBP ≥160 mmHg                        | 37 (32.7)                | 25 (52.1)            | 5.32             | 0.02 |
| NIHSS ≥10                            |                          |                     |                  |     |
| SBP ≥140 mmHg                        |                          |                     |                  |     |
| DBP ≥80 mmHg                         | 86 (76.1)                | 42 (87.5)            | 2.68             | 0.13 |
| FBG ≥6.1 mmol/L                      | 42 (37.2)                | 27 (56.2)            | 5.00             | 0.03 |
| Outcome after RCT, n (%)             |                          |                     |                  |     |
| Large artery occlusion               | 13 (11.5)                | 14 (29.2)            | 7.53             | 0.01 |
| Completely recanalization            |                          |                     |                  |     |
| Partial recanalization               |                          |                     |                  |     |
| Nonrecanalization                    |                          |                     |                  |     |
| Death, n (%)                         | 2 (1.8)                  | 5 (10.4)             | –                | 0.02 |
| mRS ≥5, n (%)                        | 5 (4.4)                  | 13 (27.1)            | 17.4             | <0.01 |

*Student’s t-tests, otherwise Pearson Chi-square test or Fisher’s exact test; IV rt-PA group: Admission NIHSS cutoff value 7.5, sensitivity 50.0%, specificity 70.0%; admission SBP cutoff value 159.5 mmHg, sensitivity 52.1%, specificity 67.3%; admission FBG cutoff value 78.5 mmHg, sensitivity 89.6%, specificity 23.0%; FBG cutoff value 6.1 mmol/L, sensitivity 56.3%, specificity 65.5%. So NIHSS ≥8. So, SBP ≥160 mmHg, DBP ≥80 mmHg, and FBG ≥6.1 mmol/L were taken as cutoff values. EVT group: Admission NIHSS cutoff value 10.5, sensitivity 93.6%, specificity 12.9%; admission SBP cutoff value 142.5 mmHg, sensitivity 76.6%, specificity 58.6%; admission FBG cutoff value 79.5 mmHg, sensitivity 80.9%, specificity 37.1%; FBG cutoff value 6.66 mmol/L, sensitivity 80.9%, specificity 45.7%. So, NIHSS ≥10, SBP ≥160 mmHg, DBP ≥80 mmHg, and FBG ≥7.0 mmol/L were taken as cutoff values. END: Early neurological deterioration; IV rt-PA: Intravenous recombinant tissue plasminogen activator; EVT: Endovascular treatment; SD: Standard deviation; CVD: Cerebral vascular disease; TOAST: Trial of Org10172 in Acute Stroke Treatment; NIHSS: National Institutes of Health Stroke Scale; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; RCT: Recanalization treatment; mRS: Modified Rankin Scale; –: Not applicable.
area, which could cause cumulative damage to neurovascular unit, or the perfusion of the supplied area was vulnerable to hypoperfusion and reocclusion.\[25,26\] As a result, the risk of END increased. Therefore, patients failing to achieve a satisfactory recanalization result after treatment should be included in the key monitoring objects. In addition, continuous improvement of cerebral blood flow should be strengthened.

Once END happens, the mortality and grave outcome rates could be increased. Decompressive craniectomy can decrease the mortality of large cerebral or cerebellar hemispheric infarction and should also be considered in malignant edema.\[25\] Evacuation of a large hematoma could be life-saving for sICH.\[26\] Hypothermia may reduce CE and improve clinical outcomes.\[27\] In addition, intraventricular drainage of cerebral spinal fluid could help to resolve secondary hydrocephalus. However, it is still a complicated task to treat END.

The present study focused on the incidence, composition, risk factors, and outcomes of END after IV rt‑PA and EVT, which found that END was not an uncommon event and associated with adverse outcomes at discharge. High admission SBP and unsatisfactory recanalization of occluded arteries might predict END. We proposed that with the further development of EVT technologies, it is imperative to intensify the monitoring and prevention awareness for END. This study is a retrospective cohort study, and the sample size was limited; therefore, there might be deviations in the results. For this reason, we will conduct single-center and multi-center prospective studies to enlarge the sample size to certify and explain the importance of prediction, monitoring, and treatment for END in the future.

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**Conflicts of interest**

There are no conflicts of interest.

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