Quantitative electroencephalograph in acute ischemic stroke treated with intravenous recombinant tissue plasminogen activator

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Abstract: To examine whether quantitative electroencephalograph (QEEG) can be applied to predict ischemic stroke patients responding to intravenous recombinant tissue plasminogen activator (iv rt-PA) treatment or not. 86 cases of ischemic stroke patients were treated with iv rt-PA and examined by QEEG and the United States National Institutes of Health Stroke Scale (NIHSS) score before treatment and 2 hours (h), 24 h, 7 days (d), 14 d, and 90 d after the treatment. Continuous EEG was recorded 10 min prior to therapy and at 2 h, 24 h, 7 d, 14 d, and 90 d after rt-PA treatment; each time point was recorded for 10 minute, and the brain symmetry index (BSI), δ+θ and α+β wave ratio (DTABR) and delta: alpha power ratio (DAR) were analyzed. By retrospective analysis, in the evaluation time point (14 d) after thrombolytic therapy with rt-PA, if NIHSS score with 1 or 0 points and NIHSS score reduced eight points, patients are enrolled to the improvement group; if not, patients are divided into non-improvement group. Finally, a total of 86 patients were divided into two groups: improvement group (n = 52) and non-improvement group (n = 34). The EEG changes at each time point were recorded in the two groups. In the improvement group, BSI and ADR exhibited greater improvement at 2 h, and continued improved to 90 d; DTABR exhibited greater improvement at 24 h, which was later than BSI and ADR; however, BSI, ADR and DTABR exhibited greater deterioration at 2 h in non-improvement group (P < 0.01). QEEG indices, especially, earlier improvement of BSI or DAR, could predict ischemic stroke patients well respond to rt-PA treatment. It is indicated that BSI or DAR was associated with the 14 d NIHSS score; while early deterioration (at 2 h) of BSI, DTABR or DAR indicated that NIHSS scores would not improve at 14 days.

Keywords: Ischemic stroke, tissue plasminogen activator (rt-PA), thrombolysis, EEG introduction

Introduction

Intravenous recombinant tissue plasminogen activator (iv rt-PA) treatment is recognized as a direct and effective treatment for acute cerebral infarction [1, 2]. The National Institute of Health Stroke Scale (NIHSS), Barthel index (BI) and Modified Rankin Scale (MRS) are usually used to evaluate the severity of stroke, dependency and the functional status/outcome of stroke patients but not for assessment of improvement in brain functions [3]. Besides, NIHSS is infeasible for special testing, especially in stroke patients with aphasia and drowsiness. Therefore, to a certain extent, evaluation using NIHSS is imprecise. Increased awareness indicates that continuous brain monitoring might be beneficial for neurological patients, because it may allow detection of brain dysfunction when the dysfunction is in a possible reversible state, Such as that qEEG-specifically the delta/alpha ratio (DAR) - was found to improve within minutes when reperfusion therapy was successful, but not improve when not successful [4]. Given the fact that the period during which this state is reversible may vary from minutes to hours, repeated clinical examinations, typically performed one to four times per day, often fail to detect dysfunction during this reversible period. While quantitative electroencephalograph (QEEG) provides information with high temporal resolution which allows real-time monitoring of brain activities, it neither requires adequate patient cooperation, nor it has contraindications for its application. Additionally, the EEG apparatus is portable,
Quantitative EEG in stroke treatment could be used to identify responses of ischemic stroke patients to iv rt-PA treatment.

Materials and methods

Patients

Patients with acute ischemic stroke within 4.5 hours of symptom onset received Computed Tomography (CT) scan and Magnetic Resonance Imaging (MRI) test to exclude cerebral hemorrhage and determine cerebral infarction. The inclusion criteria for the patients in the study were as follows: (1) age was between 18 and 80 years; (2) acute ischemic stroke occurred within 4.5 hours of symptom onset; (3) neurological symptoms and/or physical examination findings lasted at least more than one hour and NIHSS scores were between 4 and 24; (4) no or early stage cerebral ischemic changes were found by brain CT scan; and (5) informed consent provided by family members. The exclusion criteria were as follows: (1) History of cerebral hemorrhage; (2) History of stroke within the previous three months; (3) History of hemorrhagic disease within the previous six months; (4) Currently taking oral anticoagulation drug and the value of international normalized ratio was more than 1.5; (5) Platelet count was less than 100,000/mm$^3$; (6) Patients with severe diseases or conditions such as heart, lung, liver, or kidney diseases; (7) Cardiovascular shock or uncontrolled hypertension (blood pressure was greater than 185/110 mmHg); (8) Blood glucose was less than 50 mg/dL (2.7 mmol/L) or greater than 400 mg/dL (22.2 mmol/L); (9) Pregnancy.

86 patients accepting iv rt-PA treatment were recruited from the People’s Hospital of Pudong between July 2010 and July 2013. This study was approved by the hospital ethics committee. All patients received rehabilitation services from the physiotherapist in our hospital, and rehabilitation services were equivalent between the arms.

Inclusion criteria and exclusion criteria of patients treated with iv rt-PA

Grouping and intravenous thrombolysis: The patients in the treatment group received thrombolytic therapy with rt-PA. The total dosage of rt-PA was 0.9 mg/kg in a 10% water solution and administered intravenously. Ten percent of the total dosage was administered in one min-
ute, and then the reminder was infused continuously over 60 minutes. The patients without contraindications received antiplatelet therapy (300 mg/qd Aspirin during days 2-7, 100 mg/qd after day 7) after 24 h of rt-PA administration. The patients in the control group received anti-platelet therapy (300 mg/qd during days 1-7, 100 mg/qd after day 7) without rt-PA treatment.

Observational index

The pairwise-derived BSI (pdBSI) is calculated only from homologous channel pairs. DTABR, and NIHSS were analyzed in this study.

Method of EEG recording

Continuous EEG was recorded from 10 min prior to therapy until 2 h after therapy. EEG was also recorded for 10 min at 24 h, 7 d, 14 d, and 90 d after rt-PA treatment; each time point was recorded for 10 minutes. Prior to intravenous thrombolysis treatment, the doctor will discuss the risks and benefits of rt-PA treatment to the patients and their family members and a consent form is signed. The duration of consent took approximately 8-10 min; EEG examination was performed during this period in order not to delay treatment. EEG was recorded according to the International 10-20 system (with Ag/AgCl electrodes, using a bipolar 10-channel subset, and derivations F4-C4, F3-C3, C4-P4, C3-P3, P4-O2, P3-O1, F4-T4, and F3-T3). Impedance was kept less than 5 kOhm to avoid polarization effects. Recording was performed using a Nation 7128 WH EEG recorder. The sampling frequency was set to 250 Hz and filter settings were 0.16 to 70 Hz. The BSI and the DTABR were analyzed.

Measurement of the brain symmetry index

As a measure for the amount of ischemic damage, we used the BSI that was recently introduced to monitor possible brain ischemia in carotid surgery [11, 14, 15]. This measurement was made as described previously [16]. It is defined as the mean of the absolute value of the difference in mean hemispheric power in the frequency range from 1 to 25 Hz. Because the power spectral density is estimated by fast Fourier transform, we wrote for the power of the signal obtained from a particular hemispheric bipolar channel pair i (with i = 1, 2, . . . , N) at frequency j (or Fourier coefficient with index j = 1, 2, . . . , M), Rij(t) and Lij(t) for the right and left hemisphere, respectively. We define the BSI as:

$$BSI(t) = \frac{1}{M} \sum_{j=1}^{M} \left| \sum_{i=1}^{N} R_{ij}(t) - L_{ij}(t) \right|$$

with N being the number of channel pairs and M being the number of Fourier coefficients. The lower bound for the BSI is zero (perfect symmetry for all channels), whereas for the upper bound we found that BSI equaled 1, which implied maximal asymmetry.

Measurement of DTABR and DAR

The frequency ranges of delta, theta, alpha and beta were 0.5-3 Hz, 4-8 Hz, 8-13 Hz and above 14 Hz, respectively. δ+θ and α+β wave ratio was DTABR value, and Delta/alpha power ratio was DAR. All wave ratios were relative power.

Grouping of the improvement and non-improvement groups

According to the European Cooperative Acute Stroke Study (ECASSIII) reported in 2008 [17], improvement of cerebral infarction clinical function was evaluated by NIHSS score. By retrospective analysis, patients would be grouped into the improvement group if the NIHSS score is recorded as 1 or 0 point or reduced eight points at 14 d after rt-PA therapy [18]; Otherwise, patients were grouped the into non-improvement group.

Statistical analysis

The statistical software IBM SPSS Statistics 19.0 was used in this study. Need to describe whether data were expressed by mean ± standard errors or standard deviation. Chi-square test and t-test were used to analyze the data between the two groups. The difference was considered statistically significant if the P-value was less than 0.05.

Results

Patient characteristics (Table 1)

Eighty-six patients with acute ischemic stroke referred to our stroke unit between July 2010 and July 2014 were recruited in the present study. At 14 d after thrombolytic therapy with rt-PA, by retrospective analysis, 52 cases (27
men and 25 women, mean age: 57.9 years old, range: 51-79 years old) were grouped into the improvement group, and 34 cases (18 men and 16 women, mean age: 59.1 years old, range: 55-75 years old) were grouped into non-improvement group (Table 1). Five patients developed symptomatic intracerebral hemorrhage, which accounted for 5.26% of overall rt-PA treated patients. Three patients were dead at 15 d, 17 d and 22 d after treatment, which accounted for 3.95% of the overall rt-PA-treated patients. Therefore, the non-improvement group included 31 cases in the statistics at 90 d, since the three dead patients were not included in the analysis.

In the improvement group, risk factors included hypertension (n = 40), diabetes mellitus (n = 2), heart disease (n = 6), and hyperlipidemia (n = 50). In the non-improvement group, risk factors included hypertension (n = 29), diabetes mellitus (n = 1), heart disease (n = 4), and hyperlipidemia (n = 25). No significant difference in age and risk factors was observed between the two groups. The EEG starting time was 4 ± 0.1 h and the IV-starting time was 4 ± 0.4 h. 34 patients suffered ischemic stroke in the anterior cerebral artery (ACA), 52 cases in the middle cerebral artery (MCA), and no stroke was observed in the posterior cerebral artery.

Analysis of clinical outcomes

NIHSS score in two groups at each time point (Table 2): The NIHSS score in the two groups at each time point is shown in Table 2. The NIHSS score in the improvement group was 3.70 ± 2.15 at day 14 and 0.43 ± 0.63 at day 90, which was significantly lower than the non-improvement group (11.52 ± 3.02 at day 14; 7.90 ± 3.09 at day 90; P < 0.05).

BSI significantly improved early in the improvement group after rt-PA treatment (Table 3; Figure 1): Before treatment, the mean baseline value of BSI was 0.12 ± 0.13 in the improvement group and 0.12 ± 0.05 in the non-improvement group (Table 3); no significant difference was observed between the two groups. When compared with the mean baseline value (0.12 ± 0.03) before treatment, there was a significant decrease in the mean BSI at 2 h (0.09 ± 0.02; P < 0.01), 24 h (0.07 ± 0.01; P < 0.01), day 7 (0.05 ± 0.01; P < 0.01), day 14 (0.04 ± 0.02; P < 0.01), and day 90 (0.02 ± 0.01; P < 0.01) in the improvement group after rt-PA treatment, respectively. There was a significant increase at 2 h (0.16 ± 0.02; P < 0.01), 24 h (0.23 ± 0.02; P < 0.01) and 7 d (0.17 ± 0.02; P < 0.01) in the non-improvement group.

A decrease in BSI in the improvement group started at 2 h; however, in the non-improvement group, the decrease began at day 14, which was significantly later than the improvement group (P < 0.001).

DTABR changed after rt-PA treatment in each time point (Table 3; Figure 2): Before treatment, the mean baseline DTABR recorded by QEEG was 0.75 ± 0.14 in the improvement group and 0.74 ± 0.19 in the non-improvement group; no significant difference was observed between the two groups. When compared with the mean baseline value before treatment, there was a significant decrease beginning at 24 h in the mean DTABR which was later than BSI in the improvement group (0.68 ± 0.11; P < 0.01). There was a significant increase at 2 h (0.97 ± 0.20; P < 0.01), 24 h (1.03 ± 0.27; P < 0.01) and 7 d (0.82 ± 0.21; P < 0.01) in the non-improvement group.

A decrease in DTABR in the improvement group started at 24 h; however, in the non-improvement group, it began at day 14, which was significantly later than the improvement group (P < 0.001).
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Table 2. Comparison of NIHSS score at each time point (x ± S)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Baseline</th>
<th>2 h</th>
<th>24 h</th>
<th>7 d</th>
<th>14 d</th>
<th>90 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement</td>
<td>11.67 ± 2.88</td>
<td>11.83 ± 2.63</td>
<td>11.60 ± 2.97</td>
<td>7.40 ± 2.77 ▲ △</td>
<td>3.70 ± 2.15 △</td>
<td>0.43 ± 0.63 △</td>
</tr>
<tr>
<td>Non-improvement</td>
<td>11.52 ± 2.79</td>
<td>11.68 ± 2.56</td>
<td>11.50 ± 2.95</td>
<td>11.47 ± 3.66</td>
<td>11.52 ± 3.02</td>
<td>7.90 ± 3.09 ▲</td>
</tr>
</tbody>
</table>

Note: ▲ P < 0.01, △ P < 0.01, compared to baseline; Improvement group (n = 52) vs. non-improvement group (n = 34); only 31 cases were included in the statistics at 90 d for the non-improvement group due to three cases of patient death.

Table 3. Comparison of BSI, DTABR and ADR recorded by QEEG for rt-PA at different time points (x ± S)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Baseline</th>
<th>2 h</th>
<th>24 h</th>
<th>7 d</th>
<th>14 d</th>
<th>90 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSI</td>
<td>0.12 ± 0.13</td>
<td>0.09 ± 0.02 ▲</td>
<td>0.07 ± 0.01 ▲</td>
<td>0.05 ± 0.01 ▲</td>
<td>0.04 ± 0.02 ▲</td>
<td>0.02 ± 0.01 ▲</td>
</tr>
<tr>
<td>DTABR</td>
<td>0.75 ± 0.14</td>
<td>0.76 ± 0.23</td>
<td>0.68 ± 0.11 ▲</td>
<td>0.60 ± 0.12 ▲</td>
<td>0.50 ± 0.14 ▲</td>
<td>0.34 ± 0.10 ▲</td>
</tr>
<tr>
<td>ADR</td>
<td>6.4 ± 0.18</td>
<td>4.8 ± 0.21 ▲</td>
<td>4.0 ± 0.29 ▲</td>
<td>3.5 ± 0.21 ▲</td>
<td>3.0 ± 0.11 ▲</td>
<td>2.0 ± 0.19 ▲</td>
</tr>
<tr>
<td>Non-improvement group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSI</td>
<td>0.12 ± 0.05</td>
<td>0.16 ± 0.02 ▲</td>
<td>0.23 ± 0.02 ▲</td>
<td>0.11 ± 0.03 ▲</td>
<td>0.07 ± 0.02 ▲</td>
<td>0.03 ± 0.02 ▲</td>
</tr>
<tr>
<td>DTABR</td>
<td>0.74 ± 0.19</td>
<td>0.97 ± 0.20 ▲</td>
<td>1.03 ± 0.27 ▲</td>
<td>0.82 ± 0.21 ▲</td>
<td>0.54 ± 0.21 ▲</td>
<td>0.30 ± 0.17 ▲</td>
</tr>
<tr>
<td>ADR</td>
<td>6.4 ± 0.22</td>
<td>7.3 ± 0.11 ▲</td>
<td>7.19 ± 0.29 ▲</td>
<td>6.21 ± 0.24 ▲</td>
<td>4.0 ± 0.15 ▲</td>
<td>3.1 ± 0.08 ▲</td>
</tr>
</tbody>
</table>

Note: ▲ P < 0.01 and △ P < 0.01, compared to baseline; Improvement group (n = 52) vs. non-improvement group (n = 34); only 27 cases were included in the statistics at 90 d for the non-improvement group due to three cases of patient death.

Figure 1. Comparison of BSI recorded by QEEG for rt-PA responder and non-responder groups.

Figure 2. Comparison of DTABR recorded by QEEG for rt-PA responder and non-responder groups.

DAR changed after rt-PA treatment at each time point (Table 3; Figure 3): Before treatment, the mean baseline DAR recorded by QEEG was 6.4 ± 0.18 in the improvement group and 6.4 ± 0.22 in the non-improvement group; no significant difference was observed between the two groups (Table 3). When compared with the mean baseline before treatment, there was a significant decrease in the mean DAR at 2 h (4.8 ± 0.21; P < 0.01), 24 h (4.0 ± 0.29; P < 0.01), day 7 (3.5 ± 0.21; P < 0.01), day 14 (3.0 ± 0.11; P < 0.01), and day 90 (2.0 ± 0.19; P < 0.01) in the improvement group after rt-PA treatment. There was a significant increase at 2 h (7.3 ± 0.11; P < 0.01), 24 h (7.19 ± 0.29; P < 0.01) compared with the mean baseline before treatment in the non-improvement group.

A decrease compared with the mean baseline before treatment in DAR in the improvement group started at 2 h after treatment, however, in the non-improvement group, the decrease began at day...
14 after treatment, which was significantly later than the improvement group ($P < 0.001$).

Discussion

In the present study, the neurological functions in patients with ischemic stroke were compared prior to and after treatment with iv rt-PA. It was found that the patients whose BSI and DAR score of QEEG improved early (at 2 h) after receiving treatment with iv rt-PA would have early improvement of NIHSS score (at 14 day), but patients whose BSI, DTABR and DAR of QEEG deteriorated at 2 h or 24 h would have no improvement of NIHSS score at 14 day. QEEG indices, especially the BSI and DAR, may be applied to predict outcome of ischemic stroke patients who respond to iv rt-PA treatment, early deterioration of BSI, DTABR and DAR could be applied to predict patients who are not improved early. In the present study, we demonstrated a significant correlation between acute change in EEG data (BSI, DTABR and DAR) and NIHSS scores at 14 days post iv rt-PA treatment in stroke patients, which is consistent with previous study conclusions [13, 19]. It has been showed that EEG delta (1-4 Hz) [16] and delta: alpha power ratio (DAR) [13] was strongly correlated with NIHSS scores at 30 days post-stroke. The time for BSI and DAR improvement was approximately 2 h, which was later than that in the previous study [19], in which a significant delta power reduction was observed 25 min after IV alteplase treatment, the reduction preceded any notable symptomatic change by approximately 2 h when cerebral response to reperfusion following recanalization and MRI indicate reperfusion [19]. The cause of the delay may be due to the fact that we did not follow up the patients with recanalization after reperfusion using CT or MRI, so that we could not group the patients according to recanalization or non-recanalization after the patients received thrombolytic therapy, therefore, the BSI changes we observed were not simply the results of BSI and DAR from the patients with recanalization after CT or MRI reperfusion after thrombolysis, the BSI and DAR changes may be also obtained from the patients with non-recanalization after CT or MRI reperfusion after thrombolysis, and thus it is possible that the delayed improvement in BSI occurs in the patients with iv rt-PA treatment without vascular recanalization. Moreover, reperfusion may not occur timely following re-canalisation in the patients with acute ischemic stroke with NIHSS score improvement at 14 days post iv rt-PA treatment. Additionally, in the present study, continuous EEG was recorded 10 min prior to therapy after iv rt-PA treatment, whereas the recording was incontinuous from prior to therapy to 2 h, we only recorded EEG at 2 h, therefore, the improved EEG may occur when 25 min after IV or earlier; however, we did not record the improvement until in continuous recording was made.

Previous studies [20, 21] have shown that QEEG detection is the most sensitive technique for the clinical detection of ischemic stroke and is extremely sensitive to the reversible phase of physiological and pathological changes of brain tissue. Sheorajpanday et al. [14] found that BSI was significantly associated with lesion area and volume of cerebral infarction by studying sub-acute cerebral infarction, transient ischemic attack patients and healthy people. In another study [20], the accuracy of BSI to determine the NIHSS score of 1 and 0 on stroke patients was 80% and on classification of neurological deterioration was 95%, indicating that BSI is a good predictive index of ischemic stroke. BSI emerged as an independent predictor for definite stroke in patients presenting with lacunar and posterior circulation dysfunction [20], and DTABR predicted unfavorable outcome at day 7 with an accuracy of 83% in lacunar stroke [20]. BSI and DTABR were significantly correlated with the modified Rankin Scale (mRS) score at

Figure 3. Comparison of ADR recorded by QEEG for rt-PA responder and non-responder groups.
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six months after stroke [21]. NIHSS and BSI were independently associated with disability six months after stroke [20]. Dependence was independently indicated by NIHSS and DTABR [20]. Six-month mortality was independently indicated by age at stroke onset, NIHSS and DTABR [20]; however, to date, few studies have been performed to examine the role of QEEG analysis especially BSI change in ischemic stroke patients after iv rt-PA treatment. Current research has only analyzed the δ, α and β wave [22, 23] or provides preliminary evidence that continuous EEG/QEEG monitoring during thrombolysis could provide real-time information about the efficacy of iv tPA in acute clinical management of ischaemia prior to potential clinical changes [24], but the BSI, DTABR, and NIHSS were not analyzed in these previous studies. Therefore, in our study, we intended to examine whether QEEG can be applied to predict whether ischemic stroke patients eventually respond to iv rt-PA treatment or not.

Our study has some limitations. First, we used the change in clinical scales (NIHSS) as the criteria of response, but NIHSS is infeasible for respective testing, especially in stroke patients with aphasia, drowsiness, etc. Therefore, it is imprecise to a certain extent. Second, we measured the change in EEG index and NIHSS scores; however, we did not record the changes in CT perfusion scanning images or MRA after iv rt-PA treatment. If we had recorded these CT or MRA changes, we could grouping patients into improvement and non-improvement groups more accurate.

In the present study, it was found that QEEG (BSI, DTABR and DAR) was correlated with NIHSS scores at 14 days. Early improvement (at 2 h) of BSI or DAR indicated that NIHSS scores would improve at 14 day, while early deterioration (at 2 h) of BSI, DTABR or DAR indicated that NIHSS scores would not improve at 14 days. BSI, DTABR and DAR are clinically relevant and it is a sensitive or specific indicator for predication prognosis of stroke, moreover, it would also predicate progress of patients with or without treatment; however, further study of the association between BSI and long-term outcome of stroke need to be performed. Additionally, QEEG may uniquely guide acute stroke management as well. QEEG can indicate lack of favorable response to therapy and, thus, it may inform and expedite decisions regarding further reperfusional strategies, such as clot retrieval.

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Disclosure of conflict of interest

None.

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