Effects of atorvastatin and aspirin on post-stroke epilepsy and usage of levetiracetam

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Abstract

Objective: Atorvastatin and aspirin have been used in treating different forms of epilepsy. However, their effect on post-stroke epilepsy (PSE) still needs to be validated by large-scale clinical studies. In addition, their impact on the use of the antiepileptic drug levetiracetam for post-stroke epilepsy remains to be explored. Thus, the aim of this study was to further evaluate the effect of atorvastatin and aspirin on PSE and their effect on the usage of the antiepileptic drug levetiracetam in PSE patients.

Methods: Patients, aged 65 to 85 years, with newly diagnosed post-ischemic stroke epilepsy from August 30, 2014 to August 30, 2018 were included in the study, with the exclusion of those with coexisting conditions.

Results: Initially, 1321 patients were included, and 780 remained in the study at the 1-year follow-up. During the study, atorvastatin treatment with or without aspirin reduced the number of clinical epileptic episodes in PSE patients. It also reduced the dosage of levetiracetam and achieved better control of epilepsy compared to levetiracetam mono-treatment. Aspirin co-treatment with levetiracetam did not result in a significant improvement. However, the combination of aspirin with atorvastatin significantly reduced the number of seizures compared to aspirin treatment alone.

Conclusion: Atorvastatin and aspirin co-treatment with levetiracetam can reduce epilepsy in PSE patients and reduce the dosage of levetiracetam required for effective control of PSE.

Abbreviations: CDR = concentration-dose ratio, LEV = levetiracetam, NSAIDs = non-steroidal anti-inflammatory drugs, PSE = post-stroke epilepsy.

Keywords: aspirin, atorvastatin, levetiracetam, post-stroke epilepsy

1. Introduction

With the aging of the global population and modern lifestyle changes, the incidence of stroke has gradually increased. Notably, the incidence of epilepsy in the elderly is higher than that in all other ages except infants, and stroke is one of the main causes of seizures in the elderly. Post-stroke epilepsy (PSE) has become a hot topic in the field of epilepsy. After an ischemic stroke, patients often require long-term therapy with an oral antiplatelet drug, such as aspirin, and anti-atherosclerotic drugs, such as statins. Thus, long-term use of oral aspirin and statins is common in the patients with PSE caused by ischemic stroke. Statin treatment can reduce the hospitalization rate among elderly patients with epilepsy, the mortality rate of status epilepticus, and the incidence of sudden death of epilepsy. Statins, traditional antiepileptic drugs, and other drugs mutually influence their efficacy, blood concentrations, and side effects. In addition, aspirin can increase the free concentration of sodium valproate in plasma. Thus, statins and aspirin have a significant impact on epilepsy and antiepileptic drugs. However, to date there has been no large-scale clinical studies to determine this impact. In addition, there has been no investigation of co-application of statins and aspirin with new anti-epileptic drugs, such as levetiracetam (LEV), commonly used to treat PSE. Therefore, this study focused on the clinical evaluation of the effects of long-term atorvastatin and aspirin treatment on epilepsy and the usage of LEV in patients with PSE.

2. Materials and methods

2.1 Inclusions and grouping

This project was approved by the ethics committee of the First hospital of Jilin university, and every enrolled patient signed an informed consent. Patients with newly diagnosed post-ischemic stroke epilepsy, aged 65 to 85 years, who received outpatient and...
inpatient care in the Department of Neurology and Epilepsy of the First Hospital of Jilin University from August 30, 2014 to August 30, 2018 were included in the study. All received only LEV as anti-epilepsy therapy. The patients were divided into 4 groups based on whether they were further co-treated with atorvastatin and/or aspirin in addition to LEV during the 1-year follow-up: Group A: no co-treatment medication; group B: co-treatment with aspirin; group C: co-treatment with atorvastatin; and group D: co-treatment with both aspirin and atorvastatin.

2.2. Exclusion criteria
Patients were excluded if they had:
1. other types of stroke, including spontaneous intracranial hemorrhage, subarachnoid hemorrhage, and transient ischemic attack;
2. traumatic brain injury, an intracranial tumor, or central nervous system infection;
3. metabolic diseases, neurodegenerative diseases, poisoning, alcoholism, cortical dysplasia, or other condition that may cause seizures;
4. new infarcts that appeared during the 1-year follow-up; or
5. uncontrollable epilepsy during the follow-up period that required switching to other antiepileptic drugs or surgical treatment.

Ischemic stroke patients without epilepsy aged between 65 and 85 years and treated at the same time were randomly selected as the control group.

2.3. Demographic and clinical data collection at baseline
The demographic data collected included: gender, age, home address, and phone number, and the clinical data collected included: previous history of cerebral infarction, hypertension, diabetes, and hyperlipidemia; severity of stroke at baseline, graded as mild (NIHSS score < 5 points), moderate (NIHSS score 5–15 points), moderate to severe (NIHSS score 16–20 points), or severe (NIHSS score > 20 points); and the stroke site of either cortical or subcortical infarction based on the scan results obtained using a Siemens MAGNETOM Avantol 1.5T magnetic resonance scanner. The criteria used for the diagnosis and classification of PSE were based on the new definition and classification of epilepsy proposed by the 2017 International Antiepileptic Coalition.

2.4. Clinical data collection during the follow-up period
Face-to-face follow-up was performed 12 months after the baseline period for the collection of clinical data along with the measurement of the blood concentration of LEV, a 2-hour electroencephalogram (EEG), and head magnetic resonance imaging (MRI) examination. The specific follow-up data included: stroke severity (NIHSS score), usage and dosage of aspirin, usage and dosage of atorvastatin, and usage and dosage of LEV. All 3 drugs were administered orally for more than 5 days within 1 week, as regular medication. The blood concentration of LEV was measured by ultra-high-performance liquid chromatography using the following reagents and equipment: LEV tablets (UCB Pharma SA, 500 mg/tablet); LEV reference samples (UCB Pharma SA, lot number: Y0001256; purity ≥98%); methanol and acetonitrile (Fisher Scientific, USA); and protein precipitant (Abbott Company, USA). The H-CLASS Ultra High-Performance Liquid Chromatograph (Waters Company, USA), the FJY1002-UVF Ultrapure Water System (Qingdao Fulham Company), the 5430R Eppendorf Refrigerated Centrifuge (Eppendorf, Germany), and the Agilent 1200 HPLC Chromatograph (Agilent, USA) were employed. The column was a Hibar C18 bonded silica column (150 mm × 4.6 mm, 5 μm). The concentration-dose ratio (CDR) and steady valley concentration (Css) of LEV in the blood were measured. MRI of the head was also performed, and the number of clinical epilepsy episodes that had occurred from baseline to the follow-up examination was recorded.

2.5. Statistical analysis
The data were analyzed using SPSS 22.0 (SPSS, Inc., USA). Categorical variables are expressed as percentages, and Chi-Squared test was used for comparison between 2 groups. The dosage, CDR, and Css of LEV are presented as the mean and standard deviation based on the number of clinical epilepsy episodes. The comparisons among groups were performed by one-way analysis of variance (ANOVA), followed by Tukey post-hoc test. Logistic regression analysis was used to detect the relationships between atorvastatin use, aspirin use, and PSE risk. Other clinical data that may affect the results of the study were collected, including gender, age, hypertension, diabetes, hyperlipidemia, smoking, living environment, NIHSS score, and infarct site and were used as co-variants for regression analysis. The results are expressed as odds ratio (OR), 95% confidence interval (95% CI), and P value. All tests were two-way, and P values less than .05 were statistically significant.

3. Results
3.1. Patient demographic and other clinical data
According to the inclusion and exclusion criteria, a total of 1323 patients were included in the baseline period, and eventually, 780 patients met the inclusion criteria after 12 months of follow-up. Specifically, during the 1-year follow-up period, 128 patients showed obvious new infarcts on MRI and were excluded; 229 patients were excluded due to uncontrollable epilepsy that required a switch to other antiepileptic drugs or surgery. Among the 186 patients who were lost during follow-up, 56 died, 102 could not be reached due to a phone number change, and 28 refused to participate in the follow-up examination. According to the grouping criteria, 89 patients were included in group A, 253 patients in group B, 62 patients in group C, and 376 patients in group D. A total of 125 non-epileptic ischemic stroke patients were included in the control group.

The data for gender, age, place of residence, history of hypertension, diabetes, hyperlipidemia, and smoking in each group were collected (Table 1). There were no statistical differences among the groups in terms of gender, age, history hypertension, diabetes, and hyperlipidemia. However, the proportion of urban residents was significantly lower in group A than in the other groups, indicating that the urban population had better compliance with taking aspirin and atorvastatin for secondary prevention after stroke than did the non-urban population. The proportion of smokers was significantly higher in group A than in the other groups, indicating that there were fewer smokers in the urban population.
### Table 1

**Patient demographic and clinical data.**

|                          | Group A (n = 89) | Group B (n = 253) | Group C (n = 62) | Group D (n = 376) | Control (n = 125) | χ²/F | P value |
|--------------------------|-----------------|-------------------|-----------------|------------------|------------------|------|---------|
| Gender (M, %)            | 53 (40.45%)     | 148 (41.5%)       | 38 (63.11%)     | 202 (46.28%)     | 69 (44.8%)       | 2.582| .63     |
| Age (y, mean ± SD)       | 85±22.12±23     | 75±36±17.55       | 74±89±16.85     | 72±66±9.63       | 76±34±10.28     | 4.477| .001    |
| Cty residents (%)        | 21 (76.4%)      | 189 (25.3%)       | 26 (57.3%)      | 60 (60.08%)      | 3 (9.68%)        | 118.13| <.001  |
| Hypertension (%)         | 53 (40.45%)     | 169 (33.2%)       | 42 (32.26%)     | 256 (31.91%)     | 78 (37.6%)       | 3.257| .516    |
| Diabetes (%)             | 38 (57.3%)      | 118 (53.36%)      | 25 (59.68%)     | 179 (52.39%)     | 55 (56%)         | 1.823| .768    |
| Hyperlipid (%)           | 28 (68.54%)     | 101 (60.08%)      | 28 (59.57%)     | 152 (59.57%)     | 46 (63.2%)       | 3.754| .44     |
| Smoking (%)              | 25 (71.91%)     | 51 (79.84%)       | 14 (77.42%)     | 78 (79.26%)      | 28 (77.6%)       | 2.889| .577    |

*P < .05 compared to group A.

### Table 2

**Stroke severity and stroke location.**

| Stroke severity | Group A (n = 89) | Group B (n = 253) | Group C (n = 62) | Group D (n = 376) | Control (n = 125) | χ²/F | P value |
|-----------------|-----------------|-------------------|-----------------|------------------|------------------|------|---------|
| Stroke severity |                 |                   |                 |                  |                  |      |         |
| Light           | 22 (75.28%)     | 53 (79.05%)       | 14 (77.42%)     | 26 (79.26%)      | 52 (68.4%)       | 4.58 | .971    |
| Intermediate    | 34 (61.8%)      | 102 (59.68%)      | 26 (58.06%)     | 153 (59.31%)     | 52 (68.4%)       | 1.823| .768    |
| Intermediate-severe | 28 (68.54%) | 79 (68.77%)       | 15 (75.81%)     | 107 (71.54%)     | 36 (71.2%)       | 63.011| <.001  |
| Severe          | 5 (94.35%)      | 19 (92.49%)       | 7 (88.71%)      | 38 (69.39%)      | 11 (91.2%)       |      |         |
| Infarction site |                 |                   |                 |                  |                  |      |         |
| Cortical        | 68 (23.6%)      | 208 (79.57%)      | 48 (25.58%)     | 310 (37.5%)      | 62 (60.4%)       |      |         |
| Subcortical     | 21 (76.4%)      | 45 (20.21%)       | 14 (77.42%)     | 66 (27.6%)       | 63 (30.6%)       |      |         |

*P < .05 compared to control.

### Table 3

**CDR and Css values for LEV in each study group.**

|                          | Group A (n = 89) | Group B (n = 253) | Group C (n = 62) | Group D (n = 376) | F     | P value |
|--------------------------|-----------------|-------------------|-----------------|------------------|-------|---------|
| Number of epilepsy events| 12.2±2.8**       | 10.6±5.0*         | 8.6±2.3**       | 6.2±2.1**        | 172.08| <.001   |
| LEV dosage (mg/kg/d)     | 22.3±2.98**      | 21.45±16.96**     | 16.26±7.26**    | 12.22±6.14**     | 88.386| <.001   |
| LEV Css (mg/mL)          | 26.44±6.13**     | 25.13±5.22**      | 19.26±5.06**    | 14.72±4.47**     | 279.87| <.001   |
| LEV, CDR (kg/L)          | 0.85±0.56        | 0.82±0.38         | 0.81±0.69       | 0.80±0.46        | 0.298 | .827    |

*P < .05 compared to group A.

**P < .05 compared to group B.

*P < .05 compared to group C.

*P < .05 compared to group D.

### 3.2. Stroke and epilepsy data

Stroke severity, infarct location, number of clinical epileptic episodes, and LEV medication use from the baseline to follow-up period were recorded in each group (Table 2). Stroke severity did not differ significantly among the groups by Chi-Squared test. In terms of infarct site, no significant difference was observed between PSE groups A, B, C, and D, but the percentage of cortical infarction in each study group was significantly higher than that in the control group, indicating that cortical infarction is closely related to PSE.

### 3.3. Effects of co-treatment of atorvastatin and aspirin with LEV on PSE and LEV usage

The effects of the different treatment combinations on the number of clinical epileptic episode are described in Table 3, along with the dosage, Css, and CDR of LEV. Aspirin co-treatment (group B) slightly reduced number of epileptic events compared to that with LEV treatment alone (group A). However, the difference was not statistically significant. Atorvastatin co-treatment (group C) significantly reduced the number of epileptic events compared to LEV treatment alone (group A) and aspirin co-treatment (group B). Atorvastatin + aspirin co-treatment (group D) further reduced the epileptic frequency significantly compared with the frequencies observed in the other 3 groups (A, B, and C). Thus, co-treatment with atorvastatin or aspirin and atorvastatin can reduce the number of clinical episodes of PSE, and the combination of both is more effective, while aspirin co-treatment alone showed no significant effect.

Similarly, the average dose of LEV used in the aspirin co-treatment group (group B) was not significantly different from that in the LEV alone group (group A). Atorvastatin co-treatment (group C) significantly reduced the LEV dose used compared with that used with LEV treatment alone (group A) and with aspirin co-treatment (group B). Atorvastatin + aspirin co-treatment (group D) further reduced the LEV dosage significantly compared with the doses in the other 3 groups (A, B, and C). The Css of LEV also significantly differed among the groups, consistent with the results for the dosage of LEV. However, no significant difference in CDR was found among the groups. Thus, co-treatment with
atorvastatin or aspirin and atorvastatin can reduce the required dosage of LEV and still provide better control of epilepsy in PSE patients, and the combination of both is more effective, whereas aspirin co-treatment alone showed no significant effect. However, aspirin and atorvastatin alone or in combination did not significantly affect the LEV plasma concentration.

4. Discussion

The majority of patients with epilepsy after ischemic stroke require long-term oral antplatelet drugs and lipid-lowering drugs, of which aspirin and atorvastatin are 2 of the most commonly used in these classes of drugs, respectively. Atorvastatin and aspirin have been used in treating PSE, but their effectiveness still needs to be validated by large-scale clinical studies. In addition, their impact on antiepilepsy treatment with the drug LEV in PSE patients remains to be explored. To this end, in the present study, we further evaluated the effect of atorvastatin and aspirin on PSE as well as their effect on the use of the antiepilepsy drug LEV. Our results demonstrated that atorvastatin treatment without or with aspirin reduced the number of clinical epileptic episodes in PSE patients. It also reduced the dosage of LEV given to PSE patients and achieved better control of epilepsy compared to LEV treatment without atorvastatin. Aspirin co-treatment with LEV did not result in significant improvement. However, when combined with atorvastatin, aspirin treatment significantly reduced the number of seizures more effectively than only atorvastatin with LEV, suggesting that aspirin and atorvastatin have a synergistic effect in controlling epilepsy. Our results are consistent with previous studies and further confirmed the role of statins in controlling PSE with a large clinical sample size.

Regarding the relationship between aspirin and epilepsy, an animal study found that aspirin can reduce the onset of chronic temporal lobe epilepsy in mice by promoting hippocampal nerve regeneration and inhibiting inflammatory response mediated by the COX-PGE2 pathway. In animal models of pilocarpine-induced epilepsy, non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, can reduce the number of spontaneous seizures by protecting hippocampal nerves and reducing mossy fiber sprouting. However, some studies have shown that the effects of non-selective NSAIDs, such as aspirin, on epilepsy are affected by various factors such as the type of seizures, timing of medication, and clinical research methods. Our study showed that aspirin co-treatment did not significantly reduce seizures in the PSE patients, but aspirin combined with atorvastatin did significantly reduce the number of seizures. Moreover, the use of both drugs was more effective than atorvastatin co-treatment with LEV alone, suggesting that aspirin may have a synergistic effect with atorvastatin in controlling post-stroke seizures. The specific reason may be related to the aforementioned mechanisms of the activities of aspirin and atorvastatin, which may prevent non-infarct cerebral ischemia to the greatest extent.

Regarding the relationship between atorvastatin and epilepsy, studies have shown that statins can have an anti-epileptic effect through multiple mechanisms. They can reduce the excitability and toxicity of glutamate via their anti-inflammatory action, reduce the permeability of the blood-brain barrier, and regulate intracellular calcium levels and the activity of NMDA receptors. They can also down-regulate the pro-apoptotic Mst1 gene and thereby reduce hippocampal cell death. Other studies have shown that statins prevent the onset of PSE by inhibiting the pathophysiological processes of PSE, such as reactive astrocyte proliferation.

LEV, as a representative of the new anti-epileptic drugs, has been widely used in clinical practice due to its reliable efficacy and minimal side effects, especially in elderly epilepsy patients. LEV is a pyrroldione derivative with good pharmacokinetic properties, high bioavailability, low protein-binding rate (<10%), linear metabolic characteristics, and no liver enzyme induction. Because a large proportion of LEV (approximately 66%) is excreted by the kidney as a prototype, abnormal renal function and the combined use of other drugs that are mainly excreted by the kidney may slow its elimination from the body. Because aspirin and atorvastatin are mainly metabolized in the liver, theoretically, it is unlikely that they will interact with LEV to affect its metabolism. However, potential interactions between aspirin, atorvastatin and LEV have not been investigated. A study of aspirin and sodium valproate showed that aspirin can increase the concentration of free sodium valproate in plasma by competing for protein-binding sites. However, this effect should be very small for LEV, since it has an extremely low protein binding affinity. Another study showed that enzyme-inducing anti-epileptic drugs (EIAEDs) can interact with simvastatin and atorvastatin to affect drug effectiveness. However, LEV is a non-enzyme-induced antiepileptic drug (non-enzyme-inducing AEDs; NEIAEDs). Thus, there is no possibility of this type of interaction. Our study also confirmed that co-treatment with aspirin and/or atorvastatin did not affect the CDR of LEV, indicating that aspirin and atorvastatin do not affect the blood concentration and unit efficacy of LEV.

The present study has some limitations to consider when interpreting the results. In this study, patient age ranged from 65 to 85 years; thus, it is unknown whether the conclusions drawn from this study will be applicable to other age groups. In addition, the number of people lost to follow-up was somewhat large due to death or poor compliance during follow-up, which may also have impacted the results. The next steps are to include patients of other age groups and perform randomized controlled studies to further verify the conclusions of this study.

5. Conclusion

In summary, our study confirms that atorvastatin alone or in combination with aspirin can prevent PSE and reduce the required dosage of LEV medication without affecting the blood concentration of LEV. Notably, the combination of aspirin and atorvastatin was found to be more effective than atorvastatin alone for treating PSE patients receiving LEV. The detailed underlying mechanisms remain to be explored.

Author contributions

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Corrections
The corresponding author has been updated from Ying Ding to Weihong Lin. Ying Ding has also been corrected to the second author in the author list.

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