Anti-inflammatory effects of Simvastatin in patients with acute intracerebral hemorrhage in an intensive care unit

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Abstract. Intracerebral hemorrhage is one of the most common types of cerebrovascular disease in humans and often causes paralysis, a vegetative state and even death. Patients with acute intracerebral hemorrhage are frequently monitored in intensive care units (ICUs). Spontaneous intracerebral hemorrhage is associated with a higher rate of mortality and morbidity than other intracephalic diseases. The expression levels of inflammatory factors have important roles in inflammatory responses indicative of changes in a patient's condition and are therefore important in the monitoring and treatment of affected patients at the ICU as well as the development of therapeutic strategies for acute cerebral hemorrhage. The present study investigated the anti-inflammatory effects of Simvastatin in patients with acute intracerebral hemorrhage at an ICU, and inflammatory factors and cellular changes were systematically analyzed. The plasma concentrations of inflammatory factors, including interleukin (IL)-4, IL-6, IL-8 and IL-10, were evaluated by ELISAs. The plasma concentrations of inflammatory cellular changes were detected by using flow cytometry. The results demonstrated that after Simvastatin treatment of patients with acute cerebral hemorrhage at the ICU, the plasma concentrations of IL-4, IL-6, IL-8 and IL-10 were downregulated compared with those in placebo-treated controls. In addition, Simvastatin treatment at the ICU decreased lymphocytes, granulocytes and mononuclear cells in patients with acute cerebral hemorrhage. The levels of inflammatory factors were associated with brain edema in patients with acute cerebral hemorrhage treated at the ICU. In addition, the amount of bleeding was reduced in parallel with the inflammatory cell plasma concentration of lymphocytes, granulocytes and mononuclear cells. Importantly, Simvastatin treatment produced beneficial outcomes by improving brain edema and reducing the amount of bleeding. In conclusion, the present study demonstrated the efficacy of Simvastatin in treating acute intracerebral hemorrhage and evidenced the association between inflammatory responses and the progress of affected patients at the ICU, thereby providing insight for applying effective therapies for patients with acute intracerebral hemorrhage.

Introduction

Cerebral hemorrhage is the most common type of cerebrovascular disease in humans (accounting for 20-30%) and the least treatable subtype of hemorrhagic stroke (mortality rate, 30-40%) (1). The most common manifestations in the clinic are cerebral arteriosclerosis, hypertension and intracranial vascular malformations (2). Cerebral hemorrhage is often induced by exertion and emotions, and most patients show sudden onset during activity. Cerebral hemorrhage usually causes severe dysfunction of the cerebral nervous system and loss of social functioning, self-care ability and further increases the burden on the family of affected patients (3,4). Subarachnoid hemorrhage is one of the most serious types of cerebral hemorrhage and usually leads to death, as it is a devastating cerebrovascular disease with bleeding into the subarachnoid space (5,6). While oral administration of anti-coagulants and surgical resection are the mainstay of cerebral hemorrhage treatment in the clinic, no effective therapeutic schedule is currently available to improve functional outcomes in patients with cerebral hemorrhage, particularly subarachnoid hemorrhage (7-9). Therefore, the development of therapeutic agents targeting cerebral hemorrhage is urgently required and the underlying molecular mechanisms require further elucidation in order to provide novel targets for identifying novel treatment approaches of human cerebrovascular diseases.

Patients with acute intracerebral hemorrhage are frequently monitored in intensive care units (ICUs) (10). Sudden intracerebral hemorrhage is associated with higher rates of mortality and morbidity than other intracephalic diseases (11). The expression levels of inflammatory factors have important roles in the inflammatory response associated with changes in a patient's condition and are important during monitoring and treatment at the ICU as well as for the development of

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therapeutic strategies for acute cerebral hemorrhage (12). In the majority of patients with cerebral hemorrhage, the condition triggers an immune activation sufficient to induce systemic inflammatory response syndrome (13). Inflammatory response has been reported to be associated with extra-cerebral organ dysfunction as well as delayed cerebral ischemia and the amount of bleeding, which is associated with poor outcome for patients with cerebral hemorrhage at an ICU (14). Leukocytosis has long been associated with adverse events after acute intracerebral hemorrhage (15). Therefore, controlling and monitoring inflammatory responses is essential for patients with acute intracerebral hemorrhage at the ICU.

As is known, the beneficial effects of statin drugs in reducing cardiovascular diseases have been predominantly attributed to their lipid-lowering effects (16). Recent studies suggested that the beneficial effects of statins are associated with their anti-inflammatory properties (17,18). In addition, statins have important roles in changes in endothelial dysfunction, stabilizing the plaque and immune system regulation as well as anti-oxidant effects (19). Simvastatin is a statin drug that produces beneficial outcomes due to its anti-neoplastic effects and overcomes the resistance to serum withdrawal-induced apoptosis of lymphocytes from Alzheimer's disease patients (20). Numerous studies have investigated the anti-inflammatory effects of Simvastatin in different types of human diseases, such as cancer, chronic heart failure, diabetes and traumatic brain injury (21-24).

Furthermore, Simvastatin inhibited the aggregation of amyloid-β in extracellular cortical and hippocampal plaques in cerebral hemorrhage, which is a widely accepted mechanism of action of cerebral hemorrhage pathology inhibitors and associated with the lowering of brain cholesterol levels in patients with cerebral hemorrhage (25,26).

The present study investigated the anti-inflammatory effects of Simvastatin administered to patients after cerebral hemorrhage and hypothesized that it may protect neurons by regulating the inflammatory response. The anti-inflammatory properties of Simvastatin, including its capacity to inhibit inflammatory factor expression, decrease the inflammatory cellular plasma concentration of lymphocytes, granulocytes and mononuclear cells, and improve brain edema as well as reduce the amount of bleeding, were studied in patients with cerebral hemorrhage at the ICU. The results demonstrated that Simvastatin treatment led to the decrease of the levels of inflammatory factors, including interleukin (IL)-4, IL-6, IL-8 and IL-10. Furthermore, inflammatory factor levels were found to be associated with brain edema in patients with acute cerebral hemorrhage. The amount of bleeding was significantly depended on the inflammatory cellular plasma concentration of lymphocytes, granulocytes and mononuclear cells. Importantly, Simvastatin treatment produced beneficial outcomes with regard to improving brain edema and the amount of bleeding. However, further evaluation of additional clinical data is essential to fully elucidate the efficacy and tolerability of Simvastatin.

Materials and methods

Ethical approval and patient consent. This study was approved by the Ethics Committee of the People's Hospital of Changle County (ref no. 10/CC06/124; Weifang, China). The phase-I study was performed from February 2006 to June 2012 according to the Guide for Chinese Clinical Experiments of Weifang People's Hospital (Weifang, China). The study was also performed in accordance with the European Medicines Agency requirements. All patients provided written informed consent prior to undergoing any procedures associated with the study.

Patients. A total of 146 patients who presented with intracerebral hemorrhage at the ICU were randomized into two groups, which were treated with Simvastatin or placebo, respectively. The inclusion criteria were patients with no heart disease or previous history of intracerebral hemorrhage. At baseline, patient age, body mass index and time since epilepsy diagnosis were similar between the two groups. In total, 101 patients who completed the maintenance period of the phase I study post-surgery (minimal invasive puncture and drainage vs. endoscopic surgery) were included in the analysis of the therapeutic effects of Simvastatin. Patients received Simvastatin at dosages of 0.08, 0.16, 0.24, 0.30 and 0.36 mg/kg based on a previous clinical trial (26).

[18]F-Fluorodeoxyglucose positron emission tomography imaging (FDG-PET). FDG-PET was used to analyze brain edema and the amount of bleeding by using statistical parametric mapping (SPM) software (SPM, version 2; Wellcome Department of Imaging Neuroscience, University College London, London, UK). FDG-PET images were spatially normalized onto the Montreal Neurological Institute (MNI) PET brain template (MNI, McGill University, Montreal, QC, Canada), which defined regions of interest. Normalized images were smoothed by convolution with a 10-mm full width at half maximum Gaussian kernel to increase the signal-to-noise ratio. Detailed procedures for FDG-PET acquisition and image processing were described in a previous study (27).

Vasospasm analysis. In the present clinical study, vasospasm in patients with intracerebral hemorrhage was defined using clinical and angiographic criteria for vasospasm. Symptomatic vasospasm was diagnosed and recorded as abnormal neurological status as described in a previous study (28).

ELISA. The levels of IL-4 (cat no. D4050), IL6 (cat no. D6050), IL-8 (cat no. D8000C) and IL-10 (cat no. DY417) (all from R&D Systems, Inc., Minneapolis, MN, USA) in the peripheral blood of patients with intracerebral hemorrhage was assessed by using commercialized human interleukin ELISA kits. The ELISAs were performed according to the manufacturer's instructions. The results were measured at 450 nm with an ELISA reader and finally converted to concentrations of IL-4, IL6, IL-8 and IL-10.

Modified neurological severity score (MNSS) analysis. The patients with intracerebral hemorrhage at the ICU were subjected to MNSS assessment at 7, 14, 21, 28, 35 and 42 days of treatment (n=26 in Simvastatin and n=18 in placebo group). MNSS analysis comprised sensory, motor, reflex and balance experiments. A scale of 0-18 was used to grade neurological function (normal score, 0; maximal deficit score, 18). The

higher the score, the higher was the severity of injury in patients with intracerebral hemorrhage at the ICU.

Behavioral assessment. Behavioral assessment was performed on post-operative days 7, 14, 21 and 28, 35 and 42 for intracerebral hemorrhage patients. The assessment parameters, including left limb movement and coordination of movement, were evaluated using the modified Tarlov scores as follows: Severe level, possible limb movement and partial limb paralysis (1-4 points); moderate level, failure to jump and stand normally (4-7 points); primary level, failure to stand while being capable of joint movement (7-9 points); normal function (9-10 points). According to the study design, the assessment and Tarlov scoring were performed for each patient at the ICU independently and then averaged.

Efficacy and safety assessment. Efficacy assessment included determination of the maximum tolerated dose (MTD) in cerebral hemorrhage patients and dose-limiting toxicity in the presence of Simvastatin. Safety assessments included the incidence rates (≥10%) of the most frequent treatment-associated adverse events in a 42-day treatment period in the drug treatment groups. The efficacy and safety data included all patients with cerebral hemorrhage receiving Simvastatin.

Flow cytometry. Peripheral blood was drawn from patients with cerebral hemorrhage and total leukocytes were extracted using a Human Leukocyte Extraction kit (Invitrogen; Thermo Fisher Scientific, Inc., Waltham, MA, USA). Inflammatory cellular plasma concentrations of lymphocytes, granulocytes and mononuclear cells were analyzed by flow cytometry (BD FACSDiva™ v. 6.1.3 software; BD Biosciences, San Jose, CA, USA) as previously described (29).

Statistical analysis. Statistical analysis was performed by using SPSS 19.0 software (IBM Corp., Armonk, NY, USA) and Excel (2010 version; Microsoft Corporation, Redmond, WA, USA). Values are expressed as the mean ± standard error of the mean. Statistical tests for data analysis included Fisher's exact test, log-rank test, Chi-square test, and Student's 2-tailed t-test. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of patients with cerebral hemorrhage. A total of 146 patients with cerebral hemorrhage who were candidates for intravenous injection were included in the present clinical study. The mean age of the patients was 47 years. All patients were randomized into two groups and treated with Simvastatin (n=88) or placebo (n=58) by intravenous injection. The number of male patients with cerebral hemorrhage (n=94, 64.4%) was slightly higher than that of female patients (n=52, 35.6%). The characteristics of patients with cerebral hemorrhage are summarized in Table I. Furthermore, 101 (69%) patients with cerebral hemorrhage continued to complete the maintenance period of the phase-I study.

Duration of treatment, dose-limiting toxicities and MTD. The median overall duration of Simvastatin treatment was

Table I. Characteristics of patients with intracerebral hemorrhage (n=146).

Parameter	Value
Gender	
Male	94 (64.4%)
Female	52 (35.6%)
Mean age (years)	47.4 (Range: 35.4-65.8)
Drug therapy	
Simvastatin	88 (60.3%)
Placebo	58 (39.7%)
Trial participation	
Complete	101 (69.2%)
Incomplete	35 (30.8%)
Plasma glucose (mmol/l)	5.4-8.7 (normal range: 3.9-6.1)
Blood pressure (mmHg)	142±6 (normal range: 90-140)

Values are expressed as n (%), range or mean ± standard error of the mean.

four weeks for patients with cerebral hemorrhage at the ICU. Within the cohort, subgroups were treated with 0.08, 0.16, 0.24, 0.30 and 0.36 mg/kg Simvastatin. As presented in Table II, 0.30 mg/kg Simvastatin once a day was identified as the MTD and 0.24 mg/kg of Simvastatin once a day was identified as dose-limiting toxicity. The group treated with the lowest dose of Simvastatin presented with the lowest number of adverse reactions. It was observed that the common treatment-associated adverse events of Simvastatin injection were hypertension, proteinuria, fatigue, diarrhea, vomiting, rash, constipation and peripheral edema. For most of the patients with cerebral hemorrhage, a reduction of the drug dose was required due to cumulative toxicity after treatment with the MTD. Therefore, most of the patients that were subsequently enrolled in the study were treated with Simvastatin at a dose of 0.20 mg/kg to ensure tolerability and therapeutic efficacy of Simvastatin. The most common grade ≥3 adverse events in patients with cerebral hemorrhage according to Common Toxicity Criteria were hypertension and proteinuria (15% each; Table III).

Efficacy of Simvastatin in patients with cerebral hemorrhage. The efficacy of Simvastatin treatment in patients with acute cerebral hemorrhage was assessed in this clinical study. Clinical examination demonstrated that compared with the placebo group, arthralgia and body pain were markedly improved in the drug treatment groups after 4 weeks of therapy regimen. Furthermore, the levels of the inflammatory factors IL-4, IL-6, IL-8 and IL-10 were decreased after treatment with Simvastatin in patients with acute cerebral hemorrhage in the ICU (Fig. 1). Furthermore, systemic inflammatory response syndrome was found to be associated with brain edema in the patients with acute cerebral hemorrhage. Simvastatin treatment improved the degree of brain edema and the amount of bleeding (Fig. 2). Of note, the results indicated that the inflammatory cellular plasma concentration of lymphocytes, granulocytes and mononuclear cells was recovered to normal levels after

Table II. Adverse events (n) occurring during treatment with an overall incidence of ≥10%.

| | | Simvastatin (mg/kg) | | |
Adverse event	Total (%) n=40	0.08-0.16 (%) n=14	0.24-0.30 (%) n=16	0.36 (%) n=10
Hypertension	10 (25)	2 (5)	3 (7.5)	5 (12.5)
Proteinuria	8 (20)	2 (5)	2 (5)	4 (10)
Fatigue	4 (10)	1 (2.5)	1 (2.5)	2 (5)
Diarrhea	5 (12.5)	1 (2.5)	2 (5)	2 (5)
Vomiting	4 (10)	1 (5)	1 (2.5)	2 (5)
Rash	6 (15)	2 (5)	2 (5)	2 (5)
Constipation	7 (17.5)	2 (5)	2 (5)	3 (7.5)
Peripheral edema	8 (20)	2 (5)	3 (7.5)	3 (7.5)

Table III. Treatment-associated hypertension and proteinuria graded by Common Toxicity Criteria (≥20%).

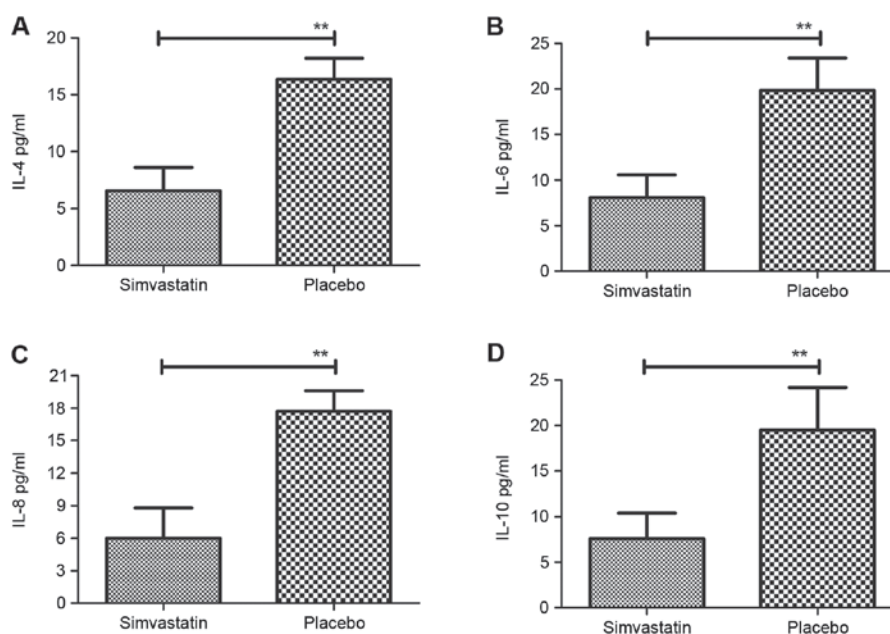| | | Simvastatin (mg/kg) | | |
Adverse event/grade	Total (%) n=40	0.08-0.16 (%) n=14	0.24-0.30 (%) n=16	0.36 (%) n=10
Hypertension				
1	3 (7.5)	0 (0)	1 (2.5)	2 (5)
2	3 (7.5)	1 (2.5)	1 (2.5)	1 (2.5)
3	4 (10)	1 (2.5)	1 (2.5)	2 (5)
Total	10 (25)	2 (5)	3 (7.5)	5 (12.5)
Proteinuria (%)				
1 (2.5)	2 (5)	0 (0)	1 (2.5)	2 (5)
2 (5)	3 (7.5)	1 (2.5)	0 (0)	1 (2.5)
3 (7.5)	2 (5)	1 (2.5)	1 (2.5)	1 (2.5)
Total	8 (20)	2 (5)	2 (5)	4 (10)

Figure 1. Analysis of the plasma concentration of inflammatory factors in patients with intracerebral hemorrhage treated with Simvastatin or placebo at the ICU. Plasma concentration of (A) IL-4, (B) IL-6, (C) IL-8 and (D) IL-10 in patients with intracerebral hemorrhage in ICU after a 42-day treatment period. Values are expressed as the mean ± standard error of the mean determined from triplicate samples. **$P<0.01$, Simvastatin vs. placebo group. ICU, intensive care unit; IL, interleukin.
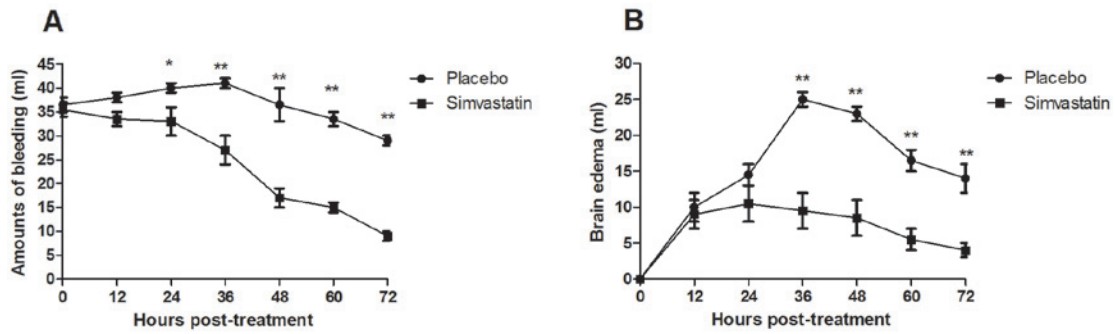
Figure 2 Analysis of brain edema and amount of bleeding in patients with intracerebral hemorrhage after treatment with Simvastatin or placebo at the ICU. (A) Brain edema was analyzed after a 42-day treatment period in patients with intracerebral hemorrhage at the ICU. (B) Amount of bleeding of patients with intracerebral hemorrhage at the ICU as determined by ^{18}F-fluorodeoxyglucose positron emission tomography imaging. Values are expressed as the mean ± standard error of the mean determined from triplicate samples. *$P<0.05$ and **$P<0.01$, Simvastatin vs. placebo group. ICU, intensive care unit.
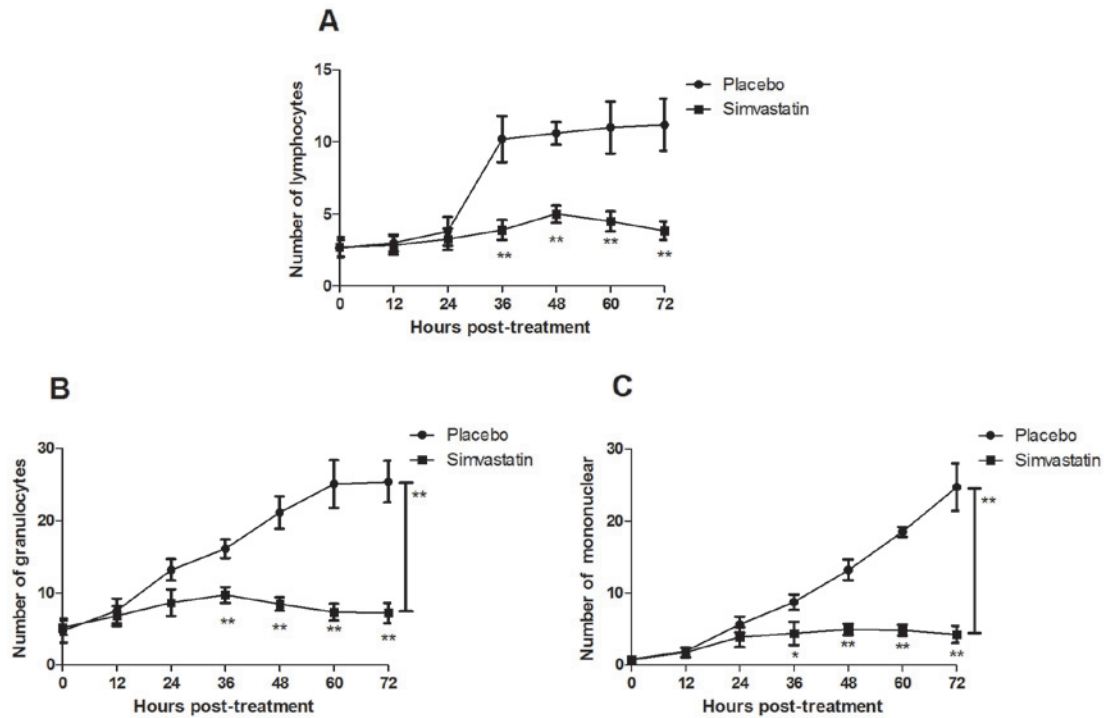

Figure 3. Analysis of leucocytes in plasma of patients with intracerebral hemorrhage after treatment with Simvastatin or placebo. (A-C) Inflammatory cellular plasma concentration of (A) lymphocytes, (B) granulocytes and (C) mononuclear cells was measured after treatment with Simvastatin or with placebo as a control. Values are expressed as the mean ± standard error of the mean determined from triplicate samples. *$P<0.05$ and **$P<0.01$, Simvastatin vs. placebo group.

treatment with Simvastatin (Fig. 3). Furthermore, the results revealed that Simvastatin treatment significantly improved the frequency of vasospasms in patients with acute cerebral hemorrhage compared with that in the placebo group (Fig. 4). Collectively, the results indicated that Simvastatin was efficient in treating acute intracerebral hemorrhage and that the inflammatory response was in parallel with the progress of patients with acute intracerebral hemorrhage in an ICU setting, which may provide insight for applying effective therapies for patients with acute intracerebral hemorrhage.

Simvastatin treatment improves the survival of patients with cerebral hemorrhage. In order to explore whether therapy with Simvastatin was effective for patients with cerebral hemorrhage *in vivo*, the recurrent activity of convulsion in cerebral
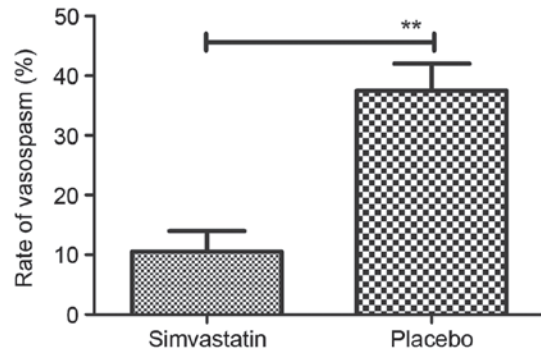

Figure 4. Rate of symptomatic vasospasms associated with an increasing inflammatory response burden on day 42. Values are expressed as the mean ± standard error of the mean determined from triplicate samples. **$P<0.01$, Simvastatin vs. placebo group.
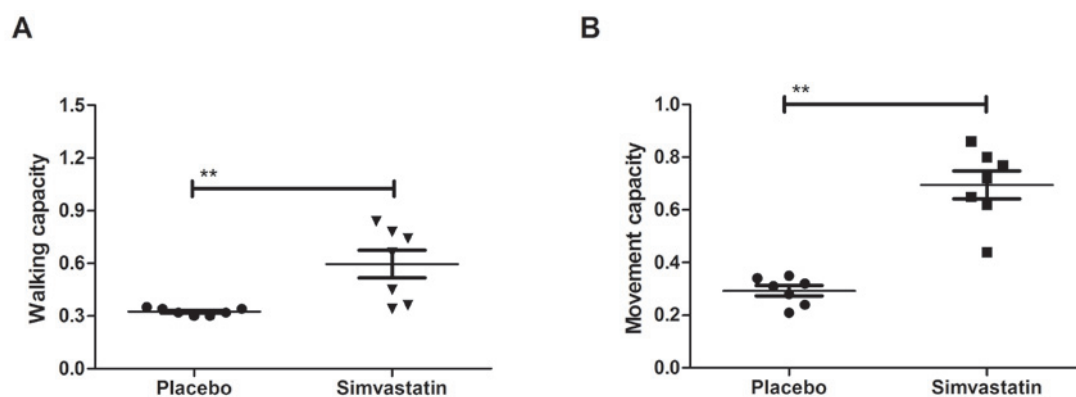
Figure 5. Walking and movement capacities of patients with intracerebral hemorrhage after treatment with Simvastatin or placebo. (A) Walking capacity on day 42. (B) Movement capacity on day 42. Values are expressed as the mean ± standard error of the mean determined from triplicate samples. **P<0.01, Simvastatin vs. placebo group.
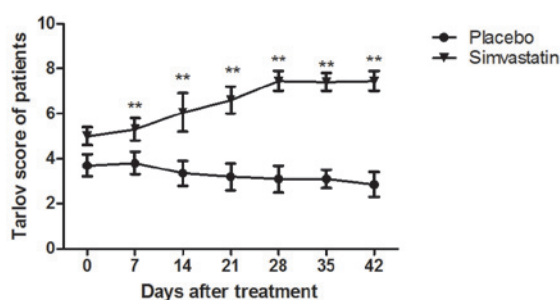

Figure 6. Behavioral assessment of patients with cerebral hemorrhage at the intensive care unit through evaluation of motor function. Behavioral assessment was performed by the modified Tarlov scale. The assessment parameters included left limb movement. Values are expressed as the mean ± standard error of the mean determined from triplicate samples. **P<0.01, Simvastatin vs. placebo group.
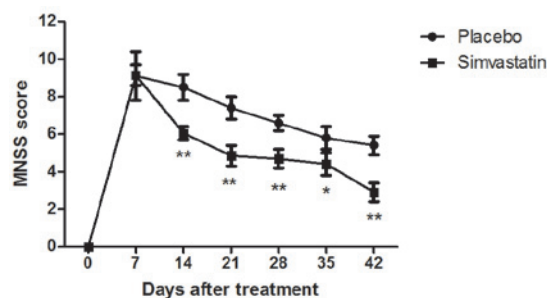

Figure 7. Treatment with Simvastatin promoted functional recovery, decreased brain water content and reduced the hemorrhage volume after intracerebral hemorrhage. The MNSS was determined to determine the therapeutic effects of Simvastatin from 1 to 42 days after intracerebral hemorrhage with placebo as control. Values are expressed as the mean ± standard error of the mean determined from triplicate samples. *P<0.05 and **P<0.01, Simvastatin vs. placebo group. MNSS, modified neurological severity score.

hemorrhage patients was assessed. The results in Fig. 5 demonstrated that movement capacities, including limb coordination and walking, were significantly improved in Simvastatin-treated patients with hemorrhage lesions compared with those in patients treated with placebo (P<0.01). However, no significant changes in arterial blood pressure, body weight and body temperature were observed (data not shown). As presented in Fig. 6, the Tarlov scores revealed that the therapeutic effects of Simvastatin were significant in patients with cerebral hemorrhage compared with those in the placebo group (P<0.01). The MNSS test demonstrated that the Simvastatin-treated patients with cerebral hemorrhage exhibited significant functional improvement compared with the placebo group (Fig. 7). Furthermore, a long-term survival observation over a 1,664-day period after treatment with Simvastatin in patients with cerebral hemorrhage was performed. The results in Fig. 8 revealed that the survival of patients was prolonged after treatment with Simvastatin. Taken together, the results suggested that Simvastatin was efficient in patients with cerebral hemorrhage in an ICU setting.

Discussion

Intracerebral hemorrhage is the most common type of cerebrovascular disease in humans and patients with acute intracerebral hemorrhage are frequently monitored in ICUs (30). Spontaneous
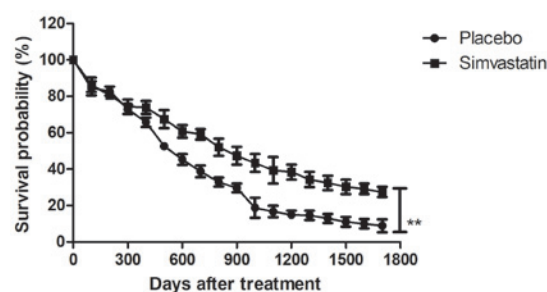

Figure 8. Survival rates of patients with intracerebral hemorrhage over a 1,664-day survival period after Simvastatin or placebo treatment. Values are expressed as the mean ± standard error of the mean determined from triplicate samples. **P<0.01, Simvastatin vs. placebo group.

and acute cerebral hemorrhage leads to high morbidity and mortality in ICUs worldwide (31,32). It was previously indicated that systemic inflammatory response syndrome is associated with intracerebral hemorrhage (13). Simvastatin is an efficient drug that improves the neurological outcome after experimental intracerebral hemorrhage (33). In addition, Simvastatin was reported to reduce the inflammatory response in the treatment of various human diseases (34). The present study investigated the anti-inflammatory effects of Simvastatin in patients with

acute intracerebral hemorrhage in an ICU. Recurrent bleeding after acute intracerebral hemorrhage is a major cause of morbidity and mortality in ICUs and a previous study suggested that the inflammatory response is associated with spontaneous intracerebral hemorrhage patients in an ICU setting (35). The present study revealed that Simvastatin treatment improved the inflammatory response and had beneficial effects in intracerebral hemorrhage patients in an ICU. Furthermore, numerous studies have shown that cerebral hemorrhage caused neuronal damage and further aggravated brain damage to even lead to the development of contralateral limb dysfunction (36-38). In cerebral hemorrhage, the blood often overflowed directly into the brain parenchyma. The clinical data of the present study demonstrated that contralateral limb dysfunction, frequency of vasospasm, degree of brain edema and the amount of bleeding were improved by treatment with Simvastatin once a day.

A previous study indicated that the possible mechanism underlying the dysfunction of the inflammatory response may be associated with leakage from small intracerebral arteries (39). Dysfunction of the inflammatory response may be an important pathophysiological factor in intracerebral hemorrhage and other human cerebrovascular diseases. A previous study has indicated that early inflammation contributes to edema after intracerebral hemorrhage in an ICU setting (40). A review on inflammation after intracerebral hemorrhage based on available evidences from preclinical and clinical studies suggested that inflammatory mechanisms are involved in the progression of intracerebral hemorrhage-induced secondary brain injury (41). In addition, the therapeutic benefit of anti-inflammatory and angiogenesis-inducing treatments in intracerebral hemorrhage has been investigated (42). The present study first assessed the anti-inflammatory effects of Simvastatin in patients with acute intracerebral hemorrhage in an ICU. The results revealed that IL-4, IL-6, IL-8 and IL-10 levels were downregulated by Simvastatin compared to those in the placebo group. Furthermore, in parallel with the decrease of inflammatory factors, the degree of brain edema and the amount of bleeding in patients with intracerebral hemorrhage was also reduced, along with an increased survival rate. These findings suggested that inhibition of inflammatory factors is beneficial for reducing the degree of brain injury and promoting functional recovery (43).

In the present study, Simvastatin was evaluated as a therapeutic agent for treating patients with intracerebral hemorrhage. In the majority of cases, cerebral hemorrhage is non-traumatic and caused by rupture of vessels in the brain parenchyma (44). The findings of the present study were consistent with those of previous studies in terms of Simvastatin exerting beneficial effects by inhibiting the expression of inflammatory factors in clinical trials (45,46). The number of detection methods used for measuring the disease progression of intracranial hemorrhage has been expanding to include imaging cerebral physiology, PET, computed tomography and magnetic resonance imaging (47). In addition, numerous molecular markers were found to be associated with cerebral hemorrhage, which may support its diagnosis and determination of its extent, and may further be utilized for treating hemorrhage via target cells associated with hemostasis (48,49). However, in terms of the overall survival rate of patients, further development or combined therapies are required for achieving better outcomes for patients with intracerebral hemorrhage in an ICU setting.

Of note, the present and previous studies indicated that Simvastatin is a prospective candidate drug for clinical therapy of patients with cerebrovascular disease (50,51).

In conclusion, the present study proved the efficacy of Simvastatin in treating acute intracerebral hemorrhage and indicated that the inflammatory response was in parallel with the progression of patients with acute intracerebral hemorrhage in an ICU setting, which may provide insight for applying effective therapies for patients with acute intracerebral hemorrhage. Taken together, these findings indicated that Simvastatin exerted beneficial effects in patients with intracerebral hemorrhage by improving survival, vasospasm, brain edema, the amount of bleeding as well as limb coordination and walking.

Acknowledgements

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