INTRODUCTION

Hypertensive cerebral hemorrhage refers to cerebral parenchymatous hemorrhage induced by the rupture of arteriole in the brain on the basis of hypertension, which is featured by high fatality rate, high disability rate, rapid onset and serious disease condition. There would be severe sequela even when patients survived from hypertensive cerebral hemorrhage. It severely affects the living quality of patients and also brings heavy burden to the society.\(^1\)\(^-\)\(^3\) Currently, the main therapies for hypertensive cerebral hemorrhage include conservative treatment, surgery and minimally invasive hematoma evacuation; however, those therapies have certain limitations in practical application, especially in recovering neurological
function. The clinical efficacy of neuroprotective drugs in recovering neurological impairment of patients with stroke is always the hotspot in clinics. Oxiracetam as a neurotrophic drug is usually used for treating brain function degradation diseases and injury induced neurological deficit.

It has been pointed out that, single use of oxiracetam is not so effective in recovering neurocognitive function. But nerve growth factor (NGF) as an extensively applied neurotrophic factor (NTF) has been found playing an important role in the survival, growth, differentiation and regeneration of neurons. Currently, NGF has been extensively applied in treating cerebral infarction and spinal and peripheral nerve injury, but few studies are available concerning the clinical efficacy of NGF in treating intracranial hemorrhage. This study selected patients with hypertensive cerebral hemorrhage as the research subjects and investigated the clinical efficacy of NGF in combination with oxiracetam in the treatment of hypertensive cerebral hemorrhage and its influence on the levels of serum inflammatory factors high-sensitivity C-reactive protein (hs-CRP), interleukin (IL)-8 and tumor necrosis factor (TNF)-α.

METHODS

One hundred and forty patients with hypertensive cerebral hemorrhage who were admitted to our hospital from July 2015 to September 2016 were selected. Patients who satisfied the criteria of hypertensive cerebral hemorrhage formulated in the 4th National Conference of Cerebrovascular Disease, have been verified by CT, were admitted to the hospital within 48 hours after onset, were scored as 8 points higher by Glasgow Coma Scale (GCS), and were examined having normal hepatic and renal function were included. Those who had vascular malformation, chronic disease or disturbances of blood coagulation, had blood flowing into subarachnoid space or ventricle, whose GCS score no higher than three points, had symptoms such as bilateral pupils dilatation, disappearance of light reflex and severe disorder of vital signs, or had mental disorder or nerve dysfunction including impairment of nervous system function induced by other existing systemic diseases such as peripheral neuropathy previously were excluded.

This study was carried out after the patients and their family members signed informed consent and it was reviewed and approved by the ethics committee. All the patients were divided into a treatment group and a control group using random number table, 70 in each group. In the treatment group, there were 38 males and 32 females, with an average age of (68.5±4.8) years (50~83 years), average blood loss of (23.5±2.2) ml (10~31 mL) and average onset-to-door time of (5.4±1.5) h (2~36 hour); as to the bleeding sites, there were 44 cases of basal ganglia, 18 cases of blood brain and 8 cases of cerebral lobe. In the control group, there were 42 males and 28 females, with an average age of (69.2±5.3) years (51~82 years), an average blood loss of (23.2±1.9) ml (11~32 mL) and an average onset-to-door time of (5.8±0.5) hour (2~38 hour); as to the bleeding sites, there were 45 cases of basal ganglia, 16 cases of blood brain and 9 cases of cerebral lobe.

Baseline data such as gender, age, blood loss and bleeding sites of the two groups had no statistically significant difference (P>0.05); the results were comparable.

Treatment methods: Patients in the two groups were given continuous oxygen inhalation in a low or medium flow. Moreover, they were given relevant treatment such as blood pressure and glucose control, intracranial pressure reduction, brain cells nourishing and hemostasis. Water and electrolyte were kept stable and balanced, enough nutritional supply was provided, and infection was carefully prevented.

In addition to conventional treatment, each patient in the treatment group were intramuscularly injected with the liquid containing 50 μg of NGF (Weiming Biomedical Co., Ltd., China) and 2 mL of 0.9% sodium chloride injection, once a day. Moreover, 5 g of oxiracetam injection which was dissolved by 0.9% sodium chloride injection was intravenously injected, once a day, for four weeks.

In addition to conventional treatment, each patient in the control group was intravenously dripped with 5 g of oxiracetam (Oulaining, Ouyi Pharmaceutical Co., Ltd. of China Shijiazhuang Pharmaceutical Group) which was dissolved with 0.9% sodium chloride injection, once a day, for four weeks.

Nursing after drug administration: Patients in the two groups were given effective nursing during drug administration. The nursing content was as follows. The first content was respiratory tract nursing. The patients were given turnover and backslap nursing, once every two hours. Respiratory secretions were timely removed to ensure smooth respiration and reduce risks of pulmonary infection. Next was nursing of vital signs. The respiration, blood pressure, heart rate, blood oxygenation concentration and body temperature were closely.
monitored. Patients whose temperature was higher than 38°C were given ice compress on the occiput or great vessels of four limbs; ice blanket or drugs could be used if necessary. The consciousness and pupils of the patients were observed, hourly; the critically ill patients were observed once every 30 minutes. The disturbance of consciousness was evaluated. Once symptoms of increased intracranial pressure such as abnormal diameter of pupils, weakened pulse, increase of blood pressure and emesis were observed, therapies for lowering intracranial pressure and relieving dehydration were adopted to prevent the occurrence of cerebral hernia. The disturbance of consciousness was evaluated. Once symptoms of increased intracranial pressure such as abnormal diameter of pupils, weakened pulse, increase of blood pressure and emesis were observed, therapies for lowering intracranial pressure and relieving dehydration were adopted to prevent the occurrence of cerebral hernia. The disturbance of consciousness was evaluated.

Observation indicators: NIHSS score, GCS score and muscle strength grade were taken as the evaluation indicators for clinical efficacy. The evaluation was performed once before and after drug administration to understand the improvement of neurological function. 2 mL~4 mL of fasting venous blood was collected from each patient in the morning and centrifuged at 3000 r/min at 4°C for 10 min. The supernate was collected and preserved at -60°C. The serum high-sensitivity C-reactive protein (hs-CRP) level was detected using double antibody enzyme linked immunosorbent assay. The levels of serum interleukin (IL)-8 and tumor necrosis factor (TNF)-α were detected using radioimmunoassay.

Table I: Comparison of NIHSS score, GCS score and muscle strength grade between the two groups before and after treatment.

| Group            | NIHSS score | GCS score | Muscle strength grade |
|------------------|-------------|-----------|----------------------|
| Treatment group  |             |           |                      |
| (N=70) Before    | 11.43±3.61  | 8.45±3.48 | 2.12±0.71            |
| After            | 6.90±2.93*  | 13.16±3.57* | 4.84±0.79*         |
| Control group    |             |           |                      |
| (N=70) Before    | 10.32±3.48  | 8.36±3.87 | 1.93±0.87            |
| After            | 8.13±2.92   | 9.17±4.05 | 3.36±0.41            |

Note: * indicated P<0.05 compared to the control group.
fourteen patients in the control group died, seven in the 4th month after treatment, two in the 8th month after treatment, one in the 9th month after treatment and four in the 13th month after treatment. The Kaplan-Meier survival curves of the two groups are shown in Fig.1. The Log-rank test suggested the two groups had statistical significance (P<0.05).

DISCUSSION

Patients with hypertensive cerebral hemorrhage may have pathological changes such as cerebral tissue injury, neuron injury and inflammatory reaction, which can accelerate the death of brain cells and disorder of brain cognitive function. Oxiracetam, a neurotrophic drug which can promote the abnormality of central nervous system, can regulate excitement of nervous system, inhibiting transmission of neural signals and neurohormones, and affect cognitive and neurological function by directly acting on neuroceptors. Moreover, oxiracetam can accelerate the recovery of function of nerve cells by affecting the energy metabolism of nervous system. But a clinical study found that single use of oxiracetam may be limited in recovering neurological function of patients with hypophrenia or Alzheimer’s disease.

NGF, the neuroactive factor which was discovered earliest, plays a key role in the growth and phenotype maintenance of peripheral nerves as well as the complexity of cholinergic neurons in central nervous system. NGF has been extensively applied in treating many diseases such as diabetic peripheral neuropathy, acute spinal cord injury and injury of optic nerve. The research results suggested that the treatment group which were treated by oxiracetam in combination with NGF obtained significant treatment effect; the indicators for the recovery of neurological function of the treatment group were superior to those of the control group, which further suggested that NGF in combination with oxiracetam was effective in recovering neurological function. That was because that NGF could protect nerve cells, inhibit cerebral injury induced neuronal death, promote the growth of nerve cells and the proliferation of neurogliocyte, and increase the communication between synapse.

In recent years, the role of inflammatory reactions in the occurrence and development of cerebral hemorrhage has been more and clearer. The formation of hematoma after the occurrence of acute cerebral hemorrhage can promote the release of a large amount of inflammatory factors and inflammatory mediators which participate in secondary brain injury that is the key factor influencing the prognosis of patients. TNF-α, IL-8 and hs-CRP as the important regulatory factors in inflammatory reaction and immune response plays important roles in the occurrence of secondary brain injury induced by intracranial hemorrhage. Therefore, levels of TNF-α, IL-8 and hs-CRP can reflect edema around intracranial hematoma of patients with intracranial hemorrhage, which is of great significance to studies on the treatment of acute cerebral hemorrhage. In this study, the reduction of levels of TNF-α, IL-8 and hs-CRP can reflect edema around intracranial hematoma of patients with intracranial hemorrhage, which is of great significance to studies on the treatment of acute cerebral hemorrhage. In this study, the reduction of levels of TNF-α, IL-8 and hs-CRP was more obvious than that of the control group, indicating the combination therapy had stronger inhibitory effect on the serum cytokines than single use of drug, indicating NGF could reduce inflammatory reaction, weaken peroxidatic reaction and relieve neuron damage. A study found that timely neuroprotection had a great effect on the prognosis of patients. The

| Group                      | hs-CRP (ng/L) | IL-8 (ng/L) | TNF-α (ng/L) |
|----------------------------|--------------|-------------|--------------|
| Treatment group (N=70)     | Before       | 42.03±7.83  | 21.03±5.11   | 22.12±3.77   |
|                           | After        | 18.02±4.01* | 7.78±2.55*   | 7.24±3.18*   |
| Control group (N=70)      | Before       | 41.97±8.01  | 20.35±4.83   | 21.18±3.51   |
|                           | After        | 30.97±6.02  | 14.31±3.18   | 14.47±2.86   |

Note: *indicated P<0.05 compared to the control group.
survival analysis suggested that the survival rate of the treatment group was much higher than that of the control group, suggesting NGF was helpful to improve the long-term treatment efficacy of patients with hypertensive cerebral hemorrhage.

CONCLUSION

In conclusion, NGF in combination with oxiracetam has significant effect in the treatment of hypertensive cerebral hemorrhage as it can effectively reduce the levels of inflammatory factors, improve neurological function and enhance living quality. The therapy is worth clinical promotion. But the medication safety has not been considered. Therefore, multi-center clinical experiments involving a large size of samples should be carried out in the future to investigate the adverse reactions occurring in the treatment of hypertensive cerebral hemorrhage with NGF in combination with oxiracetam.

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REFERENCES

1. Naranjo D, Arkuszewski M, Rudzinski W, Melhem ER, Krejza J. Brain ischemia in patients with intracranial hemorrhage: Pathophysiological reasoning for aggressive diagnostic management. Neuroradiol J. 2013;26(6):610-628. doi: 10.1177/197140091302600603.
2. Yoo HS, Kim YD, Lee HS, Song D, Song TJ, Kim BM, et al. Repeated thrombolytic therapy in patients with recurrent acute ischemic stroke. J Stroke. 2013;15(5):182-188. doi: 10.5853/jos.2013.15.3.182.
3. Song JW, Zhao XM. Analysis on clinical effects of two therapies in the treatment of hypertensive cerebral hemorrhage. National Med Frontiers China. 2012;7(1):40-42. doi: 10.3969/j.issn.1673-5552.2012.01.0026.
4. Zhang RJ, Wang XF, Tang RC, Liu JX, Yang SZ, Peng YB, et al. Clinical characteristics of 6374 patients with hypertensive intracerebral hemorrhage and their treatment choice. Chin J Neuromed. 2013;12(1):57-61. doi: 10.3760/cma.j.is sn.1671-8925.2013.01.013.
5. Said A, Amer AJ, Masood UR, Dirar A, Faris C. A brain-dead pregnant woman with prolonged somatic support and successful neonatal outcome: A grand rounding case with a detailed review of literature and ethical considerations. Int J Crit Illn Inj Sci. 2013;3(3):220-224. doi: 10.4103/2229-5119.119205.
6. Shan RY. Effect of oxiracetam in combination with vinpocetine on the mild cognitive disorder of patients with cerebral infarction. Chin J Pract Neruous Dis. 2015;18(11):77. doi: 10.3969/j.issn.1673-5110.2015.11.050.
7. Gouliav Ah, Senning A. Piracetam and other structurally related nootropics. Brain Res Rev. 1994;19(2):180-222. doi: 10.1016/0165-0173(94)90011-6.
8. Aloe L, Rocco ML, Bianchi P, Manni L. Nerve growth factor: from the early discoveries to the potential clinical use. J Transl Med. 2012;10(1):239. doi: 10.1186/1479-5876-10-239.
9. Kawahara M, Mizuno D, Koyama H, Konoha K, Ohkawara S, Sadakane Y. Disruption of zinc homeostasis and the pathogenesis of senile dementia. Metallomics. 2014;6(2):209-219. doi: 10.1039/c3m00257h.
10. Siegler JE, Martin-Schild S. Daily National Institutes of Health Stroke Scale Examination at Stroke Centers: Why not do them? Int J Stroke. 2015;10(2):140-142. doi: 10.1111/ijs.12416.
11. Zhang YJ, Xue RM. Clinical observation on nimodipine combined with oxiracetam in the treatment of hypertensive cerebral hemorrhage patients recover cognitive function. Chin J Front Med Sci (Elect Vers). 2014;6(7):109-111. doi: 10.3969/j.issn.1674-7372.2014.07.040.
12. Malykh G, Sadaie MR. Piracetam and piracetam-like drugs: from basic science to novel clinical applications to CNS disorders. Drugs. 2010;70(3):287-312. doi: 10.2165/11319230-000000000-00000.
13. Chiaretti A, Antonelli A, Genovese O, Fernandez E, Giuda D, Mariotti P, et al. Intraventricular nerve growth factor infusion improves cerebral blood flow and stimulates doublecortin expression in two infants with hypoxic-ischemic brain injury. Neurol Res. 2008;30(3):222-228. doi: 10.1179/101614107X249748.
14. Huang KG, Huang YH, Lian WX, Ye SP. The clinical research of nar nerve growth factor in the treatment of moderate to severe neonatal anaerobic ischemic encephalopathy. Clin Med Engin. 2013;20(3):391-392. doi: 10.3969/j.issn.1674-4659.2013.03.0338.
15. Taepavarapruk P, Song C. Reductions of acetylcholine release and nerve growth factor expression are correlated with memory impairment induced by interleukin-1beta administrations: effects of omega-3 fatty acid EPA treatment. J Neurochem. 2010;112(4):1054-1064. doi: 10.1111/j.1471-4159.2009.06524.x.
16. Wei X. Analysis on the effectiveness of mouse nerve growth factor in the treatment of cerebral hemorrhage. Heilongjiang Med J. 2015;39(1):71-72. doi: 10.3969/j.issn.1004-5775.2015.01.036.
17. Naranjo D, Arkuszewski M, Rudzinski W, Melhem ER, Krejza J. Brain ischemia in patients with intracranial hemorrhage: pathophysiological reasoning for aggressive diagnostic management. Neuroradiol J. 2013;26(6):610-628. doi: 10.1177/197140091302600603.
18. Zhou Y, Wang Y, Wang J, Anne Stetler R, Yang QW. Inflammation in intracerebral hemorrhage: from mechanisms to clinical translation. Prog Neurobiol. 2014;115(2):25-44. doi: 10.1016/j.pneurobio.2013.11.003.
19. Lckic T, Hartman R, Rojas H, Manaenko A, Chen W, Ayer K, et al. Protective effect of melatonin upon neuropathology, striatal function, and memory ability after intracerebral hemorrhage in rats. J Neurotrauma. 2010;27(3):627-637. doi: 10.1089/neu.2009.1163.

Authors’ Contribution:

YZS & QZ: Study design, data collection and analysis.
YZS, BQX & QZ: Manuscript preparation, drafting and revising.
YZS: Review and final approval of manuscript.