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Original Research Article

Efficacy of co-administration of oxiracetam and butylphthalide in the treatment of elderly patients with hypertensive intracerebral hemorrhage, and its effect on NIHSS and ADL scores

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Abstract

Purpose: *To investigate the effect of combined use of oxiracetam and butylphthalide on hypertensive intracerebral hemorrhage (HICH) in elderly patients, and its influence on NIHSS and activities of daily living (ADL) scores of patients.*
Methods: *Ninety (90) elderly patients with HICH who were admitted to Renmin Hospital of Wuhan University, Wuhan, China served as study subjects, and were randomly assigned to control and study groups, with 45 patients per group. The patients in the control group were treated with oxiracetam alone, while patients in the study group received a combination of oxiracetam and butylphthalide. Clinical efficacy, undesirable side effects and serum indices were determined. The NIHSS and ADL rating scales were used to evaluate cerebral nerve function and ADL score before and after treatment.*
Results: *There were significantly higher total treatment effectiveness and lower incidence of adverse reactions in the study group than in control group, while tissue inhibitor of metalloproteinase-1 (TIMP-1) index, matrix metalloproteinase-9 (MMP-9) index and NIHSS score were reduced in study patients, relative to controls ($p < 0.001$). However, ADL score in the study group was higher than that in the control group ($p < 0.001$).*
Conclusion: *Treatment of elderly patients with HICH using a combination of oxiracetam and butylphthalide improves various serum indices, cerebral nerve function and ADL, as well as clinical efficacy. Further research on the combined medication will help to establish a reliable treatment plan for these patients.*

Keywords: *Oxiracetam, Butylphthalide, Elderly hypertensive intracerebral hemorrhage, National Institutes of Health Stroke Scale (NIHSS)*

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INTRODUCTION

Hypertensive intracerebral hemorrhage (HICH) refers to intracerebral hemorrhage caused by hypertension and atherosclerosis, mainly in the aged population, with the characteristics of high mortality, rapid onset, rapid progression and high disability rate [1]. The etiology of HICH is that long-term emotional excitement and overwork in elderly patients with hypertension induce

elevated blood pressure, leading to bleeding or rupture of diseased blood vessels. The clinical manifestations of HICH comprise limb paralysis, vomiting, headache and disturbance of consciousness [2].

Research has shown that overexertion, climate change, alcohol intake, excitement and overwork are factors that induce HICH [3-5]. The treatments used for HICH are divided mainly into surgical treatment and medical treatment. At present, most patients receive medical treatment through hemostasis, sedation and prevention of complications, in order to alleviate clinical symptoms after medication and improve their neurological function [6-8].

Relevant studies have demonstrated that the use of combination of oxiracetam and butylphthalide results in remarkable clinical curative effects. This research was done to investigate the influence of the combined therapy on 90 elderly HICH patients, and its effect on NIHSS and ADL) scores, from January 2019 to January 2020.

METHODS

Patients

Ninety elderly patients with HICH were chosen for this study, and were randomly but equally divided into control and study groups. Approval for this investigation was received from the ethical authority of Renmin Hospital of Wuhan University, Wuhan, China (approval no. 20181139). The study was implemented according to the guidelines in Helsinki Declaration [9]. Subjects and their family members were well briefed on the purpose and procedures of the study, and informed consent was obtained from them.

Inclusion criteria

The included patients were those aged over 60 years, with HICH onset time less than 24 h, and presence of supratentorial hemorrhage confirmed *via* cranial CT scan; and patients with drug sensitivity consistent with the World Health Organization (WHO) diagnosis and medication criteria for hypertensive intracerebral hemorrhage.

Exclusion criteria

Patients with mental disorders, subjects with organ diseases such as severe kidney and liver diseases, and patients with severe organ dysfunction, were excluded from the study.

Treatments

All patients were treated with 5 g of oxiracetam (Biomedical Engineering Center of Hebei Medical University; NMPA approval no. H20143243; specification: 1 g/5 mL) via intravenous infusion. Before treatment, 5 % glucose injection or 0.9 % sodium chloride solution (100 - 250 mL) was added, and the dose was increased or decreased based on the patient's condition.The study group was given additional treatment with 25 mL of butylphthalide (25 mg/100 mL), and 0.9 % sodium chloride solution via intravenous infusion. Each infusion time was longer than 50 min, and the interval between infusions was not less than 6 h. Both groups were treated for 3 weeks.

Determination of indices/parameters

Treatment efficacy

If the clinical symptoms disappeared, and the living ability was normal, with 91 – 100 % reduction in neurological deficit score, the treatment was deemed to have resulted in a cure. If the clinical symptom basically disappeared, and the living ability was basically normal, with 51 – 90 % reduction in neurological deficit, the treatment was markedly effective. If the clinical symptoms and living ability were improved, and the neurological deficit score was decreased by 18 - 50 %, the treatment was effective. However, if the clinical symptoms and living ability were not improved, and the neurological deficit score was decreased by less than 18 %, the treatment was ineffective. Total effectiveness was calculated as shown in Eq 1.

$$TE = [(\underline{C + ME + E})/N] \quad \ldots\ldots\ldots (1)$$

where *TE* = total effectiveness, *C* = cured cases, *ME* = markedly effective cases, *ER* = effective cases, and *N* = total number of patients in a group.

Incidence of adverse reactions

The adverse reactions seen were slightly elevated transaminase, skin pruritus, sleep disorder and nausea.

Serum indices

Following overnight fast, 3 mL of venous blood was taken from each patient, pre- and post-treatment, and the serum was collected after centrifugation. Serum indexes in both groups were determined before and after treatment by professional doctors using enzyme-linked

immunosorbent assay (ELISA) kits (Shanghai Jiang Lai Bio-Technology Co. Ltd) according to the instructions on the kit manuals. The serum indexes assayed were tissue inhibitor of metalloproteinase-1 (TIMP-1) and matrix metalloproteinase-9 (MMP-9).

Cerebral nerve function

Cerebral nerve function was assessed before and after treatment using the *NIHSS Rating Scale* which had full score of 42 points [10]. The score directly reflected the severity of nerve function injury in the patient.

Activities of daily living (ADL)

The *ADL Rating Scale* [11] was used to compare the patients' ADL pre- and post-administration of drugs. The maximum score was 100, out of which a score of 34 or less indicated that the patients did not have daily living ability or limb motor function, while scores of 35 - 64 indicated severe dysfunction in ADL, and scores of 65 - 74 indicated moderate dysfunction in ADL. Mild ADL dysfunction was indicated in scores of 75 - 94, and scores of 95 - 100 represented normal ADL. The higher the score, the better the living ability of patients.

Statistical analysis

The SPSS version 20.0 software was used to process data in this study, while GraphPad Prism 7 was employed for plotting graphs. Counted data are expressed as numbers and percentages [n (%)], and were compared between the 2 groups using χ^2 test, while measured data are expressed as mean ±SD, and were compared using *t*-test. Statistical significance was assumed at $p < 0.05$.

RESULTS

General profile of patients

As shown in Table 1, the 2 groups did not differ markedly in age, gender, BMI, Glasgow Coma Scale (GCS) score, blood loss, smoking and alcohol drinking.

Clinical (Treatment) efficacy

As presented in Table 2, total clinical efficacy in patients in the study group was superior to that in control patients.

Incidence of adverse reactions

After treatment, there was markedly lower incidence of adverse events in the study group than in control group *($p < 0.05$*, Table 3).

TIMP-1 index

The TIMP-1 indexes of study group patients before and after therapy were 234.12 ± 35.24 pg/mL and 81.33 ± 14.23 pg/mL, respectively,

Table 1: Patient profiles in both groups

Parameter	Study group (n=45)	Control group (n=45)	χ^2	*P*-value
Age (years)	71.75±3.32	71.69±3.29	0.086	0.932
Gender			0.044	0.833
Male	22(48.89)	23(51.11)		
Female	23(51.11)	22(48.89)		
BMI (kg/m^2)	26.27±1.59	25.91±1.63	1.061	0.292
GCS score	8.14±1.28	8.19±1.24	0.188	0.851
Blood loss (mL)	42.33±4.35	42.28±4.41	0.054	0.957
Smoking			0.045	0.832
Yes	20(44.44)	21(46.67)		
No	25(55.56)	24(53.33)		
Alcohol drinking			0.178	0.673
Yes	22(48.89)	24(53.33)		
No	23(51.11)	21(46.67)		

Table 2: Clinical efficacy in each group (n (%); n = 45)

Group	Cured	Markedly effective	Effective	Ineffective	Total effectiveness
Study	66.67% (30/45)	17.78% (8/45)	11.11% (5/45)	4.44% (2/45)	95.56% (43/45)
Control	40.00% (18/45)	15.56% (7/45)	17.78% (8/45)	26.67% (12/45)	73.33% (33/45)
χ^2					8.459
P-value					0.004

Table 3: Incidence of undesirable events in both groups [n (%); n = 45]

Group	Slightly elevated transaminase	Skin pruritus	Sleep disorder	Nausea	Overall incidence
Study	2.22% (1/45)	0.00% (0/45)	0.00% (0/45)	2.22% (1/45)	4.44% (2/45)
Control	6.67% (3/45)	4.44% (2/45)	6.67% (3/45)	8.89% (4/45)	26.67% (12/45)
χ^2					8.459
P-value					0.004

while the corresponding values in controls were 232.25 ± 36.67 pg/mL and 168.25 ± 17.23 pg/mL. Following treatment, TIMP-1 index was significantly lower in the study group than in the control group ($p < 0.05$; Figure 1).

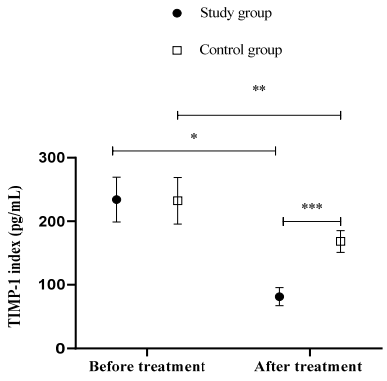

Figure 1: TIMP-1 index values in both groups (mean ± SD). *$P < 0.001$, TIMP-1 index before therapy vs TIMP-1 index after therapy (study patients); ** $p < 0.001$, TIMP-1 index before therapy vs the TIMP-1 index after therapy (control patients); *** $p < 0.001$, TIMP-1 index of control patients after therapy vs the TIMP-1 index of the study group after therapy

MMP-9 index

The MMP-9 index values of patients in study group before and after therapy were 239.44 ± 31.12 pg/mL and 90.25 ± 11.22 pg/mL, respectively, while the corresponding control values were 240.27 ± 30.88 pg/mL and 169.32 ± 21.11 pg/mL, respectively. Thus, post-treatment MMP-9 index was markedly lower in study patients, when compared to controls, as shown in Figure 2.

NIHSS score

The NIHSS scores of patients before and after therapy were 31.22 ± 2.11 and 5.37 ± 1.22 points in the study group, respectively, and 30.99 ± 2.23 and 13.28±1.98 points, respectively in control patients. Thus, post-treatment NIHSS rating was markedly reduced in study patients, relative to controls, as shown in Figure 3.

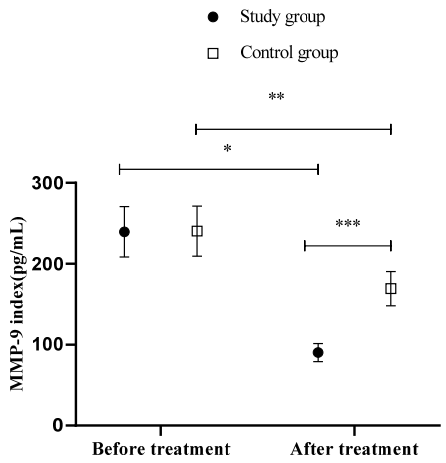

Figure 2: MMP-9 index values (mean ± SD). *$P < 0.001$, the MMP-9 index of the study group before therapy vs the MMP-9 index of the study group after therapy; ** $p < 0.001$, MMP-9 index before therapy vs the MMP-9 index after therapy in control patients; *** $p < 0.001$, MMP-9 index (control) post-therapy vs MMP-9 index of the study group after therapy

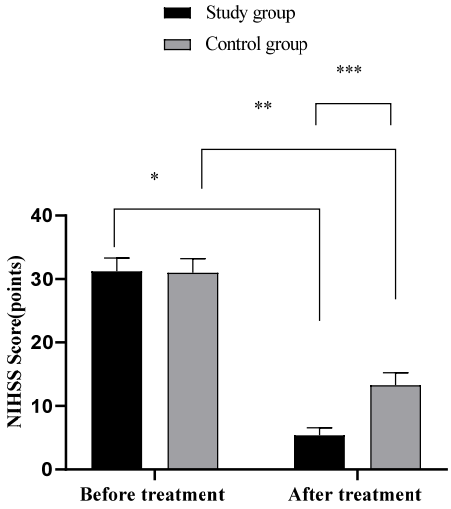

Figure 3: NIHSS scores (mean ± SD). *$P < 0.001$, NIHSS rating of study patients before therapy vs NIHSS score of the study group after therapy; **$p < 0.001$, the NIHSS score of the control group before therapy vs their NIHSS score after therapy; ***$p < 0.001$, control NIHSS score post-therapy vs NIHSS score of study group post-therapy

ADL scores

The ADL ratings of subjects in study group pre- and post-therapy were 41.27 ± 5.25 and 86.22 ± 7.28 points, respectively, while the corresponding control scores were 40.88 ± 5.61 and 62.12 ± 6.34 pints, respectively. Thus, post-therapy ADL rating was markedly superior in study group, in relation to control patients, as presented in Figure 4.

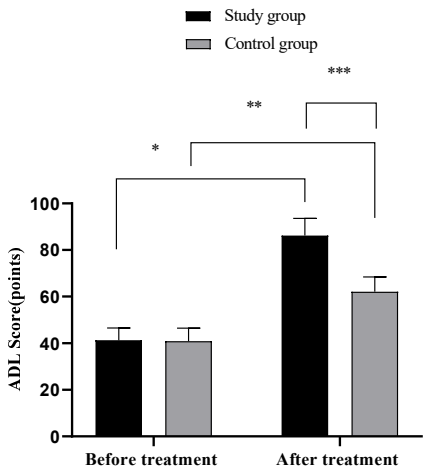

Figure 4: Comparison of ADL scores (mean ± SD). *P < 0.001, ADL rating of study group before therapy vs ADL rating after therapy; **p < 0.001, control ADL ratings before and after therapy; ***p < 0.001, ADL rating of control patients after therapy vs that of the study patients after therapy

DISCUSSION

Patients with hypertensive intracerebral hemorrhage (HICH) usually face the threat of severe brain damage and poor quality of life. For such patients, timely and effective treatment is essential to control brain edema and reduce the possibility of disability or death [12]. Intracerebral hemorrhage is a serious complication which occurs in the third stage of hypertension, accounting for 30% of incidence of cerebrovascular diseases. If it is not treated in time, hematoma will compress the cranial nerves and cause intracranial hypertension.

In severe cases, symptoms such as cerebral hernia and nerve dysfunctions may occur, thereby seriously endangering the lives of patients and reducing their quality of life [13]. In addition, elderly patients are susceptible to HICH due to advanced age, decreased body immunity and organ dysfunctions, poor vascular compliance, and prolonged high blood pressure. At present, drug therapy is mainly adopted in clinical practice to remove the hematoma and reduce the secondary brain tissue injury in perihematoma.

Oxiracetam, a well-known drug for enhancing brain metabolism and soothe cranial nerves, is widely used in clinical treatments. It effectively promotes the synthesis of phosphorylcholine and phosphorylethanolamine, increases the ratio of ATP/ADP, increases protein and nucleic acid in the brain, and repairs brain cell lesions in patients [14]. Moreover, oxiracetam keeps the patients' brain awake, and it enters the brain tissues through blood-brain barrier. This is conducive for improving the activities of daily living and cognitive function in patients. However, the use of oxiracetam drug alone leads to high incidence of adverse reactions.

Studies have revealed that the combined use of oxiracetam and butylphthalide produced significant clinical efficacy and effectively reduced the severity of undesirable side effects [15,16]. In the present research, the study patients were treated with oxiracetam in combination with butylphthalide, while the control patients were treated with oxiracetam alone. The clinical efficacy of both groups was significant, but the incidence of adverse reactions in the study group after treatment was obviously lower than that in the control group. This showed that the combined medication was safer than single medication, and that butylphthalide may effectively make up for shortcomings of oxiracetam.

Butylphthalide is a potent drug which is effective against several pathologies associated with severe ischemic stroke, and it improves ischemic cerebral perfusion and mitigates neurological deficits. It is produced as a racemic form of n-butylphthalide which blocks cerebral ischemia-induced brain injury, protects the nervous system, scavenges ROS, improves antioxidant defenses, and reduces central nerve injury [17,18].

A study has found that butylphthalide produced a significant clinical effect on HICH, and effectively enhanced cerebral energy metabolism, microcirculation of ischemic area, and the recovery of patients [19]. The present study showed superior post-treatment NIHSS rating in the study group, when compared with control patients. This is in agreement with the findings in a previous study in which the NIHSS score of the study group (14.14 ± 2.57) after treatment was better than that of the control group (31.73 ± 4.82) [20]. This indicates that oxiracetam, when used in combination with butylphthalide,

improved cerebral nerve activity, cognition and ADL in HICH subjects.

CONCLUSION

This study has shown that the combination treatment using oxiracetam and butylphthalide improves the clinical indices of HICH patients, and produces significant clinical efficacy by repairing damaged cranial nerves and enhancing patients' activities of daily living. Moreover, the combination treatment has higher safety than the monotherapy. Further research on the combined medication will help to establish a reliable treatment plan for HICH patients.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Qiong Huang and Zhixiong Chen conceived and designed the study, and drafted the manuscript. Qiong Huang, Zhixiong Chen and Jing Yao collected, analyzed and interpreted the experimental data. Zhixiong Chen and Jing Yao revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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