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Original Article

Therapeutic effectiveness of Donepezil hydrochloride in combination with butylphthalide for post-stroke cognitive impairment

Yuxin Pang[1], Zhibin Han[2], Chen Xu[3], Jincheng Meng[1], Jiping Qi[1]

[1]Department of Pathology, The First Affiliated Hospital of Harbin Medical University, Harbin 150001, Heilongjiang, China; [2]Department of Neurosurgery, The First Affiliated Hospital of Harbin Medical University, Harbin 150001, Heilongjiang, China; [3]Department of Neurology, The First Affiliated Hospital of Harbin Medical University, Harbin 150001, Heilongjiang, China

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Abstract: Objective: To study the therapeutic effectiveness of donepezil hydrochloride (DPZ) in combination with butylphthalide (BP) for the treatment of post-stroke cognitive impairment (PSCI). Methods: In this retrospective study, the clinical data of 125 PSCI patients treated at the First Affiliated Hospital of Harbin Medical University from December 2019 to December 2023 were collected and analyzed. The patients were grouped into a joint group (n=75, receiving DPZ + BP) and a control group (n=50, receiving DPZ alone) according to their treatment regimen. Inter-group comparisons were then carried out from the perspectives of therapeutic effectiveness, safety (constipation, abdominal distension and pain, and gastrointestinal reactions), cognitive function (Montreal Cognitive Assessment Scale [MoCA], Chinese Stroke Scale [CSS]), Activities of Daily Living Scale (ADL), and serum biochemical indexes (neuron-specific enolase [NSE], high-sensitivity C-reactive protein [hs-CRP], nitric oxide [NO], and malondialdehyde [MDA]). In addition, a univariate analysis was carried out to identify factors affecting therapeutic effectiveness in PSCI patients. Results: The joint group showed significantly better therapeutic effectiveness compared to the control group ($P<0.05$). There was a significant correlation between the type of stroke, treatment method, and therapeutic effectiveness in PSCI patients ($P<0.05$). There was no significant difference in the total incidence of adverse reactions ($P>0.05$). After the treatment, compared to the control group, the joint group demonstrated significant improvements in MoCA and ADL scores (all $P<0.05$) and reductions in CSS scores and levels of NSE, hs-CRP, NO, and MDA (all $P<0.05$). Conclusions: DPZ in combination with BP is highly effective for the treatment of PSCI. It positively affects cognitive function and ADL, alleviates neurological deficits, and reduces abnormal serum biochemical indices without increasing the risk of adverse reaction.

Keywords: Donepezil hydrochloride, butylphthalide, stroke, cognitive impairment, therapeutic effectiveness

Introduction

Stroke, a brain dysfunction caused by cerebral blood flow disorders, is associated with high rates of mortality and disability [1]. Post-stroke cognitive impairment (PSCI) is a major complication following a stroke, with an incidence rate ranging from 20% to 80% [2]. PSCI is pathologically complex, potentially involving neuroanatomic lesions in critical areas such as the hippocampus and white matter, and the contributing factors may include cerebrovascular disease-associated cerebral microbleeds, acute neuroinflammation, and cerebral hypoxia events [3-5]. PSCI not only hinders patients' physical recovery but may also affect their overall health outcome [6]. PSCI can be divided into post-stroke dementia-free cognitive impairment and post-stroke dementia, with a 19.3% probability of developing post-stroke dementia within 10 years following a stroke [7, 8]. To effectively prevent dementia, it is necessary to provide scientific and effective treatment and preventive management for PSCI patients.

The recovery from stroke varies, particularly in aspects such as language recovery and cognitive repair [9]. Pharmacotherapy can accelerate

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recovery from PSCI and aid in the further repair of damaged neurologic function for therapeutic purposes [10]. Donepezil hydrochloride (DPZ), as a reversible, noncompetitive acetylcholinesterase inhibitor, acts as a cognitive enhancer by increasing acetylcholine to modulate dopamine receptors in the nucleus accumbens (NAc) [11]. It can also alleviate cognitive impairment in rat models by modulating inflammatory/oxidative/apoptotic cascades [12]. In addition, DPZ can be used for the treatment of Alzheimer's disease-induced moderate dementia and is well tolerated by patients [13]. Butylphthalide (BP), a chemical component of celery oil, possesses multiple pharmacologic effects such as protecting mitochondrial function and inhibiting oxidative stress and neuronal apoptosis [14]. It can be used not only to treat diabetes, diabetes-related cataracts, and atherosclerosis, but also to manage ischemic stroke, helping to ameliorate cognitive decline caused by adverse events such as epilepsy and brain edema [15].

This study intends to analyze the therapeutic effectiveness of DPZ in combination with BP for PSCI, addressing the current research gap to offer more effective treatment options for these patients.

Patients and methods

General information

This retrospective study involved 125 PSCI patients who were treated at the First Affiliated Hospital of Harbin Medical University from December 2019 to December 2023. 75 cases in the joint group received a combination of donepezil hydrochloride and butylphthalide (DPZ + BP), and 50 cases in the control group were treated with DPZ alone. Ethical approval was granted by the First Affiliated Hospital of Harbin Medical University Ethics Committee, and informed consent was obtained from all subjects.

Patient selection and exclusion criteria

Patients eligible for this study met the following criteria: diagnosis of PSCI according to established diagnostic standards, confirmed by cranial computed tomography (CT) or magnetic resonance imaging (MRI); onset of cognitive impairment within 6 months following a hemorrhagic or ischemic stroke; adequate visual and auditory abilities to comply with testing; mobility with or without the assistance of a walker; and stable enough to cooperate with medical history documentation and related evaluations.

Patients were excluded if they had malignant tumor; severe cardiac, pulmonary, or renal diseases; known allergies to the study drug; metabolic disorders, or infectious disease; mental retardation or severe mental illness that hinder compliance and cooperation with the study protocols; or participation in other clinical studies in the past month.

Treatment methods

The control group was treated with DPZ alone. DPZ tablets (Shanghai Yuanmu Biotechnology Co., Ltd., YM-BZ0650) were given 5 mg/time, once a day. The joint group was treated with BP (Shanghai Yuanmu Biotechnology Co., Ltd., YM-BZ101035) in addition to DPZ: 2 BP soft capsules (0.2 g) were administered orally, 3 times/day. Both groups were treated continuously for 3 months.

Detection indicators

The two groups of patients were evaluated and compared in terms of therapeutic effectiveness, safety, cognitive function, degree of neurological deficits, activities of daily living (ADL), and serum biochemical indexes.

(1) Therapeutic effectiveness [16]. An obvious improvement in clinical symptoms and signs as well as an increase in the Montreal Cognitive Assessment Scale (MoCA) score by ≥6 points from baseline was determined as markedly effective; an improvement in clinical symptoms and signs, along with an increase of 4-6 points of MoCA from baseline was defined as effective. Scores not meeting these criteria are rated as ineffective.

(2) Safety [17]. The incidences of constipation, abdominal distension and pain, and gastrointestinal reactions during treatment were recorded, and the total incidence of adverse reactions was calculated.

(3) Cognitive function [18]. Cognitive function assessment was assessed with the MoCA scale, which evaluates attention and concentration, executive function, memory, language,

Table 1. Baseline data comparison

Indicator	Joint group (n=75)	Control group (n=50)	χ^2/t	P
Gender			0.776	0.378
Male	39 (52.00)	30 (60.00)		
Female	36 (48.00)	20 (40.00)		
Age (years)	65.12±8.94	65.88±8.20		
Years of education	7.17±3.09	7.98±2.85		
Type of stroke			0.387	0.534
First	52 (69.33)	32 (64.00)		
Recurrent	23 (30.67)	18 (36.00)		
Hypertension			0.442	0.506
Yes	30 (40.00)	23 (46.00)		
No	45 (60.00)	27 (54.00)		
Diabetes			0.286	0.593
Yes	25 (33.33)	19 (38.00)		
No	50 (66.67)	31 (62.00)		

Table 2. Comparison of therapeutic effectiveness

Indicator	Joint group (n=75)	Control group (n=50)	χ^2	P
Markedly effective	37 (49.33)	20 (40.00)		
Effective	30 (40.00)	18 (36.00)		
Ineffective	8 (10.67)	12 (24.00)		
Total	67 (89.33)	38 (76.00)	3.968	0.046

visuoconstructional skills, conceptual thinking, calculations, and orientation with a total score of 30 points. A lower score suggests a poorer cognitive function.

(4) Degree of neurological deficits [19]. Patients were assessed for neurological deficits by the Chinese Stroke Scale (CSS) before and after treatment. On a scale ranging from 0-45 points, a higher score is indicative of more serious neurologic deficits.

(5) ADL [20]. Patients' ADL was evaluated with the ADL scale with a total score of 100. A higher score indicates better daily living capabilities.

(6) Serum biochemical indexes [21]. 3 mL of fasting venous blood was collected from each patient before and after treatment, and the supernatant was collected after centrifugation to quantify neuron-specific enolase (NSE) and high-sensitivity C-reactive protein (hs-CRP) by chemiluminescent immunoassay, nitric oxide (NO) by colorimetry, and malondialdehyde (MDA) by enzyme-linked immunosorbent assay (ELISA).

Statistical analysis

In this study, measured and counted data were described as the mean ± SEM and the rate (percentage), respectively. Statistical comparisons of continuous variables were performed using independent sample t-tests for inter-group analyses and paired t-tests for intra-group analyses pre- and post-treatment. Categorical data were analyzed using the chi-square (χ^2) test. Univariate analysis was carried out to identify factors influencing therapeutic effectiveness in patients with PSCI. The collected data were analyzed by SPSS21.0. Statistical significance was determined at $P<0.05$.

Results

Baseline data comparison

As shown in **Table 1**, the two groups were comparable in terms of sex, age, years of education, type of stroke, hypertension, and diabetes (all $P>0.05$).

Comparison of therapeutic effectiveness

The total effective rate was 89.33% in the joint and 76.00% in the control group with a notable inter-group difference ($P<0.05$, **Table 2**).

Univariate analysis of factors influencing therapeutic effectiveness in PSCI patients

As indicated by univariate analysis (**Table 3**), the type of stroke and treatment method were strongly associated with therapeutic effectiveness in PSCI patients (both $P<0.05$), rather than gender, age, years of education, hypertension, and diabetes (all $P>0.05$).

Comparison of medication safety

The joint group experienced fewer adverse events such as constipation, abdominal distension and pain, and gastrointestinal reactions than the control group; However, the difference

Table 3. Univariate analysis of factors influencing therapeutic effectiveness in patients with post-stroke cognitive impairment

Indicator	Effective group (n=105)	Ineffective group (n=20)	χ^2	P
Sex			0.925	0.336
Male	56 (53.33)	13 (65.00)		
Female	49 (46.67)	7 (35.00)		
Age (years)			0.113	0.736
<65	43 (40.95)	9 (45.00)		
≥65	62 (59.05)	11 (55.00)		
Years of education			1.165	0.280
<7	39 (37.14)	10 (50.00)		
≥7	66 (62.86)	10 (50.00)		
Type of stroke			14.948	<0.001
First episode	78 (74.29)	6 (30.00)		
Recurrent	27 (25.71)	14 (70.00)		
Hypertension			0.534	0.465
Yes	46 (43.81)	7 (35.00)		
No	59 (56.19)	13 (65.00)		
Diabetes			3.968	0.297
Yes	39 (37.14)	5 (25.00)		
No	66 (62.86)	15 (75.00)		
Treatment method			3.968	0.046
Donepezil hydrochloride	38 (36.19)	12 (60.00)		
Donepezil hydrochloride + butylphthalide	67 (63.81)	8 (40.00)		

Table 4. Comparison of medication safety

Indicator	Joint group (n=75)	Control group (n=50)	χ^2	P
Constipation	4 (5.33)	2 (4.00)		
Abdominal distension and pain	2 (2.67)	3 (6.00)		
Gastrointestinal reactions	3 (4.00)	2 (4.00)		
Total	9 (12.00)	7 (14.00)	0.108	0.743

in the total incidence was not significant (P>0.05, **Table 4**).

Comparison of cognitive function

The MoCA assessment of patients' cognitive function revealed no marked inter-group difference before treatment (P>0.05). Both groups showed elevated MoCA scores after treatment, with a more significant increase found in the joint group (P<0.05, **Figure 1**).

Comparison of neurological deficits

By using the CSS scale, the neurological deficits of both groups were evaluated. There was no significant difference in pre-treatment CSS score between the two groups (P>0.05). Both groups showed a marked reduction in CSS score after treatment, particularly in the joint group (P<0.05, **Figure 2**).

Comparison of ADL

The comparison of ADL scores showed no significant inter-group difference before treatment (P>0.05). After treatment, both groups showed an increase in ADL scores, with the joint group achieving a higher score (P<0.05, **Figure 3**).

Comparison of serum biochemical indexes

Before treatment, there were no significant differences in serum biochemical indexes (NSE,

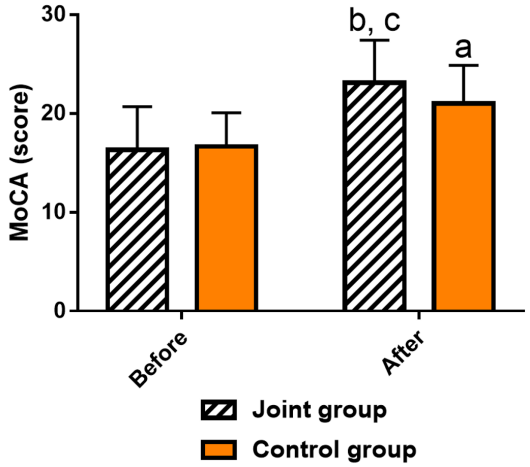

Figure 1. Comparison of cognitive function. Note: [a]P<0.05 *vs.* before treatment; [b]P<0.01 *vs.* before treatment; [c]P<0.05 *vs.* control. MoCA, Montreal Cognitive Assessment Scale.

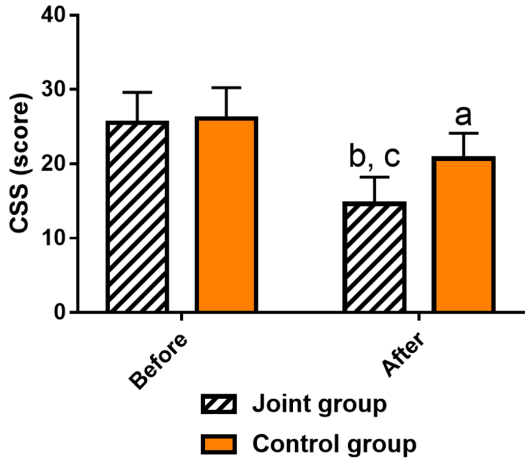

Figure 2. Comparison of neurological deficits. Note: [a]P<0.05 *vs.* before treatment; [b]P<0.01 *vs.* before treatment; [c]P<0.05 *vs.* control. CSS, Chinese Stroke Scale.

hs-CRP, NO, MDA) between the groups (P>0.05). After treatment, all indexes showed reductions in both groups, with more substantial decreases observed in the joint group (P<0.05, **Figure 4**).

Discussion

Post-stroke cognitive impairment (PSCI) adversely affects various cognitive domains including language, memory, attention, executive functions, and visuospatial abilities, thereby diminishing the independence of affected

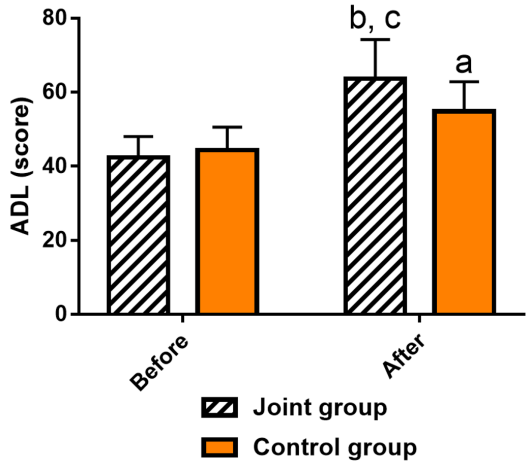

Figure 3. Comparison of ADL. Note: [a]P<0.05 *vs.* before treatment; [b]P<0.01 *vs.* before treatment; [c]P<0.05 *vs.* control. ADL, Activities of Daily Living Scale.

individuals and constraining their daily lives [25]. Age, education level, occupation, smoking, hypertension, and diabetes mellitus have been identified as factors associated with PSCI [22-24]. Therefore, effective treatment is crucial for improving the ADL of PSCI patients.

In this study, the total effective rate was significantly higher in the joint group compared to the control group (89.33% *vs.* 76.00%), suggesting that DPZ + BP for PSCI is more effective in enhancing therapeutic effectiveness. This enhanced efficacy may be attributed to the active ingredient in BP, DL-3-n-BP, which improves cerebral blood flow, alleviates ischemia and hypoxia, and supports microcirculation while also inhibiting cell apoptosis and platelet aggregation [26, 27]. Consistent with our results, Liu et al. [28] found that the combination of DPZ and BP increased the overall clinical efficacy in patients with vascular dementia compared to DPZ alone. The comparable incidence of total adverse events like constipation, abdominal distension and pain, and gastrointestinal reactions in the two groups suggests that DPZ + BP is well tolerated in the treatment of PSCI without increasing the risk of total adverse events. We speculate that there may be a mechanism that counteracts the side effects of DPZ + BP in the treatment of PSCI, although this requires further investigation. Zhang C et al. [29] also supported our findings, noting that a cocktail therapy (i.e., DPZ + BP + oxiracetam + Ginkgo biloba extract) in patients

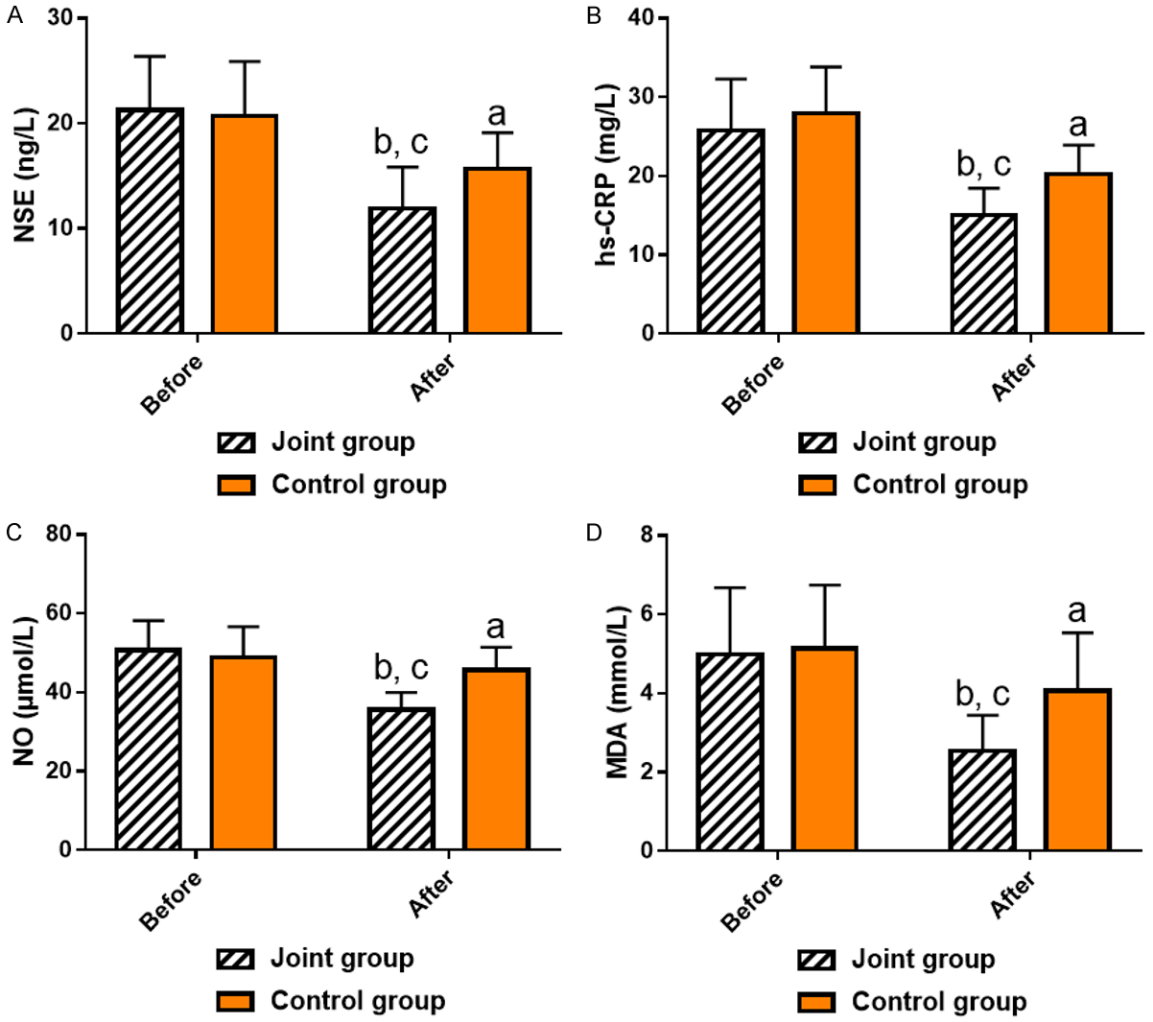

Figure 4. Comparison of serum biochemical indexes. The joint group showed markedly reduced NSE (A), hs-CRP (B), NO (C), and MDA (D) levels after treatment, lower compared to the control group. Note: [a]P<0.05 *vs.* before treatment; [b]P<0.01 *vs.* before treatment; [c]P<0.05 *vs.* control. NSE, neuron-specific enolase; hs-CRP, high-sensitivity C-reactive protein; NO, nitric oxide; MDA, malondialdehyde.

with Parkinson's disease and dementia did not increase the incidence of liver function abnormalities compared with DPZ alone. In addition, the MoCA score of the joint group increased statistically after treatment, significantly higher that the control group, ascertaining the effectiveness of DPZ + BP in improving cognitive function in PSCI patients. Furthermore, the CSS score of the joint group was markedly reduced after treatment, and was lower compared to the control group, demonstrating that the intervention of DPZ + BP is conducive to alleviating neurological deficits in PSCI patients. The joint group also experienced a significant increase in ADL scores post-treatment, demonstrating a more substantial improvement compared to DPZ alone. In a systematic review and meta-analysis, Fan et al. [30] concluded that BP, either in the form of monotherapy or combination therapy, which significantly improved cognitive function and ADL, and reduced neurological deficits in patients with PSCI, consistent with our findings.

NSE is a specific biochemical marker for nerve cell injury, and its level is inversely correlated with cognitive function in patients with cognitive impairment and intracranial tumors [31]. High hs-CRP levels are strongly associated with cognitive decline following a stroke [32]. NO is closely related to brain injury, and reducing NO content is helpful in enhancing cognitive function, particularly learning and memorizing [33]. A high serum level of MDA, an index of oxidative

stress, is also a risk factor for PSCI one month after the episode [34]. In our study, the serum biochemical indexes such as NSE, hs-CRP, NO, and MDA dropped markedly in the joint group after treatment, and were significantly lower compared with the control group, suggesting DPZ + BP could validly inhibit these abnormally increased serum biochemical indexes in PSCI patients. Similar to our findings, Tian et al. [35] reported that DPZ + BP played a neuroprotective role in the treatment of diabetic rat models, significantly reducing the levels of MDA and inflammatory cytokines while improving cognitive dysfunction in rats. Another prospective study [36] showed that BP treatment for patients with acute ischemic stroke significantly improved their cognitive function in memory, attention, and language skills, while helping to downregulate hs-CRP levels, similar to our observations. Through univariate analysis, factors influencing therapeutic effectiveness in PSCI patients were identified. Recurrence and DPZ monotherapy were significantly related to ineffective treatment in PSCI patients, suggesting that the use of combination therapy, preferably in non-recurrent patients, can substantially enhance treatment effectiveness.

Conclusion

DPZ in combination with BP outperforms DPZ monotherapy in the treatment of PSCI, offering clinical advantages in terms of safety, improvement of cognitive function, alleviation of neurological deficits, and enhancement of ADL. These benefits are partly attributed to the ability of the two drugs to effectively downregulate serum biochemical markers such as NSE, hs-CRP, NO, and MDA. This suggests a synergistic effect of DPZ and BP in mitigating the pathologic processes associated with PSCI.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jiping Qi, Department of Pathology, The First Affiliated Hospital of Harbin Medical University, No. 23 Youzheng Street, Nangang District, Harbin 150001, Heilongjiang, China. Tel: +86-0451-85556000; E-mail: qijiping2003@163.com

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