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Original Article

Clinical effect and risk factors of irbesartan in patients with ischemic cerebral infarction complicated with hypertension

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Abstract: Objective: To analyze the clinical effect and risk factors of irbesartan in ischemic cerebral infarction (ICI) complicated with hypertension. Methods: One hundred patients with acute ICI with hypertension admitted to Jilin City Central Hospital from February 2016 to December 2017 were selected and retrospectively analyzed. Among them, 58 cases were treated with irbesartan in addition to enalapril as the OB group, while 42 cases received only enalapril as the NC group. Another 100 healthy individuals were enrolled as normal control groups for the logistic regression analysis. The indices of blood pressure (BP), heart rate (HR), National Institutes of Health Stroke Scale (NIHSS) scores, and adverse reactions were recorded before and after treatment in NC group and OB group. The recurrence rate and mortality of cerebral infarction in the treatment groups were examined by computer tomography. The clinical data of the patients and controls were analyzed by univariate and multivariate analyses. Results: No difference was seen in the BP and HR between the NC and OB groups prior to treatment (both $P > 0.05$). After treatment, however, the reduction in BP was significantly lower in the NC group compared with the OB group ($P < 0.05$), while no significant difference was seen in HR ($P > 0.05$). The total effective rate of patients in the OB group was significantly higher than that in the NC group ($P < 0.05$). There was no difference in the pre-treatment NIHSS scores between the two groups ($P > 0.05$), but the post-treatment scores decreased significantly in both groups relative to their respective scores before treatment (both $P < 0.05$). In addition, the OB group had significantly lower NIHSS scores than the NC group after treatment ($P < 0.05$). There was no difference in the post-treatment dizziness, kidney injury, headache and diarrhea between the NC and OB groups (all $P > 0.05$), but the mortality and recurrence rate were higher in the NC group (both $P < 0.05$). Univariate analysis showed a significant difference between the patients and normal control groups in terms of smoking history, diabetes, history of alcoholism, age, and high-sensitivity C-reactive protein and low-density lipoprotein levels as potential prognostic factors (all $P < 0.05$). Multivariate logistic regression analysis found that smoking, alcoholism, and diabetes were the independent risk factors for ICI complicated with hypertension. Conclusion: History of smoking, alcoholism and diabetes are independent risk factors for ICI and hypertension. Irbesartan can safely and effectively control the BP and reduce the neurological impairment in patients with ICI and hypertension.

Keywords: Irbesartan, ischemic cerebral infarction, hypertension, risk factors

Introduction

As a chronic cardiovascular and cerebrovascular disease, the incidence of essential hypertension (EH) has significantly increased in recent years with changes in lifestyle and accompanying stresses, and the age of onset is decreasing steadily [1]. With a globally aging population, the patients with EH have increased worldwide. China has the highest number of patients with hypertension, around 200 million [2]. Long-term hypertension can damage the heart, brain, kidney, blood vessels, and other organs [3]. A study has shown that hypertension is an important factor in the development of cerebrovascular diseases and can easily cause cerebral ischemia and lead to infarction, which is life threatening [4].

Cerebral infarction is the most common cerebrovascular disease in the elderly, and mainly caused by thrombosis in the blood vessels

Table 1. Assignment table

Group	Assignment
ICI with hypertension	0=No, 1=Yes
Smoking history	0=No, 1=Yes
Diabetes history	0=No, 1=Yes
History of alcoholism	0=No, 1=Yes
Age (years)	0 ≥ 65, 1 ≤ 65
hs-CRP (mg/L)	1 ≤ 3.00, 2=3.00, 3=3.5~
LDL-C (mmol/L)	1 ≤ 3.00, 2=3.00, 3=3.5~

Note: ICI, ischemic cerebral infarction; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein.

which blocks the blood flow to the brain, causing thrombotic lesions and brain tissue anoxia, and finally leading to neurological dysfunctions [5]. There are many risk factors of cerebral infarction, including lifestyle, diet, blood pressure (BP), blood glucose, blood lipid etc., which make prevention difficult [6]. At present, enalapril is commonly used to treat patients with hypertension. It can reduce the anterior and posterior load of the heart, improve heart function, and improve the patient's condition. However, most hypertensive patients often have other cerebrovascular diseases, and studies show that enalapril alone does not work well [7, 8]. Irbesartan is an antagonist of angiotensin II and specifically inhibits the angiotensin-converting enzyme I receptor. This effectively reduces the expression of angiotensin II and thereby the BP by inhibiting vasoconstriction and reducing aldosterone release [9]. Down-regulation of angiotensin II can also inhibit the inflammatory response in the brain and reduce tissue injury [10]. Few studies have been conducted on the combination of enalapril and irbesartan in treating ICI with hypertension. Therefore, limitations of this treatment and the risk factors are not clear.

Therefore, we subjected the patients with ICI complicated with hypertension to two medication modes, involving enalapril and the combination of enalapril and irbesartan, and evaluated the treatment outcomes in order to provide a basis for clinical management.

Methods

Clinical data of patients

The study was approved by the Medical Ethics Committee of Jilin City Central Hospital, and all patients and their families signed informed consent.

One hundred patients with ICI complicated with hypertension who were treated in Jilin City Central Hospital from February 2016 to December 2017 were retrospectively analyzed. The NC group (n=42; 25 males and 17 females; aged 60-78; average age 65.42006.27) received enalapril, while the OB group (n=58; 39 males and 19 females; aged 62-81; average age 66.12±7.67) were given irbesartan in addition to enalapril. All patients met the clinical diagnostic criteria for hypertension of the *Guidelines for Prevention and Treatment of Hypertension in China* issued in 2010, as well as the diagnostic criteria for cerebral infarction in *Key Diagnostic Points of Various Types of Cerebrovascular Diseases* [11, 12]. In addition, clinical data and indicators of 100 healthy individuals were also collected for risk factor analysis.

Inclusion criteria: a) Age over18 years; b) no recent drug treatment; c) no other hereditary diseases; d) compliance with treatment and follow-up; e) availability of complete clinical data.

Exclusion criteria: a) Malignant tumors; b) chronic infection and pulmonary embolism; c) immune dysfunction; d) history of thrombolytic therapy; e) allergic to the drugs used in this experiment, and f) presence of incontinence, dizziness and other symptoms before the experiment.

Treatment protocols

Patients in the NC group were given enalapril (Jiangsu Pharmaceutical Co., Ltd., 10 mg/tablet) twice a day (10 mg/time), and those in the OB group were given irbesartan (Jiangsu Hengrui Pharmaceutical Co., Ltd., 150 mg/tablet) once a day (150 mg/d) along with the enalapril regimen above. The treatment lasted for 6 months, and the therapeutic effects in both groups were recorded. In case a patient experienced adverse reactions, a suitable treatment was given, and the hypertensive medications were continued after the patient's condition improved.

Observation indices

Primary observation indices included BP, heart rate (HR) changes. The therapeutic effect was graded as: a) markedly effective: diastolic bold pressure (DBP) decreased by 10 mmHg to normal levels or the DBP decreased by 20 mmHg;

Table 2. General clinical data of patients (n, %)

Group	NC group (n=42)	OB group (n=58)	t/x^2	P
Gender			0.630	0.428
Male	25 (59.52)	39 (67.24)		
Female	17 (40.48)	19 (32.76)		
Age (years)			0.037	0.848
≥ 65	29 (69.05)	39 (67.24)		
< 65	13 (30.95)	19 (32.76)		
BMI (kg/m^2)	22.58±1.96	22.94±1.38	0.284	1.078
Smoking history			0.630	0.428
Yes	25 (59.52)	39 (67.24)		
No	17 (40.48)	19 (32.76)		
Diabetes history			3.303	0.074
Yes	20 (47.62)	38 (65.52)		
No	22 (52.38)	20 (34.48)		
History of alcoholism			0.041	0.839
Yes	8 (19.05)	12 (20.69)		
No	34 (80.95)	46 (79.31)		
hs-CRP (mg/L)	2.94±1.23	3.18±1.58	0.414	0.820
LDL-C (mmol/L)	3.58±0.84	3.75±1.12	0.829	0.409
TG (mmol/L)	1.82±0.83	1.71±0.98	0.590	0.557
TC (mmol/L)	5.48±0.92	5.18±0.89	1.640	0.104
Cr (μmol/L)	91.02±16.84	95.18±18.39	1.156	0.250
UA (μmol/L)	312.28±98.23	305.39±102.36	0.338	0.736

Note: BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein; TG, triglyceride; TC, cholesterol; Cr, creatinine; UA, uric acid.

Table 3. Change of blood pressure and heart rate before and after treatment

Group	NC group		OB group	
	Pre-therapy	Post-treatment	Pre-therapy	Post-treatment
SBP (mmHg)	189.31±13.52	138.52±11.23$^{\#}$	192.57±12.24	129.52±13.21$^{*,\#}$
DBP (mmHg)	112.82±10.55	83.53±6.91$^{\#}$	109.24±11.25	75.93±6.54$^{*,\#}$
HR (time/min)	96.24±11.13	75.32±4.21$^{\#}$	95.31±10.83	75.15±3.94$^{\#}$

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. Compared with NC group, $^{*}P \leq 0.001$; compared with the same group before treatment, $^{\#}P < 0.001$.

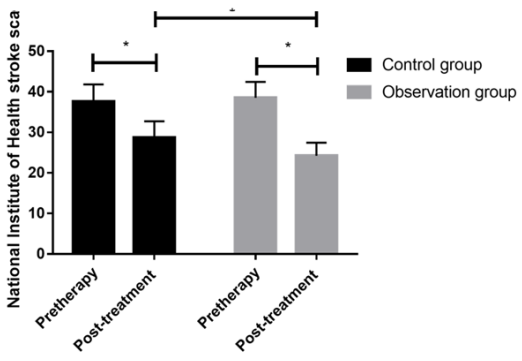

Figure 1. NIHSS scores before and after treatment. NIHSS, national institutes of health stroke scale; $^{*}P < 0.05$.

b) effective: the DBP decreased by < 10 mmHg but was still restored to normal levels or the DBP decreased by 10-20 mmHg, systolic blood pressure (SBP) by ≥ 30 mmHg; c) ineffective: none of the above targets were met [13]. The total effective rate was calculated as: (markedly effective number + effective number)/total number * 100%.

Secondary observation indces were the National Institu-tes of Health Stroke Scale (NIHSS) scores and adverse reactions, body mass index, recurrence rate and mortality after treatment. The neurological function of the patients was scored according to NIHSS, with a total score of 42 points and higher scores incating more serious neurological impairment [14]. The recurrence rate (recurrencenumber/total number * 100%) and mortality (death/total number * 100%) due to ICI were examined by computer tomography. High-sensitivity C-reactive protein (hs-CRP), low-density lipoprotein (LDL-C), triglyceride (TG), cholesterol (TC), creatinine (Cr), and uric acid (UA) levels were tested by Hitachi 7600 automatic biochemical analyzer. The patients' history of smoking, alcoholism, diabetes, and hypertension were analyzed statistically.

Statistical analysis

All statistical analysis was conducted using the SPSS20.0 software package, and the data was plotted using graphpad prism 7. The counting data were expressed as percentage (%), com-

Table 4. Comparison of therapeutic effect between the NC group and OB group

Group	Markedly effective	Effective	Ineffective	x^2	P
OB group	38 (65.52)	10 (17.24)	10 (17.24)	4.433	0.035
NC group	13 (30.95)	14 (33.33)	15 (35.71)		

Table 5. NIHSS scores in NC and OB groups before and after treatment

Group	NC group	OB group
Pre-therapy	37.58±4.25	38.54±3.88
Post-treatment	28.69±4.05	24.21±3.22*
t	9.814	21.645
P	0.000	0.000

Note: NIHSS, National Institutes of Health Stroke Scale. Compared with NC group, *P < 0.05.

Table 6. Adverse reactions, recurrence rate and mortality of patients between the NC and OB group after treatment

Group	OB group (n=58)	NC group (n=42)	P
Dizziness	2 (3.45)	3 (7.14)	0.647
Kidney injury	3 (5.17)	5 (11.90)	0.275
Headache	1 (1.72)	1 (2.38)	1.000
Diarrhea	0	1 (2.38)	0.420
Recurrence	2 (3.45)	7 (16.67)	0.033
Mortality	1 (1.72)	6 (14.29)	0.040

Note: Tested by fisher exact probability method.

pared using the chi-square test and the Fisher exact probability method, and expressed as x^2. The numerical data were expressed by mean ± standard deviation ($\bar{x}$ ± sd). The data following normal distribution were analyzed by t test, expressed as t. For the univariate analysis, the index of P < 0.05 was taken as the independent variable and cerebral infarction complicated with hypertension as the dependent variable. Stepwise logistic regression was used for multivariate analysis. The details were shown in **Table 1**. P < 0.05 is considered statistically significant.

Results

Comparison of general clinical data

We found no significant difference in the general clinical data between the NC and OB groups (all P > 0.05), which indicated comparability between the two groups (**Table 2**).

Comparison of primary indices before and after treatment

There were no significant differences in the pre-treatment BP and HR between the NC and OB groups (both P > 0.05). A pairwise comparison in each group showed that these indicators were significantly decreased after treatment in both groups (all P < 0.001). After treatment, the reduction in BP was significantly less in the NC group compared with the OB group (P < 0.05), although no significant difference was seen in the HR of the two groups (P=0.807) (**Table 3**, **Figure 1**). In addition, the total effective rate of the OB group was significantly higher than of the NC group (P < 0.05) (**Table 4**).

NIHSS in NC and OB groups before and after treatment

We found no significant difference in the pre-treatment NIHSS scores between the NC and OB groups (t=0.407, P=0.685). The NIHSS scores significantly decreased in both groups after treatment compared with that before treatment (both P < 0.05), and was significantly lower in the OB group than the NC group (t=6.158, P=0.000) (**Table 5**, **Figure 1**).

Comparison of the adverse reactions, recurrence rate and mortality

We found no significant differences in the incidences of post-treatment dizziness, kidney injury, headache, and diarrhea between the two groups (all P > 0.05), but the mortality and recurrence rate of the NC group were significantly higher than that of the OB group (both P < 0.05) (**Table 6**).

Univariate and multivariate logistic regression analysis

Univariate analysis showed that smoking history, diabetes, history of alcoholism, age, hs-CRP, and LDL-C were significant prognostic factors (all P < 0.05, **Table 7**). Multivariate logistic regression showed that smoking history, alcoholism, and diabetes were the independent risk factors for patients with ICI complicated with hypertension (**Table 8**).

Discussion

Hypertension is the most common clinical cardiovascular disease, and frequently afflicts the

Table 7. Univariate analysis of patients in two groups

Group	NC + OB group (n=100)	Normal control group (n=100)	t/x^2	P
Gender			0.340	0.560
Male	64 (64.00)	60 (60.00)		
Female	36 (36.00)	40 (40.00)		
Age (years)			18.065	0.000
≥ 65	68 (68.00)	38 (38.00)		
< 65	32 (32.00)	62 (62.00)		
BMI (kg/m^2)	22.68±2.15	23.15±2.01	1.597	0.112
Smoking history			23.204	0.000
Yes	64 (64.00)	30 (30.00)		
No	36 (36.00)	70 (70.00)		
Diabetes history			9.715	0.002
Yes	58 (58.00)	36 (36.00)		
No	42 (42.00)	64 (64.00)		
History of alcoholism			10.286	0.001
Yes	20 (20.00)	5 (5.00)		
No	80 (80.00)	95 (95.00)		
hs-CRP (mg/L)	3.84±1.84	3.15±0.95	3.332	0.001
LDL-C (mmol/L)	3.98±1.55	3.33±1.05	3.472	0.001
TG (mmol/L)	1.82±0.93	1.63±0.79	1.557	0.121
TC (mmol/L)	5.15±1.02	5.37±0.69	1.787	0.076
Cr (μmol/L)	93.54±12.25	90.64±13.09	1.618	0.107
UA (μmol/L)	335.84±96.54	315.51±87.66	1.559	0.121

Note: BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein; TG, triglyceride; TC, cholesterol; Cr, creatinine; UA, uric acid.

Table 8. Multivariate logistic regression analysis of patients

Group	β	SD	x^2	df	Sig	Exp (β)
Smoking history	2.301	0.925	6.846	1	0.008	14.960
Diabetes history	1.433	0.454	13.441	1	0.000	6.855
History of alcoholism	2.455	0.526	14.853	1	0.000	14.359
Age (years)	1.175	0.918	1.637	1	0.201	3.237
hs-CRP	0.008	0.004	0.362	1	0.534	1.012
LDL-C	-0.432	0.232	2.293	1	0.682	0.130

Note: hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein.

elderly. It is mainly caused by the remodeling of blood vessels and atherosclerosis, which results in insufficient blood supply and can be debilitating [15]. Hypertension can be classified as secondary which has known etiology, and essential hypertension with unknown etiology. Patients with essential hypertension account for 90% of all cases [16]. An epidemiological study shows that the number of elderly patients with hypertension has exceeded 120 million in China, which is the highest in the world [17]. In 2010, the number of deaths due to hypertension exceeded 9 million globally, accounting for 18% of the total deaths in the same period. This is a health problem that medical workers need to solve urgently [18]. Cerebral infarction, also called ischemic stroke, is caused by cardiovascular and cerebrovascular sclerosis due to long-term hypertension. One study has shown that the incidence of cerebral infarction in patients with hypertension is significantly higher than that in healthy individuals [19].

ICI complicated with hypertension accounts for about 75% of all acute cerebrovascular diseases, with the mortality of 10% in acute phase patients [20]. The patient is most likely to relapse in the first year after the first onset of cerebral infarction, with a recurrence rate as high as 30%, which seriously impacts patients' life quality [21]. Since the incidence of hypertension is closely related to diet, controlling a patient's diet is one of the important means to reduce the incidence rate [22]. Irbesartan, an angiotensin II receptor antagonist, can selectively block vasoconstriction and aldosterone release [23]. In recent years, one study has shown that irbesartan increases perfusion in cerebral vascular lesions and significantly improves cerebral infarction [24]. A study has shown that the use of irbesartan can increase the blood flow in the lesion area and has no effect on normal blood supply [25].

In this study, we observed significant improvement in several indices of the patients following irbesartan treatment. While both enalapril and irbesartan were effective in terms of reducing the BP and HR, the combination of the medicines further decreased BP compared with the

NC group while no significant difference was seen in HR. Taken together, irbesartan combined with enalapril has better antihypertensive efficacy than conventional treatment alone. Beer et al. also showed that irbesartan was effective in the treatment of ICI with hypertension [26]. The total effective rate of NC group was significantly lower than that of the OB group, thus validating that irbesartan is effective in treating ICI with hypertension. NIHSS score is a commonly used neurological scale for patients with cerebral infarction. The NIHSS score of NC group was significantly higher than that of OB group. Cheng et al. found that NIHSS scores were significantly lower in patients with acute cerebral infarction treated with irbesartan, which indicates that irbesartan improves neurological function in patients with cerebral infarction [27]. In addition, we found that there was no difference in the incidence of adverse events between the two groups, although the recurrence rate and mortality in NC group was significantly higher than that in OB group, further illustrating the therapeutic effect of irbesartan. At the end of the study, we conducted logistic regression analysis on patients. Univariate analysis showed that smoking history, diabetes, alcoholism history, age, hs-CRP and LDL-C were prognostic factors, and multivariate logistic regression analysis showed that smoking, diabetes and alcoholism history were independent risk factors for ICI with hypertension. A study has shown that alcohol and smoking are important risk factors of hypertension, and proper diet control plays an important role in the prognosis of patients [28].

However, this study still has some limitations. As a retrospective study, the sample number was limited and therefore the results may have a certain bias. Second, the follow-up time of the treatment was relatively short, and we were unable to follow long-term adverse reactions and deaths. Therefore, we aim to conduct randomized controlled trials in future, increase the number of samples, and follow-up the patients for longer durations to verify the results of this study. In conclusion, history of alcoholism is an independent prognostic factor of ischemic cerebral infarction complicated with hypertension. Irbesartan can safely and effectively control BP and reduce neurological impairment in patients with ICI complicated with hypertension.

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Disclosure of conflict of interest

None.

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