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Therapeutic effect of early intensive antihypertensive treatment on rebleeding and perihematomal edema in acute intracerebral hemorrhage

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Abstract

To observe the effect of early intensive blood pressure (BP)–lowering treatment on rebleeding and perihematomal edema (PE) in patients with acute intracerebral hemorrhage (ICH). A total of 121 patients with ICH were randomly assigned to an early intensive antihypertensive treatment group (IG) (n = 62) or control group (CG) (n = 59). For both groups, 25 mg of urapidil injection was slowly administered intravenously in 6 hours of the onset. For the IG, 100 mg of urapidil and 30 mL of 0.9% sodium chloride were then slowly administered. Repeat computed tomography imaging was performed at 24 hours, 72 hours, day 7, and day 14 to detect any rebleeding via changes in hematoma volume and the changes in PE. Finally, NIHSS scores and Barthel Index (BI) were calculated at 24 hours, 72 hours, day 7, day 14, day 30, and day 90. The average hematoma volume in IG patients was significantly smaller than that of CG patients after 24 hours ($P < .05$). The volume of PE in the CG increased more than in the IG within 24 hours of onset, but was not statistically significant ($P > .05$); however, this trend was statistically significant after 72 hours ($P < .05$). On day 30 and day 90, the average NIHSS score of IG patients was lower than that of CG patients, and the BI was higher ($P < .05$) than that of CG patients. There was no significant difference in mortality between the two groups. Early intensive antihypertensive treatment in ICH patients reduces rebleeding and PE, improving short-term quality of life.

1 | INTRODUCTION

The mortality and disability rates in patients with acute intracerebral hemorrhage (ICH) are concerningly high. Neurological deterioration is mainly caused by enlargement of the hematoma and brain edema in the early stages of ICH, and an increase in blood pressure (BP) is especially common after ICH. An increasing BP not only promotes hematoma enlargement, but also aggravates brain edema; therefore, neurological dysfunction is significantly associated with increased BP in the early stages of ICH. About 83% of ICH patients experience early hematoma expansion.[1] Several studies[2-5] have found that cerebral edema after ICH was highly associated with elevated BP within 24 hours and a history of hypertension. The risk of an enlarging hematoma in patients with ICH when systolic BP (SBP) ≥ 160 mm Hg was significantly higher than that of those with SBP ≤ 150 mm Hg. It was thought that decreasing elevated SBP after ICH could decrease the enlargement of a hematoma and improve the clinical outcome.Other studies showed that early intensive antihypertensive treatment within 72 hours of ICH onset could prevent hematoma enlargement, but had no obvious effect on surrounding edema.[3,6,7] Therefore, 100 mg of urapidil and 50 mL of 0.9% sodium chloride were slowly administered via micropump to intensively lower BP in patients with elevated SBP in early stages (<6 hours) after ICH in this study. The goal of our study was to assess whether this method

could reduce rebleeding and perihematomal edema (PE) after 24 hours, and whether improvement of clinical outcome could be observed on day 30 and day 90.

2 | MATERIALS AND METHODS

2.1 | Enrollment randomization and allocation

A total of 121 cases with hospitalization for ICH were consecutively recruited from January 2013 to January 2016. This research was approved by the Ethics Committee of the Second Hospital of Baoding, and written informed consent was obtained from the patients or their family members. The third-party physicians are responsible for the randomized grouping of patients with ICH.

Participants were enrolled by ICH specialists in the research team. The third-party physicians carried out the randomization, but were not involved in the enrollment, diagnosis, assessment, or intervention of the participants. The third-party physicians generated random number sequences using SAS software for the participants with ICH, respectively. Then, the third-party physicians produced sealed envelopes with the serial number on the outside and group number on the inside, and kept the envelopes in a locked drawer that was inaccessible to all researchers. The envelopes were opened sequentially by the third-party physicians after baseline assessments, and participants were assigned to the groups equally according to the group number printed inside the envelopes. Outcome subjects, their families, evaluators, investigators, and data analysts were blinded to the group assignment. Researchers designed experiments, conducted treatments, and observed adverse reactions. The NIHSS scores and BI scores were assessed by qualified evaluators who were not involved in randomization or inpatient clinical treatment. All investigators and coordinators were asked to sign confidentiality agreements to ensure that no data were disclosed to the researchers before the main results were released.

Criteria for admission: (a) patients with spontaneous ICH confirmed by head computed tomography (CT), and elevated SBP level (150-220 mm Hg) within 1 hour of onset; (b) age ≥18 years old; (c) hospitalization within 5 hours of ICH onset, allowing for monitoring of vital signs; (d) surgical treatment was not considered; (e) for rising BP in ICH patients in an early stage, symptoms should first be assessed—such as headache, vomiting, tension, irritability, urinary retention, and elevated intracranial pressure and corresponding treatment given; the changes in BP should then be monitored. After the above treatment, if SBP was still ≥150 mm Hg, hypotensive treatment under careful monitoring should be administered; (f) the Glasgow Coma Scale (GCS) was ≥8 points; and (g) in cases of hemorrhage of the brain stem, the amount of bleeding was ≤3 mL.

Exclusion criteria: (a) hospitalization within >5 hours of ICH onset; (b) possibility of death in 24 hours; (c) surgical treatment; (d) contraindications of intensive antihypertensive therapy, such as significant decrease in BP, severe arterial stenosis, high stenosis of valvular heart disease, in addition to others; (e) GCS < 8, sequelae of stroke, or dementia; (f) ICH caused by tumor, arteriovenous malformation, aneurysm, trauma, blood disease, cerebral venous thrombosis, anticoagulant, or thrombolytic therapy; (g) acute hydrocephalus caused by ICH or solitary ventricle hemorrhage; (h) supratentorial hemorrhage of cerebral lobes accompanied by a serious occupying effect, and ICH secondary from cerebral infarction; (i) ischemic stroke within 2 weeks, major surgery within 6 weeks, or other hemorrhagic strokes or intracranial hemorrhage; (j) the patients are not able to tolerate or are allergic to urapidil, are pregnant, or have heart, liver or renal dysfunction or convulsions.

2.2 | Treatment methods

The groups were treated with routine supportive treatment; different doses of dehydrating agents were initially given to reduce brain edema and reduce intracranial pressure according to the amount of hemorrhage. Patients were given inhaled oxygen and were lying in bed with the position of head lifted moderately. The setting was quiet, and the respiratory tract was unobstructed; patients were monitored for vital signs, consciousness, pupil condition, nutritional support, prevention and treatment of stress ulceration, and other symptomatic treatment. In the IG, when SBP was ≥150 mm Hg within 6 hours, 25 mg of urapidil (Guangdong DaRi Biochemical Pharmaceutical Co., Ltd. Chinese medicine quasi-word: 20010806, 25 mg/5 mL) was slowly intravenously injected. Next, 100 mg (20 mL) of urapidil and 30 mL of 0.9% sodium chloride injection were slowly administered via micropump (2-7 mL/h). When SBP reached the target value of 135-140 mm Hg within 1 hour,[8,9] this SBP was maintained for 72 hours. Next, 10 or 20 mg extended-release nifedipine tablets were administered orally for SBP that remained was ≥140 mm Hg, once every 12 hours. The same protocol was performed in the CG when SBP was ≥180 mm Hg, and the target SBP was <140 mm Hg within 1 hour[8] and maintained for 72 hours.

2.3 | Observation index and evaluation

(a) The main observation index: the hematoma volume after 24 hours of onset (Tada formula: length × width × piles × 0.5, unit: mm^3, the one layer is 10 mm, each layer of CT scan is 5 mm), indicating whether there is rebleeding or not. The volume of edema around the hematoma after 24 hours of onset (CT showed low density around the hematoma length × width × piles × 0.5, unit: mm^3, one layer is 10 mm, and layer of CT scan is 5 mm). Computed tomography was reexamined at 24 hours, 72 hours, day 7, and day 14 after ICH onset in both groups to assess for rebleeding (changes in hematoma volume) and changes in PE, and then was compared. Computed tomography scans, which were taken at baseline and 24 hours, 72 hours, day 7, and day 14, were transmitted to the core image analysis center. The reader did not know the patient's grouping, condition, treatment, and time point of treatment; the reader only determined the site of bleeding, the presence or absence of blood in the ventricle, parenchymal hematoma volume, and volume of PE. (b) Secondary observation: neurological deficit, quality of life, and mortality measured on day 30 and day 90.

TABLE 1 Comparison of two groups of general data

	IG	CG		
Cases	62	59		
Age (y)	61.8 ± 10.1	61.7 ± 10.3	$t = 0.005$	$P > .05$
Sex				
Male	35	31	$\chi^2 = .186$	$P > .05$
Female	27	28		
Medical history				
Hypertension	55	50	$\chi^2 = .203$	$P > .05$
Diabetes	12	8		
Coronary heart disease	7	6		
Cerebral infarction	4	5		
SBP (mm Hg)	182.15 ± 16.31	180.83 ± 17.26	$t = 0.433$	$P > .05$
The onset time (h)	3.71 ± 1.29	3.58 ± 1.42	$t = 0.529$	$P > .05$
Hematoma volume on CT (mm^3)	25.41 ± 10.52	25.36 ± 10.41	$t = 0.026$	$P > .05$
Hemorrhagic site				
Basal ganglia	52	50	$\chi^2 = .135$	$P > .05$
Cerebral lobe	5	5		
Cerebellum	4	3		
Brainstem	1	1		
Blend sign on CT	12	10	$\chi^2 = .117$	$P > .05$
GCS	10.34 ± 2.27	10.39 ± 2.16	$t = 0.124$	$P > .05$
NIHSS (score)	8.74 ± 2.32	8.69 ± 2.36	$t = 0.118$	$P > .05$
BI (score)	58.72 ± 12.32	58.61 ± 12.01	$t = 0.375$	$P > .05$

Abbreviations: BI: Barthel Index; CG, control group; GCS: Glasgow Coma Scale; IG: early intensive antihypertensive treatment group; NIHSS: National Institutes of Health Stroke Scale.

NIHSS scores were compared at 24 hours, 72 hours, day 7, day 14, day 30, and day 90, and the Barthel Index (BI) was compared at 72 hours, day 7, day 14, day 30, and day 90.

2.4 | Statistical methods

SPSS 13.0 statistical software was used for data processing. The measurement data were represented by the mean ± standard deviation. The ANOVA of repeated measurement design data was used for multiple follow-up indexes at different time points, and t test was used for comparison between the groups. The count data were tested by chi-square test. The difference was statistically significant for $P < .05$.

3 | RESULTS

3.1 | Grouping and baseline data comparison

The patients were randomly divided into an early intensive antihypertensive treatment group (IG) (n = 62) and control group (CG) (n = 59). There were no significant differences in age, sex, medical history, bleeding site, bleeding volume, GCS, NIHSS score, BI, average SBP level, and the time and routine treatment between the groups, $P > .05$ (Table 1).

3.2 | Comparison of hematoma volume (rebleeding) between the two groups

The average volume of hematomas in the CG was larger than that in the IG at 24 hours, and the average volume of hematomas was gradually reduced after 72 hours for both groups. Furthermore, the average volume of hematomas in the IG was decreased more than that in CG ($P < .05$) (Table 2).

3.3 | Comparison of the volume of PE (brain edema) between the two groups

The volume of PE in the CG was larger than that in the IG at 24 hours, but the difference was not statistically significant ($P > .05$). The volume of the PE in the CG increased significantly compared with that in the IG ($P < .05$) at 72 hours and day 7. The volume of PE in the two groups on day 14 was smaller than that on day 7, and the volume of PE in the IG was decreased compared with that in the CG ($P < .05$) (Table 3).

3.4 | Comparison of the NIHSS score in two groups

The NIHSS scores gradually decreased in the IG after 72 hours; the NIHSS scores increased in the CG at 72 hours, day 7, and gradually decreased after day 14. The average NIHSS score in the IG was

TABLE 2 Comparison of the volume of hematoma between the two groups (mm^3)

	n	Before treatment	24 h after onset	72 h	7th day	14th day
IG	62	25.41 ± 10.52	25.46 ± 9.51	25.17 ± 8.62	20.32 ± 7.19	13.41 ± 5.47
CG	59	25.36 ± 10.41	27.98 ± 9.37	27.51 ± 8.17	24.05 ± 7.04	16.53 ± 6.15
Between the two groups	$F = 4.125$			$P < .05$		
Between different time points	$F = 9.203$			$P < .01$		
Between the two groups • different time	$F = 6.824$			$P < .01$		

Abbreviations: CG, control group; IG: early intensive antihypertensive treatment group.

TABLE 3 Comparison of the volume of the PE between the two groups (mm^3)

	n	24 h after onset	72 h	7th day	14th day
IG	62	5.28 ± 1.25*	8.05 ± 2.65	10.82 ± 2.51	7.14 ± 1.36
CG	59	5.49 ± 1.53*	9.28 ± 2.49	12.73 ± 2.68	9.27 ± 1.56
Between the two groups	$F = 3.986$		$P < .05$		
Between different time points	$F = 8.437$		$P < .01$		
Between the two groups • different time	$F = 5.012$		$P < .05$		

Abbreviations: CG, control group; IG: early intensive antihypertensive treatment group.
*$P > 0.05$.

significantly lower than that in the CG, and the difference between the groups was statistically significant ($P < .05$) (Table 4).

3.5 | Comparison of the BI score in two groups

The BI scores increased after 72 hours in the IG; the BI scores decreased slightly in the CG at 72 hours, and gradually increased after 7 days. The average BI score in the IG was significantly higher than that of the CG, and the difference between the groups was statistically significant ($P < .05$, Table 5).

3.6 | SBP values within 1 hour

Patients in the IG group achieved the target SBP value of 135-140 mm Hg (137.21 ± 1.95 mm Hg) within 1 hour, and SBP value within 1 hour in the CG group was 130-140 mm Hg (134.86 ± 3.57 mm Hg), and there was statistically significant difference between the two groups ($t = 8.700$, $P < .01$).

3.7 | Safety analysis

Two patients died in the IG, and four patients died in the CG. Abnormal liver function was reported in three patients in the IG and two patients in the CG. The difference in abnormal liver, renal function and mortality between groups was not statistically significant ($P > .05$) (Table 6).

4 | DISCUSSION

Intracerebral hemorrhage refers to primary cerebral parenchymal hemorrhage, one of the most serious manifestations of stroke; ICH

TABLE 4 Comparison of the NIHSS between the two groups

	n	Before treatment	72 h	7th day	14th day	30th day	90th day
IG	62	8.74 ± 2.32	8.51 ± 2.29	8.02 ± 2.31	7.03 ± 2.25	4.87 ± 2.17	3.25 ± 1.22
CG	59	8.69 ± 2.36	9.16 ± 2.30	9.39 ± 2.26	8.47 ± 2.32	6.15 ± 2.24	4.19 ± 1.28
Between the two groups	$F = 4.083$			$P < .05$			
Between different time points	$F = 8.507$			$P < .01$			
Between the two groups • different time	$F = 5.106$			$P < .05$			

Abbreviations: CG, control group; IG: early intensive antihypertensive treatment group.

TABLE 5 Comparison of the BI between the two groups

	n	Before treatment	72 h	7th day	14th day	30th day	90th day
IG	62	58.72 ± 12.32	59.85 ± 12.19	65.12 ± 13.22	75.03 ± 12.45	80.87 ± 11.17	85.25 ± 10.24
CG	59	58.61 ± 12.01	57.11 ± 12.13	60.31 ± 12.96	68.47 ± 13.02	76.01 ± 11.28	81.19 ± 10.65
Between the two groups	$F = 5.836$			$P < .05$			
Between different time points	$F = 11.162$			$P < .01$			
Between the two groups • different time	$F = 8.294$			$P < .05$			

Abbreviations: CG, control group; IG: early intensive antihypertensive treatment group.

TABLE 6 Comparison of the abnormal liver function and death between the two groups

	n	Normal	Abnormal liver function	χ^2	*P*	Improve	Death	χ^2	*P*
IG	62	59	3	.185	>.05	60	2	.810	>.05
CG	59	57	2			55	4		

Abbreviations: CG, control group; IG: early intensive antihypertensive treatment group.

accounts for 10%-30% of strokes, and its mortality is high. Most survivors experience different degrees of disability afterward. An increasing SBP after ICH is common, but an increase in SBP after ICH is an important risk factor for poor outcome. An increasing SBP after ICH not only promotes hematoma enlargement, but also aggravates brain edema. Previous studies[3,5] found that the rate of neurological deterioration and hematoma enlargement when BP < 160/90 mm Hg in 6 hours and 6-24 hours was lower than that of the CG, and the patients were treated with antihypertensive medication within 6 hours were more likely to recover their neurological function at 1 month. The INTERACT-2 test[10] subgroup found that the clinical outcome was poor when SBP dropped to 130 mm Hg or lower within 24 hours of ICH onset. The ATACH-2 trial[11] showed that if average SBP dropped to 120-130 mm Hg within 24 hours of ICH onset, there was no benefit. Previous studies[12-14] showed that the antihypertensive therapy administered during a hypertensive emergency should follow the principles of achieving a stable, controlled hypotensive state rapidly. It is recommended that the average arterial BP drop rapidly not more than 25% within 1-2 hours, and the greater the range of fluctuation of BP, the greater the variability of BP, and the higher the risk of death or serious disability in 90 days. Therefore, the SBP goal in our study was determined to 135-140 mm Hg within 6 hours of the onset of ICH in the IG and maintained for 72 hours after reaching the target value in both groups.

One study[9] found that enlargement of the hematoma and brain edema in the early stage (within 72 hours) of ICH are the important causes of aggravation of the disease and poor prognosis. Rincon's study[15] showed that there was PE within 2 hours after the onset of ICH, and brain edema reached its peak between day 2 and day 7. Anderson's study[5] showed that early intensive antihypertensive treatment within 72 hours after the onset of ICH could prevent hematoma enlargement, but had no obvious effect on PE. After the onset of ICH, there was a variety of pathophysiological changes: (a) BP increased notably; (b) the hematoma volume continued to increase, and the condition worsened; (c) the hematoma oppressed the brain tissue surrounding it and caused nerve dysfunction; (d) thrombin activation, hemoglobin, erythrocyte decomposition products in the hematoma, inflammatory reaction, complement, and other factors all made the brain edema more serious, aggravating the condition. Other researchers[5,16] found that the occurrence of cerebral edema after ICH is independently associated with increasing BP within 24 hours after the ICH onset. The risk of hematoma enlargement in patients with SBP ≥ 160 mm Hg is significantly higher than that in those with SBP ≤ 150 mm Hg. It is believed that hematoma enlargement could be reduced by lowering the increased BP after the onset of ICH, reducing edema around hematoma, and ultimately decreasing outcomes of mortality and poor quality of life.

In the current study, we found that early intensive antihypertensive treatment significantly decreased the average hematoma volume at 24 hours, day 7, and day 14 after ICH onset, indicating that rebleeding in the IG was significantly lower than that in the CG. Many studies[17-19] have found that brain edema after ICH is a major hinderance of neurological recovery and aggravates the condition of the disease. Therefore, it is particularly important to reduce brain edema. Our results showed that the volume of PE in the IG decreased significantly compared with that in the CG, especially at 72 hours and day 7, indicating that the degree of brain edema in the IG was less than that in the CG. These data suggest that early intensive hypotension can prevent hematoma enlargement and reduce brain edema, consistent with previous studies.[2,4,5,16]

The pathophysiology leading to hematoma expansion progression remains poorly understood. In spontaneous ICH, rebleeding

from a single site of arterial rupture may be the primary force of hematoma expansion. In 1971, Fisher[20] have proposed an "avalanche" model for hematoma expansion. This model describes the process of hematoma growth as secondary mechanical shearing of periphery vessels caused by expansion of initial bleeding. So, hematoma expansion is a key factor affecting key ICH outcome, and prevention of hematoma expansion is a major therapeutic target. The mechanisms for the beneficial effect of early intensive antihypertensive treatment may be that early intensive antihypertensive treatment prevents enlargement of the hematoma, reducing oppression of the brain tissue surrounding the hematoma and slightly reducing blood flow in the brain tissue around the hematoma.[5-7,16]

In the current study, we found that the NIHSS scores were significantly lower, and the average BI score was significantly higher in the IG group than those in the CG at 72 hours, day 7, day 14, day 30, and day 90; the results indicated that the degree of neural function defects in the IG was lower than that in the CG; the self-care ability of patients in the IG was higher than those in the CG; and this result is consistent with previous studies.[2,4,5,16] However, this result was inconsistent with finding from previous studies [3,6,7,10,11,21] which did not find the benefit effect of early intensive antihypertensive treatment on 3-month clinical outcome. This may be due to the complex relationship between BP target and outcome, and a SBP target of less than 130 mm Hg may lead to poor outcome of ICH.[10] Furthermore, BP variability also exerts an influence on clinical outcome,[22,10] but in the present study, we did not calculate the BP variability, and the beneficial effect of early intensive antihypertensive treatment for clinical outcome needs further elucidation.

From a molecular perspective, inflammation and excitotoxicity could play a role in the pathophysiology of ICH, which are associated with poor outcomes of ICH.[23] Previous studies [24,25] have confirmed that antihypertensive medications, such as imidazoline receptor (IR) agonists and angiotensin receptor blockers (ARBs), exert neuroprotective effects on ICH through inhibiting inflammatory, reducing cell apoptosis, excitotoxicity, and brain edema. Early intensive antihypertensive treatment using antihypertensive agents that have the above-mentioned additional effects beyond BP lowering may provide neuroprotective and anti-inflammatory effects, and improve clinical outcomes, which deserve further study.

5 | LIMITATIONS

There are some limitations in the current study. (a) The number of patients in this study is small, and the follow-up period is short. The time of antihypertensive treatment, antihypertensive drug, and dose, lowered SBP goals for the patients with ICH, duration of treatment, and ischemic lesions developed during the follow-up period should be studied further. (b) Blood pressure variability is associated with clinical outcomes in patients with ICH.[23,24] However, we did not calculate the BP variability in the current study, and further studies are needed to assess associations between early BP variability and clinical outcomes in ICH patients after antihypertensive therapy and confirm our results. (c) Factors affecting clinical outcomes in patients with ICH are complex. Many variables, such as electrolyte imbalance, inflammatory markers, and metabolic factors, may adversely affect the clinical outcomes of ICH,[26-29] and future work needs to be done to control the confounding effects of factors using multivariate analysis.

6 | CONCLUSION

Our study shows that early intensive antihypertensive treatment of ICH can prevent rebleeding, prevent hematoma enlargement, reduce brain edema, reduce disability, and improve the quality of life of ICH patients.

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CONFLICT OF INTEREST

The authors have no funding and conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

FG designed the experiments. FG, YZ, and CZ conducted the experiments. YZ, QS, and JZ analyzed the data. HL, CZ, and SF interpreted the results, YZ wrote the manuscript. All authors reviewed and approved the manuscript.

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