Effects of Different Early Blood Pressure Control Targets on Hematoma Expansion and Prognosis in Patients with Hypertensive Intracerebral Hemorrhage: Postprint

Authors: Zhang Hongtao, Yu Meng, Ren Yafang, Zhang Bin, Zhang Shuling, Fu Shengqi, Zhang Daopei

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Abstract

Objective: To investigate the effects of different early blood pressure control targets on hematoma expansion and prognosis in patients with hypertensive cerebral hemorrhage (HCH).

Methods: From January 2013 to July 2016, 102 HCH patients admitted to the Department of Neurology at Zhengzhou People' s Hospital were randomly assigned to group A (n=51) and group B (n=51). Within 48 hours of admission, the two groups received different systolic blood pressure (SBP) control targets: group A underwent early intensive antihypertensive therapy with an SBP target of (130-140) mmHg; group B underwent standard antihypertensive therapy with an SBP target of (170-180) mmHg. Hematoma changes and prognosis were observed in both groups.

Results: After 48 hours of treatment, SBP, hematoma volume, and National Institutes of Health Stroke Scale (NIHSS) scores in group A were significantly lower than those in group B, while the Glasgow Coma Scale (GCS) score was significantly higher than that in group B ($P<0.01$ or $P<0.05$). After 30 days of treatment, the efficacy grade index in group A was superior to that in group B ($Z=2.331$, $P=0.020$), with a statistically significant difference; the mortality rate in group A was lower than that in group B ($^{2}=2.772$, $P=0.096$), but the difference was not statistically significant.

Conclusion: Early intensive antihypertensive therapy for patients with hypertensive cerebral hemorrhage is safe and feasible, can reduce hematoma expansion, alleviate neurological deterioration, and improve prognosis.

Full Text

Preamble

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Authors: Zhang Hongtao, Yu Meng, Ren Yafang, Zhang Bin, Zhang Shuling, Fu Shengqi, Zhang Daopei
Affiliation: First Division, Department of Neurology, Zhengzhou People' s Hospital, Zhengzhou, Henan 450000, China

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Objective: To investigate the effects of different early blood pressure control targets on hematoma expansion and prognosis in patients with hypertensive cerebral hemorrhage (HCH).

Methods: A total of 102 HCH patients admitted to the Department of Neurology at Zhengzhou People' s Hospital between January 2013 and July 2016 were randomly divided into Group A (n=51) and Group B (n=51). Within 48 hours of admission, the two groups received different systolic blood pressure (SBP) control targets: Group A received early intensive antihypertensive therapy with an SBP target of 130-140 mmHg, while Group B received standard antihypertensive therapy with an SBP target of 170-180 mmHg. Hematoma changes and patient prognosis were observed in both groups.

Results: After 48 hours of treatment, Group A showed significantly lower SBP, hematoma volume, and National Institutes of Health Stroke Scale (NIHSS) scores, and significantly higher Glasgow Coma Scale (GCS) scores compared with Group B ($P<0.01$ or $P<0.05$). After 30 days of treatment, Group A demonstrated superior efficacy grades compared with Group B ($Z=2.331$, $P=0.020$), a difference that was statistically significant. The mortality rate in Group A was lower than in Group B (2=2.772, P=0.096), though this difference was not statistically significant.

Conclusion: Early intensive antihypertensive treatment is safe and feasible for patients with HCH, and can reduce hematoma expansion, alleviate neurological deterioration, and improve prognosis.

Keywords: blood pressure, control target, hypertensive cerebral hemorrhage, hematoma enlargement, prognosis

Introduction

Hypertensive cerebral hemorrhage (HCH) patients often experience further elevation of blood pressure levels in the early stage. However, recommendations

for managing hypertension in the acute phase vary considerably across guidelines, and no consensus has been fully reached. The 2006 *Chinese Guidelines for the Prevention and Treatment of Cerebrovascular Diseases* [1] advised against urgent blood pressure reduction, recommending maintenance at slightly above pre-illness levels or around 180/105 mmHg, arguing that elevated blood pressure in the acute phase of HCH represents a protective physiological response that ensures adequate blood supply to perihematomal brain tissue in the early hemorrhage period. In contrast, the 2010 *AHA/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage* [2] recommended controlling blood pressure below 140/90 mmHg, positing that excessive blood pressure in the acute phase of HCH promotes plasma extravasation into brain tissue and facilitates hematoma expansion. Clinical practice has revealed that maintaining a hypertensive state can lead to continuous hematoma enlargement in one-third of HCH patients during the early stage [3-4]. Whether intensive antihypertensive therapy is suitable for the acute phase of HCH in Chinese populations remains controversial. Therefore, our hospital conducted a randomized group study on HCH patients with different early blood pressure control targets to compare their effects on hematoma expansion and prognosis.

1. Materials and Methods

1.1 Study Subjects

Inclusion criteria: (1) Age 18–80 years; (2) Documented history of hypertension with at least two measurements of systolic blood pressure (SBP) 180 mmHg using a mercury sphygmomanometer at admission (1 mmHg=0.133 kPa), with measurements taken 2 minutes apart; (3) First acute onset with time from onset to CT examination <6 hours; (4) Diagnosis consistent with the *Diagnostic Criteria for Various Cerebrovascular Diseases* revised at the 4th National Cerebrovascular Disease Academic Conference in 1995 [5], confirmed by cranial CT or MRI; (5) Patients and family members provided informed consent.

Exclusion criteria: (1) Non-hypertensive cerebral hemorrhage or hemorrhage secondary to structural brain abnormalities: traumatic cerebral hemorrhage, subarachnoid hemorrhage, post-thrombolysis hemorrhage, hemorrhagic cerebral infarction, intracranial tumors, intracranial aneurysms, cerebral arteriovenous malformations, Moyamoya disease, coagulation dysfunction, long-term anticoagulation, and other secondary cerebral hemorrhages; (2) Primary intraventricular hemorrhage with critical condition, cerebral hemorrhage breaking into cerebrospinal fluid circulation, brainstem hemorrhage, large hemorrhage volume or secondary brain herniation, deep coma at presentation with GCS score of 3–5; (3) Hemorrhage location and volume suitable for or requiring surgery with family consent, already scheduled for surgical hematoma evacuation; (4) Contraindications to intensive antihypertensive therapy: severe stenotic valvular heart disease, severe carotid, vertebral, or cerebral artery stenosis, Takayasu arteritis; (5) Coexisting conditions that may interfere with efficacy evaluation: severe cardiac, pulmonary, hepatic, or renal insufficiency, advanced malignancy, history

of cerebral infarction or previous brain surgery; (6) Indications for emergency blood pressure reduction: such as aortic dissection, hypertensive encephalopathy; (7) Known severe dementia or severe disability prior to this stroke; (8) Non-compliance with treatment, examination, and follow-up, or self-administration of non-study medications.

Between January 2013 and July 2016, 102 HCH patients admitted to the Department of Neurology at Zhengzhou People' s Hospital were selected and randomly divided into Group A and Group B, each with 51 cases, using a numerical table method. This study was approved by the Medical Ethics Committee of Zhengzhou People' s Hospital.

1.2 Treatment Methods

All patients received identical conventional treatment, including bed rest, vital signs monitoring, oxygen administration, mannitol for intracranial pressure reduction, and maintenance of water-electrolyte balance. Within 24 hours of admission, all patients received continuous intravenous infusion of urapidil injection (Heilongjiang Fuhua Huaxing Pharmaceutical Group Co., Ltd., H20040501) via micropump for blood pressure control. The infusion rate was adjusted according to the patient' s blood pressure, with an initial rate of 1–2 mg/min and a maintenance rate of 5–9 mg/h. Intravenous furosemide was administered when necessary. The two groups had different blood pressure control targets within 48 hours: Group A target SBP 130–140 mmHg; Group B target SBP 170–180 mmHg. All patients in both groups achieved target SBP within 1 hour of admission and maintained it within the target range for the subsequent 48 hours. After 48 hours, the target SBP for both groups was <140 mmHg. Patients with controlled blood pressure and clear consciousness after 48 hours were switched to oral (or nasogastric) angiotensin-converting enzyme inhibitors (ACEI), calcium channel blockers, and diuretics, while those with consciousness disturbances continued micropump infusion of urapidil. Subsequent maintenance therapy was continued for 30 days, with surgical treatment administered when necessary according to disease progression.

1.3 Outcome Measures

1.3.1 Blood Pressure Monitoring Both groups underwent vital signs monitoring using the German Eagle 4000 electrocardiogram monitor, with continuous blood pressure monitoring within 48 hours of admission. When blood pressure fluctuated, the healthy side brachial artery blood pressure was measured using a mercury sphygmomanometer for comparison. Blood pressure was measured every 5 minutes from the start of urapidil infusion until target blood pressure was achieved, after which measurements were taken every 30 minutes while maintaining the target blood pressure.

1.3.2 Hematoma Volume Patients underwent cranial CT scans at admission and 48 hours after treatment, with immediate CT re-examination if their con-

dition changed. Hematoma volume was calculated using the Tada formula [6]: Hematoma volume = maximum length (cm) × maximum width (cm) × number of slices × /6. Early hematoma expansion was defined as: for hematomas with initial volume <20 mL, an increase >33% in hematoma volume; for hematomas with initial volume >20 mL, an increase >10% in hematoma volume, when comparing CT at 48 hours with initial CT.

1.3.3 Clinical Prognosis Assessment At admission and 30 days after treatment, assessments were performed by a physician who was blinded to randomization and not involved in patient clinical management: Glasgow Coma Scale (GCS) score [7]; National Institutes of Health Stroke Scale (NIHSS) score [7]; and modified Rankin Scale (mRS) score [7].

1.4 Efficacy Determination

Efficacy was evaluated using the following formula [8]: (Pre-treatment score - Post-treatment score) / Pre-treatment score × 100%. (1) Cure: Symptoms and signs reduced by >81% after treatment; (2) Markedly effective: Symptoms and signs reduced by 56-80%; (3) Effective: Symptoms and signs reduced by 11-55%; (4) Ineffective: Symptoms and signs reduced by <11% or worsened.

1.5 Statistical Analysis

Data were analyzed using SPSS 22.0 statistical software. Count data were expressed as rates and analyzed using the 2 test. Efficacy grade data were analyzed using the rank-sum test. Measurement data were expressed as mean ± standard deviation and compared between groups using independent samples t-test. P<0.05 was considered statistically significant.

2. Results

2.1 Baseline Data

Comparisons of baseline characteristics including sex, age, body mass index, hypertension duration, long-term alcohol consumption, diabetes history, onset time, fibrinogen, prothrombin time, platelet count, hemorrhage site, and complications within 24 hours showed no statistically significant differences between the two groups (P>0.05,), indicating comparability.

2.2 Clinical Efficacy

Before treatment, no statistically significant differences were observed between the two groups in SBP, hematoma volume, GCS, NIHSS, or mRS scores (P>0.05), confirming comparability. After 48 hours of treatment, Group A showed significantly lower SBP, hematoma volume, NIHSS, and mRS scores, and significantly higher GCS scores compared with Group B (P<0.01 or P<0.05,).

2.3 Clinical Prognosis

Clinical efficacy was evaluated 30 days after treatment. (1) In Group A (51 patients), 22 were cured, 18 showed marked improvement, 9 showed improvement, and 2 were ineffective. In Group B (51 patients), 15 were cured, 14 showed marked improvement, 12 showed improvement, and 10 were ineffective. The difference was statistically significant according to rank-sum test for grade data (Z=2.331, P=0.020). (2) Group A had 23 disabled cases with a disability rate of 45.10%, while Group B had 35 disabled cases with a disability rate of 68.63%. The disability rate in Group A was significantly lower than in Group B (2=4.620, P=0.032). (3) Group A had 2 deaths with a mortality rate of 3.92%, while Group B had 8 deaths with a mortality rate of 15.69%. The mortality rate in Group A was lower than in Group B, but this difference was not statistically significant (2=2.772, P=0.096).

3. Discussion

Previous misconceptions existed regarding cerebral hemorrhage. Misconception 1: It was believed that bleeding stops spontaneously within 30 minutes of cerebral hemorrhage onset. However, with continuous development of imaging technology, dynamic observation of cerebral hemorrhage using cranial CT in recent years has revealed that most cerebral hemorrhages represent active bleeding. The hematoma can continue to expand dynamically over time, either continuously or in stages, rather than occurring instantaneously and stopping spontaneously [9]. Twenty to forty percent of patients experience active bleeding within the first 24 hours after initial hemorrhage, particularly within 6 hours (approximately 83%), while the possibility of continued bleeding after 48 hours is minimal (approximately 17%) [10]. Active bleeding within the first 24 hours is the primary cause of clinical deterioration and death, and represents an important factor influencing the degree of disability in surviving patients. Therefore, this study selected a 48-hour observation period. Pathophysiologically, cerebral hemorrhage progresses through three stages: hematoma formation, hematoma expansion, and perihematomal edema. The driving force for hematoma expansion originates from hypertension; as long as blood pressure remains elevated, the early-formed hematoma cannot easily stabilize [11]. Whether the hematoma can be contained depends on whether biomechanical equilibrium can be achieved, which is determined by two biomechanical factors: the spontaneous hemostatic mechanism after vascular rupture, and the increased intracavitary pressure within the hematoma that reduces the pressure gradient across the ruptured vessel. After initial cerebral hemorrhage, if the coagulation force at the site of vascular rupture is weaker than the intracavitary pressure within the hematoma, slow leakage of blood becomes inevitable, representing the mechanism of early hematoma expansion after cerebral hemorrhage [12]. Of course, multiple factors contribute to early hematoma expansion after cerebral hemorrhage: hypertension, hemorrhage location, regularity of hematoma morphology, coagulation mechanism disorders, vascular injury, vascular structural lesions,

use of anticoagulant and dehydrating agents, cerebral amyloid angiopathy, etc. [13]. Among these, hypertension is the only factor independently associated with hematoma enlargement that we can intervene upon and control.

Misconception 2: It was believed that elevated blood pressure in the acute phase of cerebral hemorrhage might be a transient natural course, with blood pressure showing a spontaneous downward trend 3–7 days after onset, and two-thirds of patients could return to pre-illness levels within one week. This blood pressure elevation was considered a compensatory need to maintain cerebral perfusion pressure, as intracranial pressure rises reactively at this time. If peripheral blood pressure decreases significantly, cerebral perfusion pressure would decrease and cerebral blood flow would reduce, potentially aggravating ischemia in perihematomal tissue. Consequently, the 1999 American Heart Association (AHA) guidelines [14] recommended initiating treatment only when SBP >180 mmHg. However, recent clinical observations have found that although elevated blood pressure in the acute phase typically decreases automatically within several days after cerebral hemorrhage onset, a considerable proportion of patients maintain persistently elevated blood pressure, which precisely constitutes the driving force for hematoma expansion [15]. Furthermore, many studies have questioned the notion that reducing peripheral blood pressure to normal (140/90 mmHg) would aggravate ischemia in perihematomal tissue. Imaging monitoring (SPECT and PET techniques) in cerebral hemorrhage patients has not shown insufficient perfusion in perihematomal brain tissue when peripheral blood pressure is reduced. Animal experiments have demonstrated that although cerebral blood flow in perihematomal tissue decreases after cerebral hemorrhage in rats, it remains above the threshold for ischemic damage and recovers rapidly, insufficient to cause ischemic injury. The presence of hypoperfusion in the perihematomal region is more likely the result of mitochondrial dysfunction and reduced metabolic demand rather than the effect of blood pressure reduction [16].

Possible mechanisms of blood pressure elevation after cerebral hemorrhage include: (1) Toxic cytotoxic edema caused by cerebral hemorrhage leads to increased intracranial pressure and cerebral tissue hypoxia, which shifts the set point upward via the brainstem blood pressure regulation center [17]; (2) Ischemia in perihematomal tissue after cerebral hemorrhage causes the cerebral blood pressure regulation center to reflexively maintain continuous blood pressure elevation to sustain perfusion in the ischemic area [18]; (3) Patient pain, fear, restlessness, or involvement of the autonomic regulation center by cerebral hemorrhage causes autonomic nervous system dysfunction, leading to overactivation of the sympathetic nervous system, peripheral vasoconstriction, and reactive blood pressure elevation [19]. Indeed, elevated blood pressure maintains normal intracranial blood perfusion, but it also aggravates cerebral tissue edema and causes secondary brain injury. Within the first 24 hours after cerebral hemorrhage onset, elevated blood pressure after cerebral hemorrhage exacerbates the elevation of static pressure at the hemorrhage site, further leading to increased initial bleeding and early hematoma expansion, causing more severe cerebral edema [20]. Therefore, hematoma expansion is an independent

risk factor for delayed cerebral edema after cerebral hemorrhage [21] and represents the most important factor for neurological deterioration within 24 hours after cerebral hemorrhage and for predicting prognosis [22]. Hematoma expansion increases the probability of neurological deficit symptom deterioration by four times compared with non-expansion. Each 1 mL increase in hemorrhage volume increases mortality by 1%. SBP exceeding 140–150 mmHg within 12 hours after cerebral hemorrhage onset can double the subsequent risk of death or dependency [23].

Therefore, theoretical analysis suggests that early intensive antihypertensive treatment can prevent hematoma expansion, reduce cerebral edema, and protect neurological function. The results of this study demonstrate that after 48 hours of early intensive antihypertensive treatment in Group A, SBP, hematoma volume, and NIHSS scores were significantly lower than in Group B, while GCS scores were significantly higher. After 30 days of treatment, Group A showed superior efficacy grade indicators and lower mortality than Group B. These findings indicate that controlling blood pressure below 140/90 mmHg in the acute phase of HCH is safe and feasible, and that early intensive antihypertensive treatment can effectively reduce hematoma volume, decrease neuronal apoptosis, thereby reducing neurological function damage and effectively improving prognosis. These results are consistent with recent peer studies [24-26]. The ATACH (Antihypertensive Treatment in Acute Cerebral Hemorrhage) trial published in 2010 [27] also confirmed that early intensive antihypertensive treatment is safe and feasible, reducing rebleeding risk and in-hospital mortality. Thus, early intensive antihypertensive therapy holds promise as an intervention without major harm. Consequently, the *Chinese Guidelines for the Diagnosis and Treatment of Cerebral Hemorrhage (2014)* [28] proposed recommendations for blood pressure control in Chinese cerebral hemorrhage patients: rapidly reducing SBP from 150–200 mmHg to 140 mmHg in acute cerebral hemorrhage patients is likely safe (Class IIa recommendation, Level B evidence).

This study employed urapidil administration via micropump, which can smoothly and effectively control patients' blood pressure to target levels without increasing heart rate, causing first-dose reactions, or producing many adverse effects. Urapidil is a uracil derivative substituted with phenylpiperazine, possessing dual peripheral and central antihypertensive effects. Peripherally, it primarily blocks postsynaptic 1 receptors, significantly dilating vessels, and secondarily blocks presynaptic 2 receptors, blocking the vasoconstrictive effect of catecholamines. Centrally, it primarily activates 5-hydroxytryptamine-1A (5-HT1a) receptors, reducing sympathetic feedback regulation in the medullary cardiovascular center to lower blood pressure [29]. This drug has greater venodilatory than arteriodilatory effects, does not affect intracranial pressure when lowering blood pressure, does not cause reflex tachycardia, and has no hypotensive effect on normotensive individuals [30]. It simultaneously reduces pulmonary capillary wedge pressure, decreases myocardial oxygen consumption, increases cardiac output, reduces renal vascular resistance, and does not affect glucose or lipid metabolism or impair renal function [31]. Therefore, urapidil is

a relatively safe and effective antihypertensive agent for patients in the acute phase of cerebral hemorrhage.

This study has several design limitations and deficiencies, with insufficient depth and breadth. Cerebral perfusion pressure was not monitored, so the effects of intensive antihypertensive therapy on cerebral perfusion pressure and cerebral edema cannot be determined. Additionally, the sample size was small, the observation period was short, and many cases were excluded, which may affect statistical power. Future studies should expand the sample size, reduce excluded cases, increase monitoring of cerebral perfusion pressure, blood pressure control targets, and observation time points. If invasive blood pressure monitoring could be used to accurately track blood pressure fluctuations, it would provide more scientific evidence-based data for determining reasonable targets for blood pressure regulation in the acute phase of cerebral hemorrhage. In summary, controlling SBP below 140 mmHg in acute cerebral hemorrhage patients may be beneficial for prognosis, but evidence remains insufficient and awaits further large-scale multicenter studies to guide the establishment of more scientific and rational blood pressure control targets [32].

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Note: Figure translations are in progress. See original paper for figures.