



The association between blood pressure decreasing rates and survival time in patients with acute intracerebral hemorrhage

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ARTICLE INFO

Keywords:

Acute intracerebral hemorrhage
Blood pressure
Decreasing rate
Survival time
Systolic blood pressure
Diastolic blood pressure

ABSTRACT

Aims: There was no established consensus on the optimal blood pressure management protocol in patients with acute intracerebral hemorrhage (ICH). This study was to explore the association between blood pressure decreasing rates and survival time in patients with acute ICH.

Methods: 786 acute ICH patients were enrolled in the study and hospitalized from 2004 to 2006. K-means clustering was used to classify the subjects according to the decreasing rates of blood pressure within 14 days of acute ICH patients. Cox regression was used to screen the independent influencing factors of 14-day survival in the univariate analysis among acute ICH patients.

Results: There was significant difference in the decreasing rates of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in 1–2 d and 2–3 d after admission in patients with acute ICH ($P < .05$) between blood pressure decreasing stability and instability groups. The independent factors of 14-day survival in patients with acute ICH included: age, 24 h the National Institutes of Health Stroke Scale (NIHSS) score, bleeding volume, blood glucose, low density lipoprotein cholesterol, serum albumin, fasting, bleeding position and lowering rates of SBP ($P < .05$). And the risk of death within 14 days in the SBP decreasing instability group was 1.71 (1.02 to 2.86) times than those in stability group.

Conclusion: Compared with DBP decreasing rates, SBP decreasing rates had a greater impact on the survival time in patients with acute ICH. In addition, patients with instable SBP decreasing rates had inferior survival than those with stable SBP decreasing rates.

1. Introduction

Stroke was one of the leading causes of global death [1]. Intracerebral hemorrhage (ICH), as a form of destructive stroke, its incidence was high, especially among Asians, including Chinese [2]. By 2013, 27 of 33 provinces in China had stroke as the leading cause of death [3]. ICH usually had a poor prognosis and one-month mortality rate of ICH was about 40% [4], and the disability rate was 44.82% 3–6 months after the operation in around 2008 [5]. Extensive research has been done on the factors of ICH prognosis, including the bleeding volume and position, increasing heart rate, atrial fibrillation, ischemic heart disease and the hypertension [6–8].

Chronic hypertension was a major risk factor for ICH incidence and recurrence, and the acute ICH usually occurred during the hypertensive

crisis and short-term elevation of blood pressure [9]. Blood pressure was often raised to markedly elevated levels on hospital admission in acute ICH, with systolic blood pressure (SBP) > 160 mmHg and > 184 mmHg in 50% and 15% of patients, respectively [10,11]. However, there was a tendency for blood pressure to decline spontaneously within several days after acute ICH occurred, with the steepest decline in the first 24 h [10].

AHA guidelines (2015) recommend that for ICH patients presenting with SBP ranged from 150 to 220 mmHg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mmHg is safe (Class I; Level of Evidence A) and can be effective for improving functional outcome (Class II a; Level of Evidence B) [12]. Acute ICH anti-hypertension clinical trials suggested that the area of hematoma in the intensive antihypertensive therapy group showed a declining trend

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[13,14]. It was also indicated that antihypertensive treatment in the acute ICH was a potentially modifiable means of meliorating outcomes, and its underlying presumption was to limit early hemorrhage dilation [15]. However, excessively low levels of blood pressure may lead to insufficient perfusion of brain tissue, making brain tissue hypoxia more serious and aggravating cerebral edema, and this concerns limited active antihypertensive therapy in the acute phase of ICH [16].

There was no consensus on the relationship between blood pressure management and clinical outcomes in the acute phase of ICH, and no uniform standard for blood pressure management [17,18]. Few studies have focused on the effect of blood pressure decreasing rates on the survival time, and our study was to explore the association between blood pressure decreasing rates and survival time in patients with acute ICH, which might provide helpful suggestion on the clinicians' treatment decision for the patients with acute ICH.

2. Methods

2.1. Subjects

A total of 786 acute ICH patients (486 males, 300 females) were enrolled in the study and they were hospitalized in a clinical hospital from January 2004 to December 2006.

The mean age of the patients was 59 [51, 68] (means \pm standard deviations) years old. During the follow-up period, 30 subjects were lost and 70 died. The mean survival time was 13.13 (12.92–13.34) (means \pm standard deviations) days.

The subjects selected in this study strictly adhere to the following standards. Inclusion criteria: (a) Conformed the criteria of the Fourth National Conference on Cerebrovascular Disease in 1995 and confirmed by CT or MRI; (b) The first time for onset of ICH; (c) Visited to the hospital within 24 h after onset of ICH; (d) The bleeding volume ranged from 15 ml to 45 ml; (e) Given dehydration to reduce intracranial pressure, nutritional nerve treatment, and antihypertensive treatment if necessary. Exclusion criteria: (a) Tumor stroke; (b) Subarachnoid hemorrhage; (c) Traumatic brain hemorrhage; (d) Arteriovenous malformation and the hemorrhage caused by smoke disease; (e) Patients with minimally invasive treatment; (f) The heart, lung, liver, kidney and other important viscera serious injury; (g) The diagnosis was not clear, incomplete data.

2.2. Data information

This study was a retrospective cohort study. The clinical data of

patients with acute ICH who met the inclusion criteria were collected, including: (a) Basic patient information (age, sex, smoking, drinking history, etc.). The history of smoking was defined as a smoker who smoked more than one cigarette a day for more than one year. The history of drinking was defined as a drinker whose alcohol consumption were more than 50 g per day for more than one year. (b) Past history (hypertension, diabetes, kidney disease, cerebral infarction history, etc.); (c) 24 h the National Institutes of Health Stroke Scale (NIHSS) score, which is a 15-item impairment scale used to measure stroke severity and is recommended as a valid tool to assess stroke severity in emergency departments [19]; (d) ICH situation: bleeding position, the area of hematoma, bleeding volume, the blood pressure within 14 days of hospitalization, complications, and survival at 14 days after admission; (e) The laboratory examination at the time of admission: triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), blood glucose, blood urine nitrogen (BUN), creatinine (Cre), uric acid (UA), serum bilirubin, serum albumin, blood sodium, blood potassium content, etc.; (f) Treatment program (including the use of antihypertensive drugs, hypoglycemic agents, etc.).

Ethical approval: For this type of study formal consent is not required.

Informed consent: Informed consent was obtained from all individual participants included in the study.

2.3. Statistical analysis

Median and quartile were used to described the characteristics of the continuous variables and percentages of the categorical variables. The k-means clustering was used to classify the subjects according to the decreasing rates of SBP and DBP within 14 days of acute ICH patients [20]. Repeated measures one-way ANOVA test was used to investigate the blood pressure decreasing rates of the groups, and the differences between the groups were evaluated with post hoc multiple comparison analysis. Cox regression was used in the univariate analysis of the 14-day survival in acute ICH patients. Multivariate Cox regression was used to screen the independent influencing factors of 14-day survival among acute ICH patients. All statistical analyses were performed by R version 3.4.3, using the package "AMAP" [21] and "survival" [22]. Statistical significance was set at $P < .05$.

3. Results

Fig. 1 showed that, blood pressure decreased and the decreasing of

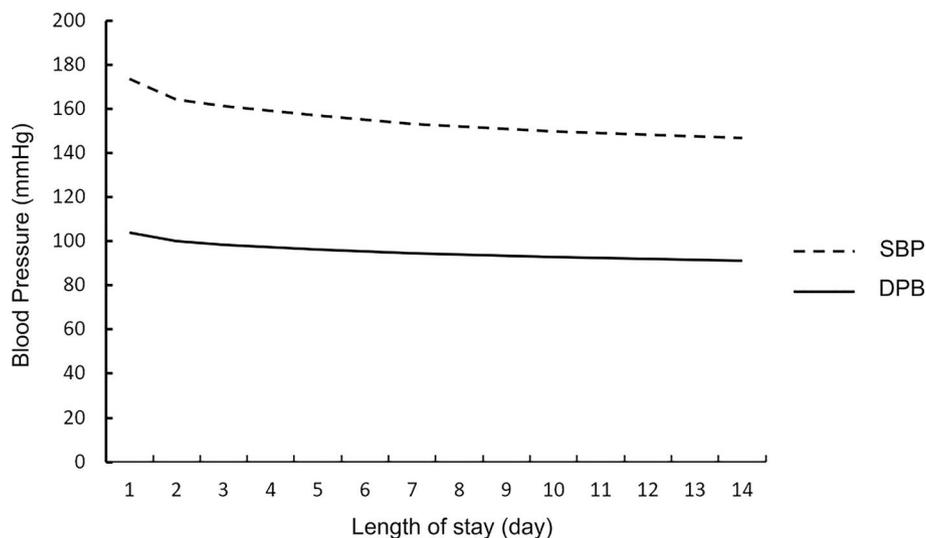


Fig. 1. Blood pressure levels of patients with acute ICH in 14 days after admission.

Table 1
Clustering analysis of the change rates of blood pressure between the time points of measurement in patients with acute ICH.

Measurement time points	SBP(mmHg/d)				DBP(mmHg/d)			
	I ^a (608n)	II ^b (178n)	F	P	I ^a (265n)	II ^b (521n)	F	P
1–2 d	1.11	–44.12	864.08	< 0.001	3.43	–19.11	675.93	< 0.001
2–3 d	–7.35	–14.81	214.75	< 0.001	–6.05	8.13	274.62	< 0.001
3–5 d	–1.68	–2.91	2.44	0.119	–0.75	–1.61	3.28	0.071
5–7 d	–2.12	–3.78	5.61	0.018	–1.02	–1.46	1.17	0.28
7–10 d	–1.47	–1.59	0.07	0.798	–0.93	–0.95	0.01	0.941
10–14 d	–0.44	–0.13	0.56	0.454	–0.16	–0.05	0.21	0.643

^a Blood pressure decreasing stability group.

^b Blood pressure decreasing instability group.

blood pressure tended to be steady as the number of days after admission. Compared with DBP, SBP decreased more marked. The patients were divided into two groups via k-means clustering based on the decreasing rates of SBP and DBP, respectively. There was significant difference between time points of measurement with same blood pressure group (SBP: $F = 276.437$, $P < .001$; DBP: $F = 106.242$, $P < .001$). Group I was the patients whose blood pressure decreased stably, whereas group II was the patients whose blood pressure decreased unstably (Table 1). In addition, it was significantly different in the decreasing rates of SBP and DBP in 1–2 d and 2–3 d after admission among patients with acute ICH between group I and group II, respectively.

Table 2 listed the factors that may have an impact on survival among patients with acute ICH for 14 days. It was showed that there were statistically significant difference between the two groups in age, residence, 24 h NIHSS score, time of onset to admission, bleeding volume, hematoma area, blood glucose, TG, LDL-c, serum albumin, serum potassium, hematoma appearance, dehydration diuretics, anti-hypertensive drugs, complications, bleeding position, fasting, SBP decreasing rates and DBP decreasing rates ($p < .05$) via univariate analysis (70 patients of death group and 716 patients of censored group).

And finally, Table 3 showed that age, 24 h NIHSS score, bleeding volume, blood glucose, LDL, serum albumin, fasting, bleeding position and decreasing rates of SBP are associated with the survival time via multivariate analysis. Noteworthy, the risk of death within 14 days of the group with unstable SBP decreasing rates was 1.71 (1.02 to 2.86) times of those with stable SBP decreasing rates instability among the acute ICH patients.

4. Discussion

This study aimed to investigate the association between blood pressure decreasing rates and survival time among patients with acute ICH. The main findings of this study included the following points. Firstly, the decrease of SBP and DBP in 1–2 d and 2–3 d after admission among patients with acute ICH were significant between the group with stable blood pressure decreasing rates and the one with unstable blood pressure decreasing rates. Secondly, SBP decreasing rates had a greater impact on the survival time among patients with acute ICH than DBP decreasing rates. Thirdly, patients with instable SBP decreasing rates had inferior survival than those with stable SBP decreasing rates.

Previous studies have shown that blood pressure had a spontaneous reduction tendency after admission to hospital in patients with acute ICH [23], which was consistent with our study. But the spontaneous reduction of blood pressure over the next few days was inconsistent with the performance of chronic hypertension in most patients [24,25]. In addition, blood pressure lowering treatment was proven to be an intervention which could reduce the risk of ICH recurrence [26]. It was suggested that increased blood pressure may lead to persistent bleeding and hematoma enlargement, and hematoma enlargement was a strong predictor of poor prognosis [27–29]. Furthermore, the main hypothesis

for the decreasing blood pressure at the acute phase of ICH to improve the prognosis may be that its reduction in hydrostatic pressure at the site of the hemorrhage subsequent attenuation of early hematoma expansion [15,30,31].

In our study, the decreasing of SBP rather than DBP had impact on the survival time among patients with acute ICH. Some studies have shown an association between high SBP and prognosis of ICH patients [27,32], which was consistent with our study. However, some studies have shown no correlation between the two [16,33], which might be indicated that the beneficial effect of early lowering of blood pressure may take some time to manifest [34]. It was pointed out that the greater the variation of SBP, the stronger the association with a poor prognosis (death or major disability at 90 days) [31,35], which was generally consistent with our results. An observational study has found out that unsteady blood pressure (and baroreceptor sensitivity) was associated with cerebral edema in patients with ICH [36], which might lead to subsequent worse outcomes. However, the exact mechanism of the SBP instability lowering influencing the outcome of acute ICH was unclear. A possible hypothesis was that large fluctuations in SBP may contribute to the formation of brain edema due to impaired brain autoregulation in the microvascular channel that may promote hematoma expansion and osmotic pressure or hydrostatic pressure gradients in the surrounding area [37]. Although there was no established consensus on the optimal blood pressure management protocol [38], it was suggested that early blood pressure lowering management after ICH diagnosis was the key factor of prognosis and it should be extended to the first week after ICH [39]. Therefore, based on the clinical importance of decreasing SBP soon after the onset of acute ICH, it is more meaningful to ensure the stability of SBP decreasing over the several days [31,34].

Some limitations should be noted in present study. Firstly, this was a retrospective study and participants were selected from a hospital in Jilin Province, hence, selection bias could exist and limit the results generalize to other populations. Secondly, in this study, patients were only divided into whether or not to use drugs, without subdividing the types of drugs used.

5. Conclusion

Compared with DBP decreasing rates, SBP decreasing rates had a greater impact on the survival time in patients with acute ICH. In addition, patients with instable SBP decreasing rates had inferior survival than those with stable SBP decreasing rates.

Statement of ethics

Subjects (or their parents or guardians) have signed their written informed consent and the study protocol has been approved by the research committee.

Table 2
Univariate analysis of survival in patients with acute ICH for 14 days (M [P₂₅, P₇₅]/n (%)).

Variables	Death (n=70)	Censored (n=716)	Wald χ^2	P
Age	63.50[53.00, 75.25]	58.00[51.00, 68.00]	12.26	< 0.001
Gender			0.70	0.404
Male	40(57.14)	446(62.29)		
Female	30(42.86)	270(37.31)		
Residence			6.72	0.01
Urban	60(85.71)	486(67.88)		
Rural	10(14.29)	230(32.12)		
NIHSS	13.33[11.00, 15.25]	8.00[4.00, 12.00]	96.19	< 0.001
Time of onset to admission (days)	2.00[2.00, 4.00]	3.00[2.00, 6.00]	7.68	0.006
Bleeding volume	28.75[13.97, 39.75]	8.75[4.88, 15.08]	139.60	< 0.001
Area of hematoma	8.06[4.73, 13.52]	6.68[3.92, 10.92]	10.36	0.001
BUN	5.64[4.53, 7.62]	4.60[3.70, 5.73]	2.32	0.128
Cre	86.78[64.11, 107.06]	77.10[64.00, 94.00]	1.47	0.226
UA	260.50[226.98, 311.00]	267.63[220.70, 320.40]	0.09	0.766
Blood glucose	8.28[7.18, 10.13]	6.50[5.56, 7.80]	50.46	< 0.001
TG	1.88[1.50, 2.26]	1.23[0.84, 1.72]	12.32	< 0.001
TC	5.29[4.71, 6.92]	4.77[4.21, 5.39]	1.16	0.282
LDL	3.00[2.64, 4.10]	2.92[2.40, 3.34]	18.32	< 0.001
HDL	1.45[0.95, 1.71]	1.31[1.07, 1.60]	0.04	0.843
TBil	20.04[20.04, 20.04]	20.04[19.70, 20.04]	0.01	0.929
Serum Albumin	42.26[39.17, 44.13]	39.00[36.35, 41.70]	4.84	0.028
Serum Sodium	136.24[132.38, 138.07]	138.50[135.18, 141.00]	0.67	0.413
Serum Potassium	3.51[3.12, 3.92]	3.69[3.43, 3.95]	9.93	0.002
Hematoma appearance			6.03	0.014
Regular	49(70.00)	585(81.70)		
Irregular	21(30.00)	131(18.30)		
Dehydration diuretics			11.55	0.001
Yes	67(95.71)	563(78.63)		
No	3(4.29)	153(21.37)		
Antihypertensive drugs			24.00	< 0.001
Yes	8(11.43)	280(39.11)		
No	62(88.57)	436(60.89)		
Hypoglycemic agents			0.81	0.37
Yes	23(32.86)	189(26.40)		
No	47(67.14)	527(73.60)		
Smoking history			3.48	0.062
No	69(98.57)	664(92.74)		
Yes	1(1.43)	52(7.26)		
Drinking history			2.90	0.089
No	68(97.14)	653(91.20)		
Yes	2(2.86)	63(8.80)		
Hypertension history			1.23	0.267
No	31(44.29)	275(38.41)		
Yes	39(55.71)	441(61.59)		
Diabetes history			3.76	0.053
No	62(88.57)	677(94.55)		
Yes	8(11.43)	39(5.45)		
Kidney history			1.37	0.243
No	68(97.14)	708(98.88)		
Yes	2(2.86)	8(1.12)		
CIS history			0.41	0.523
No	64(91.43)	640(89.39)		
Yes	6(8.57)	76(10.61)		
Complication			4.85	0.028
No	22(31.43)	341(47.63)		
Yes	48(68.57)	375(52.37)		
Bleeding position			118.00	< 0.001

Table 2 (continued)

Variables	Death (n=70)	Censored (n=716)	Wald χ^2	P
Basal ganglia	24(34.28)	496(69.27)		
Cerebellum	2(2.86)	13(1.82)		
Brain stem	9(12.86)	15(2.09)		
Gyrus	20(28.57)	155(21.65)		
Other	15(21.43)	37(5.17)		
Fasting			95.02	< 0.001
No	31(44.29)	615(85.89)		
Yes	39(55.71)	101(14.11)		
SBP lowering			27.94	< 0.001
Steady	38(54.29)	570(79.61)		
Unsteady	32(45.71)	146(20.39)		
DBP lowering			5.46	0.019
Steady	38(54.29)	483(67.46)		
Unsteady	32(45.71)	233(32.54)		

Table 3
Multivariate Cox regression of survival in patients with acute ICH for 14 days.

Variables	β	S.E.	Wald χ^2	HR(95%CI)	P
Age	0.05	0.01	18.87	1.05 (1.03–1.08)	< 0.001
NIHSS	0.12	0.02	29.87	1.13 (1.08–1.18)	< 0.001
Bleeding volume	0.06	0.01	50.19	1.06 (1.04–1.08)	< 0.001
Blood glucose	0.16	0.04	15.19	1.14 (1.05–1.24)	0.001
LDL	0.38	0.16	5.73	1.47 (1.07–2.01)	0.017
Serum Albumin	0.04	0.01	13.00	1.04 (1.02–1.06)	< 0.001
Fasting					
No	–	–	–	1.00	–
Yes	1.04	0.27	14.74	2.82 (1.66–4.79)	< 0.001
Bleeding position					
Basal ganglia	–	–	–	1.00	–
Cerebellum	1.89	0.77	6.01	6.62 (1.46–29.98)	0.014
Brain stem	2.54	0.43	34.46	12.71 (5.44–29.70)	< 0.001
Gyrus	0.95	0.32	8.83	2.58 (1.38–4.83)	0.003
Other	2.01	0.38	27.70	7.47 (3.53–15.78)	< 0.001
SBP lowering					
Steady	–	–	–	1.00	–
Unsteady	0.54	0.26	4.15	1.71 (1.02–2.86)	0.042

Author contributions

Xin Guo, Lijuan Wang, Mengzi Sun, Lina Jin and Yan Yao had the original idea for the study, and with all co-authors, carried out the design. Fang Yang and Yan Yao provided valuable insight regarding the methodological approach and organization of the manuscript. Mengzi Sun and Xin Guo carried out the statistical analysis and reviewed the consistency of data included in the paper. Mengzi Sun, Xin Guo and Li Shen wrote the first draft of the manuscript. Fang Yang, Mengzi Sun, Jing Dou, Liyuan Pu, Chunli Bi and Shuo Li performed the interpretation of the results and wrote the final version of article in collaboration with Yan Yao and Lina Jin. Mengzi Sun, Fang Yang, Jing Dou, Li Shen, Lijuan Wang, Yan Yao and Lina Jin revised the manuscript. All authors read and approved the final manuscript.

Acknowledgement and funding

This work was supported by the Natural Science Foundation of Science and Technology Department of Jilin Province, China (grant number: 20180101129JC), the Outstanding Youth Foundation of Science and Technology Department of Jilin Province, China (grant number: 20170520049JH), the National Natural Science Foundation of China (grant number: 11301213 and 11571068), the National Key Research and Development Program of China (grant number: 2016YFC1303800).

Declaration of Competing Interest

All authors stated that they have no conflict of interest.

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