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Intensive blood pressure control reduces the risk of progressive hemorrhage in patients with acute hypertensive intracerebral hemorrhage: A retrospective observational study

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ABSTRACT

Objective: To investigate the impact of intensive blood pressure control on progressive intracerebral hemorrhage and outcome in patients with high blood pressure and intracerebral hemorrhage.

Patients and methods: A retrospective study was conducted recruiting 659 patients with acute hemorrhagic stroke between Jan. 2012 and May 2018. Patients recruited before May 2015 were treated with a target systolic level of < 180 mm Hg, while those recruited after May 2015 received intensive blood pressure control treatment with a target systolic level of < 140 mm Hg within 1 h. Uni- and multi-variate analysis were conducted to illustrate the association between intensive blood pressure control and progressive intracerebral hemorrhage. Mortality, rates of operation, length of ICU stay, modified Rankin scores at 90 days, and the rate of serious adverse events were also compared between the two groups.

Results: A total of 351 and 308 patients with acute hypertensive intracerebral hemorrhage were recruited before and after May 2015, respectively. Progressive intracerebral hemorrhage was identified among 111 out of 659 patients. Patients who received intensive blood pressure control showed a statistically lower rate of hematoma enlarging (43 of 308, 13.9% *vs.* 74 of 351, 21.1%, p = 0.018). The rates of operation and modified Rankin scores at 90 days were statistically lower with intensive blood control, while the mortality, length of ICU stay and rate of serious adverse events were similar between the two groups. Intensive BP control is an independent factor in predicting hematoma growing, with a more favorable discrimination (AUC = 0.889; 95%CI, 0.859–0.917) than other two models (AUC = 0.821; 95%CI, 0.791–0.852; and AUC = 0.635; 95%CI, 0.588–0.682).

Conclusion: Intensive blood pressure control reduce the risk of progressive intracerebral hemorrhage and improved functional outcomes in patients with acute hemorrhagic stroke.

1. Introduction

Spontaneous intracerebral hemorrhage (ICH), which affects over one million people worldwide annually, remains a significant cause of morbidity and mortality [1,2]. It has been proven that the volume and the growth of underlying hematoma are independent determiners of ICH patients' outcome [3–5]. A history of hypertension is common among ICH patients, and the blood pressure (BP) often become elevated after intracranial hemorrhage. Previous INTERACT1 (intensive blood pressure reduction in acute cerebral hemorrhage 1) and INTERACT2 studies have shown that intensive BP control (with a goal of achieving systolic pressure < 140 mm Hg within 1 h and maintaining this level for the next 7 days) improved functional outcome without increasing occurrence of severe adverse events [6,7]. The latest guidelines also recommend acute lowering of systolic blood pressure (SBP) to 140 mmHg, if there is no contraindication for ICH patients [8]. However, it is not clear whether the improvement of functional outcome is related to the control of hematoma enlargement.

In our center, patients with spontaneous ICH and elevated blood pressure admitted before May 2015 received treatment according to the previous guidelines with a target systolic level of < 180 mm Hg [9,10]. Since May 2015, a new target (SBP < 140 mm Hg within 1 h, last for 7

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days) has been adopted according to INTERACT1, INTERACT2, and updated guidelines [6–8,11,12]. It is reasonable that such updated blood pressure reduction protocol may reduce the risk of progressive hemorrhage, thus, we retrospectively investigated the effects of the new blood pressure control protocols on progressive intracerebral hemorrhage and functional outcome in patients with spontaneous ICH.

2. Methods and patients

2.1. Study design and participants

Between May 2012 and May 2018, a retrospective study was conducted in Fudan University Huashan Hospital. This study was approved by the Ethical Review Boards of Fudan University Huashan Hospital. Informed consent was obtained from all individual participants. Adult patients (age ≥ 14) with acute spontaneous ICH (within 6 h since the onset of hemorrhage) and elevated blood pressure (SBP > 140 mmHg) on admission were recruited. ICH was diagnosed by computed tomography (CT) and computed tomography angiography (CTA) scans on admission. Intracranial hemorrhage cases due to trauma, tumor apoplexy, ruptured aneurism, cavernous hemangioma, or arteriovenous malformation were not included. Patients with the following situations were also excluded from this study: deep coma (Glasgow Coma Scale, GCS 3–5); bilateral pupil dilation; cerebral herniation that requires emergency operation; pregnancy; and other contraindications to blood-pressure-lowering treatment.

2.2. Blood control treatment

Recruited patients were under neurointensive care with blood pressure measurement every 10 min. Before May 2015, patients with spontaneous ICH received treatment with target SBP level < 180 mmHg. Since May 2015, the blood-pressure-lowering protocols have been changed according to INTERACT1, INTERACT2, and updated guidelines (target SBP < 140 mmHg within 1 h and maintaining for the next 7 days). Intravenous treatment and therapy with oral agents were applied according to the availability of agents and physicians' choice.

2.3. Assessments

Demographic characteristics, lifestyle risk factors, medical history, clinical features, standard clinical laboratory tests, CT scan images were collected on admission. Baseline stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) and GCS. Coagulopathy was defined as one or more of the following: platelet counts (PLT) < 100×10^9/L, international normalized ratio (INR) > 1.25, prothrombin time (PT) > 14 s, or activated partial thromboplastin time (APTT) > 36 s [13]. Head CT scans were performed at admission, 6 h, 24 h, and 72 h after admission. CT scans were mandatory when neurological deficits occurred. Hematoma volumes were calculated by 2 independent neuroradiologists using the formula ABC/2 [14]. Progressive intracranial hemorrhage was defined as an increase in the full film appearance of lesion size, which amounted to no less than 10% increase in hematoma volume, or more hemorrhagic lesions seen on the follow-up CT scans.

The primary outcome measure was the mortality and functional outcome at 90 days after admission by using the modified Rankin scale at 90 days after randomization. The rates of operation, length of ICU stay, severe hypotension (defined as hypotension with clinical consequences that required corrective therapy with intravenous fluids, vasopressors, or hemodialysis) [6] and the rate of serious adverse events, including kidney dysfunction, kidney injury and brain infarction, were collected at discharge.

Table 1
Baseline characteristics at admission comparison between intensive BP reduction group and control BP group patients.

	Intensive BP reduction	Control BP reduction	P value
Patients	308	351	
Age, year	66.1 ± 14.7	63.9 ± 13.3	0.154
Male	211 (68.5%)	256 (72.9%)	0.229
Current smoking	43 (13.9%)	58 (16.5%)	0.387
Medical history			
History of diabetes mellitus	21 (6.8%)	38 (10.8%)	0.077
History of stroke	22 (7.1%)	15 (4.3%)	0.128
History of atrial fibrillation	17 (5.5%)	13 (3.7%)	0.349
Hematoma volume at admission, ml	22.8 ± 10.1	21.6 ± 9.9	0.140
Hematoma location			
Lobar	71 (23.1%)	97 (27.6%)	0.181
Basal ganglia	113 (36.7%)	151 (43.1%)	0.111
Thalamus	121 (39.3%)	159 (45.3%)	0.134
Cerebellum	48 (15.6%)	72 (20.5%)	0.107
Brain stem	5 (1.6%)	8 (2.3%)	0.588
Intraventricular extension	38 (12.3%)	63 (17.9%)	0.082
Clinical features			
Time from onset to admission, hour	4.0 (2.0–5.0)	3.0 (1.5–4.5)	0.092
Systolic BP, mm Hg	163.8 ± 29.7	166.1 ± 27.3	0.289
Diastolic BP, mm Hg	99.4 ± 25.1	101.6 ± 24.9	0.053
TG, mmol/L	1.19 (0.67–1.56)	1.05 (0.74–1.75)	0.032*
TC, mmol/L	4.77 (3.57–5.69)	4.38 (3.69–5.48)	0.301
LDL-C, mmol/L	2.89 (2.13–3.49)	3.18 (2.01–3.97)	0.049*
HDL-C, mmol/L	1.35 (1.01–1.63)	1.29 (1.14–1.58)	0.182
GLU, mol/L	5.3 (4.2–6.6)	6.0 (5.2–7.0)	0.021*
White blood cell, 10^9/L	13.9 (8.9–17.3)	12.6 (8.3–16.9)	0.233
Coagulopathy	67 (21.8%)	94 (26.8%)	0.146
Creatinine, mmol/L	97.8 ± 87.2	88.2 ± 73.4	0.029*
Uric acid, μmol/L	294.2 ± 101.6	301.3 ± 90.3	0.053
Baseline NIHSS score	17.4 (11.3-28.1)	19.2 (9.7-29.3)	0.497
Baseline GCS score	10.2 ± 3.2	9.3 ± 4.3	0.365

Data are given as mean ± SD, n (%), or median (IQR) unless otherwise noted. GLU = glucose; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride.
* $p < 0.05$.

2.4. Prediction models

We constructed three predictive models, based on patients' baseline characteristics, to assess the prognostic value of intensive BP reduction in predicting the enlargement of hematoma in hypertensive ICH patients. Model A included standard predictors such as age, gender, lifestyle risks, medical history, hematoma locations, and baseline clinical features; model B included the BP reduction protocols in addition to the predictors from model A; and model C contained only BP reduction methods.

2.5. Statistical analysis

Continuous variables are expressed as means ± standard deviations or as median (interquartile range), whereas categorical variables are expressed as frequency (percentage). For group comparisons, the analysis of variance was used for continuous variables with a normal distribution, and the Wilcoxon rank-sum test was used for continuous variables with skewed distributions. Meanwhile, χ^2 test or Fisher exact test was used for categorical variables.

A multivariable logistic regression was used to assess the associations between hematoma volume changes and BP treatment. Potential confounders, such as age, gender, time from onset to admission, baseline NIHSS score, were adjusted in the multivariable model. Odds ratios

Table 2
3-month outcomes and safety of two BP control protocols.

	Intensive BP reduction, n = 308	Control BP reduction, n = 351	P value
Progressive intracerebral hemorrhage			
Hematoma enlargement	43 (13.9%)	74 (21.1%)	0.018*
Hematoma enlarged volume	3.1 ± 1.4	5.1 ± 2.2	< 0.001*
New hemorrhagic lesion	28 (9.1%)	53 (15.1%)	0.024*
Operation, (n, %)	49 (15.9%)	82 (23.4%)	0.019*
Length of ICU stay	8 (6–17)	10 (7–21)	0.057
Systolic BP after 1-hour therapy	118.3 ± 9.4	153.7 ± 10.3	< 0.001*
Diabolic BP after 1-hour therapy	75.6 ± 8.8	87.6 ± 10.9	< 0.001*
Hypotension	7 (2.3%)	4 (1.1%)	0.363
Complications			
Kidney dysfunction	13 (4.2%)	6 (1.7%)	0.063
Kidney failure	5 (1.6%)	2 (0.6%)	0.261
Brain infarction	15 (4.9%)	29 (8.3%)	0.087
Others	12 (3.9%)	16 (4.6%)	0.703
Modified Rankin Scale at 90 days (n, %)			0.006*
0: No symptoms at all	36 (11.7%)	31 (8.8%)	
1: No substantive disability despite symptoms	73 (23.7%)	49 (13.9%)	
2: Slight disability	88 (28.6%)	101 (28.8%)	
3: Moderate disability requiring some help	52 (16.9%)	68 (19.5%)	
4: Moderate–severe disability requiring assistance with daily living	34 (11.0%)	49 (13.9%)	
5: Severe disability, bed–bound and incontinent	17 (5.5%)	38 (10.8%)	
6: Death by 90 days (mortality)	8 (2.6%)	15 (4.3%)	0.242

Data are given as mean ± SD, n (%), or median (IQR) unless otherwise noted.
BP = blood pressure; ICU = intensive care units.
* $p < 0.05$.

(ORs) and 95% confidence intervals (CIs) were computed for each group. Specificity and sensitivity of predicting models were evaluated by constructing receiver operative curves (ROC) and the areas under the curve (AUC). A 2-sided P-value < 0.05 was considered as the level for statistical significance. Statistical analyses were performed using SPSS 23.0 (IBM, USA) and MedCalc statistical software (version 15.2.2, MedCalc Software bvba, Ostend, Belgium).

3. Results

Between Jan. 2012 to May 2015, 351 patients with acute ICH were recruited in this study. These patients underwent BP control therapies with target SBP level of < 180 mmHg. There were 308 patients suffered meeting the same inclusion criteria recruited between June 2015 and May 2018, receiving intensive BP control treatment (SBP < 140 mmHg within one hour, lasting for 7 days). The mean age of all samples (467 men and 192 women) was 64.8 ± 15.1 years (range: 16–86 years). The baseline characteristics of recruited patients at admission are shown in Table 1. It is shown that there was no statistical difference in patients age, gender, medical history, initial hematoma volumes, results of laboratory tests, and NIHSS/GCS on admission ($p > 0.05$), but significant differences were detected in triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), glucose (GLU) and creatinine between two groups ($p < 0.05$).

We next compared the safety and outcomes in patients undergoing intensive BP control treatment. Table 2 showed that there is a statistically lower rate of hematoma enlargement (43 of 308, 13.9% *vs.* 74 of 351, 21.1%, p = 0.018) and occurrence of new hemorrhagic lesions (28 of 308, 9.1% *vs.* 53 of 351, 15.1%, p = 0.024) for patients receiving intensive BP control. Hypotension is considered to be one of most harmful complications induced by intensive BP reduction, but in our study, no significant differences were founded between the occurrence of two groups (7 of 308, 2.3% *vs.* 4 of 351, 1.1%, p = 0.363). The number of patients who had to receive surgical interventions to evacuate hematoma were statistically lower in intensive BP reduction group (49 of 308, 15.9% *vs.* 82 of 351, 23.4%, p = 0.019). The 90 days outcome of ICH patients were assessed by using modified rankin scale, it is shown that patients who received intensive BP reduction had a more favorable outcome, however, the 3-month mortality showed no significantly differences between the two BP reduction protocol. During the therapy of intensive BP control, only a few patients developed complications, including kidney dysfunction, brain infarction and et al, but no statistical differences were detected between the two groups (Table 2).

By performing univariate analysis between hematoma enlarging and non-enlarging patients, and such results are shown in Table 3. Intracerebral hematomas of male patients with elder age, history of stroke, intraventricular extending hematoma, shorter time from onset to admission and et al were more likely enlarging. Moreover, coagulopathy, higher baseline NIHSS or lower GCS scores are more likely to induce hematoma expanding. Meanwhile and utmost, the number of patients who received intensive BP reduction was statistically lower in patients with hematoma expanding, compared with patients with hematoma non-expanding (43 of 154, 27.9% *vs.* 265 of 505, 52.5%, $p < 0.001$). It is indicated that hematoma volume of acute hypertensive ICH patients with rapid BP reduction is less likely to increase after admission.

To further investigate the association between intensive BP control and progressive intracerebral hemorrhage, multivariate logistic regression analyses were performed (Table 4). Potential confounders were also adjusted in the analysis. The analysis indicated that intensive BP control treatment could reduce the risk of progressive intracerebral hematoma enlarging. Meanwhile, the enlargement of hematoma or occurrence of new hemorrhagic lesions were also related to patients' age, history of stroke, time from onset to admission, coagulopathy, cerebral hemorrhage and breaking into ventricle, baseline GCS and NIHSS scores.

We next built three predictive models and constructed ROC to evaluate the predictive ability of intensive BP control in progressive intracerebral hemorrhage (Fig. 1). By calculating AUC, model B showed a more discriminative ability (AUC = 0.889; 95%CI, 0.859–0.917; $P < 0.001$) than that of model A (AUC = 0.821; 95%CI, 0.791–0.852; $P < 0.001$) and model C (AUC = 0.635; 95%CI, 0.588–0.682; $P < 0.001$). These results further confirmed the prognostic value of multivariate logistic regression.

Table 3
Univariate analysis of hematoma expanding.

Independent variables	Expanding (n = 154)	Non-expanding (n = 505)	P value
Age, year	69.7 ± 13.1	61.8 ± 14.3	< 0.001*
Male	92 (59.7%)	375 (74.3%)	< 0.001*
Current smoking	21 (13.6%)	80 (15.8%)	0.609
Medical history			
History of diabetes mellitus	15 (9.7%)	44 (8.7%)	0.747
History of stroke	16 (10.4%)	21 (4.1%)	0.008*
History of atrial fibrillation	4 (2.6%)	26 (5.1%)	0.268
Hematoma volume at admission, ml	21.4 ± 9.8	22.5 ± 10.1	0.335
Hematoma location			
Lobar	45 (29.2%)	123 (24.3%)	0.245
Basal ganglia	61 (39.6%)	188 (37.2%)	0.635
Thalamus	58 (37.7%)	222 (43.9%)	0.192
Cerebellum	31 (20.1%)	89 (17.6%)	0.476
Brain stem	2 (1.3%)	11 (2.2%)	0.743
Intraventricular extension	36 (23.4%)	75 (14.8%)	0.019*
Clinical features			
Time from onset to admission, hour	3.5 (2.0–5.5)	4.0 (2.0–5.0)	< 0.001*
Systolic BP, mm Hg	168.7 ± 27.2	161.8 ± 31.3	0.075
Diastolic BP, mm Hg	95.4 ± 25.1	103.6 ± 36.7	0.093
TG, mmol/L	1.04 (0.73–1.31)	1.13 (0.65–1.79)	0.032*
TC, mmol/L	4.61 (4.02–5.63)	4.27 (3.75–6.29)	0.061
LDL-C, mmol/L	2.77 (2.34–3.18)	2.85 (2.13–3.42)	0.012*
HDL-C, mmol/L	1.28 (1.02–1.59)	1.42 (0.99–1.53)	0.055
GLU, mol/L	6.1 (5.4–6.7)	6.3 (5.1–7.3)	0.401
White blood cell, 10^9/L	16.3 (11.5–19.4)	12.4 (7.2–16.5)	0.032*
Coagulopathy	54 (35.1%)	107 (21.2%)	< 0.001*
Creatinine, mmol/L	83.2 ± 72.3	93.2 ± 68.1	0.073
Uric acid, μmol/L	299.2 ± 97.6	312.3 ± 101.7	0.081
Baseline NIHSS score	23.3 (10.4–35.1)	11.2 (9.8–20.6)	< 0.001*
Baseline GCS score	8.6 ± 3.2	10.5 ± 2.9	< 0.001*
Intensive BP reduction	43 (27.9%)	265 (52.5%)	< 0.001*

Data are given as mean ± SD, n (%), or median (IQR) unless otherwise noted. GLU = glucose; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride.
* $p < 0.05$.

Table 4
Multivariate analysis of hematoma expanding.

Independent variables	OR (95% CI)	P value
Age	0.721 (0.532–0.958)	< 0.001*
Gender	0.939 (0.594–1.571)	0.103
History of stroke	0.653 (0.318–0.996)	0.034*
Time from onset to admission	0.718 (0.477–0.981)	0.013*
Intraventricular extension	0.631 (0.367–0.859)	0.017*
TG, mmol/L	1.107 (0.786–1.458)	0.643
LDL-C, mmol/L	1.109 (0.599–2.091)	0.087
White blood cell, 10^9/L	1.039 (0.798–1.602)	0.104
Coagulopathy	0.618 (0.501–0.828)	< 0.001*
Baseline NIHSS score	0.632 (0.304–0.962)	0.004*
Baseline GCS score	0.566 (0.366–0.847)	< 0.001*
Intensive BP reduction	0.524 (0.324–0.846)	0.008*

CI = confidential interval; OR = odds ratio.
* $p < 0.05$.

4. Discussion

In this retrospective cohort study of Chinese acute hypertensive ICH patients, the primary finding of our study is that the hematoma volume is less likely to expand when acute hypertensive ICH patients received rapid BP reduction under 140/90 mm Hg within 1 h after admission. Meanwhile, intensive BP reduction is confirmed to be an independent predictor of preventing hematoma enlarging in hypertensive ICH patients.

According to recent epidemiological studies, the prevalence of hypertension and associated intracranial hemorrhage continuously increased during recent decades [15–17]. In addition, hypertension has been proven as not only one of the etiological factors, but also an independent risk factor for outcome [5,11,18]. It is reported that 1% increase of the size of hematoma would lead to 5% increase in mortality and morbidity [11,19]. Moreover, patients' outcome has been approved to be correlated with the site of bleeding in primary ICH [20]. Therefore, it is advocated that efficient BP control would reduce the risks of disease progression and improve patients' outcome. Under this background, a series of RCT studies have been conducted to elucidate the benefits of BP lowing in ICH patients. The INTERACT1, INTERACT2 studies [6,7] advocated intensive BP lowing treatment for hypertensive ICH patients, of which the recommendation was adopted by updated guidelines. However, the direct association between intensive BP control and progressive ICH has not been verified.

We have demonstrated that the progressive ICH is less likely to occur when patients receive intensive BP control. In addition, intensive BP control also lowered the requirement for surgical hematoma evacuation and improved functional outcome at 90 days assessed by using the modified Rankin scores. The underlying mechanisms of such benefits are not clear. It is hypothesized that the hematoma not only causes primary brain parenchyma injury, but also compressed the ruptured intracranial arteries so that temporary and vulnerable hemostasis is achieved. If the BP remains high, the hemostasis could be compromised and new bleeding may occur, which may consequently lead to an emergency operation, prolonged ICU stay and poor outcome.

According to baseline characteristics of all included patients at admission shown in Table 1, it was indicated that TG, LDL-C, GLU and creatinine showed statistical differences between intensive BP and control BP reduction groups; also, as results from univariate analysis (Table 3), the hematoma volume was significantly affected by TG, LDL-C and white blood cell counts. The potential reasons that induced these biases maybe that the study we performed is retrospective, and data we collected cannot absolutely follow our requirements as prospective studies. Moreover, the time course of our study was relatively long, thus, results of these lab tests may be affected by different test methods or equipment.

Consist with previous studies [19,21], we found that age, time from onset to admission, baseline GCS scores, and et al were independently risk factors of hematoma expanding, which indicated that predictive models of our study is convincing, and thus, results from such models are convincing. By performing multivariate analysis, building ROC curves and calculating the area under the curve (AUC), the abilities of discrimination and prediction are more favorable when BP control protocols are included; also, it is indicated that intensive BP reduction will independently prevent hematoma expanding after ICH. Such results also confirmed that rapidly lower BP under 140 mmHg within one hour and maintaining BP under this level is reasonable in hypertensive ICH patients.

Despite the benefits, there have been worries about the side effects of intensive BP control. The primary concern is that intensive BP lowering may lead to insufficient cerebral perfusion pressure (CPP), secondary ischemic injury [22,23], and acute kidney dysfunction [24–26]. However, the INTERACT 2 study proved that intensively lowering SBP under 140 mmHg within one hour was safe [6], and results from our retrospective study have further confirmed this finding. Consist of previous studies, we additionally verified that patients' age, time from onset to admission, baseline GCS scores, and cerebral hemorrhage and breaking into ventricle were independent risk factors of progressive hemorrhage. Moreover, we also confirmed intensive BP reduction is a safe protocol in avoiding hypotension as normal BP reduction. Although several intensive BP reduction patients suffered hypotension, the incidence was familiar with normal BP reduction patients. And once

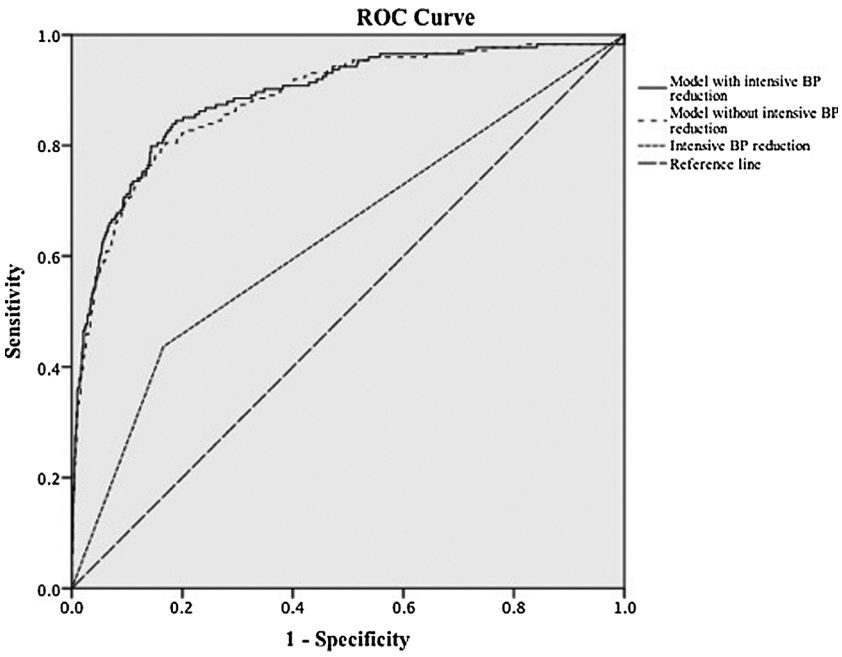

Fig. 1. Receiver operative curve (ROC) of the three predictive models. The model with intensive blood pressure reduction had a larger are under the curve (AUC) than the other two models. It is indicated that the discrimination of the model with intensive blood pressure control is more favorable than the other two models. Applying intensive blood reduction protocol may reduce the risk of progressive hemorrhage.

hypotension occurred, proper medications were applied by physicians on time.

Several limitations existed in our study. For our study is a real-world observational study applying conclusions of previous landmark studies, a further study is required to furtherly elucidate the optimal BP management of acute hypertensive ICH patients which is able to benefit patients mostly. Then, the time course of our study was relatively long, thus, even this is a one-center study, the level of emergency may be different. Lastly, patients' outcome assessing by mRS was limited and in our furtherly research, we will collect more information to make a more convincing assessment of patients' outcome.

In summary, intensive BP control has been generally accepted during management of acute spontaneous ICH. The target of SBP lowering has also been included in the latest guidelines for ICH management. This study proved that intensive BP control treatment not only reduced the requirement for surgical operations and the length of ICU stay but also improved functional outcome with no increase in the rates of severe complications.

5. Conclusion

Intensive blood pressure control reduces the risk of progressive intracerebral hemorrhage and improved functional outcomes in patients with acute hemorrhagic stroke.

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Declarations of interest

None.

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