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PRACTICAL PEARL

Rapid Blood Pressure Reduction in Acute Intracerebral Hemorrhage: Feasibility and Safety

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Abstract
Background The optimal blood pressure (BP) for treating acute intracerebral hemorrhage remains (ICH) uncertain. High BP may contribute to hematoma growth while excessive BP reduction might precipitate peri-hemorrhage ischemia. We examine here the feasibility and safety of reducing BP to lower than presently recommended levels in patients with acute ICH.
Methods Patients with ICH were prospectively randomized to standard BP treatment (mean arterial BP [MAP] 110–130 mmHg) or aggressive BP lowering (MAP < 110 mmHg) within 8 h of symptom onset. MAP was managed during the 48 h treatment period. NIHSS was obtained at baseline, 24, and 48 h. Brain CT was done 24 h after symptoms. A modified Rankin Scale (mRs) was obtained at 90 days. A clinical decline (NIHSS drop $\geq$ 2 points) within the first 48 h was the primary endpoint. Hematoma enlargement at 24 h was a secondary endpoint.
Results We enrolled 21 patients into each group. Mean age was 60.6 $\pm$ 12.3 years and MAP on presentation was 147.6 $\pm$ 18.2 mmHg. Treatment was started on average 3.2 $\pm$ 2.2 h after symptom onset. Baseline clinical variables were identical between the 2 treatment groups. Target blood pressure was achieved within 87.1 $\pm$ 59.6 min in the standard group and 163.5 $\pm$ 163.8 min in the aggressive BP treatment group. There were no significant differences in early neurological deterioration, hematoma and edema growth, and clinical outcome at 90 days.
Conclusion A more aggressive reduction of acute hypertension after ICH does not increase the rate of neurological deterioration even when treatment is initiated within hours of symptom onset. Lowering BP aggressively did not affect hematoma and edema expansion but this possibility deserves further study.

Keywords Intracerebral hemorrhage · Hypertension · Hematoma growth

Despite recent advances in the treatment of intracerebral hemorrhage (ICH) the optimal management of blood pressure (BP) in acute parenchymal bleeding remains uncertain. The argument to lower BP aggressively to prevent hematoma growth is countered by concerns about reducing cerebral perfusion pressure in the setting of increased intracranial pressure, thus causing cerebral ischemia. Expert guidelines at the time this study was designed, suggest that maintaining a mean arterial blood pressure (MAP) goal below 130 mmHg as a reasonable compromise [1]. However, this BP parameter was rated as a grade C recommendation since it is based on data from anecdotal case series (level of evidence V). For this reason, trials evaluating BP reduction were considered among the main medical research priorities in ICH by the participants of a recent workshop sponsored by the National Institute of Neurological Disorders and Stroke [2].

In approximately one-third of patients presenting with acute intracerebral hemorrhage the hematoma expands by more than 33% within the first hours. Such expansion is strongly associated with worsening outcome [3, 4]. It is presently unknown if prompt aggressive reduction of BP

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after cerebral hemorrhage is safe, prevents hematoma expansion, and improves clinical outcome.

Studies assessing the effect of acute hypertension on outcome after ICH have produced conflicting results. Most studies reported worse outcome with increased BP on presentation [5–11], but others found no correlation between BP and hematoma growth [3, 12, 13]. Despite clear evidence that hematomas are often surrounded by an area of hypoperfusion [14–16], experimental models [17–19] and recent studies using perfusion imaging and PET scanning mostly argue against the presence of a perihemorrhagic penumbra and suggest that acute BP reduction after ICH may not induce ischemia [20–22]. Only one small study has examined the safety of acute BP reduction in patients with ICH [23] but this study did not include a control group and antihypertensive treatment was initiated relatively late after symptom onset.

Additionally, the feasibility and efficacy of lowering blood pressure rapidly in the setting of an acute ICH has largely remained unexamined. Various intravenous agents administered intermittently or by continuous infusion are presently recommended [24], but little is known about their usefulness to rapidly reduce blood pressure in this setting. We therefore undertook the present study to determine the safety and feasibility of aggressive BP lowering in patients with acute spontaneous ICH.

Methods

Study Population

We enrolled consecutive patients 18 years of age or older with radiologically confirmed acute spontaneous supratentorial ICH within 8 h of symptom onset. The following criteria excluded patients from study participation: history of head trauma, coma with signs of herniation, coagulopathy defined as platelet count <50,000 mm^3 or INR $\geq$ 1.8, MAP < 110 mmHg at presentation, ICH secondary to arteriovenous malformations, trauma, aneurysms or other secondary causes, surgical hematoma evacuation, or inability to give informed consent. Patients were enrolled between January 2004 and December 2006.

Study Intervention

All patients were randomly assigned to one of two BP management groups: a standard BP treatment group with a target MAP 110–130 mmHg according to American Heart Association (AHA) guidelines for the management of ICH or an aggressive BP treatment group with a target MAP < 110 mmHg. Patients received standard BP lowering agents. Agent selection was not strictly standardized and occurred according to our routine clinical practice. Patients were typically treated initially with intermittent labetalol infusions (10–20 mg). If this failed to achieve target blood pressure a continuous infusion of nicardipine (5–15 mg/h) was started. More severe cases were treated with intravenous nicardipine from the onset according to manufacturers' recommendations, i.e. initial dose, 5 mg/h followed by titration and increases of 2.5 mg/h every 5–15 min. No bolus was administered. Most severe cases of hypertension were treated with sodium nitroprusside infusion at 0.3 mcg/kg/min IV infusion and titrated every few minutes to desired effect. BP was monitored as follows: every 15 min for the first 3 h, every 30 min from 3–6 h, and hourly from 6–48 h. Brachial BP was measured with automated cuff sphygmomanometry initially. Reaching target MAP was defined as maintaining MAP within the assigned parameters for at least 30 consecutive minutes. Allocation to treatment was concealed by numbered envelopes in random sequence prior to the onset of the study.

Measurements and Endpoints

Stroke severity was determined blinded to treatment allocation using the NIH stroke scale (NIHSS) and Glasgow coma scale (GCS) on admission. Patient and treating health care personnel were not blinded to treatment allocation. NIHSS and GCS were repeated blinded to treatment at 24 and 48 h to assess clinical evolution. Neurological deterioration was deemed present when a decline of $\geq$2 points on the NIHSS from baseline to 48 h was found. Functional outcome was determined 90 days after symptom onset by follow-up examination or phone contact employing the modified Rankin scale (mRS). Favorable functional outcome was defined as a 90-day mRS $\leq$ 2.

Hematoma and edema volumes on baseline and 24-h CT scans were measured blinded to treatment allocation using the ABC method [25]. Hematoma expansion was defined according to previous criteria as enlargement exceeding 30% of baseline volume, which has been correlated with poor outcome [3]. Edema was measured as absolute volume and relative to the size of the hemorrhage.

The primary endpoint of the study was the presence of neurological deterioration within the first 48 h. Secondary outcome measures were functional status at 90 days, and hematoma and edema growth between baseline and 24-h CT scans. We anticipated that time to target blood pressure would be significantly different between the 2 groups and did not include this as an endpoint. The study was approved by the local institutional review board and written consent was obtained from all subjects or health care proxies.

Statistical Analysis

Neurological deterioration at 48 h and favorable neurological outcome at 90 days were analyzed as nominal variables. Hematoma and edema growth were assessed by mean volume increase and as a dichotomized variable based on the occurrence of growth greater than 30% of baseline volume. Continuous normally distributed variables were compared using the independent *t*-test. Nonparametric tests were employed for data not normally distributed. Categorical variables were analyzed by Chi-square test. All *P*-values are two tailed at 0.05 level of significance.

Results

During the study period 237 patients were screened. Inclusion criteria were met by 42 patients and 21 patients were randomized into each group (Table 1). Three patients meeting inclusion criteria deteriorated prior to study enrollment and were not included in the final analysis. Mean age of the study population was 60.6 ± 12.3 years and 23/42 were men. The majority of patients were of African descent (57%) and 41% were Hispanic. Hemorrhage location was as follows: thalamus 52%, putamen 31 %, lobar 12%, and caudate 5%. Mean MAP on ER arrival was 147.6 ± 18.2 mmHg and presenting mean NIHSS severity was 11.5 ± 6.7 and initial median GCS was 15 ± 2.03. Mean baseline ICH volume was 10.5 ± 14.0 ml (median 6.7 ml). Treatment was started on average 3.2 ± 2.2 h after symptom onset and 36 (86%) patients started treatment within 6 h of symptoms. There were no significant differences between the standard and aggressive BP treatment groups in baseline clinical variables; however, ICH and edema volumes were larger in the low BP group (Table 1).

Target MAP was achieved within 87.1 ± 59.6 min in the standard group and 163.5 ± 163.8 min in the aggressive BP treatment group after starting hypertensive therapy ($P = 0.14$). In one patient (aggressive treatment group) target BP was not reached. After 3 h of treatment 7/21 (33%) and 2/21 (10%) had not attained target BP in the aggressive and standard treatment groups, respectively. An intravenous nicardipine drip was used for BP control in 34 cases; 4 patients received intravenous sodium nitroprusside infusion and the remaining 4 patients received other forms of antihypertensive treatment (most commonly intermittent boluses of intravenous beta-blocker). BP remained significantly different between the two groups throughout the study (Table 2).

All patients underwent standard glycemic management. There were no significant differences between admission, 24 and 48-h glucose levels between the standard and aggressive BP treatment groups (152.9 ± 77.0 mg/dl vs. 135.5 ± 56.2 mg/dl; 151.9 ± 87 mg/dl vs. 151.1 ± 42.5 mg/dl; 123.9 ± 45.8 mg/dl vs. 128.1 ± 43.3 mg/dl).

Clinical deterioration occurred in 3 patients at 48 h (2 in the aggressive and 1 in the standard BP treatment arm). At 90 days 6 (15%) patients had died. A favorable outcome (mRS ≤ 2) was achieved by 18 (45%) patients. There were

Table 2 Blood pressure course after treatment onset

Mean MAP	Standard ($n = 21$)	Low ($n = 21$)	*P* value
0–3 h	124.1 ± 12.8	113.8 ± 13.0	0.013
3–6 h	112.9 ± 11.9	105.1 ± 12.6	0.045
6–12 h	111.7 ± 11.0	99.5 ± 10.5	0.001
12–24 h	115.1 ± 8.6	99.7 ± 12.8	<0.001
24–48 h	113.9 ± 6.8	101.1 ± 11.5	<0.001

MAP, mean arterial pressure, values are shown as means and standard deviations

Table 1 Baseline characteristics of standard and low blood pressure treatment groups

Variable	Standard ($n = 21$)	Aggressive ($n = 21$)	*P* value
Age, mean, yr	60 ± 11	61.2 ± 13	0.75
Men, *n*	14	9	0.12
Hypertension, *n*	19	18	0.63
Diabetes, *n*	6	5	0.73
Antiplatelet therapy, *n*	4	7	0.29
Anticoagulation, *n*	0	1	0.31
NIHSS, mean	10.9 ± 6.5	12 ± 7.0	0.60
GCS, median (range)	15 (10–15)	13.5 (9–15)	0.08
Arrival MAP, mean, mmHg	150.7 ± 20.1	144.3 ± 15.8	0.45
Time to treatment,[a] mean, min	193.9 ± 134.6	187.8 ± 132.9	0.88
ICH volume, mean, ml	8.5 ± 9.8	12.5 ± 17.2	0.37
Edema volume, mean, ml	16.3 ± 18.42	26.6 ± 33.6	0.23

NIHSS, National Institute of Health Stroke Scale; GCS, Glasgow coma score; MAP, mean arterial pressure; ICH, intracerebral hemorrhage,
[a] from symptom onset

Table 3 Radiological and clinical outcome

Variable	Standard	Low	*P* value
NIHSS deterioration at 48 h, *n*	1	2	0.55
ICH volume increase, mean, ml	2.4 ± 6.7	2.4 ± 5.3	0.97
Hematoma expansion >30%, *n*	6	6	1.00
Edema volume increase, mean, ml	8.6 ± 16.5	7.5 ± 22.0	0.86
Edema volume expansion >30%, *n*	11	8	0.35
Favorable outcome (mRS ≤ 2), *n*	10	8	0.43
Mortality 90 days, *n*	3	3	1.00

ICH, intracerebral hemorrhage; NIHSS, NIH stroke scale; mRS, modified Rankin scale

no significant differences between the 2 groups in regards to clinical outcome (Table 3). We were unable to reach 3 patients (2 in the standard and 1 in the aggressive treatment groups) for the 90-day follow-up.

Hematoma volume increased by an average 2.4 ± 6.0 ml at 24 h. Hematoma expansion exceeding 30% of baseline volume occurred in 12 (29%) patients. Absolute edema volume increased by 8.1 ± 19.2 ml and 19 (45%) patients had edema growth exceeding 30% of baseline volume. There were no significant differences between the 2 groups (Table 3). A trend toward a lower relative ICH volume increase was noted with a mean percent ICH volume increase of 18.2 ± 46.8 in the standard and 11.9 ± 29.7 in the aggressive BP treatment group ($P = 0.61$). The percent of edema volume increase was 35.7 ± 48.7 and 25.7 ± 45.5 ($P = 0.50$) in the standard and aggressive treatment groups, respectively.

In a subgroup analysis of 27 treated within 3 h from symptom onset we found no differences in hematoma and edema expansion at 24 h or clinical outcome at 48 h and 90 days.

Discussion

We randomized patients with acute ICH to receive antihypertensive treatment according to current practice guidelines (MAP 110–130 mmHg) or a more aggressive approach, aiming at a lower BP (MAP < 110 mmHg). The primary goal was to show feasibility and safety of aggressive BP treatment. We found no significant differences in neurological decline or radiological outcome between the two groups. There was a significant delay to achieve a more aggressive blood pressure reduction.

Two main questions affect the decision on how aggressively BP should be treated in acute ICH: (1) does acute hypertension induce hematoma expansion; and (2) is there an area of ischemic penumbra surrounding parenchymal hematomas? A positive answer to the first question along with a negative answer to the second would support aggressive BP reduction. Conversely, the opposite answer would argue for more cautious treatment of hypertension to avoid the risk of producing secondary ischemic damage.

Severe acute hypertension after spontaneous ICH—in particular MAP >145 mmHg or systolic BP > 200 mmHg—has been found to be independently associated with worse clinical outcome in most large series [5–11]. This deleterious effect may be due to increased hematoma growth [8, 9], although the relationship between acute hypertension and hematoma enlargement has not been consistent across different studies [3, 12, 13]. In our study, the first randomized interventional trial assessing the effect of different degrees of BP lowering on clinical outcome and hematoma growth, intensity of BP lowering had no measurable effect on hematoma growth. All our patients with MAP > 130 mmHg upon presentation received antihypertensive therapy, which may have obscured a possible protective effect of BP lowering on risk of hematoma enlargement.

Various studies relying on different forms of perfusion imaging have documented areas of decreased perfusion around a parenchymal hematoma [14–16]. Yet, studies using PET scan demonstrated decreased oxygen extraction fraction in the peri-hemorrhagic brain tissue (rather than increased oxygen extraction fraction which characterizes ischemia) because of greater reduction in cerebral metabolic rate of oxygen than in cerebral blood flow [22]. Further evidence against the presence of a peri-hemorrhagic ischemic penumbra was provided by a study using diffusion-perfusion MRI [21], although peri-hematomal ischemia might have occurred in a minority of patients with larger ICH in this study [26]. In addition, moderate lowering of MAP between 6 and 22 h after ICH onset did not significantly affect global or peri-clot cerebral blood flow as assessed by PET [20]. Antihypertensive treatment initiated within the first 24 h after ICH following the AHA guidelines has been shown to be well tolerated [27]. In our trial, greater BP reduction initiated on average between 3 and 4 h after symptom onset had no measurable negative effect on neurological status.

Several reasons may explain the lack of benefit from more aggressive BP reduction observed in our study. It is possible that keeping MAP < 130 mmHg might be sufficient and further reduction does not confer additional protection. Although MAP in our groups were significantly different throughout the treatment period, it is conceivable that the differences were not large enough to produce measurable changes in the clinical or radiological outcome measures. It also appears that BP control in the standard group may have been more stringent than usual practice. MAP pressure for the standard group stabilized at approximately 110 mmHg by 3–6 h of treatment (Table 2).

Such careful BP control may have further obscured any potential differences in outcome between the groups. But most importantly, our study was primarily designed to test the safety of BP reduction and it was not powered to detect favorable changes in rate of ICH expansion or clinical outcome from aggressive BP reduction.

The hematoma size in the present study was relatively small in comparison to other studies of ICH. Prior studies have shown a baseline ICH volume of 29 ± 29 ml and 26 ± 29 ml [3, 28]. The reasons for this difference are not entirely clear. It is possible that the ethnic make-up of the study population and hematoma location might be the explanation. The study population comprised almost entirely minorities and had a larger proportions of thalamic hemorrhages than reported in previous studies [3, 28]. The small hematoma size may also affect the generalizability of the study, particularly to patients with larger hematomas. Patients with larger hematomas are probably at greater risk to experience peri-hematoma perfusion deficits as blood pressure is lowered.

Additionally, while BP control was instituted with continuous intravenous infusion in most cases there was still a considerable delay until target BP was achieved as patients were refractory to treatment. Hematoma expansion occurs in the first few hours after onset of bleeding, and it is possible that this delay may have mitigated any effect on hematoma growth. Our treatment protocol included agents commonly used in the management of hypertension in neurological disease, particularly nicardipine. The use of an intravenous bolus at onset of treatment to lower BP even more rapidly needs to be strongly considered in future studies of this nature [29].

The strengths of our study are its randomized design, blinded assessment of clinical and radiological outcome measures, and early initiation of antihypertensive treatment. Nonetheless, we acknowledge that our study also has limitations and that certain caveats apply to its interpretation. Its small size does not allow us to examine differences between subgroups (e.g. differential effect of BP lowering according to baseline ICH size or time to presentation). Use of MAP rather than systolic BP may be arguable [30]. We used MAP because this parameter had been proposed in the AHA guidelines [1]. However, while MAP is a preferred marker of perfusion, systolic BP may be a better predictor of hematoma expansion [9, 31]. Greater standardization of antihypertensive regimens could have increased the effectiveness of our intervention.

We conclude that aggressive reduction of acute hypertension after spontaneous ICH does not increase the rate of neurological deterioration. Blood pressure control by standard antihypertensive treatment regimens was not achieved rapidly in the group of aggressive blood pressure treatment. Our safety results support the changes incorporated to the new AHA guidelines for acute ICH management, which recommend reducing BP to a MAP target of 110 mmHg in patients without suspicion of increased intracranial pressure [24]. While our primary goal was to assess safety, we found no effect of aggressive BP lowering on the incidence of hematoma expansion. However, we believe that emergent treatment of hypertension in acute ICH, possibly aiming for faster and perhaps more profound lowering of elevated BP, deserves further study.

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