

Determinants of the high admission blood pressure in mild to moderate acute intracerebral hemorrhage

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Abstract

Background and Purpose: An early elevation in blood pressure (BP) is common after spontaneous intracerebral hemorrhage (ICH), has various potential causes, and is predictive of poor outcome. We aimed to determine the predictors of this phenomenon, in pooled analyses of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trials (INTERACT1 [n=404] and INTERACT2 [n=2829]).

Methods: INTERACT trials were international, open, blinded endpoint, randomized controlled trials of patients with spontaneous ICH (<6 hrs) and elevated systolic BP (SBP) (150-220 mmHg) assigned to intensive (target SBP <140 mmHg) or guideline-recommended (SBP <180 mmHg) treatment. Multivariable linear and logistic regression models were used to determine associations between baseline variables and the high admission BP, with continuous and binary SBP measures, respectively.

Results: Among 3233 patients (mean age 63 years; 37% female; baseline mean SBP 179mmHg), both analytic approaches showed significant positive associations of high admission BP with history of hypertension, admission hyperglycemia ≥ 6.5 mmol/L, elevated heart rate, and greater neurological severity (National Institutes of Health Stroke Scale scores); and significant negative associations with prior use of antithrombotic agents and longer time from onset to randomization.

Conclusion: The high admission BP of mild to moderate acute ICH is related to autonomic nervous system activated ‘stress’ rather than hematoma location and mass effect.

Clinical Trial Registration — URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00226096 and NCT00716079.

Elevated blood pressure (BP) is common early after an acute stroke,¹ and is more frequent and with higher BP levels in acute intracerebral hemorrhage (ICH) than acute ischemic stroke.²⁻⁵ Moreover, population-based data suggest that the first recorded BP after the onset of ICH is significantly higher than pre-ICH levels, which supports the notion that there is a hypertensive response to ICH.⁶ Raised BP in acute ICH has clear prognostic significance, being associated with greater hematoma expansion, neurological deterioration, death, and dependency,^{3, 7-9} but the evidence is inconsistent regarding the effects of early intensive BP lowering.⁸ Whilst various potential mechanisms have been proposed, few analyses have been undertaken to identify variables that independently predict the high admission BP in order to advance our understanding of mechanisms¹ and potential targeting on treatments in acute ICH. We aimed to determine the factors associated with the high admission BP in participants of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trials (INTERACT1 and 2).

Methods

The INTERACT studies were international, multicenter, open, blinded endpoint, randomized controlled trials, as described in detail elsewhere.¹⁰⁻¹² Briefly, 404 (INTERACT1) and 2829 (INTERACT2) patients with spontaneous ICH within 6 hours of onset and elevated systolic BP (SBP, 150-220 mmHg) were centrally randomized to receive intensive (target SBP <140mmHg) or contemporaneous guideline-recommended (target SBP <180mmHg) BP lowering treatment. Participants allocated to intensive treatment received intravenous treatment and oral drugs according to pre-specified treatment protocols based on locally available drugs, with the goal of achieving the SBP target within 1 hour of randomization and to maintain this level with oral antihypertensive drugs (or topical nitrates), and via a nasogastric tube if necessary, for 7 days (or discharge from hospital, if sooner). Treatment was stopped at a SBP <130mmHg.^{13, 14} Demographic and clinical characteristics were recorded at enrolment, with stroke severity measured by use of the Glasgow coma scale (GCS) and National Institutes of Health Stroke

Scale (NIHSS, scores range from 0 to 42; high scores indicate greater neurological deficit) at baseline, 24 hours, and Day 7 (or earlier, at discharge from hospital). Pre-existing hypertension was by self-report. BP was measured at least twice, at least two minutes apart using digital sphygmomanometers, in the non-paretic arm (or right arm in situations of coma or tetraparesis) with the patient supine, at baseline immediately prior to randomization. The studies were approved by ethics committees at each site and written informed consent was obtained from each patient or, where appropriate, an approved surrogate.

We tested associations between baseline characteristics and high admission BP (SBP as a continuous variable) using linear regression, and according to high baseline SBP >180mmHg (SBP dichotomized) with logistic regression. Significant covariates from univariate analyses and other variables chosen for their potential clinical relevance (sex, baseline hematoma volume, and randomized treatment) were included in multivariable models. We reduced the full model by successively removing non-significant covariates until all remaining predictors remained statistically significant ($P < 0.05$). All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

These analyses included 3233 patients (mean age 63 years; 36.8% female) with mean SBP 179mmHg at baseline. Higher SBP was associated with younger age, prior history of hypertension, previous ischemic stroke, and admission hyperglycemia ≥ 6.5 mmol/L). Patients with higher SBP had earlier presentation to hospital, more severe neurological deficit (higher NIHSS score) and altered level of consciousness (lower GCS score) (Table 1 and eTable 1).

Table 2 shows the independent predictors of high admission BP in acute ICH: positive associations were history of hypertension (estimate 2.295, SE 0.691, $P = 0.001$), admission hyperglycemia ≥ 6.5 mmol/L; 3.132, 0.618, $P < 0.0001$), elevated heart rate (1.238, 0.222 per 10

beats per minute increase, $P < 0.0001$), and higher NIHSS (0.154, 0.047 per 1 point increase, $P = 0.001$); and negative associations were prior use of antithrombotic agents (-3.742, 0.954, $P < 0.0001$) and time from onset to randomization (-0.992, 0.255 per 1 hour increase, $P = 0.0001$).

Table 3 shows the independent associations for high baseline SBP was dichotomized at 180mmHg: positive associations were history of hypertension (odds ratio [OR] 1.36, 95% confidence interval [CI] 1.14-1.62; $P = 0.001$), admission hyperglycemia ≥ 6.5 mmol/L; OR 1.43, 95%CI 1.22-1.68; $P < 0.0001$), elevated heart rate (OR 1.13, 95%CI 1.06-1.19; $P < 0.0001$ per 10 beats per minute increase), and higher NIHSS (OR 1.02, 95%CI 1.00-1.03; $P = 0.01$ per 1 point increase); and negative associations were use of antithrombotics (OR 0.63, 95%CI 0.49-0.80; $P = 0.0002$) and time from onset to randomization (OR 0.91, 95% CI 0.85-0.97; $P = 0.004$ per 1 hour increase).

Discussion

This study, derived from a large international clinical trial database, has shown that pre-existing hypertension combined with several manifestations of ‘stress’ are associated with a high admission BP within the first few hours after the onset of acute ICH. There was no association with the size and location of the ICH.

It has been hypothesized that the primary cause of acute hypertensive response in ICH is damage or compression of brain regions that mediate autonomic control of BP, which functionally adapts over subsequent days.^{15, 16} However, we were unable to find any association with volume, location or other morphological features of the hematoma, suggesting the hypertensive response is a complex multifactorial phenomenon. Our data suggest the postulated acute increase in sympathoadrenal activity appears not to be related to brain stem compression, which may also partly explain why such an increase is greater in ICH compared to acute ischemic stroke.⁶ In addition, greater neurological deficit is associated with high

admission BP, suggesting that sympathoadrenal activation is unlikely to be psychogenic in origin.^{6, 17}

It is well established that having a history of hypertension influences the level of BP early after acute stroke,² and poorly controlled hypertension may trigger an event,^{18, 19} particularly for ICH.⁶ Our finding of an inverse relationship between prior use of antithrombotic medication and high admission BP may be a surrogate marker for better control of vascular risk factors, including hypertension.

Factors that represent activation of the autonomic nervous system were predictive of high admission BP in the present analyses. Elevated BP, blood glucose and heart rate are markers of increased sympathoadrenal tone, and all have been shown to have independent prognostic significance in the INTERACT population.^{20, 21} Moreover, blood glucose has been associated with increased arterial contractility in animal models, which could partly explain its association with elevated BP,²² while the association of greater neurological impairment and high admission BP may also be due to central autonomic activation rather than peripheral effects of headache, urinary retention, or infection.¹ The inverse association of greater time from onset to randomization and the high admission BP is consistent with prior observations of earlier presentations with more severe illness and tendency for elevated BP to decline spontaneously over time.^{2, 4} However, as additional factors remained significant after adjustment for time from symptom onset to BP measurement, our analyses highlight the importance of other mechanisms.

Our study included a large and heterogeneous population with rigorous prospective and systematic evaluations of BP, but is limited in being based on a selected clinical trial population where the majority of participants were Chinese and had mild to moderate severity of ICH, and where self-reported hypertension was common but the use of secondary prevention was not (particularly statin use). Thus, the results may not be applicable to those with different

154 demographic and disease characteristics. In addition, we were unable to determine the
155 relationship between the cause of ICH (i.e. hypertensive arteriopathy or cerebral amyloid
156 angiopathy) and elevated BP at admission because these data were not collected.

157 In conclusion, our analyses of predictors of high admission BP in an international RCT of
158 intensive BP reduction early after the onset of ICH suggests that high admission BP at baseline
159 represents poorly controlled pre-morbid hypertension, surrogate markers of autonomic nervous
160 system dysfunction, and occurs in those with more severe neurological impairment.

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Contributors

XW did data analysis, contributed to data interpretation, and wrote the first draft of the report. ECS supervised the analyses, contributed to data interpretation and writing the report. MW, TR, JC, HA and CA obtained funding, planning of the study, supervision, data interpretation, and writing of the report. TM, GC, LS, CC, and CD provided comments on data interpretation and the report.

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Conflicts of Interest

TR is a National Institute of Health Research Senior Investigator, and reports receiving speaking fees from Bayer and Boehringer Ingelheim, and fees for Advisory Panels from Bayer and Daiichi Sankyo. M. Woodward is a consultant for Amgen. J. Chalmers reports research grants and lecture fees from Servier for the ADVANCE trial and post-trial follow-up. CA reports receiving reimbursement for travel expenses and honorarium from Takeda China, and is on Advisory Committees for Medtronic and Astra Zeneca.

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Table 1. Characteristics of patients with acute intracerebral hemorrhage and association with increasing baseline systolic blood pressure (BP)

		Systolic blood pressure			Diastolic blood pressure		
	n=3233	Estimate	SE	P value	Estimate	SE	P value
Demographic							
Age years	63 (13)	-0.652*	0.235	0.006	-4.820	0.183	<0.0001
Female	1191 (36.8)	0.786	0.625	0.208	-3.117	0.533	<0.0001
Chinese	2304 (71.3)	-1.039	0.666	0.119	7.205	0.557	<0.0001
Medical history							
Hypertension	2348 (72.7)	2.113	0.676	0.002	1.036	0.580	0.074
Acute coronary or other cardiac disease	341 (10.6)	-0.779	0.981	0.427	-5.064	0.837	<0.0001
Diabetes mellitus	339 (10.5)	0.821	0.984	0.404	-4.459	0.840	<0.0001
Prior intracerebral hemorrhage	275 (8.5)	-1.423	1.080	0.188	0.413	0.927	0.656
Prior ischemic/undifferentiated stroke	369 (11.4)	-1.947	0.945	0.040	-2.496	0.812	0.002
Admission hyperglycemia (≥6.5 mmol/L)	1552 (50.8)	3.495	0.616	<0.0001	-0.347	0.529	0.513
Medications							
Antihypertensive therapy	1449 (44.9)	-0.231	0.606	0.703	-2.440	0.518	<0.0001
Oral anticoagulant or antiplatelet therapy	368 (11.4)	-2.779	0.948	0.003	-8.547	0.800	<0.0001
Lipid lowering therapy	209 (6.5)	-2.997	1.225	0.015	-8.053	1.042	<0.0001
Clinic features							
Systolic BP, mmHg	179 (17)	-	-	-			
Heart rate, bpm	78 (14)	1.323*	0.215	<0.0001	2.029	0.182	<0.0001
NIHSS score	10 (6-15)	0.199	0.045	<0.0001	0.0005	0.0390	0.990
≥15	915 (28.4)	2.173	0.668	0.001	-0.791	0.574	0.168
GCS score	14 (12-15)	-0.594	0.131	<0.0001	-0.4087	0.1127	0.0003
<13	821 (25.4)	2.711	0.691	<0.0001	1.680	0.593	0.005
CT findings							

Hematoma volume, mL	10.7 (5.6-19.3)	0.199†	0.307	0.517	0.621	0.262	0.018
Left hemisphere	1491 (50.4)	1.115	0.629	0.076	0.635	0.536	0.236
Deep location	2470 (83.5)	-0.916	0.846	0.279	0.899	0.722	0.213
Intraventricular extension	821 (27.8)	1.156	0.702	0.100	-0.751	0.599	0.210
<i>Treatment over first 7 days post-randomization</i>							
Randomised to intensive BP lowering	1602 (49.6)	-0.816	0.602	0.176	-0.254	0.517	0.624
Time from onset to randomization, hours	3.7 (2.8-4.7)	-1.139	0.250	<0.0001	-0.704	0.215	0.001

Data are mean (SD), frequency (%), or median (interquartile range)

BP denoted blood pressure, SE denotes standard error, SD standard deviation, NIHSS National Institute for Health Stroke Scale; IQR, interquartile range; GCS, Glasgow coma scale; BP, blood pressure

Estimate: regression coefficient from Generalised linear model (GLM)

*per 10-unit increase

†per 1 log mL increase

Table 2. Independent predictors of higher baseline systolic blood pressure in acute intracerebral hemorrhage

Variable	Estimate	SE	<i>P</i> value
History of hypertension	2.292	0.691	0.001
Hyperglycemia ≥ 6.5 mmol/L)	2.980	0.619	<0.0001
Oral anticoagulant or antiplatelet therapy	-3.744	0.955	<0.0001
Heart rate, per 10-bpm increase	1.243	0.222	<0.0001
NIHSS score, per 1 point increase	0.152	0.047	0.001
Time from onset to randomization, per 1 hour increase	-1.004	0.255	0.0001

Bpm denotes beats per minute, NIHSS National Institute for Health Stroke Scale, SE standard error.

Estimate: regression coefficient from Generalised linear model (GLM)

Table 3. Independent predictors of systolic blood pressure >180 mmHg within 6 hours of onset of acute intracerebral hemorrhage

	Univariate analysis		Multivariable analysis	
	OR (95%CI)	P Value	OR (95%CI)	P Value
Sex (female vs. male)	1.12 (0.97-1.30)	0.109		
Age, per 10 year increase	0.91 (0.86-0.96)	0.001		
Prior ischemic/undifferentiated stroke	0.88 (0.70-1.09)	0.230		
History of hypertension	1.27 (1.09-1.49)	0.002	1.31 (1.11-1.54)	0.001
Admission hyperglycemia (≥ 6.5 mmol/L)	1.44 (1.25-1.66)	<0.0001	1.40 (1.21-1.62)	<0.0001
Oral anticoagulant or antiplatelet therapy	0.69 (0.56-0.87)	0.001	0.61 (0.49-0.77)	<0.0001
Lipid lowering therapy	0.67 (0.50-0.89)	0.006		
Heart rate, per 10 bpm increase	1.12 (1.07-1.18)	<0.0001	1.23 (1.06-1.18)	<0.0001
NIHSS score, per 1 point increase	1.02 (1.01-1.03)	0.001	1.01 (1.00-1.03)	0.012
Hematoma volume at baseline, per 1 log mL increase	1.03 (0.96-1.11)	0.368		
Randomised to intensive BP lowering	0.94 (0.82-1.08)	0.372		
Time from onset to randomization, per 1 hour increase	0.90 (0.84-0.96)	0.001	0.91 (0.85-0.96)	0.001

Bpm denoted beats per minute, CI confidence interval, NIHSS National Institute for Health Stroke Scale, OR odds ratio

Estimate: regression coefficient from Generalised linear model (GLM)