Early Cognitive Impairment After Intracerebral Hemorrhage in the INTERACT1 study

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Abstract

Background and purpose: Data on cognitive impairment after acute intracerebral hemorrhage (ICH) are limited. We determined the frequency and predictors of cognitive impairment among participants of the pilot phase, Intensive Blood Pressure (BP) Reduction in Acute Cerebral Hemorrhage Trial (INTERACT1).

Methods: INTERACT1 was an open randomized trial of early intensive (target systolic blood pressure [BP] <140mmHg) compared with contemporaneous guideline-recommended BP lowering in 404 patients with elevated systolic BP (150-220mmHg) within 6 hours of ICH onset. Cognitive impairment was defined by scores ≤ 24 on the Mini-Mental State Examination (MMSE) assessed by interview on follow-up at 90-days.

Results: A total of 231 (64.5%) of 358 90-day survivors had MMSE scores for analyses, and 75 (32.5%) had cognitive impairment. In multivariable analysis, older age (odds ratio [OR] 2.48, 95% confidence interval [CI] 1.73 to 3.56 per 10-year increase; $P < 0.001$), female (2.06, 1.00 to 4.23; $P = 0.049$), prior ICH (2.87, 1.08 to 7.65; $P = 0.035$), high baseline National Institute of Health Stroke Scale score (1.06, 1.00 to 1.13; $P = 0.044$), and high mean systolic BP over the first 24 hours post-randomization (1.34, 1.07 to 1.68; $P = 0.011$) were independently associated with cognitive impairment.

Conclusions: One third of patients have significant cognitive impairment early after ICH, which is more frequent in the elderly, females, those with prior ICH and more severe initial neurological deficit, and with persistently high early systolic BP.

Clinical trial registration: INTERACT1 is registered at ClinicalTrials.gov (NCT00226096).

Key words: Intracerebral hemorrhage, cognitive impairment, predictors, INTERACT, trial

Post-stroke cognitive impairment is common, carries a poor prognosis, often poorly recognized,¹ may have a relentless decline over several years.² Although intracerebral hemorrhage (ICH) is well recognized as a serious type of stroke with high burden of premature death and disability,³ data on subsequent cognitive functioning are limited. Cognitive decline is reported in 37% to 61% of patients, up to 4 years after ICH,^{4,5} but these data are from selected and small series. The pilot phase of the Intensive Blood Pressure (BP) Reduction in Acute Cerebral Hemorrhage Trial (INTERACT1) was an international, open, randomized controlled trial that investigated the effects of early intensive BP lowering in patients with acute spontaneous ICH.⁶ Herein, we report the frequency and predictors of cognitive impairment which was assessed among surviving participants at 90 days of follow-up.

Methods

The design and main results of INTERACT1 are outlined elsewhere.⁶ In brief, 404 adult patients with CT-confirmed ICH within 6 hours of onset and elevated systolic BP (150-220 mmHg) were randomly assigned to receive intensive (target systolic BP <140 mmHg within 1 hour) or contemporaneous guideline-recommended (<180 mmHg) BP lowering treatment. The study protocol was approved by the appropriate ethics committee at each participating site and written informed consent was obtained directly from the patient or an appropriate surrogate. INTERACT1 is registered at ClinicalTrials.gov (NCT00226096).

Demographic, clinical characteristics, and medical history including current medications, were recorded at the time of enrolment. Stroke severity was measured using the Glasgow

coma scale (GCS) and National Institutes of Health stroke scale (NIHSS) at baseline, 24 hours, and at Day 7 (or earlier upon discharge from hospital). Computed tomography (CT) scans were performed according to standardized techniques (recommended slice thickness: 5-8 mm) at baseline and centrally analyzed for volume and location of ICH. The primary outcome was the standard dichotomous measure of poor outcome due to death or major disability, defined as a score of 3-6 on the modified Rankin Scale (mRS), undertaken at 90 days by trained local staff who were masked to the treatment allocation. These staff used the Mini-Mental State Examination (MMSE) to assess cognitive function, with impairment defined as a score ≤ 24 .⁷ A cut-off of 18 (severe cognitive impairment) was used for a sensitivity analysis.

Multivariable logistic regression was used to determine the predictors of cognitive impairment. All the variables with $P < 0.05$ in the univariate analysis were included in multivariable analyses, with the full model developed by successively removing all non-significant covariates until all those remaining were statistically significant ($P < 0.05$). Data are reported as odds ratios (OR) with 95% confidence intervals (CI). SAS version 9.3 (SAS Institute, Cary, NC) was used for analyses.

Results

Of the 404 INTERACT1 participants, 46 patients died within 3 months and 127 patients without an MMSE score were excluded. Thus, 231 (64.5%) ICH survivors (median [IQR] age 64 [52-72] years, 35.5% female) with 90-day MMSE scores were included in analyses. Table I of the online-only Data Supplement shows that included patients were clinically less

severe (higher GCS scores, lower NIHSS scores), had smaller hematoma volume and less intraventricular extension (IVH), and lower diastolic BP, at baseline.

The Table shows the univariate predictors of cognitive impairment (MMSE score ≤ 24), present in 75 (32.5%) patients, as older age, female, history of ICH or ischemic stroke, higher baseline NIHSS score, IVH, lower diastolic BP at baseline, and higher mean systolic BP over the first 24 hours post-randomization. The variables were similar in sensitivity analysis using a MMSE cut-off of 18 (in the online-only Data Supplement Table II). In multivariable analyses, older age (OR 2.48, 95% CI 1.73 to 3.56 per 10-year increase; $P < 0.001$), female (2.06, 1.00 to 4.23; $P = 0.049$), prior ICH (2.87, 1.08 to 7.65; $P = 0.035$), higher baseline NIHSS score (1.06, 1.00 to 1.13; $P = 0.044$) and higher systolic BP over the first 24 hours post-randomization (1.34, 1.07 to 1.68; $P = 0.011$) were independently associated with cognitive impairment.

Discussion

In this secondary analysis of the INTERACT1 study dataset, over one third of ICH survivors had significant cognitive impairment, defined by standard ≤ 24 scores on the MMSE at 90 days follow-up. The independent variables associated with this adverse outcome were older age, female, prior ICH history, more severe ICH (higher NIHSS scores), and higher systolic BP over the first 24 hours.

The frequency of cognitive impairment after ICH varies widely across studies, from 37% in a French study of 167 patients⁴ to 61% in a Norwegian study of 134 patients,⁵ over approximately 4 years of follow-up. Our lower rate of 32.5% is consistent with the trial

population having predominantly mild-moderate severity of ICH who were free of major premorbid cognitive impairment, assessed relatively early after the illness, when cognitive function is known to decline over time.⁸

Interestingly, our study provides further support for the adverse consequences of the hypertensive response in ICH, in showing that high mean systolic BP over the first 24 hours was related to cognitive impairment. This is in line with related evidence of hypertension and vascular dementia and Alzheimer's disease,⁹ although long-term BP lowering has not shown to impact on the risk of dementia.^{10,11} The association between BP lowering treatment and risk of cognitive decline is complex and confounded by an interaction with stroke prevention.¹²

Limitations in this study include the small sample size and selection bias related to the inclusion in a clinical trial and of missing MMSE outcome. Furthermore, we did not have an ability to assess the impact of ICH on pre-existing cognitive impairment or in relation to education, and that the MMSE is a rather crude measure of cognitive functioning.

In summary, our study has shown there is a high frequency of cognitive impairment in the first few months after the onset of ICH, which is related not just to established factors, such as age, sex, and severity of the initial neurological deficit, but also to persistent elevation in systolic BP in the first 24 hours.

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Disclosures

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Table Patient characteristics, by cognitive function at 90-day after intracerebral hemorrhage

	MMSE >24 (n=156)	MMSE ≤24 (n=75)	<i>P</i> value	Adjusted OR (95%CI)	<i>P</i> value
Age, years	59 (11)	69 (12)	<0.0001	2.48 (1.73-3.56)*	<0.001
Female	48/156 (30.8)	34/75 (45.3)	0.030	2.06 (1.00-4.23)	0.049
History of intracerebral hemorrhage	11/156 (7.1)	15/75 (20.0)	0.004	2.87 (1.08-7.65)	0.035
History of ischemic stroke	11/156 (7.1)	12/75 (16.0)	0.033		
History of acute coronary syndrome	3/156 (1.9)	3/75 (4.0)	0.393†		
Diabetes mellitus	15/156 (9.6)	4/75 (5.3)	0.267		
History of hypertension	115/156 (73.7)	57/75 (76.0)	0.710		
Use of antihypertensive therapy	70/156 (44.9)	30/75 (40.0)	0.484		
Use of warfarin anticoagulation	0/156 (0.0)	1/75 (1.3)	0.325†		
Use of aspirin/other antiplatelet	10/156 (6.4)	10/75 (13.3)	0.080		
Baseline GCS‡	150 (13.5-15)	14 (13-15)	0.122		
Baseline NIHSS§	7 (4-13)	10 (5-15)	0.040	1.06 (1.00-1.13)	0.044
Time to CT scan, hours	1.7 (1.0-2.6)	1.6(1.2-2.3)	0.672		
Baseline SBP, mmHg	180 (18)	180 (18)	0.977		
Baseline DBP, mmHg	103 (13)	98 (13)	0.010		
Achieved SBP over 24 hours	149 (16)	155 (20)	0.028	1.34 (1.07-1.68)*	0.011
Hematoma characteristics					
Deep	116/138 (84.1)	48/60 (80.0)	0.487		
Lobar	8 (5.8)	8 (13.3)	0.090†		
Left hemisphere	71/138 (51.5)	34/60 (56.7)	0.448		
Volume, mL	8.4(3.7-13.4)	8.8(4.5-16.8)	0.460		
IVH extension	22/138 (15.9)	17/60 (28.3)	0.044		
Randomized to intensive BP lowering	79/156 (49.4)	36/75 (48.0)	0.707		

Data are n (%), mean (SD), or median (IQR). *P* values are based on chi-squared or Kruskal-Wallis test

BP indicates blood pressure, CI confidence interval, CT Computerized tomography, DBP diastolic BP, GCS Glasgow Coma Scale, NIHSS

National Institutes of Health Stroke Scale, OR odds ratio, SBP systolic BP

*Age and mean achieved BP over the first 24 hours are for every 10 units increase in multivariable analysis

†Fisher's exact test

‡GCS scores range from 3 (deep coma) to 15 (normal, alert)

§NIHSS scores range from 0 (normal, no neurological deficit) to 42 (coma with quadriplegia)

||basal ganglia or thalamus