Influence of time to achieve target systolic blood pressure on outcome after intracerebral hemorrhage: the Blood Pressure in Acute Stroke Collaboration (BASC)

Running head: Achieving and maintaining blood pressure control after acute ICH: IPD meta-analysis

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Abstract

Background: We aim to investigate whether an earlier time to achieving and maintaining systolic blood pressure (SBP) at 120-140 mmHg is associated with favorable outcomes in a cohort of patients with acute intracerebral hemorrhage (ICH).

Methods: Individual patient data from randomized controlled trials conducted between 2008 and 2020 were aggregated in the Blood Pressure in Acute Stroke Collaboration (BASC). Time was defined as time from symptom onset plus the time (hour) to first achieve and subsequently maintain SBP at 120-140 mmHg over 24 hours. The outcomes were functional status measured by the modified Rankin scale (mRS) at 90-180 days, hematoma expansion at 24 hours post randomization, and cardiac or renal adverse events. A generalized linear mixed models was used, with adjustment for covariables and trial as a random effect.

Results: 5761 patients (mean age 64.0 [SD 13.0], 2120 [36.8%] females) were included in analyses. Earlier SBP control was associated with better functional outcomes (mRS 3-6, odds ratio 0.98, 95% confidence interval 0.97-0.99, per 1 hour decrease, P=0.002) and a significant lower odds of hematoma expansion (0.98, 0.96-1.00, P=0.049). This association was stronger in patients with larger baseline hematoma volume (>10 mL) compared with those with smaller baseline hematoma volume (≤10 mL) (P=0.006 for interaction). Earlier SBP control was not associated with cardiac or renal adverse events.

Conclusions: Our research indicates a strong relationship between early control of SBP within 120-140 mmHg and better outcomes in one-third of patients with acute ICH who sustained this target range. Specifically, managing to control SBP within the first 6 hours of the first 24-hour period following ICH can increase the odds of good functional recovery at 90 days by 12%. These

data provide further support for the value of early recognition, rapid transport, and prompt initiation of treatment of patients with ICH.

Introduction

Pooled analysis of second intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) and Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-II) studies suggest that careful titration and continued smooth control of systolic blood pressure (SBP) over 24 h, potentially even to levels as low 120–130 mmHg, provides benefits to adults admitted to hospital with acute intracerebral hemorrhage (ICH) of mild-to-moderate severity. Achieving every 10 mmHg reduction in mean SBP over the first 24 hours is associated with a 10% increase in the odds of better functional recovery after ICH, down to levels of 120-130 mmHg; and similarly of improved outcomes for sustained low levels of SBP over 24 hours.[1, 2]

It has been hypothesized that any potential benefit of blood pressure (BP) lowering after acute ICH might be enhanced by earlier reductions in SBP.[3] Secondary analysis of INTERACT2 identified trends for benefit in relation to the time, intensity, and mean level of BP control on clinical outcomes and hematoma expansion (HE).[4-6] A post-hoc analysis of ATACH-II suggested that BP lowering within 2 hours of ICH onset is associated with lower odds of HE at 24 hours and improved 90-day outcomes compared with the initiation of treatment at later time points.[7] However, the window for the potential benefit of BP lowering to the optimal level of 120-140 mmHg has not been extensively studied. Our hypothesis is that the window for the potential benefit of BP lowering to the optimal level of 120-140 mmHg is likely to overlap with the period of highest risk of HE, such that the earlier to achieve and maintain such an optimal level would provide greater benefits to patients.

The international Blood pressure in Acute Stroke Collaboration (BASC) pooled individual patient data (IPD) from 16 randomized controlled trials (RCT) of BP management in acute ICH.[8, 9]

Herein, we report our assessment of whether an earlier time to achieving and maintaining SBP at 120-140 mmHg is associated with better outcomes after acute ICH.

Methods

Search strategy and selection criteria

We performed a systematic review according to a pre-specified protocol (PROSPERO registration number CRD42019141136) to identify RCTs that assessed the effects of different BP lowering strategies during the acute phase (within 7 days) of stroke.[8, 9] We identified eligible studies in the Cochrane Central Register of Controlled Trials, EMBASE and MEDLINE databases from inception to June 23 2020, and in the reference lists of published systematic and ad hoc reviews using a comprehensive search strategy, limited to humans, combining terms for ICH, BP lowering interventions, and RCTs, with no language restrictions.

We included RCTs that involved adults (age ≥18 years) with acute primary spontaneous ICH (<7 days from onset); randomized participants to fixed active agent or intensive, titrated target-based BP lowering interventions with oral, sublingual, transdermal, or intravenous agents, in single or combination therapy versus placebo or contemporaneous guideline BP management; and recorded clinical and/or radiological outcomes.

Two authors screened titles and abstracts, and assessed full-text articles for eligibility against the inclusion criteria. We sent our protocol and letters of invitation to investigators of eligible studies, inviting them to join the BASC collaboration and share IPD. This was followed by an invitation to join (online or in-person) BASC collaborator meetings at international conferences. To ensure transparency, collaborators sharing data with BASC were asked to sign a data transfer agreement for the predefined and appropriate use of their data according to our protocol.

Data management

We checked IPD with published results to ensure data were complete and transferred without error; queries were resolved with individual trial investigators. We harmonized RCT datasets according to agreed nomenclature.[8, 9] The details of the included RCTs, trial design, and available BP recording were recorded (Supplemental Table S1).[10-25]

Ethical approval for the original studies was sought and is documented by each study. Further ethical approval was not required as no new patient data were collected nor was there any deviation from the original purpose of each study.

Outcomes

The primary outcome was functional status, defined by the distribution of scores on the modified Rankin scale (mRS), which ranges from 0 (no symptoms) to 6 (death) at the end of follow-up (90-180 days). Secondary outcomes were: (i) death or dependency (mRS scores 3–6); (ii) death or severe dependency (mRS 4–6); and (iii) death. The radiological outcome was absolute (≥6 mL increase from baseline) HE at 24 hours.[24] Safety outcomes were: (i) early neurological deterioration (as defined by each individual RCT); (ii) renal serious adverse event (SAE) (as defined by each individual RCT); and (iii) cardiac SAE, as defined by individual RCT, to include those fatal, non-fatal, and treatment-related.

Data analysis

The one-stage approach provides additional statistical power and flexibility by combining all IPD into a single meta-analysis and permits subgroup analyses according to individual characteristics of interest. Descriptive statistics are described as mean (SD) or median (IQR) for continuous data,

or frequency (percentage) for categorical data, and Kruskal-Wallis or chi-squared tests are used to make comparisons.

Time was defined as the time from symptom onset to randomization plus the time from randomization to achieve and maintain SBP 120-140 mmHg. For example, if a patient was randomized at 2 hours post-ictus, achieved the SBP target at 2 hours post-randomization and have this maintained until 24 hours, the time for this patient was 4 hours. For those who achieved SBP 120-140 mmHg at some time points but not maintained until 24 hours, time was defined as the time from symptom onset to randomization plus 25. And for those who did not achieve the target, time was defined as the time from symptom onset to randomization plus 26. We used generalized linear mixed models with covariables (age, sex, region, baseline SBP, history of ischemic heart disease, time to randomization, randomized treatment, baseline National Institutes of Health Stroke Scale [NIHSS] scores of ≤10 vs. >10, baseline hematoma volume of ≤10 vs. >10 mL, history of stroke, history of hypertension, and SBP variability), and the source RCT as a random effect to account for clustering. Analyses of ordinal and binary outcome variables are presented as odds ratios (OR) with 95% confidence intervals (CI). We checked the proportional odds assumption using the likelihood ratio test before undertaking ordinal analyses of outcomes on the mRS. Patients with missing data on any of the aforementioned variables would be excluded from the multivariable analysis.

In order to test if age, NIHSS score, baseline hematoma volume, and randomized treatment modified associations, we performed the following subgroup analysis with an interaction term in models to test heterogeneity: age (≤60 vs. >60 years), NIHSS scores (≤10 vs. >10), baseline hematoma volume (≤10 vs. >10 mL), and randomized treatment (active/intensive vs. placebo/guideline).

We also conducted a sensitivity analysis to restrict patients with complete data of five BP readings at 1, 1-6, 6-12, 12-18, and 18-24 hours. All analyses were undertaken with SAS 9.4 and R studio 4.2. And the study was reported according to STROBE guidelines.[26]

Data sharing

Requests for sharing of de-identified IPD from individual trials used in these analyses should be directed to the corresponding author of the individual trial. The ATACH-II trial data, including de-identified participant data, are available indefinitely at the National Institute of Neurological Disorders and Stroke data archive (https://www.ninds.nih.gov/). To gain access, requesters will need to sign a data-access agreement.

Role of the funding source

This work was supported by a an investigator grant from the National Health and Medical Research Council (NHMRC) of Australia. The corresponding author had full access to all of the data and final responsibility to submit for publication.**Results**

We included 5761 patients with at least one BP reading in the first 24 hours post-randomization, among whom 4159 had complete BP readings (Supplementary Figure S1). Table 1 summarizes the baseline characteristics by the time to achieve and maintain the target SBP. Overall, mean age was 64.2 (SD 12.9) years and 2266 (36.4%) were female, with a median level of baseline neurological impairment defined by NIHSS scores of 11 (range 0-42, IQR 7-16). Overall, mean SBP and diastolic BP (DBP) at randomization were 177.3 mm Hg (SD 20.3) and 100.0 mm Hg (SD 15.7), respectively, and the median time from onset to randomization to various BP lowering strategies was 3.8 hours (IQR 2.6-5.3). The median hematoma volume on the diagnostic CT brain scan was 10.7 mL (IQR 5.2-20.7).

Approximately one-third of participants achieved and maintained SBP at 120-140 mmHg over 24 hours post-randomization (Supplementary tables 2 and 3). Patients who achieved SBP 120-140 mmHg within the first 24 hours after randomization were younger, had lower SBP at randomization, and lower NIHSS scores, and were less likely to have a 'do not attempt resuscitation order' compared to those in whom SBP range of 120-140 mmHg was not achieved (table 1). All the significant variables from the univariate analysis were put into a multivariate model, which left three variables remaining significant: baseline SBP (OR 0.99, 95% CI 0.98-0.99 , P<0.0001), baseline hematoma volume (0.99, 0.99-1.00, P=0.0002), and hematoma location (lobar vs. infratentorial/posterior fossa: 1.61, 1.17-2.20, P=0.02; basal ganglia/deep vs infratentorial/posterior fossa: 1.50, 1.16-1.94, P=0.04). Thus, patients with lower baseline SBP, smaller baseline hematoma volume, and lobar/ basal ganglia/deep hemorrhages compared to other locations are more likely to have achieved and maintained SBP at an optimal level of 120-140 mmHg.

Figure 1 shows the adjusted association between time to achieve SBP range of 120-140 mmHg and the primary, secondary, safety, and radiological, outcomes. As ordinal analyses of the primary outcome of functional status assessed across the 7-levels of the mRS (p=0.007) did not meet proportional odds assumption, death or dependency (mRS scores 3–6) was used instead as the primary outcome. There was a significant linear association between the time of achieving the target and functional outcomes (Figure 2). The earlier the achievement and maintenance of SBP 120-140 mm Hg was significantly associated with less risk of death or dependency (mRS scores 3–6, OR 0.98, 95%CI 0.97-0.99, p=0.002; mRS scores 4–6, 0.98, 0.97-0.99, P=0.007, for per 1 hour decrease). This finding was consistent in the sensitivity analysis restricted to patients with complete BP readings (0.99, 0.98-1.00, P=0.026, for per 1 hour decrease). The earlier the

achievement and maintenance of SBP 120-140 mm Hg was significantly associated with a lower odds of death (0.97, 0.95-0.99, P=0.005, for per 1 hour decrease). The earlier the achievement and maintenance of SBP 120-140 mm Hg was not significantly associated with neurological deterioration, cardiac or renal SAEs.

There were 2508 patients from 5 RCTs with complete IPD for the analysis of the secondary outcome of HE at 24 hours. The earlier the achievement and maintenance of SBP 120-140 mm Hg was significantly associated with less odds of HE at 24 hours (0.98, 0.96-1.00, P=0.049).

The association between achievement and maintenance of SBP 120-140 mmHg and the mRS scores 3–6, was not modified by randomized treatment (active/intensive vs. placebo/guideline, P= 0.317 for interaction), NIHSS scores (≤10 vs. >10, P= 0.132 for interaction), and age (≤60 vs. >60 y, P=0.43 for interaction). However, the association was stronger in patients with larger baseline hematoma volume (>10 mL, 0.98, 0.96-0.99) than in those with smaller baseline hematoma volume ≤10 mL, 0.99, 0.97-1.01) (P= 0.006 for interaction).

Discussion

In this meta-analysis of IPD from RCTs of various BP lowering interventions in adults with predominantly mild-to-moderate severity acute ICH, we found a clear time relation between an earlier SBP control (120-140 mm Hg) and a reduced odds of HE/improved functional recovery. Achieving and maintaining SBP within the range of 120-140 mmHg, starting within 6 hours of the initial 24-hour period after an ICH occurs, may lead to a 12% improvement in the chances of good functional recovery at 90 days. The treatment was safe without evidence of an increase in neurological deterioration, cardiac, and renal SAEs.

BP lowering could have a larger effect when initiated within the first few hours of ICH onset, as this is when HE is likely to be greatest.[3] However, no clear time-relation of BP control on outcomes for patients randomized early versus late was identified in individual RCTs (INTERACT2[27], ATACH-2[28]), the pooled data from INTERACT2 and ATACH-II,[1, 2] nor in BASC studies overall.[8, 9] These current analyses could explain this inconsistency as less than 2% of participants had achieved and maintained SBP to an optimal level of 120-140 mmHg within 1 hour post-randomization in RCTs. In fact, this level was achieved and maintained in only 10% of participants at 12 hours after the initiation of treatment, and more than 15 hours after the onset of ICH, which is outside the time window of greatest occurrence of HE. It may not only be time to initiation of treatment that matters,[7] but also the intensity of BP reduction to a desirable target that is crucial to affecting outcome from ICH.[29]

Our findings provide evidence for the knowledge gap highlighted in the latest ICH management guidelines uncertainty as to whether ultra-early BP lowering is beneficial.[3] We found that earlier achievement and maintenance of SBP 120-140 mmHg was associated with greater reductions in HE and improved functional status. Our analyses add to existing evidence that the earlier to achieve SBP 120-140 mm Hg after ICH is beneficial, with the persistence of control (maintenance) also being important, as evidenced by improved functional outcomes. Our findings confirm those from a previous IPD meta-analysis of 5435 patients which showed that 0.5-3 hours after symptom onset is the time frame when most HE occurs and thus, when the effect on attenuating HE is likely to be the greatest.[30] This informs the design of future RCTs in ICH that assess treatments targeting HE to enrich the study population with patients at the highest risk of HE, and in more broadly highlighting the value of early recognition, rapid transport, and prompt initiation of treatment of patients with ICH.

We found the time relation between an earlier SBP control (120-140 mm Hg) and an improved functional recovery was stronger in patients with baseline hematoma volumes >10mL than those with baseline hematoma volume ≤10 mL, although patients with smaller baseline hematoma volume were more likely to have achieved and maintained SBP at an optimal level of 120-140 mmHg. However, as our study predominantly included small-to-medium sized hematomas, these results require confirmation in patients with large and more severe ICH.

Key strengths of our study include the broad inclusion criteria and availability of IPD from most high-quality ICH and mixed stroke RCTs in the area. Our study had a sample of patients with ICH of 6221, compared with 4360 in a previous study-level meta-analysis of studies only with ICH.[31] The unique dataset facilitated robust covariable-adjusted analyses, which provided reliable evidence about achieving and maintaining SBP 120-140 mmHg on HE. However, our study is limited by selection bias related to RCT populations where patients with severe ICH or early planned surgery were excluded. Furthermore, the heterogeneity of different BP lowering interventions used in the RCTs creates uncertainty on the most desirable strategy, timing, agent and BP lowering dosing protocol. To overcome this, we have included SBP variability in the multivariable analysis to minimize heterogeneity. In addition, the imprecise and low frequency of BP measurements, and the categorization of patients, may have been influenced by how frequently BP was monitored across trials. Finally, the post hoc observational nature of these analyses, raise the potential for random error and residual confounding from imbalances between groups, despite sensitivity analysis restricted to patients with complete BP readings showing consistent results.

In summary, our study has shown that an earlier achievement and maintenance of this target reduces the likelihood of growth of small-medium sized hematomas, which translates into

improved odds of recovery. These data provide further support for the value of early recognition, rapid transport, and prompt initiation of treatment of patients with ICH.[17]

Author Contributions

XW did the planning, systematic review, analyses, and data interpretation, and wrote the first draft of the report. JY contributed to planning, data interpretation, and the first draft of the report. TJM, ECS and LJW contributed to planning, analyses and data interpretation, and provided comments on the report. ZKL contributed to the systematic review, data interpretation and provided comments on the report. PMB, CSA, and JC conceived the study, obtained funding for some of the original trials, and supervised planning, analyses, data interpretation, and writing of the report. All other authors contributed to data collection, analysis, interpretation and writing of the report.

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PMB, NS, JMW; SCAST: Eivind Berge (deceased), ECS; VENUS: Janneke Horn.

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Author Contributions

XW contributed to planning, systematic review, analyses, data interpretation and wrote the first draft of the report. JY contributed to planning, data interpretation and the first draft of the report. TJM, ECS and LJW contributed to planning, analyses and data interpretation and provided comments on the report. ZKL contributed to the systematic review, data interpretation and provided comments on the report. PMB, CSA, and JC conceived the study, obtained funding for some of the original trials, and supervised planning, analyses, data interpretation, and writing of the report. All other authors contributed to data collection, analysis, interpretation and writing of the report.

Competing interests

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448 Figure legends

449 **Figure 1** Association of time to achieve SBP of 120-140 mmHg and maintained until 24 h, and
450 the primary and secondary clinical, and safety and radiological outcomes

451 Footnote: SBP systolic blood pressure; mRS modofied Rankin Scale; SAE serious adverse event

452 **Figure 2** The predicted probability of poor outcome (mRS 3-6) by time to achieve and maintain
453 SBP of 120-140 mmHg

454 Footnote: SBP systolic blood pressure

455

Table 1. Baseline characteristics by the time in achieving target SBP and maintaining until 24 hours

Characteristics	Achieving target SBP and maintaining until 24 hours (n=1780)	Achieving target SBP but not maintaining until 24 hours (n=1632)	Not achieved (n=2349)	P
Age (yr)	63.7 (13.1)	63.9 (12.7)	64.2 (13.2)	0.452
Sex (% female)	664/1780 (37.3)	640/1632 (39.2)	816/2349 (34.7)	0.014
Geographical region[1]				<0.001
America	235/ 1780 (13.2)	314/ 1632 (19.2)	475/ 2349 (20.2)	
Asia	1153/1780 (64.8)	970/1632 (59.4)	1226/2349 (52.2)	
Europe	392/1780 (22.0)	348/1632 (21.3)	648/2349 (27.6)	
SBP at randomization (mmHg)	174.5 (19.7)	175.6 (20.1)	180.9 (20.5)	<0.0001
DBP at randomization (mmHg)	99.0 (15.0)	99.4 (15.6)	101.1 (16.3)	0.0004
NIHSS score	11.0 (6.0 - 15.0)	11 (6-16)	12 (8-17)	<0.0001
GCS score	14.0 (13.0 - 15.0)	14.0 (13.0 - 15.0)	15.0 (13.0 - 15.0)	0.250
History of hypertension	1286/1763 (72.9)	1216/1629 (74.6)	1696/2307 (73.5)	0.520
History of diabetes mellitus	221/1756 (12.6)	207/1593 (13.0)	304/2281 (13.3)	0.785
History of stroke	285/1769 (16.1)	310/1622 (19.1)	367/2294 (16.0)	0.021
History of ischemic heart disease	201/1756 (11.4)	145/1585 (9.1)	194/2245 (8.6)	0.008
Current use of antihypertensive drugs	805/1767 (45.6)	685/1490 (46.0)	879/2030 (43.3)	0.214
Current use of antiplatelet drugs	112/1148 (9.8)	114/1162 (9.8)	109/1122 (9.7)	0.997
Current use of anticoagulant drugs	41/1147 (3.6)	31/1162 (2.7)	34/1119 (3.0)	0.449
Hematoma volume (mL)	10.0 (5.0 - 18.2)	11.1 (5.7 - 21.0)	10.4 (5.0 - 20.2)	0.002
Hematoma location				0.001

Lobar	169/1389 (12.2)	175/1180 (14.8)	159/1276 (12.5)	
Basal ganglia/deep	1165/1389 (83.9)	926/1180 (78.5)	1030/1276 (80.7)	
Infratentorial/posterior fossa	55/1389 (4.0)	79/1180 (6.7)	87/1276 (6.8)	
Intraventricular hemorrhage	445/1661 (26.8)	438/1530 (28.6)	683/2091 (32.7)	0.0003
Time from ICH onset to randomization (hr)	3.6 (2.7 - 4.6)	3.5 (2.5 - 4.7)	3.8 (2.4 - 5.9)	<0.0001
DNAR	77/1606 (4.8)	63/1362 (4.6)	102/1395 (7.3)	0.002
Intubation	140/1678 (8.3)	119/1422 (8.4)	116/1526 (7.6)	0.677
Neurosurgery	89/1678 (5.3)	89/1422 (6.3)	82/1524 (5.4)	0.455

Data are numbers (%), mean (standard deviation), or median (IQR)

GCS denotes Glasgow coma scale; NIHSS National, Institute of Health Stroke Scale; SBP, systolic blood pressure; ICH, intracerebral hemorrhage; DNAR, do not attempt resuscitation order

[1] Geographical region denotes the country in which they were treated