Location of Hemorrhage as Predictive Factor for Refractoriness to Blood Pressure Control in Acute, Non-lobar, Hypertensive Intracerebral Hemorrhages

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ABSTRACT

Background. Uncontrolled hypertension in acute intracerebral hemorrhages (ICH) may cause hematoma expansion within the first 24 hours, and increase patient mortality. We investigated whether there was an association between ICH location and the difficulty in lowering BP in patients with acute hypertensive non-lobar ICH.

Methods. This is a retrospective cohort study of adults diagnosed with non-lobar ICH admitted at a tertiary hospital over a 2-year period. We documented the time to attain target mean arterial pressure (MAP) of 110–130 mmHg, as well as the use of antihypertensive medications.

Results. Of 357 patients admitted for non-lobar ICH, 47 patients fulfilled the study criteria. Basal ganglia hemorrhages were the most common (47%), followed by thalamic (34%), cerebellar (11%), and pontine hemorrhages (8%). While there were no significant differences in baseline MAP among the different sites of hemorrhage, those with thalamic ICH had a significantly longer time-to-target MAP ($p=0.02$) and required three or more classes of oral antihypertensive medications ($p<0.001$).

Conclusions. Acute thalamic intracerebral hemorrhages may require multiple classes of antihypertensives to lower blood pressure to safer levels.

Key Words: intracerebral hemorrhage, refractory hypertension, thalamic, hemorrhage, blood pressure control

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Background

Uncontrolled hypertension in acute spontaneous intracerebral hemorrhages (SICH) largely contributes to the continued expansion of hematoma volume within the first 24 hours and leads to increased mortality.[1,2] Continued hematoma growth up to 6 hours following the initial hemorrhage has been attributed to uncontrolled hypertension and localized coagulopathy. Hematoma volume of greater than 60 mL as well as initial Glasgow Coma Score (GCS) of 9 or less have been associated with increased mortality.[3] Current clinical practice guidelines for SICH recommend careful lowering of the blood pressure (BP) using titratable antihypertensive medications such as labetalol, hydralazine, and nicardipine, while maintaining adequate cerebral perfusion pressure.[4] Recent trials such as INTERACT and ATACH demonstrated that lowering systolic BP to less than 140 mmHg is safe and reduces risk of hematoma expansion.[5,6]

To our knowledge there are no published articles on the relationship between the location of intracerebral hemorrhage and the difficulty of lowering blood pressure in patients with acute hypertensive SICH. It is unclear whether patients with different sites of non-lobar SICH will have the same response to antihypertensive therapy during the first 48 hours of stroke onset. Our aim was to investigate whether there was an association between the location of the hematoma and the difficulty in lowering the blood pressure in patients with acute hypertensive non-lobar intracerebral hemorrhage.

Methods

This is a retrospective cohort study of patients diagnosed with non-lobar hemorrhagic stroke admitted at a tertiary hospital from January 2006 to December 2007. The study was approved by the hospital's committee on research implementation and development, comprising the technical and ethics review boards. The study included all patients (aged over 45 years), diagnosed with non-lobar intracerebral hemorrhages (ICH) by neuroimaging (cranial computed tomography), and admitted within 48 hours post-ictus, regardless of initial Glasgow coma score (GCS). Patients

demonstrated to have secondary hypertension and/or bleeding diatheses or coagulopathies were excluded, as well as those with compelling indications for stricter blood pressure control (hypertensive encephalopathy, aortic dissection, acute renal failure, acute pulmonary edema, or acute myocardial infarction).[7] Cerebral infarcts with extensive hemorrhagic transformation were likewise excluded. Any neurosurgical intervention such as evacuation of hematoma and external ventricular drainage for hydrocephalus was recorded. The hospital records of patients who fulfilled the inclusion criteria and data regarding their co-morbidities was reviewed.

We documented the initial systolic, diastolic, and mean arterial blood pressure recorded at the emergency room as well as the antihypertensive medications administered. Based upon the 2010 guidelines of the American Heart Association and American Stroke Association, adequate BP control was defined as achieving the target MAP of 110–130 mmHg within 48 hours of admission.[8] We used the following as outcome measures: (1) the time in hours to achieve the target MAP; (2) the use of more than one class of antihypertensive medications to lower the BP; (3) neurosurgical interventions such as external ventricular cerebrospinal fluid drainage or surgical evacuation of the hematoma; and (4) mortality from all causes.

Statistical Analysis

We used Kruskal-Wallis test for non-normally distributed continuous data such as BP and MAP, and Fisher test for categorical data. Multivariate analysis using linear regression was performed to determine predictors for the time to achieve target MAP. Log rank analysis was also used to determine significant differences in time to target MAP among the different sites of ICH. Statistical significance was set at $p<0.05$. We used the open source CRAN R statistical software for our data analysis (http://www.R-project.org/).

Results

A total of 357 non-lobar hemorrhagic stroke patients aged 46 and above were admitted at a tertiary hospital from January 2006 to December 2007. Ninety-one charts were available and obtained for review, of which 47 patients satisfied the inclusion criteria for the study. Most of these patients were male (64%). In this study, basal ganglia hemorrhages were most common (47%), followed by thalamic (34%), cerebellar (11%), and pontine hemorrhages (8%). This data is comparable to both Western and Asian data regarding the common locations of non-lobar hemorrhages.[9,10] Table 1 summarizes the demographics of the population in the study. There were no significant differences in the initial hematoma volume among the different sites of ICH (chi-squared=53.8482, df=66, p=0.86).

The MAP on admission was 128±21 mmHg. There were no significant differences in baseline MAP among the different sites of hemorrhage (Kruskal-Wallis chi-squared=21.8637, df=21, p=0.41), and all the patients received intravenous nicardipine infusion titrated to a maximum of 15 mg/hour to achieve the desired MAP of 110–130 mmHg. The target MAP was attained within the first 48 hours of admission in 65% of the patients. The patients with thalamic hemorrhages received nicardipine infusions for a mean duration of 4.4 days, as compared to the patients with basal ganglia (2.3 days), pontine (2.0 days), and cerebellar hemorrhages (1.7 days).

The patients with thalamic hemorrhages had a mean time to target MAP of 93 hours, which was significantly longer than patients with hemorrhages in other areas (p=0.02) (Figure 1). Log rank analysis did not show significant differences in the survival curves of the different locations of ICH (chi square=3.6, p=0.30, Figure 2). Patients with thalamic hemorrhages were more likely to be on more than two classes of oral antihypertensive medications ($p<0.001$) compared with patients with non-thalamic hemorrhages. There was no association between hemorrhage volume and the time to target MAP. The length of time to reach target MAP did not lead to any increase in neurosurgical intervention or mortality. The linear regression analysis is summarized in Table 2.

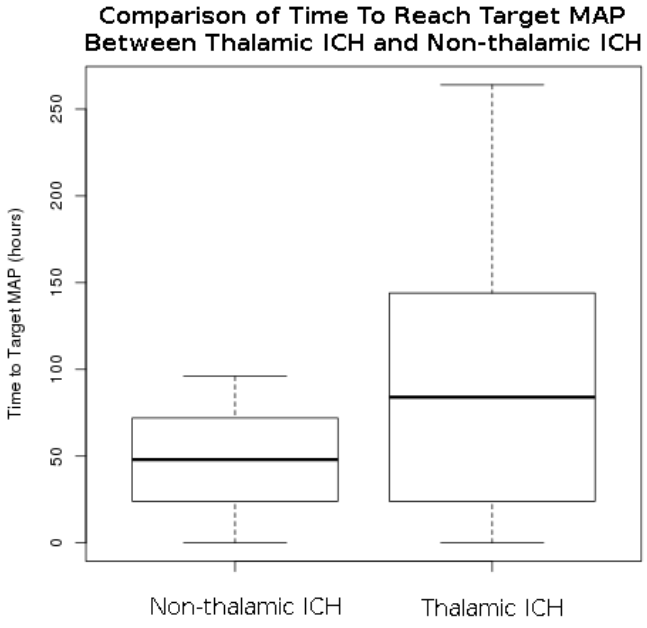

Figure 1. Comparison of Time to Target MAP in Thalamic SICH vs. Non-Thalamic SICH

Table 1. Baseline Characteristics

	Thalamus (N = 16)	Basal Ganglia (N = 22)	Pons (N = 4)	Cerebellum (N = 5)
Median age (IQR) (years)	58 (55 - 71)	50 (48 - 56)	56 (54 - 58)	61 (60 - 69)
Female, *n* (%)	4 (25)	7 (32)	1 (25)	0 (0)
Hypertension, *n* (%)	14 (88)	15 (68)	4 (100)	5 (100)
Diabetes, *n* (%)	0 (0)	2 (9)	0 (0)	2 (40)
Initial Systolic BP, mean, s.d. (mm Hg)	185.0 ± 27.3	177.7 ± 28.4	200.0 ± 58.9	156.4 ± 16.3
Initial Diastolic BP (mm Hg)	105.3 ± 16.7	100.9 ± 17.7	107.5 ± 38.6	93.6 ± 11.6
Initial MAP (mm Hg)	131.9 ± 18.7	126.5 ± 19.2	138.3 ± 42.6	114.5 ± 12.9
Median Glasgow Coma Score	11	14	12	11
Initial hematoma volume (mL)	9.8 ± 7.3	15.9 ± 9.1	3.0 ± 1.3	12.2 ± 6.6
	Thalamus (N = 16)	**Basal Ganglia (N = 22)**	**Pons (N = 4)**	**Cerebellum (N = 5)**
Nicardipine, *n (%)*	11 (68)	16 (73)	3 (75)	3 (60)
Beta blockers, *n (%)*	9 (56)	12 (54)	4 (100)	2 (40)
ACE inhibitors, *n (%)*	11 (69)	15 (68)	3 (75)	3 (60)
Calcium channel blockers, *n (%)*	11 (69)	6 (27)	3 (75)	2 (40)
Angiotensin II receptor blockers, *n (%)*	9 (56)	2 (9)	0 (0)	1 (20)
Single antihypertensive agent, *n (%)*	1 (6)	11 (50)	0 (0)	2 (40)
2 antihypertensive agents, *n (%)*	4 (25)	8 (36)	2 (50)	3 (60)
≥3 antihypertensive agents, *n (%)*	11 (69)	3 (14)	2 (50)	0 (0)

Table 2. Linear Regression Analysis for Clinical Endpoints

	More than 3 antihypertensive class of drugs	More than 48 hrs to target MAP	Underwent Neurosurgery	Mortality
Age	1.00 (0.98 – 1.03)	0.99 (0.97 – 1.01)	0.99 (0.98 – 1.00)	1.00 (0.99 – 1.02)
Female gender	0.92 (0.54 – 1.56)	0.89 (0.63 – 1.26)	1.68 (0.47 – 5.94)	1.09 (0.76 – 1.56)
DM	0.51 (0.21 – 1.25)	0.87 (0.49 – 1.56)	0.86 (0.66 – 1.13)	0.94 (0.51 – 1.71)
Initial GCS	1.06 (0.97 – 1.16)	0.98 (0.92 – 1.04)	**0.93 (0.91 – 0.96)*****	0.95 (0.89 – 1.01)
Volume of ICH	1.00 (0.97 – 1.03)	0.99 (0.97 – 1.01)	0.99 (0.98 – 1.00)	1.00 (0.97 – 1.02)
Location of ICH				
Thalamus	**3.06 (1.76 – 5.30)*****	0.70 (0.49 – 1.01)	2.15 (0.53 – 8.68)	0.96 (0.66 – 1.40)
	2.65 (1.01 – 6.97)			
Pons	1.23 (0.54 – 2.78)	0.56 (0.30 – 1.06)	1.46 (0.33 – 6.39)	1.36 (0.71 – 2.60)
Cerebellum		1.37 (0.81 – 2.33)	**1.43 (1.12 – 1.83)****	0.89 (0.52 – 1.55)

*** $p < 0.001$
** $p < 0.01$

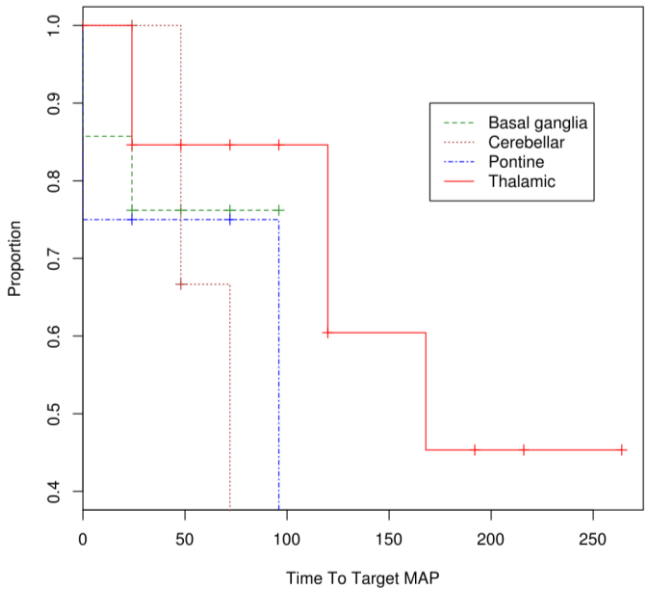

Figure 2. Survival Curve of SICH Patients' Time to Target Mean Arterial Pressure

Discussion

Patients with acute thalamic hemorrhages may have markedly refractory hypertension requiring combinations of antihypertensive drugs on top of intravenous nicardipine. The refractoriness of hypertension in this subset of hypertensive intracerebral hemorrhages may be due to increased sympathetic drive in the nearby diencephalic structures such as the hypothalamus. The paraventricular nucleus (PVN) of the hypothalamus has been shown to be the master controller of the autonomic nervous system functions,[11] with spinally projecting pre-autonomic neurons (SPAN)[12] that target the cardiovascular system. Either increased stimulation by excitatory neurotransmitters or loss of GABA-mediated inhibition of the PVN may lead to increased heart rate and hypertension.[13-21] One experimental study showed that the overexpression of diencephalic thyroliberin (dTRH) induced arterial hypertension in rats.[22] Thalamic hemorrhages with compression upon the hypothalamus have been shown to present clinically with miosis by disrupting the descending sympathetic fibers.[23] It may be possible that other homeostatic mechanisms of the

hypothalamus may be disrupted by such compression, leading to increased sympathetic drive and elevated blood pressure.

Conclusions

There is an association between the thalamic site of intracerebral hemorrhage and difficulties in lowering markedly elevated blood pressures during the first 48 hours of admission. While the patients with thalamic intracerebral hemorrhages did not differ in baseline blood pressure and MAP from the patients with non-lobar hemorrhages at other sites, this subset of patients took significantly longer and needed more than two classes of antihypertensives to lower the BP to the target MAP. The findings of this study may impact future clinical trials investigating the efficacy of BP lowering in the acute phase of SICH, as patients with thalamic hemorrhages may have increased sympathetic drive and may require combinations of several classes of oral antihypertensive medication to achieve the target mean arterial or systolic blood pressures.

Limitations and recommendations

As this was a retrospective study with low chart retrieval rates, the sample sizes for each group of ICH site was small, particularly for the pontine and cerebellar hemorrhages. Although the selection of oral antihypertensive drug classes was based on existing clinical practice guidelines during the study period, the administration of the drugs may have been inconsistent and dependent on the patients' financial status.

We recommend further research into the control of hypertension in acute thalamic hemorrhages using a prospective cohort design, with a larger sample size for each location of non-lobar intracerebral hemorrhage. A prospective study would allow standardization in the dosing and titration of intravenous antihypertensives such as nicardipine, as well as the utilization of the different classes of oral antihypertensive medications. We also recommend the addition of clinical endpoints of hematoma expansion as well as the development of worsening perilesional edema, to further delineate the importance of refractoriness of hypertension in ICH patients.

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