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ORIGINAL ARTICLE

Nationwide survey of antihypertensive treatment for acute intracerebral hemorrhage in Japan

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Acute hypertension is associated with hematoma enlargement and poor clinical outcomes in patients with intracerebral hemorrhage (ICH). However, the method of controlling blood pressure (BP) during the acute phase of ICH remains unknown. The aim of this study is to show current strategies about this issue in Japan. Questionnaires regarding antihypertensive treatment (AHT) strategies were sent to neurosurgeons, neurologists and others responsible for ICH management in 1424 hospitals. Of 600 respondents, 550 (92%) worked at hospitals wherein acute ICH patients are managed and 548 (99.6%) of them agreed with the application of AHT within 24 h of ICH onset. Most answered that the systolic BP threshold for starting AHT was 180 mm Hg (36%) or 160 mm Hg (31%), which differed significantly between neurosurgeons (median, 160 mm Hg) and neurologists/others (180 mm Hg, $P<0.001$). The goal of lowering systolic BP was to reach a maximum of 140, 150 or 160 mm Hg according to 448 respondents (82%) and 209 (38%) intensively lowered systolic BP to $\leqslant$140 mm Hg. Nicardipine was the first choice of intravenous drug for 313 (57%) and the second choice for 146 respondents (27%). However, 141 (26%) thought that nicardipine is inappropriate mainly because of a conflict with a description of contraindications on the official Japanese label for this drug. In conclusion, the present Japanese respondents, especially neurosurgeons, lower BP more aggressively than recommended in domestic and Western guidelines for managing acute ICH patients. Nicardipine was the most frequent choice of antihypertensive agent.
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INTRODUCTION

Intracerebral hemorrhage (ICH) is not only life threatening but also causes major disability. The annual incidence of ICH in Japan is several-fold higher than that in Caucasian populations.[1–5] Chronic hypertension is a leading risk factor for ICH[2,6,7] and such patients often have high blood pressure (BP) on admission. Acute high BP might enhance active intracranial bleeding and hematoma growth, which could be a determinant of poor clinical outcome.[8–12] In contrast, some investigators insist that high BP might work to maintain normal cerebral blood flow and prevent peri-hematomal ischemic damage.[13,14] However, pharmacologically mediated BP reduction apparently has no adverse effects on cerebral blood flow in humans or other animals.[15,16] Control of BP for acute ICH remains controversial.

American Heart Association/American Stroke Association (AHA/ASA) guidelines[17] and the Japanese Guidelines for the Management of Stroke 2004[18] both recommend lowering of BP for ICH patients with systolic blood pressure (SBP) of $>$180 mm Hg or mean arterial pressure of $>$130 mm Hg. The target BP level has not been defined. The European Stroke Initiative (EUSI) advocates an upper recommended limit of 180/105 mm Hg and a target BP of 160/100 mm Hg for acute ICH patients with known earlier hypertension or signs of chronic hypertension.[19] However, these recommendations are based on limited information and neither their usefulness nor their effects are well established.

Another concern regarding the lowering of BP in acute ICH patients is of the differences in recommendations for intravenous (i.v.) antihypertensive drugs among guidelines. Both the AHA/ASA and the EUSI guidelines recommend i.v. administration of the adrenergic inhibitors, labetalol and esmolol, and of the calcium channel blocker, nicardipine. In Japan, labetalol is not approved for commercial use, esmolol is used only for antiarrhythmia, and nicardipine

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administration for hyperacute ICH patients is limited by the description on the official label.

To conform to worldwide trends, BP control in ICH patients in Japan should be standardized, domestic recommendations that differ from others should be reconsidered, and an active role in international trials should be taken. Therefore, we conducted a nationwide web survey as the first step toward defining current standard strategies of BP control in Japanese patients with acute ICH.

METHODS

We surveyed 1424 certified training institutes recommended by the Japan Stroke Society, the Japan Neurosurgical Society and the Societas Neurologica Japonica. Web questionnaires (https://ssl.e-ult.jp/ICH/, for limited members) regarding acute ICH management and antihypertensive treatment (AHT) strategies were sent to hospital directors in July 2008 with a request that they encourage responsible physicians involved in stroke management to reply by September 2008.

The inquiry started by questioning whether acute ICH patients are usually treated in the respondents' hospitals. Those who responded affirmatively were required to answer seven questions about conditions surrounding acute ICH management and 14 questions about AHT for acute ICH (Table 1). When respondents disagreed with AHT for acute ICH patients in Question 10 (Q10), responses to subsequent questions were not required. All answers were multiple choice, except for Questions 2, 5 and 9, which required integral numbers.

At the end of the survey, we asked if the respondents were interested in further inquiries. Those who answered in the affirmative received a supplementary questionnaire in October 2008 to determine whether their patients experienced side effects of i.v. antihypertensive drugs during acute ICH management. Respondents were only required to e-mail a reply to this simple question if they recognized possible side effects.

Table 1 The web questionnaire in this study

Conditions for acute ICH management

- Q1. What is your specialty?
- Q2. How long is your career in clinical medicine?
- Q3. How many acute ICH patients (hospitalized within 7 days of onset) are treated in your hospital per year?
- Q4. Who mainly treats acute ICH patients at your hospital?
- Q5. How many medical physicians attend patients with acute ICH at your hospital?
- Q6. Where do you treat acute ICH patients?
- Q7. Is your medical staff for acute ICH available during the nighttime and on weekends?

Antihypertensive therapy (AHT) for acute ICH

- Q8. How do you measure BP in acute ICH patients?
- Q9. How many times do you measure BP during the initial 24 h?
- Q10. Do you agree with AHT within 24 h after ICH onset?
- Q11. When do you start AHT?
- Q12. At which SBP level or more do you initiate AHT?
- Q13. At which level or less do you lower SBP during the hyperacute stage?
- Q14. Which i.v. antihypertensive agent do you primarily choose?
- Q15. Why do you choose the agent in Q14?
- Q16. Which is your second choice of i.v. antihypertensive agent?
- Q17. Do you think the listed i.v. agent is inappropriate for acute ICH patients?
- Q18. Why do you choose the agent in Q17?
- Q19. When do you think active intracranial bleeding ceases?
- Q20. Which oral antihypertensive agent do you administer after acute i.v. AHT?
- Q21. To which level or less do you lower SBP during the chronic stage?

Abbreviations: AHT, antihypertensive treatment; BP, blood pressure; ICH, intracerebral hemorrhage.

Statistics

The BP thresholds in Questions 12, 13 and 21 were compared between neurosurgeons and respondents from other specialties using the Mann–Whitney *U*-test. Categorical variables were compared using the χ^2 test. A *P*-value of <0.05 was considered to represent a significant difference.

RESULTS

Among a total of 602 collected responses, two were excluded from the analyses because the same respondents answered twice, leaving 600 responses remaining from 1424 (42.1%) hospitals. Of these, 50 replied that they did not usually treat patients with acute ICH at their hospitals. Finally, 550 responses (38.6% of 1424 hospitals) were analyzed.

Conditions for acute ICH management

Of the 550 respondents, 457 (83.1%) were neurosurgeons (Q1; Table 2). Overall, the respondents had spent a median of 23 years in clinical medicine (Q2). The median number of ICH patients treated annually ranged between 41 and 60 (Q3). The main department for ICH management was neurosurgery (79.5%), whereas 10.5% of respondents replied that a mixed team from neurosurgery and neurology treated patients with acute ICH (Q4). The median number of ICH attending physicians was three per hospital (Q5). An ICU (intensive care unit) was the main ward (34.5%), and a SCU (stroke care unit) was used in only 12.7% of the respondent hospitals (Q6). The availability of doctors responsible for initial management of emergency ICH patients in the respondent hospitals or on call 24/7 was 61.6% (Q7).

Antihypertensive treatment for acute ICH

Blood pressure was measured during acute ICH mainly using automated equipment (81.3%, Q8; Table 2). The median number of BP measurements was 24 during the initial 24 h (Q9). Two respondents (0.4%) replied that AHT should not be performed within 24 h of ICH onset and the other 548 agreed with AHT (Q10). Thus, we analyzed the following results from these 548 respondents.

Antihypertensive treatment was started mostly in the emergency room or in the CT/MRI room immediately after a diagnosis of ICH was confirmed (85.0%, Q11). The threshold median SBP level for AHT initiation was 160 mm Hg (interquartile range: (IQR) 150–180 mm Hg), with biphasic peaks at 180 mm Hg (35.6%) and 160 mm Hg (30.8%, Q12; Figure 1, top). The median levels differed between neurosurgeons (160 mm Hg (IQR: 150–180)) and other physicians (180 mm Hg (160–180), $P<0.001$). Guideline-based initiation for patients with SBP $\geqslant$180 mm Hg was approved by 40.0% of the overall respondents, 35.3% of neurosurgeons and 63.0% of the remainder.

The target of lowering the SBP was also biphasic at 160 mm Hg (29.4%) and 140 mm Hg (29.7%); 448 respondents (81.8%) approved 140, 150 or 160 mm Hg as the target (Q13; Figure 1, middle). The median (IQR) target levels of neurosurgeons were 150 (140–160) mm Hg and those of others were 160 (150–170) mm Hg ($P<0.001$). Intensive lowering to $\leqslant$140 mm Hg was approved by 38.1% of the overall respondents, 41.0% of neurosurgeons and 23.9% of the remainder.

The most frequent first choice of i.v. drug was nicardipine (57.1%), followed by diltiazem (34.9%, Q14). The main reason for administering nicardipine was its ability to lower BP (96.2%, Q15). The second choice of respondents (26.5%) was nicardipine (Q16). Thus, nicardipine was used for acute ICH patients as the first or second choice by 83.5% of respondents, and by 396 (86.8%) neurosurgeons

Table 2 Answers to the web questionnaire

Question	*Multiple choice answers*	*Respondents*	*%*
Q1. Specialty	Neurosurgery	457	83.1
	Neurology	63	11.5
	Vascular neurology	12	2.2
	Emergency	2	0.4
	Other	16	2.9
Q2. Length of career[a]		23 (18–28) years	
Q3. Number of ICH patients	⩽20	88	16.0
	21–40	118	21.5
	41–60	113	20.5
	61–80	85	15.5
	81–100	63	11.5
	⩾101	83	15.1
Q4. Department for ICH care	Neurosurgery	437	79.5
	(Vascular) Neurology	44	8.0
	Mixed team composed of neurosurgery and neurology	58	10.5
	Emergency	2	0.4
	Other	9	1.6
Q5. Number of physicians for acute stroke care[a]		3 (2–5)	
Q6. Ward for ICH care	Stroke care unit	70	12.7
	Intensive care unit	190	34.5
	Emergency	110	20.0
	General	153	27.8
	Other	27	4.9
Q7. Nighttime/weekend availability of stroke team	Always available in hospital	182	33.1
	Always on call	157	28.5
	Occasionally	206	37.5
	Not available	5	0.9
Q8. Method of BP measurement	Manual sphygmomanometer	71	12.9
	Automated equipment	447	81.3
	Direct arterial monitor	32	5.8
Q9. Frequency of BP measurements[a]		24 (12–48)	
Q10. AHT for acute ICH	Agree	548	99.6
	Disagree	2	0.4
Q11. Timing to initiate AHT	Immediately after diagnosis	466	85.0
	Immediately after admission to ward	60	10.9
	After observation for several hours	22	4.0
Q12. Threshold SBP to initiate AHT		See Figure 1 (top)	
Q13. Target SBP during hyperacute stage		See Figure 1 (middle)	
Q14. First choice of i.v. drug	Nicardipine	313	57.1
	Nitroglycerin	38	6.9
	Diltiazem	191	34.9
	Nitroprusside	0	0.0
	Other i.v. drug	1	0.2
	Oral or transdermal drug	5	0.9
Q15-1. Reasons for choosing nicardipine in Q14[b]	Effectively reduces BP	301	96.2
	Safety	85	27.2
	Other	20	6.4
Q15-2. Reasons for choosing nitroglycerin in Q14[b]	Effectively reduces BP	19	50.0
	Safety	28	73.7
	Other	4	10.5
Q15-3. Reasons for choice of diltiazem in Q14[b]	Effectively reduces BP	72	37.7
	Safety	95	49.7
	Others	70	36.6
Q16. Second choice of i.v. drug	Nicardipine	146	26.5
	Nitroglycerin	132	24.0
	Diltiazem	159	28.9
	Nitroprusside	5	0.9
	Other i.v. drug	13	2.4
	Oral or transdermal drug	93	16.9
Q17. Inappropriate i.v. drug[b]	Nicardipine	141	25.6
	Nitroglycerin	123	22.4
	Diltiazem	55	10.0
	Nitroprusside	83	15.1
	Any drug is appropriate.	266	48.4
Q18-1. Reasons for choice of nicardipine in Q17[b]	Ineffective BP reduction	0	0.0
	Safety problems	14	9.9
	Limitations on official label	127	90.1
	Other	10	7.1
Q18-2. Reasons for choice of nitroglycerin in Q17[b]	Ineffective BP reduction	30	24.4
	Safety issues	23	18.7
	Limitation on official label	65	52.8
	Other	22	17.9
Q18-3. Reasons for choice of diltiazem in Q17[b]	Ineffective BP reduction	16	29.1
	Safety issues	19	34.5
	Limitations on official label	8	14.5
	Other	19	34.5
Q18-4. Reasons for choice of nitroprusside in Q17[b]	Less BP lowering power	10	12.0
	Safety issues	18	21.7
	Limitations on official label	44	53.0
	Other	16	19.3

Table 2 Continued

Question	*Multiple choice answers*	*Respondents*	*%*
Q19. Timing of end of active bleeding	⩽1 h after ICH onset	48	8.7
	1–3 h	74	13.5
	3–6 h	156	28.4
	6–12 h	121	22.0
	12–24 h	90	16.4
	⩾24 h	47	8.5
	Other	14	2.5
Q20. First choice of oral antihypertensive drug	Calcium channel blocker	360	65.5
	ARB	165	30.0
	ACE inhibitor	25	4.5
	β-Blocker	0	0.0
	Diuretic	0	0.0
Q21. Target SBP during chronic stage		See Figure 1 (bottom)	

Abbreviations: ACE, angiotensin-converting enzyme; AHT, antihypertensive therapy; ARB, angiotensin II receptor blocker; BP, blood pressure; ICH, intracerebral hemorrhage; SBP, systolic blood pressure.
[a]Data are expressed as medians (interquartile range).
[b]Multiple answers possible where applicable.

and 63 (68.5%) other respondents (P=0.14). Although 266 (48.4%) respondents answered that any i.v. drugs that lower BP are appropriate for patients with acute ICH, 141 (25.6%) replied that nicardipine is inappropriate, mainly because of the contraindications described on the label (90.1%, Q17, Q18). Around half of the respondents replied that active intracranial bleeding ceases within 6 h (50.5%, Q19).

After i.v. AHT, 360 respondents (65.5%) administer oral AHT using a calcium channel blocker, followed by an angiotensin II receptor blocker (30.0%, Q20). The target SBP value of 333 respondents (60.5%) was ⩽140 mm Hg (Q21). The median (IQR) target values of neurosurgeons were 140 (140–140) mm Hg and those of other physicians were 140 (130–140) mm Hg (P=0.001).

Supplementary inquiry

Among the respondents to the initial web questionnaire, 414 (75.3%) expressed an interest in further inquiries. We sent them another questionnaire to determine whether their patients experienced any possible side effects of i.v. antihypertensive drugs. A total of 32 physicians responded. Of them, 18 had patients who experienced bradycardia or atrioventricular block and one had a patient who developed arrhythmia during diltiazem administration. Nicardipine caused phlebitis (n=6), tachycardia (n=3) and liver dysfunction (n=2). One respondent described a decrease of oxygen partial pressure in arterial blood in a patient receiving nitroglycerin. A total of 10 respondents replied that i.v. drug administration did not cause side effects.

DISCUSSION

This study shows the current strategies regarding AHT for acute ICH patients in Japan. The first major finding was that 60% of the respondents start AHT on the basis of a threshold SBP level that is lower than that recommended by guidelines (180 mm Hg). The second major finding was that 80% of the respondents lowered SBP

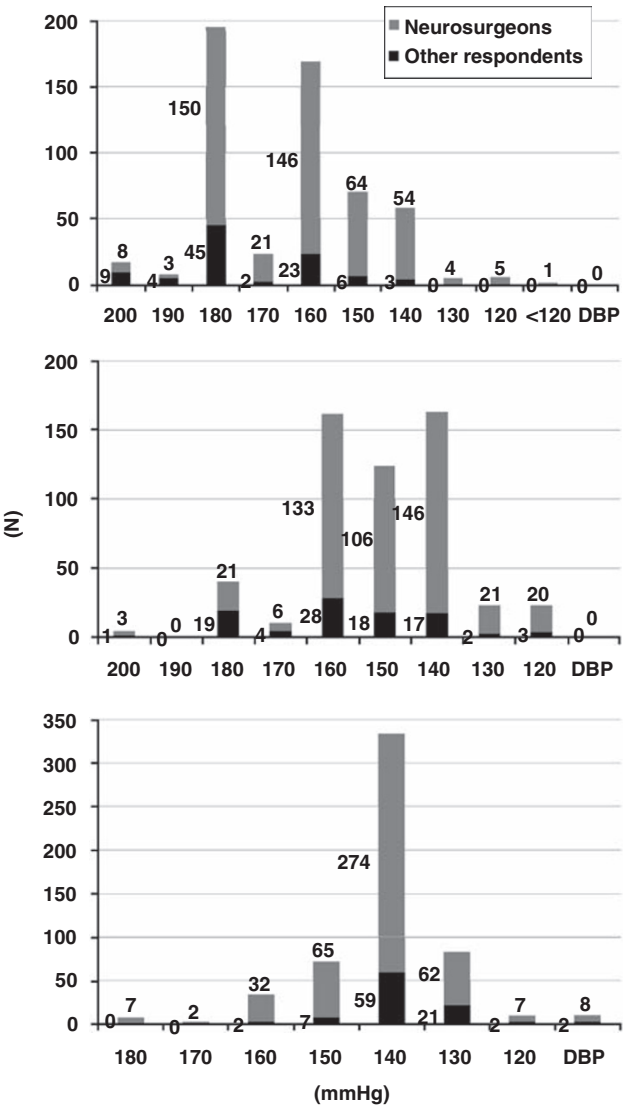

Figure 1 Answers to Questions 12, 13 and 21. Top: Threshold systolic blood pressure (SBP) required to start antihypertensive treatment (AHT). Middle: SBP during hyperacute stage by intravenous AHT. Bottom: SBP during chronic stage targeted by oral AHT. DBP: diastolic blood pressure (mm Hg) used by respondents rather than SBP as threshold or target value.

to a maximum of 140, 150 or 160 mm Hg, and 40% intensively lowered SBP to ⩽140 mm Hg. These two findings mainly reflect the opinions of neurosurgeons, as they accounted for 80% of the respondents. Both the threshold SBP level required to initiate AHT and the target SBP level were higher according to responses from other physicians (mainly neurologists and vascular neurologists) compared with those from neurosurgeons. The third major finding was that nicardipine is the most effective i.v. drug to reduce BP of patients with acute ICH, although such usage conflicts with the official Japanese label.

The threshold SBP level required to initiate AHT and the target SBP level recommended in the guidelines are not identical and are not based on sophisticated trials; over half of the respondents set lower values for these two parameters than those recommended by the AHA/ASA guidelines. The present findings indicate that most Japanese neurosurgeons prefer stricter AHT for ICH patients than that

recommended by the current guidelines. This tendency might be because a stricter AHT than the usual one is recommended when surgical therapy is scheduled for ICH in Japanese guidelines, although the evidence level is not high.[20] A lower target SBP than the guidelines recommend has been reported recently. Ohwaki *et al.*[20] assessed 76 patients with ICH and found that an SBP target of $\leqslant$150 mm Hg was less significantly associated with hematoma growth than that of $\geqslant$160 mm Hg. Our observational study of 244 patients with ICH showed that lowering SBP to $<$138 mm Hg during the initial 24 h after admission seems to predict a favorable early outcome.[21] Two major clinical trials are ongoing to determine the safety and efficacy of intensively lowering BP for acute ICH: the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT)[22] and the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH).[23] The vanguard phase of INTERACT showed that early intensive lowering of BP with a targeted SBP of 140 mm Hg and careful monitoring was feasible, safe and might have modestly attenuated hematoma growth in 346 randomized patients in the standard best practice stroke unit care.[22] Phase I of ATACH investigated the potential consequences of controlling BP with i.v. nicardipine at the sequential levels of 170–200, 140–170 and 110–140 mm Hg in 60 patients.[23] The result was announced in a recent conference.[22]

This survey clarified a contradiction regarding the prevalence of nicardipine administration to Japanese patients with ICH regardless of the following contraindications described on the official label; 'nicardipine is contraindicated for (I) ICH patients with a suspicion of ongoing intracranial bleeding not to enhance bleeding and for (II) acute stroke patients with elevated intracranial pressure not to accelerate intracranial pressure elevation.' When nicardipine was originally approved for commercial use as an ameliorant of cerebral circulation, not as an antihypertensive agent, in Japan in 1981, a description of the above contraindications was listed on the label following that of another ameliorant of cerebral circulation. As far as we can determine, the limited administration of nicardipine for patients with ongoing intracranial bleeding or high intracranial pressure is not supported by any scientific evidence. The description on the label has another problem in that the time when active intracranial bleeding ceases is not as clear as stated in the answer to Q19. On the basis of the results of this survey, a formal request for reassessment of the official label of nicardipine was submitted to the Ministry of Health, Labour and Welfare of Japan by the Japan Stroke Society, Japan Neurosurgical Society and the Japanese Society of Hypertension in October 2008. Diltiazem was the second most frequently administered drug, which seems to be associated with an influence on cardiac rhythms. On the basis of Japanese official labels, nitroglycerin is not administered to lower BP except for patients with acute heart failure, unstable angina or perioperative conditions, and nitroprusside is limited to patients with severely damaged cerebral circulation. A limitation of this study was that we did not ask in the web questionnaires whether respondents know the contraindication of nicardipine listed on the official label. It is important to know how many doctors use nicardipine with or without knowing this contraindication.

Calcium channel blockers and angiotensin II receptor blockers were the choices of oral antihypertensive drugs after i.v. administration in 65.5 and 30.0% of respondents, respectively. The most frequent target SBP according to our respondents (140 mm Hg) was identical to the level recommended by the guidelines of the Japanese Society of Hypertension[23] and higher than that in the guidelines from the European Society of Hypertension and European Society of Cardiology (130 mm Hg).[24]

In conclusion, current Japanese strategies based on this survey regarding acute BP lowering for ICH patients, especially by neurosurgeons, differ considerably from strategies recommended in various guidelines. We are planning to conduct a multicenter, randomized clinical trial of Japanese patients with ICH to determine the optimal BP target of AHT based on the results of this survey.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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