Blood pressure at hospital admission and outcome after primary intracerebral hemorrhage

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Abstract

Introduction: The importance of the admission blood pressure (BP) for intracerebral hemorrhage (ICH) outcome is not completely clear. Our objective was to analyze the clinical impact of BP at hospital arrival in patients with primary ICH.
Material and methods: We studied 316 patients (50% women, mean age: 64 years, 75% with hypertension history) with acute primary ICH. The first BP reading at admission was evaluated for its association with neuroimaging findings and outcome. A Cox proportional hazards model and Kaplan-Meier analyses were constructed to evaluate factors associated with in-hospital mortality.
Results: Intraventricular irruption occurred in 52% of cases. A high frequency of third ventricle extension was observed in patients with BP readings in the upper quartiles of the distribution (systolic, diastolic, or mean arterial pressure). Blood pressure readings did not correlate with hematoma volumes. In-hospital case fatality rate was 46% (63% among those with ventricular irruption). Systolic BP (SBP) > 190 mm Hg was independently associated with in-hospital mortality in supratentorial (n = 285) ICH (hazard ratio: 1.19, 95% confidence interval: 1.02-1.38, for the highest vs. the lowest quartile) even after adjustment for known strong predictors (age, ICH volume, Glasgow coma scale and ventricular extension). Blood pressure was not significantly associated with ventricular extension or outcome in patients with infratentorial ICH.
Conclusions: A high BP on admission is associated with an increased risk of intraventricular extension and early mortality in patients with supratentorial ICH. However, a significant proportion of patients with high BP readings without ventricular irruption still have an increased risk of death.

Key words: blood pressure, diastolic, hematoma, intracerebral hemorrhage, hypertension, outcome, systolic.

Introduction

Hypertension is the single most important risk factor for primary intracerebral hemorrhage (ICH) [1-6]. On admission to hospital most patients have the antecedent of hypertension, but nearly 10% correspond to new cases diagnosed after the brain hemorrhage has occurred [2-6]. It is well known that blood pressure (BP) readings are higher after

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acute cerebrovascular disease, as compared with the basal state [7], so a high BP in the acute state can be both the cause and the consequence of a non-traumatic brain hematoma [2, 8]. Nevertheless, the clinical relevance of BP readings upon arrival at the Emergency Department for radiological characteristics and outcome after ICH is not completely clear [8-11].

The purpose of this study was to analyze the clinical significance of the first BP reading performed at hospital admission in patients with acute primary ICH, in relation to neuroimaging characteristics and short-term outcome. Our hypothesis was that a high BP is associated with short-term mortality, mainly through extension into the ventricular system. This may help to define adequate patient selection for acute tight BP control after ICH. Our findings are relevant in view of the recent clinical trials on acute control of BP in patients with primary cerebral hematomas.

Material and methods

Patient characteristics

This is a descriptive study on patients prospectively included in a single-center research database [10]. The internal Committee of Ethics of our hospital approved the present study. Informed consent was obtained from the patients or their closest relative. We reviewed 316 consecutive adult patients hospitalized in the general wards of our institution with acute primary ICH. Inclusion criteria were: 1) ICH was defined as a sudden focal neurological deficit explained by a brain hematoma demonstrated in head computed tomography (CT) or magnetic resonance imaging (MRI) performed in the first 48 h after arrival; 2) supratentorial or infratentorial parenchymal hematomas; and 3) having available the first BP readings at hospital admission to the Emergency Department registered within the first 24 h after symptoms onset. The exclusion criteria were: 1) hematomas secondary to head trauma, arteriovenous malformations, aneurysms, vasculitis, cerebral vein and sinus thrombosis, neoplasms, hemorrhagic diathesis, anti-coagulant therapy or illicit drug abuse; 2) time from symptoms onset, neuroimaging or outcome information not available. Blood pressure readings were performed immediately following arrival at the Emergency Department, and before exposure to any anti-hypertensive therapy [12]. After a systolic BP (SBP) > 200 mm Hg or a mean arterial pressure (MAP) > 150 mm Hg was identified, aggressive BP control was applied, as recommended [7]. A standardized structured questionnaire was used to collect information on risk factors, neuroimaging characteristics, acute management, in-hospital complications and outcome at discharge.

A hypertensive etiology was defined as the patient having a history of hypertension or SBP > 140 mm Hg or diastolic BP (DBP) > 90 mm Hg maintained throughout one week or more after the hospital admission, in the absence of other potential causes [3, 4]. Intracerebral hemorrhage volume was calculated by analysis of the head CT scans according to the *ABC/2* method. The first SBP and DBP reading taken on arrival at the Emergency Department, before anti-hypertensive intervention, was used to calculate MAP, as MAP = DBP + 0.412 (SBP − DBP) [3, 4]. This MAP formula corrects for the spurious variance of calculated MAP seen in individuals with hypertension; thus, it is the ideal method in cases with hypertensive ICH.

Statistical analysis

Pearson χ^2 and Fisher exact test were used to assess nominal variables in bivariate analyses. Pearson correlation was used in continuous variables. The SBP, DBP and MAP were evaluated for their association with relevant neuroimaging findings and short-term outcome. The distributions of SBP, DBP and MAP values were divided into quartiles to compare the highest (Q4: > 190, 110, 135 and 85 mm Hg; respectively) vs. lower (Q1-Q3) or the lowest (Q1) quartiles for their clinical correlates. To test the association of BP values with short-term mortality, multivariate Cox proportional hazards models were constructed for the entire cohort and for the cases with supratentorial ICH (n = 285) separately. Input variables were those significantly associated with mortality in bivariate analyses. Actuarial analyses by Kaplan-Meier survival curves were constructed to evaluate the prognostic association of SBP with mortality observed after hospital admission. Log-rank tests were used to compare Q4 and Q1 in actuarial curves. All p values are two-sided and considered significant when p < 0.05. Except for the multivariable analysis, which implies adjustments for relevant confounders, a Bonferroni correction (multiple-comparison adjustment) was applied to all significant associations in bivariate analyses, with a correction factor derived from the number of independent variables tested for each outcome of interest (ICH location, BP estimate and mortality). SPSS (SPSS Inc., Chicago, IL.) v17.0 statistical package was used for all calculations.

Results

We studied 316 patients (mean age: 64 years, range: 18 to 99 years) with primary ICH: 159 (50.3%) women (mean age: 65 years, range: 18 to 99 years) and 157 (49.7%) men (mean age: 63 years, range: 18 to 95 years). No relevant differences were observed according to gender, except for more cases with the antecedent of hypertension in women,

as compared with men (74% vs. 60%, respectively; $p = 0.009$).

Systolic BP > 190 mm Hg was more frequently found among older patients than those aged < 45 years, but not significantly after Bonferroni correction (Table I). Irruption into the third ventricle was more common among patients with the highest (i.e., Q4) BP estimates (Table I) than those with a lower BP. Patients with SBP > 190 mm Hg and DBP > 110 mm Hg (BP > 190/110 mm Hg) had more extension into the third ventricle, as compared with patients with SBP > 190 mm Hg but with DBP ≤ 110 mm Hg (56% vs. 30%, respectively; Bonferroni $p = 0.04$). No significant correlation was found between BP (either as quartiles or crude values) and hematoma volume. In cases with supratentorial ICH ($n = 285$), intraventricular extension occurred more frequently in those with deep rather than lobar hematomas (59% vs. 38%, respectively; Bonferroni $p = 0.01$).

In patients with supratentorial ICH, 46% with lobar and 26% with deep hematomas underwent surgical evacuation ($p = 0.04$). Conversely, ventriculostomy was significantly more common among patients with deep ICH than in lobar ICH cases (11% vs. 1%, $p = 0.005$). High BP estimates were not associated with the probability of receiving any surgical intervention. Median hospital stay was 9 days (range: 1 to 82 days). Ten (3.2%) patients were discharged with total recovery, 45 (14.2%) with moderate disability, 110 (34.8%) with severe disability and 7 (2.2%) in vegetative state. The in-hospital case fatality rate was 45.6% ($n = 144$), with 4.4% of in-hospital deaths occurring within the first 48 h after admission. In-hospital mortality was higher among patients with SBP > 190 mm Hg (Table I), and in cases with any extension into the ventricular system, in bivariate analyses. Moreover, BP measures were not significantly associated with acute case fatality or with extensions into the ventricles in patients with infratentorial ICH. On the other hand, in a Cox proportional hazards model applied to patients with supratentorial ICH, the highest quartile of SBP was independently associated with a high frequency of acute case fatalities, after adjusting for known pre-

Table I. Clinical characteristics of 316 patients with ICH, according to blood pressure readings

Variables	SBP		DBP		MAP	
	> 190 mm Hg (Q4) ($n = 77$)	≤ 190 mm Hg (Q1-Q3) ($n = 239$)	> 110 mm Hg (Q4) ($n = 54$)	≤ 110 mm Hg (Q1-Q3) ($n = 262$)	> 135 mm Hg (Q4) ($n = 75$)	≤ 135 mm Hg (Q1-Q3) ($n = 241$)
GCS at arrival ≤ 8, n (%)	29 (37.7)	63 (26.4)	20 (37.0)	72 (27.5)	26 (34.7)	66 (27.4)
ICH volume > 70 ml, n (%)	13 (16.9)	25 (10.5)	8 (14.8)	30 (11.5)	12 (16.0)	26 (10.8)
Supratentorial, n (%)	65 (84.4)	220 (92.1)	46 (85.2)	239 (91.2)	62 (82.7)	223 (92.5)
Lobar	9 (13.8)	77 (35.0)[a]	3 (6.5)	83 (34.7)[a]	5 (8.1)	81 (36.3)[a]
Deep	56 (86.2)	143 (65.0)	43 (93.5)	156 (65.3)[a]	57 (91.9)	142 (63.7)[a]
Infratentorial ICH, n (%)	12 (15.6)	19 (7.9)	8 (14.8)	23 (8.8)	13 (17.3)	18 (7.5)
Ventricular irruption, n (%)	44 (57.1)	119 (49.8)	32 (59.3)	131 (50.0)	41 (54.7)	122 (50.6)
Third ventricle	32 (41.6)	65 (27.2)[a]	25 (46.3)	72 (27.5)[a]	30 (40.0)	67 (27.8)[a]
Fourth ventricle	23 (29.9)	55 (23.0)	19 (35.2)	59 (22.5)	22 (29.3)	56 (23.2)
Lateral ventricles	40 (51.9)	110 (46.0)	29 (53.7)	121 (46.2)	38 (50.7)	112 (46.5)
In-hospital mortality, n (%)	43 (55.8)	101 (42.3)	26 (48.1)	118 (45.0)	37 (49.3)	107 (44.4)

DBP – diastolic blood pressure, GCS – Glasgow coma scale, ICH – intracerebral hemorrhage, MAP – mean arterial pressure, SBP – systolic blood pressure. [a]$p < 0.05$, after Bonferroni correction; for comparison of upper vs. lower quartiles

Table II. Multivariate analysis of factors independently associated with in-hospital mortality in patients with supratentorial hemorrhage ($n = 285$): a Cox proportional hazards model[a]

Variables	Hazard ratio (95% confidence interval)	Value of p
GCS < 8 at admission	3.27 (2.08-5.14)	< 0.001
Hematoma volume > 70 ml	2.09 (1.24-3.54)	0.006
The highest vs. the lowest SBP quartile	1.19 (1.02-1.38)	0.03
Age, per one year increment	1.02 (1.00-1.03)	0.01

GCS – Glasgow coma scale, SBP, systolic blood pressure. [a]Adjusted for gender, age, extension into the ventricles (any or separate), diastolic and mean blood pressure at hospital admission, ICH location (supratentorial vs. infratentorial; deep vs. lobar; and cerebellar vs. brainstem) and surgical interventions (surgical evacuation and ventriculostomy). Only significant predictors are shown
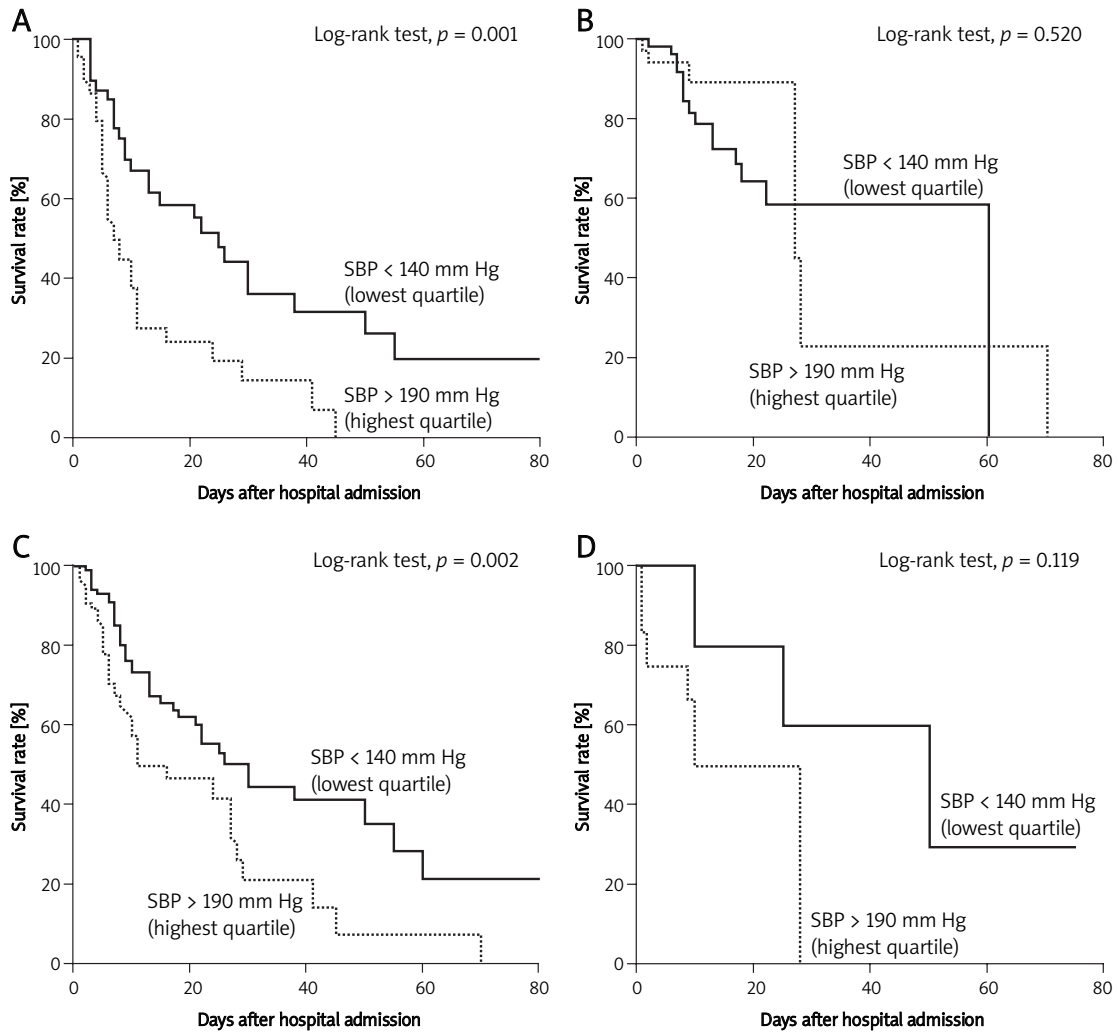
Figure 1. Kaplan-Meier estimates of short-term survival after primary intracerebral hemorrhage (ICH), according to the first systolic blood pressure (SBP) reading at hospital admission, in patients with (n = 163) (**A**) and without (n = 153) (**B**) intraventricular hematoma extension, as well as with supratentorial (n = 285) (**C**) and infratentorial (n = 31) (**D**) ICH

dictors of short-term outcome (Table II). The association of a high SBP with mortality remained significant only for supratentorial ICH and in cases with hematoma extension into the ventricular system at first brain imaging (Figure 1). We also explored the possibility that low BP levels would be associated with a high mortality, together with very high BP readings (i.e., a "J-pattern relationship" between BP levels and mortality frequency) either as quartiles, quintiles or intuitive BP cutoffs (Figure 2) in the whole cohort (n = 316). A J-shaped relationship was observed for SBP intervals and case fatality rate, but not for DBP or MAP (Figure 2).

Discussion

We found that a high BP at hospital admission is associated with an increased probability of ICH extension into the ventricular system and with
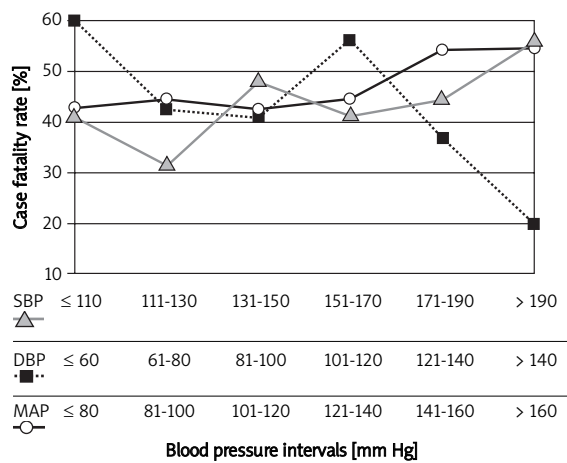
Figure 2. Case fatality rate according to blood pressure intervals (as 20 mm Hg increments)
DBP – diastolic blood pressure, SBP – systolic blood pressure, MAP – mean arterial pressure

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a high short-term mortality in patients with supratentorial ICH. The effect of a high BP is possibly mediated by a high frequency of extension into the ventricular system, especially the third ventricle. We observed a high acute case fatality rate, possibly due to the fact that all patients analyzed in this study were managed in the general wards.

Several autonomic responses have been described after acute cerebrovascular disease, including ICH [2, 6, 13]. The association of a high BP at hospital admission and early outcome after ICH has been discussed previously [2, 8-11], but the nature of this relationship is difficult to explain. It has been suggested that acute hypertension after ICH may facilitate hematoma enlargement, perihematoma edema or rebleeding, all dynamic factors associated with outcome [7]. Hematoma expansion is a strong predictor of short-term outcome [14, 15], but this factor has not been consistently associated with a high BP at hospital admission [16-19]. Alternatively, an elevated BP could be an epiphenomenal marker of early deterioration and not the cause of the neurologic impairment [20].

Clinical and experimental studies have shown that SBP increases acutely after ICH or cerebral infarction, with a natural tendency to decrease in the following days [2, 6, 21-24]. Impaired cerebrovascular reactivity [25] and baroreflex dysfunction [26] can result from ICH or cerebral infarction, which could mediate in part the acute BP response after brain injury and intracranial hypertension. Recent trials [27, 28] have failed to demonstrate a reduction in mortality with strict BP control in the acute state after ICH. This suggests that there is a tight balance that needs to be maintained between adequate cerebral perfusion after ICH [6] and the risk of hematoma expansion imposed by a high systemic blood pressure [16], which highlights the importance of adequate patient selection for strict blood pressure control in the acute management of ICH. Our results confirm the notion that patients with supratentorial ICH experience more benefit from tight BP control, as compared with those with brainstem or cerebellar hematomas.

In the mid and long term, a J-shaped relationship has been described for BP levels (below 110/70 mm Hg and above 140/90 mm Hg) with cardiovascular outcomes [1, 29]. This has challenged the "lower the better" concept in BP management. Moreover, in the acute presentation of the different forms of cerebrovascular disease (ischemic stroke, ICH, subarachnoid hemorrhage and cerebral venous thrombosis) the first SBP readings (but not DBP or MAP) at hospital admission also show a J-shaped relationship with short-term mortality, so that the risk of death is highest for SBP < 100 mm Hg, decreases between 100 mm Hg and 139 mm Hg, and gradually reaches a new zenith at SBP > 220 mm Hg [2].

In the present report we confirm this pattern in an independent population; however, here we observed very few (n = 3) cases with SBP < 100 mm Hg, and therefore Kaplan-Meier and Cox analyses did not show a significant association for low SBP levels and short-term outcome. On the other hand, the present study was about the first BP readings at hospital admittance and not about BP control in relation to outcome. A better understanding of BP and organ perfusion dynamics will help to define patient-centered cut-offs for effectively reducing cardiovascular outcomes and mortality [30-32].

This study has several limitations that should be acknowledged. First, no information could be obtained about other relevant prognostic variables, such as blood glucose levels, central temperature, premorbid brain parenchymal characteristics, withdrawal of care and timing of neuroimaging or surgery [7, 14, 19]. Also, no sequential information from brain imaging could be obtained to evaluate hematoma expansion, secondary intraventricular extension, or perihematoma edema, and the dynamic changes of BP throughout the first week after ICH were not registered. More importantly, we could not eliminate the possibility of hematoma enlargement before the first CT or MRI was performed, because neuroimaging was undertaken at different time points for each patient. Nevertheless, these findings may help to identify patients more suitable to experience benefit from strict BP control in the acute phase of ICH. Whether aggressive reduction of BP will result in better outcomes is yet to be established [27, 28].

In conclusion, a high BP is associated with an adverse short-term outcome. High BP readings are more related to irruption into the ventricular system than with hematoma volume, therefore influencing mortality risk. However, a significant proportion of deaths could not be explained by ventricular irruptions, which highlights the need for more studies to define adequate BP cutoffs to positively affect cardiovascular outcomes in patients with hypertension [30-32].

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