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β -Blockers associated with no class-specific survival benefit in acute intracerebral hemorrhage

J.P. Shoup^a, J. Winkler^a, A. Czap^a, I. Staff^b, G. Fortunato^b, L.D. McCullough^{c,d}, and L.H. Sarsing^{d,*}

J.P. Shoup: JShoup@student.uchc.edu; J. Winkler: JWinkler@student.uchc.edu; A. Czap: ACzap@student.uchc.edu; I. Staff: IStaff@harthosp.org; G. Fortunato: GFortun@harthosp.org; L.D. McCullough: LMcCullough@uchc.edu; L.H. Sarsing: Sarsing@uchc.edu

^aThe University of Connecticut School of Medicine, United States

^bHartford Hospital Research Department, United States

^cThe University of Connecticut Health Center, Departments of Neurology and Neuroscience, United States

^dThe Stroke Center at Hartford Hospital, United States

Abstract

Objectives—Despite the high mortality, there is currently no specific treatment for intracerebral hemorrhage (ICH). Research investigating optimum degree of blood pressure control in patients presenting with ICH and hypertension is ongoing. However, there is limited understanding of the potential benefits of specific classes of antihypertensive therapy. β -Adrenergic antagonists may provide neuroprotection from inflammation-induced injury by inhibiting sympathetic nervous system mediated immune activation. We examined mortality in ICH patients receiving β -adrenergic antagonists to determine whether this class of antihypertensive therapy was associated with improved survival.

Methods—A retrospective analysis of a large, prospectively collected database of patients presenting with acute ICH was performed. Patients were grouped by inpatient β -blocker treatment to determine an effect on mortality during the inpatient stay and at 3 months of follow-up. Additional analysis was conducted comparing β -blocker therapy to any other antihypertensive treatment to determine a class-specific association of β -blocker treatment with mortality.

Results—The study population included 426 patients with acute, spontaneous ICH. Inpatient β -blocker use was independently associated with decreased rates of inpatient death and mortality at 3 months of follow-up. However, univariate and multivariable analyses comparing β -blocker use to other antihypertensives failed to show any class-specific reduction in mortality at either time point.

*Corresponding author at: 263 Farmington Avenue, L4076, Farmington, CT 06030, United States. Tel.: +1 860 679 2156; fax: +1 860 679 1018.

Conflict of Interest Statement
None.

Discussion—Our study demonstrates that the improvement seen in patients treated with β -adrenergic antagonists is not an effect unique to this class. This supports ongoing trials to determine optimum levels of blood pressure control using multiple classes of antihypertensives.

Keywords

Stroke; Intracerebral hemorrhage; Antihypertensives; Beta-adrenergic antagonist; Sympathetic nervous system; Blood pressure

1. Introduction

Stroke is currently the fourth leading cause of death in the United States [1]. While the majority of strokes are ischemic, 10–15% are intracerebral hemorrhages (ICH) [2] which carry a one-month mortality of 40% [3]. This strikingly high rate has not improved over the past several decades [4]. Despite the severity of this illness, there is no specific therapy for ICH. Current clinical guidelines recommend modest blood pressure reduction, theoretically in an attempt to prevent hematoma expansion while maintaining enough pressure to ensure adequate cerebral perfusion [5]. Recent clinical trial results demonstrated that aggressive blood pressure reduction is associated with improved quality of life and a shift towards improved functional outcomes after ICH [6]. Another large trial (ATACH-II) is ongoing to further examine treatment targets for blood pressure reduction [7].

Despite the extensive work on blood pressure reduction, little attention has been paid to the choice of antihypertensive agents. It is well accepted that secondary inflammation is a major contributor to the pathophysiology of brain injury following ICH [reviewed in 8]. Given the complex interaction of the sympathetic nervous system and systemic immune response [9,10], agents that antagonize sympathetic signaling may offer anti-inflammatory benefits in ICH patients. We hypothesized that the anti-inflammatory properties of adrenergic antagonists may provide an additional benefit over other classes of antihypertensives in this critically ill population. In a large prospective database of patients with spontaneous ICH, we examined mortality in patients receiving β -adrenergic antagonists to determine whether this class of antihypertensive therapy was associated with improved survival.

2. Methods

This was a retrospective analysis of a prospectively collected stroke database at a Joint Commission Comprehensive Stroke Center. Patients were cared for in a dedicated Neuroscience ICU by a team of intensivists according to the Guidelines of the American Stroke Association [4]. Antihypertensive medications were administered to maintain systolic blood pressure < 160 mm Hg, with intravenous labetalol or nicardipine as preferred agents in the acute setting and transitioning to oral medications as the patients were able to tolerate them. Patients 18 years or older with a diagnosis of ICH between January 2, 2007 and May 18, 2011 were included in this analysis. Patients were excluded if the hemorrhage was due to an underlying lesion (e.g. tumor, ischemia, arteriovenous malformation) or if complete data was not available. Data were extracted from an on-going stroke patient registry and augmented by chart review. Data collected included: age, sex, history of diabetes, hypertension, high cholesterol, atrial fibrillation, home anticoagulant use, home β -blocker

use, initial severity of ICH (as measured by ICH score [11], ICH volume and Glasgow Coma Scale), initial systolic and diastolic blood pressure, infectious complications, placement of external ventricular drains and surgical evacuation, inpatient medications, and in-hospital mortality. ICH volume was estimated with the validated ABC/2 calculation [12]. The primary outcome was in-hospital mortality (defined as inpatient death or discharge to hospice). Secondary outcome was mortality at 3 months of follow-up. Follow-up data was acquired by review of inpatient and outpatient health care system databases and telephone calls to patients, families, and nursing facilities. If patient status could not be confirmed at 3 months the patient was excluded from the 3 month mortality analysis.

Patients were grouped by inpatient β -blocker treatment to determine an association with acute antagonism of the sympathetic activation and outcome. Patients who received β -blocker treatment (p.o. or i.v.) during the first 3 days of hospital admission were compared to patients who received no β -blockers. Descriptive statistics, presented as mean $\pm$ standard deviation if normally distributed, median [interquartile range] if skewed continuous data, and percentages for dichotomous variables, were first calculated. Univariate analyses included chi-square tests of proportion for dichotomous and categorical variables and t-tests or Wilcoxon ranked sum for functional scales and other continuous variables as appropriate. Multivariable analysis utilized backwards logistical regression including all factors associated with β -blocker use in the univariate analysis at $p < 0.15$. Variables known to significantly affect outcome were also included (components of the ICH score plus home anticoagulant use). The GCS score was skewed and thus categorized using the groups in the ICH score [11]. An *a priori* sample size calculation was not performed since we had no estimation of an effect size of β -blocker treatment. Rather, we included all patients in the database as described above. In an additional analysis to determine the class-specific effect of β -blocker treatment, patients receiving β -blocker therapy were compared to patients receiving other antihypertensives. Analysis was performed using SPSS v14.

The prospectively collected database and this sub-study were approved by the Institutional Review Board.

3. Results

560 patients were admitted with a primary diagnosis of ICH during the study period. Of these, 134 were excluded for ICH secondary to arteriovenous malformation (AVM), ruptured aneurysm, tumor, hemorrhagic conversion of ischemic stroke, lack of neurological imaging, or incomplete medical records. The final study population included 426 individuals with ICH primarily due to hypertension, cerebral amyloid angiopathy, and/or coagulopathy.

The demographics and baseline clinical characteristics of the patient population are shown in Table 1. Overall, 79.6% of patients received some form of antihypertensive within the first 3 days of hospitalization. 64.6% of patients ($n = 275$) were treated with a β -blocker during this time period. The most commonly utilized β -blockers (91%) were labetalol and metoprolol. Patients who received β -blockers were more likely to be men, younger than 80 years old, and to have a history of hypertension, and/or dementia. As would be expected, this group also had higher initial blood pressures. ICH volumes were smaller and initial GCS scores higher

in the β -blocker group, indicating a lower initial ICH severity. Despite these findings, neurosurgical intervention either through evacuation or ventriculostomy placement was more than twice as common among patients treated with β -blocker. The overall high rates of neurosurgical intervention are due to enrollment of patients in clinical trials evaluating either open or minimally-invasive evacuation. Inpatient infection rates were higher, but overall length of inpatient hospitalization was shorter. In univariate analysis, the patients treated with β -blockers had lower rates of both inpatient and 3-month mortality (Table 2). Premorbid β -blocker use was evaluated and was not associated with any difference in inpatient or 3-month mortality.

Because of the baseline inequalities in factors known to influence outcome after ICH, a multivariable model was constructed to determine an independent association of β -blocker use and mortality. Age, sex, history of hypertension, diabetes, dementia, or atrial fibrillation, home anticoagulant use, ICH volume, initial GCS score, intraventricular hemorrhage (IVH), infratentorial location, initial blood pressure, infection, and neurosurgical interventions were included in the initial model. The results of the multivariable models are shown in Tables 3A–3B. β -Blocker use remained independently associated with decreased inpatient mortality as well as mortality at 3 months after controlling for these factors.

To examine a possible interaction between β -blocker use and initial elevated systolic blood pressure (SBP), this interaction term was added to the multivariable analysis. The interaction between SBP and β -blocker use was significantly associated with decreased mortality and did not otherwise alter the results. Patients who presented with systolic blood pressure > 160 mm Hg had the strongest decrease in inpatient mortality with β -blocker treatment (β -blocker 30.1% vs. no β -blocker 62.9%, $p < 0.01$). This effect was mirrored in the 3 month mortality rates, where the strongest association with reduced mortality was among the patients with elevated blood pressure (β -blocker 37.6% vs no β -blocker 68.2%, $p < 0.01$).

In order to determine whether the beneficial association of β -blocker use on outcome was a class-specific effect or a benefit of any blood pressure treatment, we performed an additional analysis in which patients receiving β -blocker therapy ($n = 275$) were compared to those receiving any other non- β -blocker antihypertensive therapy ($n = 64$). The β -blocker therapy group contained patients who received both β -blocker alone ($n = 39$) as well as patients who received β -blocker in addition to other antihypertensives ($n = 236$). In univariate analysis, there was no difference in inpatient mortality between patients receiving β -blockers compared to those who received other antihypertensives (β -blocker 27.4% vs. other antihypertensives 29.7%, $p = 0.71$). There was also no difference between the groups in mortality at 3 months (β -blocker 33.8% mortality vs. other antihypertensives 32.8%, $p = 0.88$). However, there was an increased rate of infections among the patients treated with β -blocker therapy (β -blocker 24.0% vs. other antihypertensives 10.9%, $p = 0.02$). To ensure there was no confounding that obscured a class-specific effect of β -blocker treatment, multivariable analysis was conducted including differences in baseline presentation as well as infections and neurosurgical interventions. β -Blocker use was not significantly associated with mortality in these models (Tables 4A–4B). As before, an interaction term for elevated SBP and β -blocker use was added to the multivariable model. This term was not significant at either time point and had minimal effect on the multivariable model. In order to determine

whether the reduced number of patients in this analysis limited the ability to detect an effect, the power of this subgroup analysis was calculated. The analysis had 92% power to detect a 25% difference in mortality between the groups (the difference found in Table 2) and 84% power to detect a 20% difference between the groups. Finally, an exploratory analysis was conducted to identify any difference in mortality among the patients who received β -blocker treatment alone compared to patients who received β -blocker and additional antihypertensive medications; no difference was found.

4. Discussion

ICH is a devastating disease that led to an overall inpatient mortality of 35% in our study cohort. This is consistent with the known high mortality rate and poor functional outcomes in patients with ICH [2]. We hypothesized that inpatient treatment with β -blocker therapy would be associated with reduced mortality due to the immunomodulatory effects of antagonizing the sympathetic nervous system. In our initial analysis, patients who received β -blockers had significantly reduced inpatient mortality compared to patients who did not receive β -blockers, even after controlling for multiple potential confounders. However, further analysis of patients receiving β -blocker therapy compared to those receiving other antihypertensive revealed no class-specific advantage to β -blockade.

Antihypertensive therapy is a crucial part of acute management of ICH. Hematoma expansion, likely supported by elevated SBP, is strongly associated with poor outcomes [13–15]. Pilot clinical trials of more rigorous blood pressure control demonstrated reduced hemorrhage growth in patients treated with aggressive blood pressure reduction [8,16,17]. These studies led to late-phase randomized clinical trials (ATACH-II, INTERACT2) to determine optimal goals for blood pressure reduction [6,7]. The first of these trials to report demonstrated improvements in the distribution of patients across the ordinal modified Rankin Scale and improved quality of life after aggressive blood pressure reduction [5]. Although a majority of patients received either an α -adrenergic antagonist or a mixed α - and β -adrenergic antagonist, the trial did not evaluate for effects of individual antihypertensives. On the other hand, our study was not designed to evaluate different blood pressure treatment goals but rather to investigate whether the choice of agents had an impact. Our results demonstrate that the benefits of antihypertensive therapy are not limited to β -blockade and support the broader goal of blood pressure reduction using multiple agents as utilized in these trials [6,7].

Recent research has begun to identify the effects of sympathetic activity on patient outcomes in acute cerebrovascular disease. Sympathetic over-activation has been identified in patients with subarachnoid hemorrhage [18] and is associated with neurogenic cardiomyopathy [19] and other complications [20]. In patients with acute cerebral infarction, increased serum norepinephrine levels have been associated with poor outcome at one year [21]. β -Blocker therapy has also been associated with lower initial stroke severity scores in a prospective clinical cohort [22].

The sympathetic nervous system plays an integral role in the activation and migration of leukocytes from the spleen and bone marrow during inflammation. In rodent models of

ischemic stroke, sympathetic nervous system activation leads to splenic atrophy, leukocyte recruitment and systemic inflammation [23–25] and outcomes can be improved by carvedilol, a mixed adrenergic antagonist [23,26].

In clinical studies, the use of anti-adrenergic medications (β -blockers and clonidine) in the first 72 h of hospitalization was associated with decreased perihematomal edema at 72 h after ICH. However, there was no difference in outcome associated with anti-adrenergic medication use [27]. A recent paper reported reduced infection rates and mortality among ICH patients treated with atenolol, a β 1-selective antagonist [28]. However the comparator group included both normotensive, untreated patients as well as patients treated with other classes of antihypertensives. No analysis was performed to determine a class-specific association of β -blockers with outcome.

In our univariate analysis, patients treated with β -blockers had higher rates of infections (primarily urinary tract infections and pneumonia). This is consistent with our hypothesis of antagonism of sympathetic-induced immune responses. However, infections were not independently associated with mortality in our multivariable models. Despite this, it is possible that the increased rate of infections obscured a neuroprotective effect of β -blocker therapy.

The strength of our study lies in its large cohort, careful review of patient information, and detailed follow-up. Nearly 80% of our 426 patients received antihypertensive medication, providing a significant sample size for comparison of these treatment groups. Although our analysis was limited to a single center, the patient population fits the general profile of patients with ICH described in a recent epidemiologic study, including the high prevalence of hypertension, similar median age, and approximately equal numbers of men and women [29]. All patients were treated according to a hospital-based protocol adhering to the guidelines published by the American Stroke Association [5]. In the setting of a devastating disease such as ICH and the paucity of knowledge about treatment, retrospective analyses such as this remain an important tool to identify possibly therapeutic options and lay the groundwork for pilot clinical trials.

Despite these strengths, there are limitations to this study. We do not have data on blood pressure measurements among our study population. We did not examine DNR status in this population. Given that patients who did not receive β -blocker therapy appeared to have more severe strokes, it is possible that they were more likely to have care withdrawn. However, the similar rates of intubation in both groups and the longer length of hospitalization in patients not receiving β -blocker argue against systematically less-aggressive treatment. We also found an unexpectedly high rate of neurosurgical interventions among the group who received β -blocker therapy. It is likely that the high rate of β -blocker therapy in the surgical patients is due to institutional compliance with SCIPS measures to reduce the risk of perioperative myocardial infarctions. The overall high rate of neurosurgical evacuation in our population is a reflection of our high rates of enrollment in clinical trials. Importantly, neurosurgical evacuation was not associated with outcome in the multivariable models so it is unlikely that interventions are responsible for our findings on β -blocker therapy. The choice of antihypertensive therapy may have been biased by clinical characteristics of the

patients. We examined factors such as pre-existing hypertension, cardiac disease and atrial fibrillation, and controlled for these factors in the analyses. However, despite our attempts to identify and adjust for potential confounders, an unmeasured bias in the selection of who received this therapy could theoretically obscure an effect of β -blocker therapy. Prospective randomized study is necessary to exclude this possibility.

Overall, our study demonstrates that the improvement seen in patients treated with β -adrenergic antagonists is not an effect unique to this class. Rather, those benefits underscore the importance of appropriate antihypertensive therapy in patients presenting with ICH and elevated blood pressure. Our results support the practice of blood pressure reduction using multiple classes of antihypertensives. Continued research of antihypertensive therapy and other therapeutic targets remains crucial to future treatment of this disease.

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Table 1

Baseline characteristics.

	Patients receiving β -blocker therapy (n = 275)	Patients not receiving β -blocker (n = 151)	p value
<i>Clinical variables</i>			
Age (years)	67.51 $\pm$ 15.6	70.32 $\pm$ 18.1	NS
Female sex	46.5%	58.3%	0.02
Race			0.51
White	74.9%	81.5%	
Black	7.6%	6.6%	
Asian	1.8%	0.7%	
Hispanic	11.6%	9.3%	
Other	4.0%	2.0%	
History of			
Hypertension	82.5%	64.2%	<0.01
Hyperlipidemia	38.5%	38.4%	0.98
Coronary artery disease/MI	32.0%	27.2%	0.30
Diabetes mellitus	24.7%	16.6%	0.05
Ischemic stroke	14.9%	15.2%	0.93
Dementia	9.1%	15.9%	0.04
Aneurysm	0.7%	2.0%	0.25
Atrial fibrillation	20.7%	14.6%	0.12
Home medication use			
Antiplatelet agents	70.9%	69.5%	0.77
Anticoagulants	18.5%	14.6%	0.30
Baseline (preadmission) mBI	20 [19,20]	20 [19,20]	0.43
<i>Clinical presentation</i>			
ICH score	1 [1,2]	2 [0–3]	0.01
ICH volume > 30 mL	33.1%	37.7%	0.33
ICH volume mL	15.75 [4.75–42.65]	22.79 [4.73–82.16]	0.04
IVH	41.5%	46.4%	0.33
Infratentorial	12.4%	14.6%	0.52
Age > 80	26.2%	40.4%	<0.01
Glasgow Coma Scale:			0.01
3–4	4.8%	11.6%	
5–12	24.1%	30.1%	
13–15	71.1%	58.2%	
Median GCS	15 [11–15]	14 [8–15]	0.01
Systolic blood pressure (mm Hg)	176.2 $\pm$ 37.54	161.6 $\pm$ 38.95	<0.01
Diastolic blood pressure (mm Hg)	96.03 $\pm$ 23.98	86.75 $\pm$ 20.80	<0.01
Intubated	6.1%	8.9%	0.37
Infection rate	32.1%	16.1%	<0.01
Neurosurgical evacuation	10.5%	2.0%	<0.01

	Patients receiving β -blocker therapy (n = 275)	Patients not receiving β -blocker (n = 151)	p value
EVD placement	13.1%	4.6%	<0.01
Length of stay	3 [1–5]	7 [4–13]	<0.01

Univariate analysis of factors associated with inpatient β -blocker therapy.

Abbreviations: ICH — intracerebral hemorrhage; GCS — Glasgow Coma Scale; IVH —intraventricular hemorrhage; EVD — external ventricular drain. Data are %, mean $\pm$ SD, or median [interquartile range].

Table 2

Univariate outcome analysis.

	Patients receiving β -blocker	Patients not receiving β -blocker	p value
Inpatient mortality, n = 426	27.4%	50.0%	<0.01
3 month mortality, n = 368	39.4%	58.3%	<0.001

Univariate analysis of inpatient β -blocker use compared to no β -blocker use on inpatient and 3 month mortality.

Table 3AMultivariable model of inpatient mortality by β -blocker use.

	OR (95% CI)	p value
Treatment with β -blocker	0.21 (0.07–0.59)	<0.01
Age, per year	1.05 (1.02–1.09)	<0.01
History of diabetes mellitus	4.64 (1.50–14.41)	0.01
ICH volume, per mL	1.03 (1.01–1.05)	<0.01
GCS 5–12	5.06 (1.87–13.67)	<0.01
GCS 3–4	9.58 (0.94–97.3)	0.06
IVH	2.79 (1.09–7.19)	0.03
External ventricular drain placement	3.63 (1.18–11.23)	0.03

Multivariable models of inpatient β -blocker use compared to no β -blocker use on inpatient and 3 month mortality. Initial model included variables listed plus sex, history of hypertension, history of atrial fibrillation, history of dementia, home anticoagulant use, IVH, infratentorial location, initial systolic and diastolic blood pressures, hospital-acquired infection, ICH evacuation, and placement of ventricular drain. Abbreviations: OR — odds ratio; CI — confidence interval; GCS — Glasgow Coma Scale; IVH — intraventricular hemorrhage.

Table 3B

Multivariable model of 3 month mortality by β -blocker use.

	OR (95% CI)	p value
Treatment with β -blocker	0.36 (0.13–0.98)	<0.05
Age, per year	1.06 (1.03–1.09)	<0.01
History of diabetes mellitus	6.50 (2.00–21.18)	<0.01
ICH volume, per mL	1.03 (1.02–1.05)	<0.01
GCS 5–12	3.81 (1.35–10.78)	0.01
GCS 3–4	10.23 (0.98–107.28)	0.05
External ventricular drain placement	8.73 (2.44–31.64)	<0.01

Multivariable models of inpatient β -blocker use compared to no β -blocker use on inpatient and 3 month mortality. Initial model included variables listed plus sex, history of hypertension, history of atrial fibrillation, history of dementia, home anticoagulant use, IVH, infratentorial location, initial systolic and diastolic blood pressures, hospital-acquired infection, ICH evacuation, and placement of ventricular drain. Abbreviations: OR — odds ratio; CI — confidence interval; GCS — Glasgow Coma Scale; IVH —intraventricular hemorrhage.

Table 4A

Multivariable model of inpatient mortality comparing β -blocker to other antihypertensives.

	OR (95% CI)	p value
Inpatient β -blocker treatment	2.14 (0.57–8.09)	0.26
Age, per year	1.03 (1.00–1.06)	0.08
History of diabetes mellitus	4.96 (1.66–14.80)	<0.01
ICH volume, per mL	1.03 (1.01–1.04)	<0.01
GCS 5–12	4.07 (1.47–11.30)	0.01
GCS 3–4	9.61(0.93–99.70)	0.06
IVH	2.21 (0.84–5.83)	0.11
External ventricular drain placement	3.55 (1.12–11.26)	0.03

Multivariable models of inpatient β -blocker use compared to other antihypertensives on inpatient and 3 month mortality. Abbreviations: OR — odds ratio; CI — confidence interval; GCS — Glasgow Coma Scale.

Table 4B

Multivariable model of 3 month mortality comparing β -blocker to other antihypertensives.

	OR (95% CI)	p value
Age, per year	1.05 (1.02–1.09)	<0.01
History of diabetes mellitus	6.63 (2.06–21.28)	<0.01
ICH volume, per mL	1.03 (1.01–1.05)	<0.01
GCS 5–12	3.01 (0.98–9.30)	0.06
GCS 3–4	6.87 (0.68–69.22)	0.10
External ventricular drain placement	8.90 (2.40–32.96)	<0.01
Inpatient β -blocker treatment	1.27 (0.34–4.78)	0.72

Multivariable models of inpatient β -blocker use compared to other antihypertensives on inpatient and 3 month mortality. Abbreviations: OR — odds ratio; CI — confidence interval; GCS — Glasgow Coma Scale.