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Beta-blocker therapy is not associated with mortality after intracerebral hemorrhage

M. Sykora[1] | J. Putaala[2] | A. Meretoja[2,3] | T. Tatlisumak[2,4] | D. Strbian[2]

[1]Department of Neurology, St. John's Hospital, Medical faculty, Sigmund Freud University Vienna, Wien, Austria

[2]Department of Neurology, Helsinki University Hospital, Helsinki, Finland

[3]Department of Medicine at the Royal Melbourne Hospital, University of Melbourne, Parkville, VIC, Australia

[4]Department of Clinical Neurosciences/ Neurology, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg and Sahlgrenska University Hospital, Gothenburg, Sweden

Correspondence
M. Sykora, Department of Neurology, St. John's Hospital, Wien, Austria.
Email: marek.sykora@bbwien.at

Background: Beta-blocker therapy has been suggested to have neuroprotective properties in the setting of acute stroke; however, the evidence is weak and contradictory. We aimed to examine the effects of pre-admission therapy with beta-blockers (BB) on the mortality following spontaneous intracerebral hemorrhage (ICH).

Methods: Retrospective analysis of the Helsinki ICH Study database.

Results: A total of 1013 patients with ICH were included in the analysis. Patients taking BB were significantly older, had a higher premorbid mRS score, had more DNR orders, and more comorbidities as atrial fibrillation, hypertension, diabetes mellitus, ischemic heart disease, and heart failure. After adjustment for age, pre-existing comorbidities, and prior use of antithrombotic and antihypertensive medications, no differences in in-hospital mortality (OR 1.1, 95% CI 0.8-1.7), 12-month mortality (OR 1.3, 95% CI 0.9-1.9), and 3-month mortality (OR 1.2, 95% CI 0.8-1.7) emerged.

Conclusion: Pre-admission use of BB was not associated with mortality after ICH.

KEYWORDS
beta-blockers, intracerebral hemorrhage, mortality, outcome

1 | INTRODUCTION

Acute stroke including intracerebral hemorrhage (ICH) has been shown to elicit massive activation of the sympathetic nervous system responsible for complication as hypertensive derangement, cardiac changes, or immunodepression.[1,2] Thus, anti-adrenergic medication has been studied for neuroprotective properties in this setting. Previous reports indicate that prestroke beta-blocker (BB) therapy in ischemic stroke may be associated with decreased stroke severity and overall mortality.[3,4] However, other reports contradict these findings.[5] In ICH, BB-therapy has been proposed to reduce perihematomal edema, infection rates, and mortality.[6-8] However, a huge national registry could not verify positive effects of BB on short-term mortality after ICH.[9] Given the inconclusiveness of the previous studies, we aimed to test the hypothesis that prestroke BB-therapy is associated with mortality after ICH.

2 | METHODS

This study was based on the Helsinki ICH Study database, a retrospective collection of all consecutive patients with ICH treated at the Helsinki University Central Hospital from January 2005 to March 2010, as published in detail previously.[10] Briefly, the database is based on retrospectively retrieved data from medical records. The Glasgow Coma Scale (GCS) was systematically registered for patients at the emergency department, and the National Institutes of Health Stroke Scale was reconstructed from chart notes. Information on comorbidities and previous medications were retrieved from the province-wide hospital notes of all specialties and general practice referral notes. All scans were evaluated by neuroradiologists at our hospital, and we included all subsequent scans after the ICH in our analysis. Lesion volumes were estimated with the ABC/2 method.[11] We recorded the modified Rankin Scale (mRS) at discharge but did not have systematic follow-up visits, wherefore

functional outcome could not be evaluated after discharge. For this reason, we used mortality as our primary outcome with date of death retrieved from Statistics Finland in October 2011 for all residents of our province. The study has been approved by institutional authorities. As a routine observational quality registry with no patient contact, consent for registration was not required by Finnish legislation.

3 | STATISTICS

Due to non-normal distribution of all continuous variables, median with interquartile range is reported. Groups were compared with the Pearson chi-squared test with two-sided statistical significance set at 0.05. Multivariable logistic regression models with the dependent variables in-hospital mortality, mortality at 3 months, and mortality at 12 months were performed to test for possible impact of the prior BB-therapy after adjustment for following confounders: age, prior mRS>1, atrial fibrillation, hypertension, diabetes mellitus, ischemic heart disease, heart failure, admission glycemia, prior anticoagulants, prior antiplatelets, and previous therapy with angiotensin converting enzyme inhibitors (ACEI), angiotensin receptors antagonists (ARB), and calcium blockers (CA). Analyses were performed on IBM SPSS 20 (IBM Corp, Armonk, NY).

TABLE 1 Characteristics and mortality of BB-naïve patients vs those treated with BBs before ICH onset

Characteristic	BB-naive, n = 724 (71.5%)	BB before ICH, n = 289 (28.5%)	*P*
Male gender, n (%)	413 (57.0)	169 (58.5)	.7
Age, years, mean (range, SD)	65.4 (22-93, 13.7)	70.3 (31-97, 12.3)	<.001
Prior mRS>1	71 (9.8)	63 (21.8)	<.001
Atrial fibrillation, n (%)	52 (7.3)	90 (31.3)	<.001
Hypertension, n (%)	352 (48.6)	285 (98.6)	<.001
Diabetes mellitus, n (%)	63 (8.7)	79 (27.3)	<.001
Ischemic heart disease, n (%)	36 (5.0)	92 (31.9)	<.001
Heart failure, n (%)	18 (2.5)	30 (10.5)	<.001
Admission NIHSS, median (range, IQR)	11 (0-40, 15)	12 (0-40, 15)	.14
Admission GCS, median (range, IQR)	14 (3-15, 5)	14 (3-15, 5)	.79
ICH score, median (range, IQR)	1 (0-6, 2)	1 (0-5, 2)	.23
Hemorrhage volume, median (range, IQR)	10.4 (0-274, 22.6)	8.8 (0.1-171, 25.7)	.72
IVH, n (%)	297 (41.0)	115 (39.8)	.7
Infratentorial localization, n (%)	102 (14.1)	40 (13.8)	1.0
Basal ganglia localization, n (%)	317 (43.8)	116 (40.1)	.3
Hemorrhage growth 33% or >6 mL, n (%)	101 (28.7)	44 (32.4)	.4
Admission blood glucose, median (range, IQR)	7.9 (3.5-54.8, 3)	8.6 (2.7-28.9, 3.5)	.009
Admission systolic BP, median (range, IQR)	169 (70-280, 44)	173 (34-191, 25)	.35
Admission diastolic BP, median (range, IQR)	92 (34-191, 26)	88 (35-162, 25)	.02
Prior OAC, n (%)	60 (8.3)	83 (28.7)	<.001
Prior antiplatelet, n (%)	143 (19.8)	122 (42.2)	<.001
Prior ACEI, n (%)	63 (8.7)	91 (31.5)	<.001
Prior ARB, n (%)	59 (8.1)	57 (19.7)	<.001
Prior CA, n (%)	61 (8.4)	63 (21.8)	<.001
In-hospital mortality, n (%)	161 (22.2)	83 (28.7)	.03
Mortality at 3 mo, n (%)	206 (29.2)	111 (39.8)	.002
Mortality at 12 mo, (%)	228 (32.3)	130 (46.6)	<.001

N, frequency; SD, standard deviation; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; BP, blood pressure; OAC, oral anticoagulants; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptors antagonists; CA, calcium blockers.

4 | RESULTS

In total, 1013 patients with ICH were extracted from the database and included in the analysis. Out of 1013 patients, 289 (28.5%) were taking BB at the time of index ICH and 724 (71.5%) were BB-naïve. Compared to patients not taking BB prior to ICH, those taking BB were significantly older (70.3 vs 65.4 years, $P < .001$), had a higher premorbid modified Rankin Score (mRS>1: 21.8% vs 9.8%, $P < .001$), had more comorbidities such as atrial fibrillation (31.3% vs 7.3%, $P < .001$), hypertension (98.6% vs 48.6%, $P < .001$), diabetes mellitus (27.3% vs 8.7%, $P < .001$), ischemic heart disease (31.9% vs 5%, $P < .001$), and heart failure (10.5% vs 2.5%, $P < .001$). Furthermore, patients on BB had more often prior oral anticoagulant treatment (28.7% vs 8.3%, $P < .001$), more often antiplatelet drugs (42.2% vs 19.8%, $P < .001$), and more often other antihypertensive drugs (ACEI: 31.5% vs 8.7%, ARB: 19.7% vs 8.1%, CA: 21.8% vs 8.4%, all $P < .001$), see also Table 1. Patients on BB also had more often do-not-resuscitate orders (n = 121, 41.9% vs n = 237, 32.7%; $P = .007$). The hemorrhage characteristics as well as the clinical status on admission were comparable between the groups (hemorrhage volume 8.8 mL vs 10.4 mL, $P = .72$; admission GCS 14 vs 14, $P = .79$), see also Table 1.

In the entire study population, in-hospital mortality was 24.1%, 3-month mortality 31.1%, and 12-month mortality 35.3%. Mortality at every time point was higher in the group of patients on pre-ICH BB-therapy as compared to BB-naïve patients. In BB-pretreated patients compared to BB-naïve patients, the in-hospital mortality, 3-months mortality, and 12-month mortality were 28.7%, 39.8%, and 46.6% as compared to 22.2%, 29.2%, and 32.3% ($P = .03$, $P = .002$, and<.001), respectively. After multivariable adjustment, no effects of prior BB-therapy on in-hospital (adjusted OR 1.1, 95% CI 0.8-1.7), 3-month mortality (adjusted OR 1.2, 95% CI 0.8-1.7), and 12-month mortality (adjusted OR 1.3, 95% CI 0.9-1.9) could be observed.

5 | DISCUSSION

In animal models, prestroke beta-blockade leads to decreased stroke lesion volumes, lesser infections, better functional outcome, and lower mortality.[12,13] As increased heart rate as a surrogate for sympathetic activation has been consistently found to be associated with poor outcome and higher mortality in all stroke types,[14-16] sympatholytic therapies may appear reasonable. However, the evidence from human studies is not straight forward. Confirmatory as well as negative studies exist on the beneficial effects of the prestroke BB-therapy in acute ischemic stroke.[3-5,9] A study by Laowattana found decreased ischemic stroke severity on admission in those taking BB-therapy.[4] On the other hand, later studies could not find any association between prestroke BB-therapy and stroke severity or outcome.[5,17] In our previous study, we found no effects of pretreatment BB on stroke severity, mortality and functional outcome; however, patients newly started with BB within the first 3 days after onset had lower infections rates and lower mortality.[18] Interestingly, there are some positive studies of protective effects of beta-blockers in subarachnoidal hemorrhage (SAH) and traumatic brain injury (TBI), both pathologies inducing marked sympathetic hyperactivity. Study by Chalouhi suggested that pre-admission therapy with BBs may reduce the incidence of vasospasms after SAH.[19] Another study in SAH patients suggested improved discharge characteristics and lower mortality in those treated with BB.[20] For TBI, recent studies and meta-analyses consistently suggest mortality and outcome benefits with beta-blockade.[21-23] Data in patients with spontaneous ICH are scarce and include both positive and negative signals.[6-9] A study by Kalita suggested reduction in mortality, SIRS, and pneumonia with the in-hospital use of atenolol in patients with ICH.[6] Other studies found no association between BB pretreatment and outcome in ICH.[7,9] In line with the later studies, we found no effects of pre-admission BB on mortality after ICH, thus, contributing to the negative body of evidence within this topic. We hypothesize that the effects of random prestroke BB exposure and post-admission beta-blockade on stroke outcome may be different. This is also the point where most of the studies diverge.

Limitations of our study have to be acknowledged. BB in this cohort were principally uncontrolled, highly heterogeneous in substances and dosages as well as in indications for administration. The main source of possible bias is, therefore, the confounding by indication. Despite having adjusted the analysis for the between-group imbalances, one cannot completely rule out hidden effects. Further drawback is the retrospective, non-randomized character of the analysis. The strength of our study, however, is the data from a large homogeneous monocentric registry of consecutive ICH patients with rigorously collected clinical and radiological variables and outcomes.

6 | CONCLUSION

In the recent large monocentric non-randomized comparison, we could not find any association of pretreatment BB with mortality after ICH.

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CONFLICT OF INTEREST

none.

DISCLOSURES

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ORCID

M. Sykora http://orcid.org/0000-0003-3508-2176

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