Original Article

Labetalol Use Is Associated With Increased In-Hospital Infection Compared With Nicardipine Use in Intracerebral Hemorrhage

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Background and Purpose—Increased sympathetic tone causes hypertension after intracerebral hemorrhage, and blood pressure reduction has been studied as a way to decrease hemorrhage growth and improve outcomes. It is unknown if the antihypertensive used to achieve blood pressure goals influences either. Because sympatholytic drugs reduce death and infection in animal models, we hypothesized that labetalol would improve outcomes compared with nicardipine.

Methods—Prospective data from a single center were retrospectively reviewed. Patients receiving labetalol, nicardipine, or both during their first 3 days of hospitalization were included. Outcomes included in-hospital death; discharge modified Rankin Score >2; and in-hospital urinary tract infection, pneumonia, or bacteremia. Patients were compared with propensity scoring and analyzed with linear models adjusted for significant confounders.

Results—Of 1066 admissions, 525 were treated with labetalol or nicardipine and are included; 229 (43.6%) received labetalol, 107 (20.4%) received nicardipine, and 189 (36.0%) received both. Mortality and infection rates were 40.2% and 15.8%, respectively, 77.2% had a modified Rankin Score >2. After adjustment, compared with nicardipine alone, labetalol alone was associated with infection (odds ratio, 3.12; confidence interval, 1.27–7.64; P=0.013) but not when combined with nicardipine (odds ratio, 2.44; confidence interval, 0.98–6.07; P=0.055). Labetalol, with or without nicardipine, was not associated with death or discharge modified Rankin Score >2.

Conclusions—Compared with nicardipine, labetalol was associated with increased in-hospital infections, but not mortality or modified Rankin Score >2. These findings do not support our hypothesis that labetalol use improves outcomes relative to nicardipine in intracerebral hemorrhage. **(*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.117.017230.)**

Key Words: cerebral hemorrhage ■ hypertension ■ labetalol ■ nicardipine ■ propensity score ■ receptors, adrenergic, beta ■ stroke

Intracerebral hemorrhage (ICH) is a devastating neurological condition associated with significant morbidity and mortality.[1,2] Patients often present with increased sympathetic tone, either from direct brain injury or indirectly reduced parasympathetic tone.[3] This catecholamine surge can have pleiotropic effects on cardiac, renal, metabolic, and immune function and leads to hypertension, which may predispose to hemorrhage growth.[3–5] Optimal blood pressure goals in ICH are unclear.[6,7]

The pragmatic INTERACT2 trial (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial) randomized patients to guideline recommended treatment (systolic blood pressure<180 mm Hg) or intensive treatment (systolic blood pressure goal<140 mm Hg). Intensive systolic blood pressure lowering in INTERACT2 was associated with an improvement in modified Rankin Scores (mRS). A variety of antihypertensives were used to achieve these systolic blood pressure goals, many of which affected sympathetic tone.[6] Conversely, the ATACH-2 trial (Antihypertensive Treatment of Acute Cerebral Hemorrhage), which used only nicardipine, found no clinical benefit with intensive versus standard blood pressure control.[7]

Several less rigorous retrospective studies examining the use of β-blockers specifically for management of hypertension in ICH link their use to reductions in mortality, systemic inflammatory response syndrome, pneumonia, and perihematomal edema.[3,5,8] In animal models of ischemic stroke, β-blockers decrease mortality and the risk of infection; observational studies in humans show varying effects of β-blocker use on mortality and infection.[9–16] It is thus conceivable that part of the discrepancy between the 2 large clinical trials of blood pressure reduction in ICH is related to the specific antihypertensive agents used given the frequent use of α/β-blockers in INTERACT2 and the sole use of the calcium channel blocker nicardipine in ATACH-2.

Materials and Methods

To examine whether α/β-blockers for hypertension management in ICH result in better clinical outcomes, we compared outcomes in patients treated with nicardipine, labetalol, or both. The Institutional Review Board of the University of Washington approved this study with a waiver of informed consent. The records for all ICH admissions at a single center from July 2010 to June 2015 were prospectively collected for Get With The Guidelines-Stroke, a national prospective quality improvement database.[17] These data were combined with

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local billing and medication administration record data extracted with Microsoft AMALGA (Microsoft, Redmond, WA) and linked by medical record number.

Patients were categorized by whether or not they received labetalol, nicardipine, or both during their first 3 days in the hospital; patients receiving neither medication were excluded. The effects of these 2 specific medications were chosen because they are by far the most frequently used medications for blood pressure management in ICH at the study site. There is no local protocol specifying which antihypertensive to use, so practitioner choice varies with personal preferences, patient comorbidities/presentation, and the admitting service. Patients receiving both medications were included to help determine if 1 medication was associated with a benefit or harm; in the case of a benefit, patients receiving both would be expected to have similar outcomes to those receiving just the beneficial medication. In the case of harm, patients receiving both would be expected to have similar outcomes to those receiving just the harmful medication.

Covariates in this study included age, sex, body mass index, atrial fibrillation, coronary artery disease, diabetes mellitus, hyperlipidemia, hypertension, peripheral vascular disease, prior stroke or transient ischemic attack, smoking status, substance abuse, admission ICH score, treatment with hypertonic saline or mannitol, and any surgical management of intracranial pressure (external ventricular drain, endoscopic evacuation, conventional craniotomy and evacuation, stereotactic evacuation, hemicraniectomy without evacuation, or "other"). The only covariate with missing values was body mass index (n=168). Missing values were replaced with predictive mean matching using 5 multiple imputations with 5 iterations.[18]

The outcomes of interest were in-hospital death, mRS>2 at discharge, and infection, defined as a urinary tract infection, pneumonia, or bacteremia during the acute hospitalization. Pneumonia was recorded per Get With The Guidelines standards, which requires both the clinical mention of pneumonia by the physician and treatment with an antibiotic for pneumonia. ICD-9 codes (International Classification of Diseases) were used for urinary tract infection (590.10, 590.11, 590.80, 590.9, 599.0) and bacteremia (421.0, 421.1, 421.9, 424.90, 424.91, 424.99, 790.7, 999.32).

Using all subjects, a primary propensity weighted cohort was created to examine in-hospital death. Because some discharge mRS values were missing (n=86), a separate cohort to examine this outcome was created by excluding patients with missing mRS values. To be able to analyze downstream infection development, patients started on antibiotics on hospital day 1 (n=68) were presumed to have arrived with an infection and also excluded from another cohort to specifically analyze infections.

Statistical Analysis

R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses.[19] For univariate analyses, Pearson's χ^2, Fisher exact test, analysis of variance, and Kruskal–Wallis rank-sum tests were utilized as appropriate.

The propensity for each patient to receive nicardipine was determined with the R package Twang using all covariates associated with receiving nicardipine by univariate analysis ($P<0.05$).[20] The estimand was set to the average treatment effect on the treated, and the stop method was the maximum standardized effect size. To ensure adequate scoring, the maximum standardized effect size for each covariate was confirmed to be <0.1, and the minimum Kolmogorov–Smirnov statistic was confirmed to be >0.05.[20,21] These methods were repeated for the mRS cohort and the infection cohort. A propensity weighting approach with the TWANG package (Toolkit for Weighting and Analysis of Nonequivalent Groups) was chosen because this study includes 3 treatment groups. This approach avoids the introduction of bias that a nearest neighbor matching method could add if healthier patients from the control group are more frequently matched with 1 experimental group than the other.

Covariates not included in the propensity score were then tested for univariate associations with the outcomes of interest using Pearson's χ^2 and Fisher exact test as appropriate. Any covariate associated with an outcome ($P<0.05$) was controlled for in the analysis of that outcome. For the final analysis of all 3 outcomes, generalized linear models weighted by propensity scores and adjusted for significant confounders were created with the iteratively reweighted least squares method. All outcomes were binary, so logit links were also used. These models were used to deduce odds ratios (ORs) and 95% confidence intervals (CIs).

Results

This study included 1066 admissions. Labetalol or nicardipine was administered within the first 3 days of hospitalization for 525 admissions. The mean patient age was 62.8 years (SD, 15.7) with a median ICH score of 2 (interquartile range, 1–3). The labetalol group included 229 admissions (43.6%); the nicardipine group included 107 admissions (20.4%); and 189 admissions (36.0%) received both medications. Patients receiving exclusively labetalol were more likely to have concomitant atrial fibrillation, and patients receiving both medications were more likely to undergo a surgical intervention for intracranial pressure management, suggesting more aggressive management overall. A full comparison of the demographic characteristics of the patients in each group is presented in Table 1.

The overall mortality rate was 40.2%, with 26.5% of patients ultimately receiving comfort measures only. Infections after admission were diagnosed in 15.8% of patients. Urinary tract infections were recorded in 11.2% of patients, pneumonia in 5.0%, and bacteremia in 0.4%. An mRS>2 at discharge was recorded for 77.2% of patients. Before propensity weighting or adjustment for significant confounders, compared with nicardipine alone, labetalol use was not associated with mortality, either alone (OR, 0.77; confidence interval [CI], 0.48–1.23; $P=0.266$) or in combination with nicardipine (OR, 0.90; CI, 0.56–1.45; $P=0.657$). Infection was associated with labetalol use, both alone (OR, 2.76; CI, 1.25–6.99; $P=0.019$) and in combination with nicardipine (OR, 2.47; CI, 1.08–6.37; $P=0.043$). Labetalol use was not associated with disability (mRS>2), either alone (OR, 1.05; CI, 0.58–1.87; $P=0.862$) or in combination with nicardipine (OR, 1.23; CI, 0.66–2.24; $P=0.509$).

On univariate analysis, age, body mass index, atrial fibrillation, ICH score, and an intracranial pressure intervention were associated with treatment group allocation. Using these covariates, separate propensity weighted cohorts for all 3 outcomes were created that met the prespecified model criteria. Balance tables depicting the quality of matching for all 3 cohorts are presented in Table 2.

All of the remaining covariates were tested for associations with the outcomes of interest, with the resulting P values depicted in Figure 1. Lack of hypertonic saline/mannitol administration ($P=0.002$) and no substance abuse history ($P=0.045$) were both associated with death and controlled for in its respective model. Female sex ($P=0.050$) and hypertonic saline/mannitol administration ($P=0.029$) were associated with infection and controlled for in its respective model. Finally, female sex ($P=0.038$) was also associated with mRS>2 and controlled for in its respective model.

The results of the propensity weighted generalized linear models for each outcome, after controlling for associated covariates, are summarized in Figure 2. Death was not associated with labetalol administration (OR, 0.93; CI, 0.55–1.57; $P=0.793$) or receiving both labetalol and nicardipine (OR,

Table 1. Demographic Characteristics of the Whole Patient Cohort and the Subsets of Patients Who Received Labetalol, Nicardipine, or Both During the First 3 Days of Hospitalization

Baseline Characteristics of the Study Population Overall and the 3 Treatment Groups					
	Overall (n=1066)	Labetalol (n=229)	Nicardipine (n=107)	Both (n=189)	*P* Value
Age, mean (SD)	62.8 (15.7)	62.8 (15.4)	58.8 (15.0)	58.2 (14.5)	0.004
Male, n (%)	592 (55.5)	132 (57.6)	66 (61.7)	120 (63.5)	0.460
BMI, mean (SD)	28.1 (6.8)	27.8 (5.8)	29.5 (8.1)	29.6 (7.7)	0.024
Atrial fibrillation, n (%)	186 (17.4)	46 (20.1)	14 (13.1)	22 (11.6)	0.044
CAD, n (%)	165 (15.5)	29 (12.7)	11 (10.3)	25 (13.2)	0.749
DM, n (%)	224 (21.0)	46 (20.1)	91 (15.0)	48 (25.4)	0.096
Hyperlipidemia, n (%)	336 (31.5)	68 (29.7)	33 (30.8)	56 (29.6)	0.972
HTN, n (%)	735 (68.9)	173 (75.5)	81 (75.7)	144 (75.2)	0.988
PVD, n (%)	22 (2.1)	4 (1.7)	4 (3.7)	2 (1.1)	0.318
Prior stroke/TIA, n (%)	205 (19.2)	47 (20.5)	17 (15.9)	23 (12.2)	0.072
Smoker, n (%)	218 (20.5)	53 (23.1)	21 (19.6)	41 (21.7)	0.765
Substance abuse, n (%)	81 (7.6)	19 (8.3)	14 (13.1)	17 (9.0)	0.361
Hospital transfer, n (%)	806 (75.6)	175 (76.4)	81 (75.7)	132 (69.8)	0.280
ICH score, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	0.003
Labetalol per d (mg IV), median, (IQR)*	0 (0–6.7)	10 (3.3–26.7)	0 (0–0)	16.7 (6.7–36.7)	NA
Nicardipine per d (mg IV), median (IQR)	0 (0–3.6)	0 (0–0)	43.3 (12.7–71.6)	28.0 (9.6–71.6)	NA
Hypertonic saline/mannitol, n (%)	794 (74.5)	188 (82.1)	90 (84.1)	165 (87.3)	0.344
ICP intervention, n (%)	101 (9.5)	27 (11.8)	11 (10.3)	36 (19.0)	0.047
Length of stay, median (IQR)	7 (3–16)	10 (5–19)	9 (4–24)	12 (6–23)	0.107

P values were derived with Pearson's χ^2, Fisher exact test, analysis of variance, and Kruskal–Wallis rank-sum tests as appropriate. Abbreviations: BMI indicates body mass index; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; ICH, intracerebral hemorrhage; ICP, intracranial pressure; IQR, interquartile range; IV, intravenous; PVD, peripheral vascular disease; and TIA, transient ischemic attack.

*Oral labetalol was converted to IV labetalol at a 4:1 ratio.

0.97; CI, 0.58–1.62; *P*=0.913) relative to receiving nicardipine alone. Infections were associated with labetalol use alone (OR, 3.12; CI, 1.27–7.64; *P*=0.013) but not labetalol use in combination with nicardipine (OR, 2.44; CI, 0.98–6.07; *P*=0.055). An mRS>2 was not associated with labetalol use alone (OR, 1.17; CI, 0.62–2.20; *P*=0.634) or labetalol use in combination with nicardipine (OR, 1.17; CI, 0.60–2.29; *P*=0.639).

Discussion

We did not find a difference in mortality or disability (mRS>2) between patients who received labetalol or nicardipine for the management of hypertension after ICH. Labetalol use, however, was associated with an increase in infections after ICH. While not statistically significant, patients who received both labetalol and nicardipine tended to have an elevated risk of

Table 2. Balance Tables for Each Cohort After Propensity Scoring Based on the Covariates Associated With Treatment Group Allocation

Propensity Weighting Balance Table Summary						
	Death		Infection		mRS>2	
	Maximum Standardized Effect Size	Minimum KS *P* Value	Maximum Standardized Effect Size	Minimum KS *P* Value	Maximum Standardized Effect Size	Minimum KS *P* Value
Age	0.066	0.991	0.077	0.988	0.012	0.992
BMI	0.059	0.998	0.077	0.993	0.097	0.991
Atrial fibrillation	0.067	0.595	0.079	0.562	0.050	0.713
ICH score	0.030	1.000	0.081	0.996	0.040	0.999
ICP intervention	0.054	0.679	0.047	0.735	0.097	0.521

All maximum standardized effect sizes are < 0.1, and all minimum KS *P* values are >0.05, suggesting adequate matching. BMI indicates body mass index; ICH, intracranial hemorrhage; ICP, intracranial pressure; KS, Kolmogorov–Smirnov statistic; and mRS, modified Rankin Score.

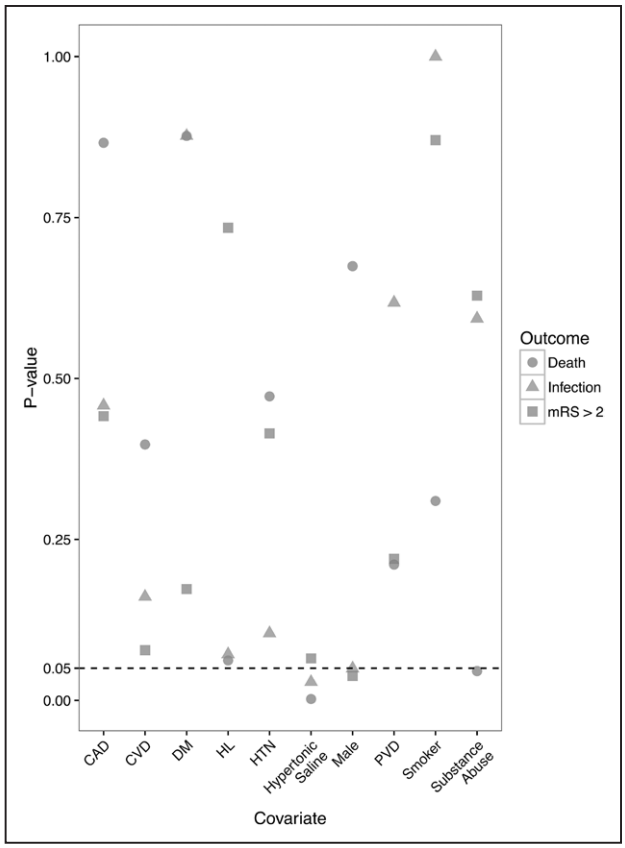

Figure 1. Results of univariate testing between outcomes and all covariates excluded from propensity weighting. Covariates associated with receiving labetalol, nicardipine, or both were included in the propensity weighting. All remaining covariates were eligible to be adjusted for in the generalized linear models for each outcome. To determine which covariates to include, we performed univariate tests between the remaining covariates and the 3 outcomes of interest. The *P* values from these tests are summarized in this figure. Covariates with $P<0.05$ were ultimately adjusted for in the final, generalized linear models. All testing was with Pearson's χ^2 test, except for peripheral vascular disease (PVD), which required Fisher exact test. CAD indicates coronary artery disease; CVD, cerebrovascular disease; DM, diabetes mellitus; HL, hyperlipidemia; HTN, hypertension; and mRS, modified Rankin Score.

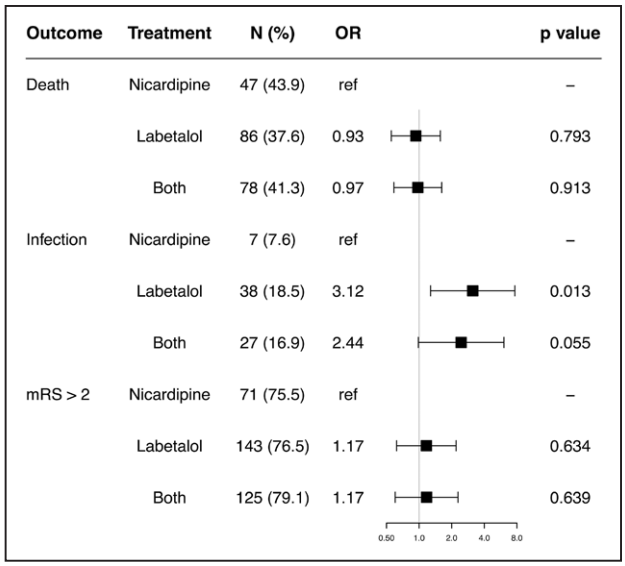

Figure 2. Results after propensity weighting and adjusting for significant confounders. For each outcome of interest, this forest plot summarizes the results for each treatment group compared with the nicardipine treatment group as the reference. The odds ratios were determined after propensity weighting and adjusting for significant confounders (death: hypertonic saline/mannitol administration, substance abuse; infection: sex, hypertonic saline/mannitol administration; mRS>2: sex). The boxes represent the odds ratios, while the whiskers represent the 95% confidence intervals. OR indicates odds ratio; mRS, modified Rankin Score; and ref, reference.

infection similar to those who received labetalol alone, suggesting labetalol use is associated with an increased risk of infection, as opposed to nicardipine use being associated with a reduced risk of infection.

The lack of a difference in mortality or disability (mRS>2) is similar to the findings of the INTERACT2 trial, although a separate ordinal regression analysis in that study suggested that intensive blood pressure control lowered the mRS.[6] An ordinal regression analysis was originally intended in this study, but the proportional odds assumption did not seem to hold, perhaps because of the relatively smaller sample size. Nevertheless, given that the odds ratios for mRS are nearly one in this study, it is unlikely that any statistical modification would have revealed a significant difference.

Our findings are also consistent with a variety of studies showing similar safety profiles for labetalol and nicardipine in ICH, subarachnoid hemorrhage, ischemic stroke, and acute hypertension.[8,22–26] These studies largely examined hemodynamic stability during the acute presentation, but Mayer et al[23] specifically did not find a survival difference between the initiation of labetalol or nicardipine for acute hypertension. Similarly, in ICH, while Shoup et al[8] demonstrated reduced mortality in those taking a β-blocker within the first 3 days, they also found that the survival benefit was not specific to the class of antihypertensive.

Poststroke immunodepression seems to be related, at least in part, to increased sympathetic tone. Previous study suggests that β-blockers may inhibit the detrimental effect of sympathetic activation on immune function and decrease the risk of infection.[11,12,14,16] In several recent retrospective studies, however, β-blocker use was found to be associated with an increased risk of infection in ischemic stroke.[8,27,28] Our findings support the relationship between β-blockers and increased infection.

One of the limitations of this study includes its inherent susceptibility to unrecognized confounders. There are certainly other factors affecting our outcomes of interest that we did not include: mechanical ventilation, peak intracranial pressure, potential use of immunosuppressive medications, etc. Data regarding these variables were not always available, and incorporating too many covariates presents its own challenges. Additionally, we did not control for other antihypertensives that may have been concurrently administered.

This study also included patients transferred from other hospitals, and medications given before transfer were not available for analysis. Almost all transfers were from outside

emergency departments, however, so the likelihood of receiving an antihypertensive that was not continued after transfer is low.

Another area of concern is the definition of an infection. Pneumonia was prospectively recorded according to the standards of Get With The Guidelines-Stroke, but ICD-9 coding was used to identify urinary tract infections and bacteremia, which has variable capture rates and definitions.[29,30] For example, asymptomatic bacteriuria or a single blood culture contaminant could be mislabeled. We chose to include these infections given their frequency after stroke and because previous studies included these data points, but other important infections, like *Clostridium difficile* or meningitis, were not included.[10,15,27,28]

The timing of antihypertensive exposure used for categorizing a patient as receiving labetalol or nicardipine is also debatable. If the whole hospitalization was chosen, treatment categorization could be adversely effected by categorizing a patient who received nicardipine for the first 3 days, but received a 1-time labetalol dose on hospital day 30, in the "both" group. If a shorter period was chosen, hospital day 1 for instance, patients could start receiving the other agent on hospital day 3, early enough to potentially influence their outcomes. Ultimately, 3 days was chosen as the therapeutic window given its frequent characterization as the acute stroke period.[8,31,32] Conclusions about effects on mRS may also be limited by the timing of disability assessment at hospital discharge, as opposed to delayed intervals after ICH occurrence.

In summary, this study of patients with ICH found labetalol use for management of hypertension, compared with nicardipine, not to be associated with differences in mortality or mRS. Labetalol use, however, was associated with an increase in infections. The findings of this study therefore argue against labetalol being superior to nicardipine for management of hypertension in ICH.

Disclosures

None.

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