Nicardipine Associated Risk of Short-Term Mortality in Critically Ill Patients with Ischemic Stroke

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Background: Hypertensive emergency is commonly associated with acute ischemic stroke and can be a predictor of poor outcome in these patients. Nicardipine and labetalol are commonly administered for the treatment of acute hypertension following stroke. Yet, data are lacking on the safety of these agents in this setting. *Objective:* This study aimed to determine all-cause in-hospital mortality, medication-related hypotensive episodes, development of hospital acquired infections and hospital length of stay between nicardipine and labetalol use for the management of hypertension after acute ischemic stroke. *Methods:* This retrospective study used a prospective database of individuals admitted to the neurointensive care unit at a university-based hospital over 39 months. Patients with confirmed ischemic strokes were included in this analysis. Data were recorded for administration of nicardipine and labetalol following acute stroke. *Results:* A total of 244 patients with acute ischemic stroke were included in this analysis (mean age, 64.3 ± 15 years; 52.2% males). Nicardipine use after acute ischemic stroke was associated with an increased risk of 30-day mortality (odds ratio [OR]: 4.6, 95% confidence interval [CI] 1.3-15.7; $P = .02$). A single episode of hypotension in the first 72 hours of admission was also significantly associated with mortality (OR 4.35 [95% CI 1.2-14.9]; $P = .02$). *Conclusions:* Nicardipine was associated with an increased risk of short-term mortality after acute ischemic stroke. This may have been due to hypotension, tachycardia, or pulmonary edema which were not apparent in our study. Further studies are required to elucidate the cause of this association.

Key Words: Ischemic Stroke—hypertension—antihypertensives—nicardipine—mortality

Introduction

Stroke is the fifth leading cause of death in the United States.[1] Approximately, 75% of patients experiencing an ischemic stroke will have an acute hypertensive response, which has been established as an independent predictor of poor clinical outcome due to the increased risk of cerebral edema and hemorrhagic transformation in stroke patients.[2-6] However, the optimal pharmacologic management of hyperacute hypertensive response after an ischemic stroke within the first 72 hours is controversial.

The low-dose beta blockade in acute stroke study that evaluated patients receiving beta blocker therapy within the first 48 hours of an ischemic stroke showed a higher mortality as compared to placebo.[7] The study concluded that the effect may have been due to the variations in baseline characteristic among the treatment groups or

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could be attributed to the negative inotropic effects of beta blockers that may worsen cerebral perfusion.[7] In contrast, the controlling hypertension and hypotension immediately post stroke study demonstrated the safety of labetalol when given in acute hypertensive phase and suggested an overall decrease in mortality; however, the study was not powered to demonstrate this effect.[8] More recently, labetalol use has been linked to increase in-hospital infection rates compared to nicardipine in patients with intracerebral hemorrhage.[9]

Intravenous calcium channel blockers initiated in patients with acute ischemic stroke were found to have an increased risk of poor outcomes if administrated at higher doses, and within 12 hours of symptom onset.[10] A prospective trial that evaluated the efficacy of labetalol versus nicardipine for blood pressure management after an acute stroke found nicardipine to be superior without any demonstrable differences in clinical outcomes.[11] However, the majority of patients in this study presented with intracerebral hemorrhage.[11]

Although the AHA/ASA guidelines for early management of patients with acute ischemic stroke recommend nicardipine and labetalol as the 2 antihypertensive of choice,[12] the impact of the type of pharmacologic agent on clinical outcomes is less well established, particularly in critically ill patients. In this study, we sought to evaluate the differences in short-term mortality in patients receiving nicardipine and labetalol.

Methods

A retrospective analysis was conducted from a prospectively maintained database. The database includes all patients admitted to the Neurocritical Care Unit (NICU) at a university-based hospital. A research coordinator was assigned to enter the data which included demographics, comorbidities, presentation, length of stay (LOS), primary and secondary diagnoses. Additional disease-specific data such as National Institute of Health Stroke Scale (NIHSS) and administration of thrombolytics was entered based on the primary diagnosis. The database was queried for all patients with an admission diagnosis of ischemic stroke between November 2013 and January 2017. A chart review was performed to collect additional data, and patients were categorized by the strategy of antihypertensive agents used in the first 48 hours of hospitalization (nicardipine, labetalol, or both). Patients were excluded if they had a concomitant intracerebral hemorrhage or lack of blood pressure data. The use of labetalol or nicardipine would likely be distributed nondifferentially and represents the treating physician's choice or patient's contraindications.

The primary outcome was all-cause in-hospital mortality after index stroke. Secondary outcomes included any medication-related hypotensive episodes (systolic blood pressure [SBP] <90 mm Hg or mean arterial pressure <65 mm Hg), development of hospital acquired infections, and hospital LOS.

Statistical Analysis

Descriptive data were reported as mean ± SD, median (interquartile range [IQR]) or number, and percentage for each treatment group. Chi-square test of comparison for categorical variables was used to compare the risk of mortality between labetalol and nicardipine therapy groups. Mortality risk according to antihypertensive regimen was assessed using multivariate logistic regression models to assess potential association between antihypertensive strategy and NICU mortality. Odds ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated. Statistical significance was defined as a P value $< .05$.

Ethics

The university institutional review board approved the study. The institutional review board waived the need for a consent.

Results

A total of 244 patients with acute ischemic stroke were included in the analysis. Out of 244 patients, 42 (17.2%) patients received only labetalol, 25 (10.2%) patients received only nicardipine, and 33 (13.5%) patients received both. In total, intravenous antihypertensive medications were administered in 41% of patients. The mean age of the cohort was 64.3 (±15) years, were predominantly male (52.2%) and 39.3% received thrombolytic therapy. The median NIHSS of the cohort was 9 (IQR 4-16), 12 (IQR 4-17) in labetalol group, and 15 (IQR 5.5-20.6) in the nicardipine group. The median admission SBP and admission mean arterial pressures were not significantly different between the groups. The baseline admission characteristics of the patients are documented in Table 1. There were no significant differences among the 2 groups with the exception of diabetics, in whom labetalol was used more commonly (23.6% versus 16.6%; $P = .03$).

The overall in-hospital mortality was 7.8%. Among patients who received either antihypertensive agents, nicardipine was associated with a significantly higher mortality (7.4% versus 1.5%; $P < .04$). In patients who received nicardipine, the mortality was 20% versus 6.4% in patients who did not receive nicardipine (OR: 3.6, 95% CI 1.2-11.2; $P = .02$). The cause of death in patients that received antihypertensives include withdrawal of care due to poor neurological status (n = 6), cerebral herniation (n = 5), cardiac arrhythmias (n = 3), sudden cardiac arrest (n = 4), pulmonary embolism (n = 1), and septic shock (n = 1).

In a logistic regression analysis adjusted for comorbidities, stroke severity (NIHSS), need for intubation, development of hospital-acquired infections and blood

Table 1. *Baseline characteristics of patients stratified by intravenous antihypertensive use*

Variable	Total cohort	Labetalol group	Nicardipine group	*P* value
Male (%)	52.5	13.3	9.4	.15
Age (years; mean ± SD)	64.3 ± 15	66 ± 17.2	65.8 ± 11.9	.94
Afib (%)	20.1	15.7	19.6	.13
CAD (%)	24.2	11.9	5.1	.52
DM (%)	36.5	23.6	16.6	.03
HLD (%)	29.5	19.4	5.6	.31
Smoking (%)	30.3	16.2	5.4	.36
Prior stroke (%)	27	21.2	9.1	.19
tPA (%)	39.3	19.8	7.3	.17
Median NIHSS (IQR)	9 (4-16)	12 (4-17)	15 (5.5-20.6)	.16
Median admission SBP (mm Hg; IQR)	153 (132-179)	162 (133-182)	159 (139.5-201.8)	.85
Median admission MAP (mm Hg; IQR)	106 (94-122)	115.5 (104-128)	114 (102.8-121.5)	.50

Abbreviations: Afib, atrial fibrillation; CAD, coronary artery disease; DM, diabetes mellitus; HLD, hyperlipidemia; IQR, interquartile range; MAP, mean arterial pressure; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure; SD, standard deviation; tPA, tissue plasminogen activator.

Table 2. *Multivariate analysis for predictors of mortality*

Predictor	OR	CI	*P* value
Any hypotensive episode (<72 hours of admission)	4.35	1.2-14.9	.02
Nicardipine use	4.6	1.3-15.7	.02

Abbreviations: CI, confidence interval; OR, odds ratio.

pressure control, nicardipine usage remained significantly associated with higher risk of mortality (OR 4.6 [95% CI 1.3-15.7]; *P* = .02; Table 2).

Episodes of hypotension were seen in 55 patients (22.5%) but did not vary based on the antihypertensive agent use (*P* = .18). However, a single episode of hypotension in the first 72 hours of admission was also significantly associated with mortality (OR 4.35 [95% CI 1.2-14.9]; *P* = .02; Table 2). The level of blood pressure control in first 72 hours (*P* = .65; Fig 1), development of

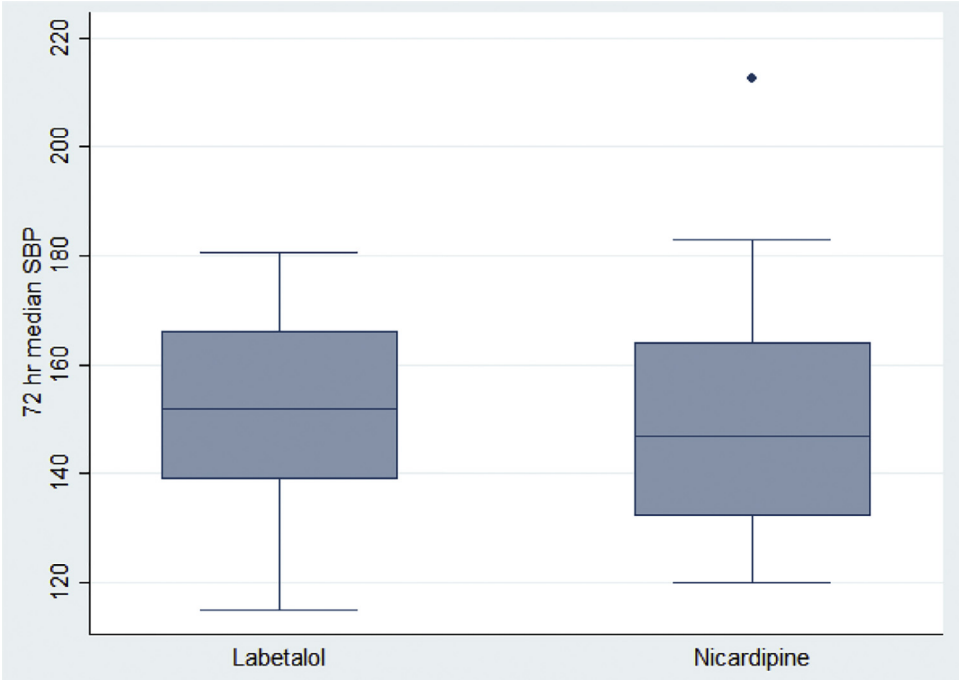

Figure 1. *Median systolic blood pressures within the first 72 hours of admission stratified by intravenous antihypertensive use. Abbreviation: SBP, systolic blood pressure.*

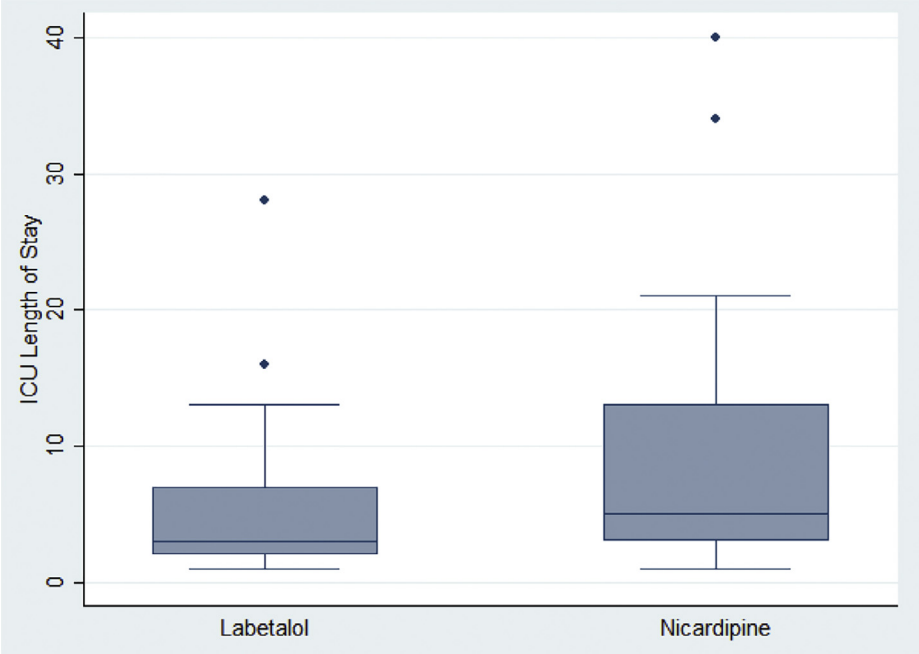

Figure 2. *Intensive care unit (ICU) length of stay stratified by intravenous antihypertensive use.*

hospital acquired infections (P = .12) and LOS (P = .11; Fig 2) did not vary between the 2 groups.

Discussion

Acute management of blood pressure during the first 72 hours after ischemic stroke is not well established. Although guidelines and prospective studies have addressed this issue in the past, definitive randomized evidence particularly in the critically ill patients is lacking. This has been further complicated by recent paradigm shifts in acute stroke care, such as the widespread use of endovascular therapies for large vessel occlusive strokes. Our analysis of 244 patients with acute stroke admitted to NICU showed a higher risk of short-term mortality in patients treated with nicardipine compared to labetalol.

Increased blood pressure is common following acute stroke, especially in those with pre-existing hypertension.[13] Prior studies have noted worse outcomes in patients with a decrease in blood pressure after admission.[14] Results from analyses on more than 17,000 patients enrolled in the International Stroke Trial showed a "U-shaped" relationship between blood pressure and mortality, with an 18% increase in mortality for every decrease of 10 mm Hg below SBP of 150 mm Hg.[15] These results are in line with findings from our study. We found a 4.5-fold increased risk of short-term mortality in acute stroke patients who experienced a hypotensive episode in the first 72 hours of intensive care unit admission.

The AHA/ASA guidelines for early management of patients with acute ischemic stroke recommend nicardipine and labetalol as the 2 antihypertensive of choice for acute blood pressure lowering.[12] Although these agents are recommended, there are little data that demonstrate the safety and efficacy for use for acute blood pressure management after ischemic stroke. In our prospective cohort of acute ischemic stroke patients, we observed a significant increase in mortality in those treated with nicardipine. These results warrant prospective study to further validate our findings.

Lui-DeRyke, et al. aimed to evaluate the therapeutic response and tolerability of labetalol and nicardipine following acute stroke in primarily hemorrhagic stroke patients.[3] Therapeutic response assessed by blood pressure goal achievement and blood pressure variability was significantly better achieved by nicardipine compared to labetalol.[3] The study also found no significant difference in clinical outcomes including LOS, clinical status at discharge, and in-hospital mortality.[3] However the study had a small sample size and was not powered to detect a difference in clinical outcomes. A more recent evaluation in hypertensive stroke patients found no difference between continuous infusion labetalol versus nicardipine in time to reach blood pressure goal.[11] The investigators did not assess mortality or infectious risk in this study.

The use of beta blockers in acute stroke is controversial and there is discrepancy among studies for mortality risk. Beta-blocker therapy within 48 hours of ischemic stroke symptom onset increases the risk of mortality.[7] However, other trials have found that beta blockers may reduce risk of early death in ischemic stroke patients. Although there was a reduction of inpatient death and 3-month follow-up mortality with labetalol use, there was no class-specific reduction in mortality with labetalol compared to other

antihypertensive medications.[16] This reduction in mortality can be explained by a reduction of cardiovascular events (myocardial infarction, heart failure, or sudden death) as a result of decreasing sympathetic tone.[11,17] In a recent study in patients with hemorrhagic stroke, labetalol was found to be associated with an increase in-hospital infection compared to nicardipine. In same study, there was no significant difference in mortality or modified Rankin Score >2 between nicardipine and labetalol groups. However, the nicardipine group had a (nonsignificant) higher rate of mortality compared to the labetalol group.[9]

The mechanism of the detrimental effect of nicardipine on mortality is unclear. Nicardipine can commonly cause hypotension, tachycardia, and pulmonary edema which could lead to adverse cardiac events. However, none of these toxicities were apparent in our cohort.

Limitations

This study was limited to patients with acute ischemic stroke admitted to the NICU, and therefore results may not be generalizable to patients treated outside critical care units. Although adjusted for baseline and comorbid conditions, our results may be affected by residual confounding. For instance, patients treated with nicardipine may have had a higher risk of complications at baseline. However, correction for major underlying baseline and stroke features have minimized this confounding. The use of labetalol or nicardipine would likely be distributed nondifferentially representing the treating physician's choice or patient's contraindications but we did not have enough data to validate this argument. Another limitation of our study is the withdrawal of care in patients who were deemed to have poor neurological outcomes. This may have contributed to the mortality burden. However, only 6 patients receiving antihypertensives and specifically only 1 patient in the nicardipine group underwent terminal weaning.

Conclusions

Our study showed a significantly increased risk of mortality that may have been associated with nicardipine use in patients with ischemic stroke. However, limitations of the study should be taken into consideration when associating causality. Most previous studies were performed in patients with intracranial hemorrhage. Our knowledge regarding the safety and efficacy of medications used for acute blood pressure management in ischemic stroke is therefore limited. Further studies using prospective randomized data are needed to validate these findings.

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