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ORIGINAL ARTICLE

A Comparison of Nicardipine and Labetalol for Acute Hypertension Management Following Stroke

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Abstract
Objective Evaluate the ease of use and tolerability of labetalol (L) and nicardipine (N) for hypertension management in patients with acute stroke.
Methods This is a retrospective, non-randomized study. Consecutive adults within 24 h of hospital admission who received intravenous bolus labetalol or nicardipine infusion as first-line antihypertensive therapy were identified. Hemodynamic data were collected through 24 h of therapy.
Results Ninety patients received either labetalol ($N = 64$) or nicardipine ($N = 26$) initially for blood pressure (BP) management. Stroke types were 54% intracerebral hemorrhage (ICH), 22% subarachnoid hemorrhage, and 23% ischemic stroke and were similar between the two drug groups. Baseline patient characteristics and disease severity (APACHE II and GCS) were similar between groups. The average total daily labetalol dose was 40 (10–340) mg and nicardipine infusion was 5 (1–14) mg/h. Initial BP was similar in the two groups. The nicardipine group had less BP variability (N 8.19 vs. L 10.78 mmHg; $p = 0.003$), fewer dosage adjustments [L 4 (1–17), N 2 (0–5); $p < 0.001$] and fewer additional antihypertensive agents (L 33%, N 8%; $p = 0.013$) administered during the 24-h observation period. In patients with ICH, 33% of nicardipine-treated patients achieved target BP within the first 60 min versus 6% of the L group ($p = 0.02$). Overall, incidence of hypotension (SBP < 90 mmHg) (L 3%; N 0%) and bradycardia (HR < 60 beats per min) (L 20.6%; N 12%) were comparable between the groups.
Conclusions Nicardipine offers an alternative to labetalol with similar tolerability and appears to provide a smoother blood pressure control compared to labetalol.

Keywords Blood pressure · Labetalol · Nicardipine · Acute stroke · Intracerebral hemorrhage · Ischemic stroke · Subarachnoid hemorrhage

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Introduction

Hypertension is observed in greater than 2/3 of acute stroke patients irrespective of their past medical history. The initial increase in the blood pressure may be a protective mechanism to maintain cerebral perfusion pressure (CPP) to the brain. However, a persistently elevated blood pressure may contribute to rebleeding [1], hematoma expansion [2–5], early neurological deterioration [6], and poor outcomes [7–9]. The management of acute hypertension therefore is a double-edged sword because both low and high admission blood pressure following acute ischemic stroke (AIS) and intracerebral hemorrhage (ICH) is associated with worsening of stroke symptoms and poor clinical outcomes [8, 10, 11].

Despite the lack of strong evidence guiding the management of acute hypertension in patients with neurological injury, many physicians do treat persistently high blood pressure. A parenteral antihypertensive agent which can produce a predictable blood pressure dose response while concurrently having minimal cerebral effects is desired because autoregulation is often impaired or lost in the area where insults occurred. In which case, cerebral blood flow (CBF) becomes pressure dependent, and any small change in blood pressure may have a detrimental effect on the perfusion of the brain. Commonly used drugs for hypertensive emergency include: sodium nitroprusside, labetalol, hydralazine, enalaprilat, and nicardipine. However, the adverse effects on CBF, intracranial pressure (ICP), unpredictability of blood pressure response, or prolonged antihypertensive effect makes sodium nitroprusside, hydralazine, and enalaprilat less desirable antihypertensive agents during the acute phase of neurologic injury [12–15]. Labetalol and nicardipine have been recommended by the American Heart Association and American Stroke Association (AHA/ASA) as the initial options following acute stroke [16–18].

Labetalol is a mixed α-1 and β-1 and 2-antagonist. Since labetalol has an effect on both adrenergic receptors, it possesses less of an effect on heart rate and cardiac output compared to other β blockers. The onset of action of labetalol is approximately 5–20 min while the duration of action is between 3 and 6 h, which makes it difficult to titrate as a continuous infusion and is commonly given as intravenous bolus instead. The cerebrovascular effect of labetalol is primarily drawn from healthy volunteers and chronic hypertensive patients. In these patients, there was no change in CBF or cerebral metabolic rate of oxygen consumption ($CMRO_2$) observed following administration of labetalol indicating that labetalol has little effect on cerebral circulation in the normal brain [19, 20].

Nicardipine, a second generation dihydropyridine calcium channel blocker, has gained popularity as a parenteral antihypertensive agent for managing hypertensive crisis in the past decade, particularly in patients with brain injury due to its calcium channel blockade property and high cerebrovascular selectivity. Both experimental and human data have indicated that nicardipine may increase CBF, however, it has little effect on ICP while lowering blood pressure. Powers et al. reported that both labetalol and nicardipine effectively reduced blood pressure up to 20% from baseline in ICH patients without compromising cerebral autoregulation [21]. The onset of action of nicardipine is within 5–10 min and it has a relatively short duration of action (about 15 min) due to its rapid redistribution [22]. In addition, the dosing of nicardipine is not dependent on body weight. These pharmacokinetic characteristics allow for a titratable intravenous infusion. Furthermore, postoperative studies have consistently reported the ease of administration and rapid blood pressure control (within 15 min) with a nicardipine infusion compared to other agents [12, 13].

Both labetalol and nicardipine are recommended as initial parenteral antihypertensive agents in the setting of acute spontaneous neurological injury [16–18, 23, 24], yet there is a paucity of data examining the efficacy and safety of these agents in this setting. Likewise, there is a paucity of data concerning different methods of drug administration (i.e., bolus versus continuous infusion). We sought to assess the utility and tolerability of these two agents in patients with acute stroke by evaluating the degree of blood pressure reduction, the ease of administration, and the incidence of adverse events following the administration of either intravenous labetalol boluses or nicardipine continuous infusion.

Methods

This retrospective study was conducted at a university-affiliated urban Level 1 trauma center. The study was approved by the Human Investigation Committee of Wayne State University. Patients were identified using the neuro-ICU admission logbook cross-referenced with the pharmacy computer database. All stroke patients including AIS, primary ICH, and unsecured aneurysmal subarachnoid hemorrhage (SAH), who were 18 years of age or older and received intravenous bolus labetalol or intravenous infusion nicardipine for initial hypertension management were retained.

The major exclusion criteria were: patients with trauma prompting the index admission, those who received other antihypertensive medications prior to either labetalol or nicardipine administration, those who were bradycardic (heart rate <60 beats per min (bpm) on admission), presented with acute transmural myocardial ischemia, those with a history of intracranial neoplasm and those with pre-identified severe aortic valve stenosis. The intention of the exclusion criteria was to create a population with neither specific indication for one drug class versus another (i.e., transmural myocardial ischemia) or contraindication to receive either one of the drugs (e.g., pre-existing bradycardia, severe aortic stenosis). Drug dosing, in this retrospective observational study was completely at the prescribing physicians' discretion. It is our institutional practice to use bolus labetalol instead of labetalol infusion, as this was the recommended method for administration in the AHA/ASA guidelines during the data collection period.

Hemodynamic data were collected for 24 h following the first dose of labetalol or nicardipine, except in aneurysmal SAH patients, where blood pressure data were

collected until the aneurysm was secured. Other data collection included: Patient demographics and medical history, stroke subtype, Glasgow Coma Scale (GCS), and illness severity (APACHE II). Baseline blood pressure was evaluated at the time of hospital admission and prior to the first dose of study medication. All available blood pressure recordings were collected and assessed during the 24-h study period. The hematoma size was collected in all ICH patients and was calculated from both the initial and acute follow-up computed tomography (CT) scans, using a standard estimation method [25]. Hematoma size was not calculated in patients with brainstem hemorrhage, patients whose initial CT scan was performed at an outside referring institution, or the films were not available for review. An increase above >33% in volume from the baseline was considered significant hematoma expansion. We calculated mean arterial pressure (MAP) for all patients (to eliminate bias from physicians' decisions to place intra-arterial pressure monitors) using the standard formula: MAP = (DBP*2 + SBP)/3.

The primary outcome included the degree of MAP reduction following study medications and the variability of blood pressure over the study period. Secondary outcomes were to assess (1) the compliance of current AHA/ASA guidelines [16–18, 26]; (2) the ease of administration; and (3) any adverse events that occurred during the study period. (1) The initial blood pressure prior to the study medication was used to assess the compliance to AHA/ASA guidelines. For AIS patients who are not eligible for thrombolytic therapy, the appropriate trigger to treat is when SBP > 220 or DBP > 120 mmHg. In patients who are eligible for thrombolytic therapy, treatment is warranted when SBP > 185 or DBP > 110 mmHg. The goal blood pressure is to maintain SBP < 180 mmHg or DBP < 105 mmHg in patients who received thrombolytic therapy, or a 10–15% reduction from the baseline MAP in non-thrombolytic eligible AIS patients [17]. In primary ICH patients, the antihypertensive regimen is suggested to be used in patients with MAP > 130 mmHg, with a goal blood pressure reduction of 10–15% from baseline MAP [16]. For patients with unsecured aneurysmal SAH, the consensus at our institution is to treat SBP > 160 mmHg and keep blood pressure below this threshold [1, 26]. (2) The ease of administration was assessed by the number of dosage adjustments defined as extra boluses of labetalol or increases in the infusion rate of nicardipine, and the necessity for additional antihypertensive agents used during the study period. (3) Safety measures included the incidence of hypotension, defined as SBP < 90 mmHg, and bradycardia, defined as heart rate <60 bpm.

For continuous variables, group means were compared using a student's *t*-test for normally distributed data, and Mann–Whitney *U* test for non-parametric data. For dichotomous variables, groups were compared using Pearson's chi-square or Fisher's exact tests. Since the number of time points for blood pressure readings differed across individuals, hierarchical linear modeling (HLM) was used to assess changes in MAP across time. Control variables for the HLM analyses included gender, race, age, admission, and immediate pre-treatment MAP, GCS, APACHE II, past medical history of hypertension, and stroke subtype. A *p*-value of 0.05 was used for statistical significance. Prism4 for Macintosh (version 4.0b, graphpad software, Inc., San Diego, CA), SPSS (version 14.0.0 SPSS, Inc., Chicago, IL) and HLM for Windows (version 6.02, Scientific Software International, Chicago, IL) were used for graphics and statistical analyses.

Results

Patient Characteristics

A total of 197 patients admitted to the Neurosciences ICU were identified as having received either labetalol or nicardipine for hypertension over the study period. After applying exclusion criteria, 90 patients who received these agents as initial therapy were included in the final analysis (Fig. 1). About 64 patients received intravenous bolus labetalol and 26 patients received intravenous infusion nicardipine. Demographic data was similar between the two groups except for age (Table 1). Patients who received labetalol were slightly older than those in the nicardipine group (L 61 ± 12 vs. N 55 ± 10 years, $p = 0.02$). Severity of illness was similar between the two groups, as evidenced by the admission APACHE II score (L 15 ± 7 vs. N 17 ± 8) and GCS (L 11 ± 4 vs. N 10 ± 5). The

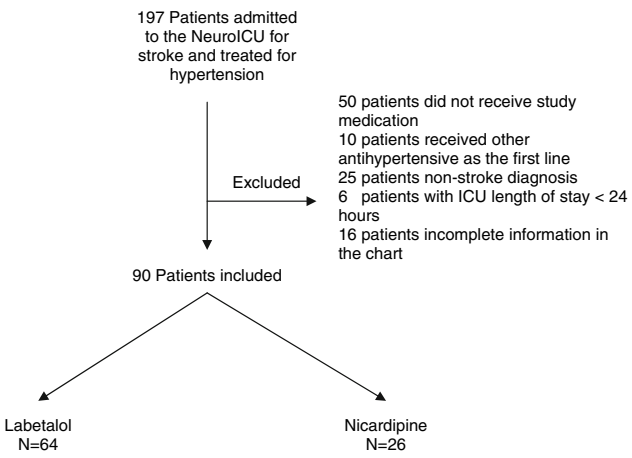

Fig. 1 Study cohort diagram

Table 1 Demographic data

Variable	Labetalol ($n = 64$)	Nicardipine ($n = 26$)	p
Age (years)	61 ± 12	55 ± 10	0.02
Gender, *n* (%)			0.55
Female	35 (54.7%)	16 (61.5%)	
Ethnicity, *n* (%)			0.52
African-American	42 (65.6%)	20 (76.9%)	
Caucasian	18 (28.1%)	4 (15.4%)	
Others[a]	4 (6.3%)	2 (7.7%)	
APACHE II	15 ± 7	17 ± 8	0.49
GCS	11 ± 4	10 ± 5	0.85
Heart rate (bpm)	81 ± 11	86 ± 15	0.11
Stroke subtype, *n* (%)			0.84
ICH	34 (53%)	15 (58%)	
SAH	14 (22%)	6 (23%)	
AIS	16 (25%)	5 (19%)	
Selected family history[b], *n* (%)			
Stroke/TIA	2 (5%)	4 (21%)	0.08
Hypertension	17 (43%)	7 (37%)	0.78
Selected past medical history[c], *n* (%)			
Stroke/TIA	14 (23%)	7 (28%)	0.78
Hypertension	48 (79%)	19 (76%)	0.78
Baseline blood pressure (mmHg)			
On admission			
SBP	185 ± 30	191 ± 37	0.44
DBP	98 ± 25	93 ± 25	0.43
MAP	127 ± 24	125 ± 28	0.73
Prior to first dose			
SBP	193 ± 24	196 ± 33	0.69
DBP	101 ± 22	90 ± 17	0.02
MAP	131 ± 20	126 ± 20	0.21

GCS: Glasgow coma scale; bpm: beats per min; ICH: intracerebral hemorrhage; AIS: acute ischemic stroke; SAH: subarachnoid hemorrhage; TIA: transient ischemic attack; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure

[a] Others include Hispanics, Indians, and Middle Easterners

[b] Labetalol $n = 40$; Nicardipine $n = 19$

[c] Labetalol $n = 61$; Nicardipine $n = 25$

Data presented as mean ± standard deviation unless otherwise noted

majority of patients (54%) included in the analysis experienced a primary ICH (Table 1). Over 70% of study patients had a past medical history of hypertension at the time of admission. In addition, about 1/3 of patients in each study arm had experienced either transient ischemic attack or stroke prior to this admission. Blood pressure (SBP, DBP, and MAP) at admission and immediately prior to study medication administration were comparable between the two groups (Table 1).

Overall Blood Pressure Response

The degree of MAP reduction and variability of blood pressure after study drugs during the 24-h study period were evaluated. Four of the subjects were missing data on past medical history of hypertension. These subjects were removed from the HLM analyses; a total of 1464 blood pressure recordings from the remaining 86 subjects were analyzed. The number of blood pressure recordings per subject during the study period ranged from 2 to 27 with median of 18.

In order to assess the change in MAP across the time following drug administration, a two level HLM was used (Table 2). Interpreting the results of a HLM analysis is similar to interpreting results from a multiple regression. The first level of the model was used to determine significant predictors of the linear change in MAP across time for each subject, which included baseline MAP and race. In the second level of the model, the prediction of the change in blood pressure across time was evaluated. Overall, in patients who received study medications, the MAP significantly dropped 0.007 mmHg/min or 0.40 mmHg/h ($p = 0.001$). Baseline MAP was significantly related to the degree of drop in blood pressure across time ($p = 0.003$). The higher the baseline MAP the greater the decrease in blood pressure across time. For each 1 mmHg increase in baseline MAP the MAP across time decreased with an additional 0.0003 mmHg/min or 0.02 mmHg/h. Lastly, the difference in MAP changes across time between the two drug groups was not different after controlling for race and baseline MAP ($p = 0.846$).

Based on the HLM analyses of change in MAP across the first 24 h of drug administration, the standard error in MAP around the estimated linear change for each patient was computed. This is an estimate of the variability in MAP during the 24-h study period. When comparing the variability between the two drug groups, a weighted least squares regression was performed, where the outcome was the standard error around the line for each patient, the weight was the number of time points, and the predictor was drug group. The nicardipine group had a significantly lower amount of variability [F (1, 84) = 9.04, $p = 0.003$] during the study period. The average variability for the labetalol group was 10.78 mmHg and the average variability for the nicardipine group was 8.19 mmHg. This variability in blood pressure can be further visualized in Fig. 2a and b, which the hourly MAP over 24-h study period was more tightly controlled in the nicardipine group compared to the labetalol group.

Immediate response in MAP within 30-min of drug administration was also evaluated for all study participants. Due to the retrospective design of this study, not all patients had blood pressure readings within 30 min of drug

Table 2 Hierarchical linear modeling analyses assessing the change across time in MAP

Fixed Effect	Coefficient	Standard error	*t* ratio	Approx d.f.	*p* value
First level model					
MAP at 30 Min[a]	110.12	2.42	45.46	82	≤0.001
Baseline MAP[b]	0.37	0.07	5.28	82	≤0.001
Race[c]	6.66	2.70	2.47	82	0.016
Drug Group[d]	−4.73	3.14	−1.41	82	0.136
Second level model					
Change across time[e]					
Intercept	−0.007	0.002	−3.45	83	0.001
Baseline MAP[b]	−0.0003	0.00008	−3.11	83	0.003
Drug group[d]	0.001	0.003	0.20	83	0.846

MAP: mean arterial pressure; d.f.: degree of freedom

[a] Intercept (estimated MAP at 30 min) is allowed to vary across patients

[b] Baseline MAP is Grand Mean Centered

[c] Race is coded as 1 for African-Americans and 0 for all other Races

[d] Drug Group is coded as 0 for Labetalol and 1 for Nicardipine

[e] Slope across time is allowed to vary across patients

administration. Of the 64 labetalol patients, 30 min data was collected for 40 patients, and of the 26 nicadipine patients, data was collected for six patients. However, multiple blood pressure recordings were collected in these patients ranging from 1 to 10 per patient with a median of 2. Based on the HLM analyses, MAP significantly dropped by 12 mmHg within 30 min of drug administration for both groups ($t = -6.69$, df $= 45$, $p \leq 0.001$). Similarly, overall percent change in MAP after drug administration was significant (mean $= -9.05\%$, $t = -6.697$, df $= 45$, $p \leq 0.001$). The amount of MAP change and percent MAP change following treatment was unrelated to drug group ($t = -1.39$, df $= 44$, $p = 0.173$ and $t = -1.168$, df $= 44$, $p = 0.249$ respectively). The average first dose given was 10 (5–40) mg for labetalol and 5 (1–15) mg/h for nicardipine. The highest total dose of labetalol used was 340 mg (average 40 mg) and the highest nicardipine infusion rate was 15 mg/h (average 5 mg/h) during the 24-h study period.

Secondary and Clinical Outcomes

The ease of administration was evaluated by the need for dosage adjustments and additional antihypertensive agents used. Labetalol treated patients required significantly more dosage adjustments and additional antihypertensive agents (Table 3). The most commonly used secondary antihypertensive agent was hydralazine in both groups, followed by enalaprilat in the labetalol-treated group and clonidine in the nicardipine treated group.

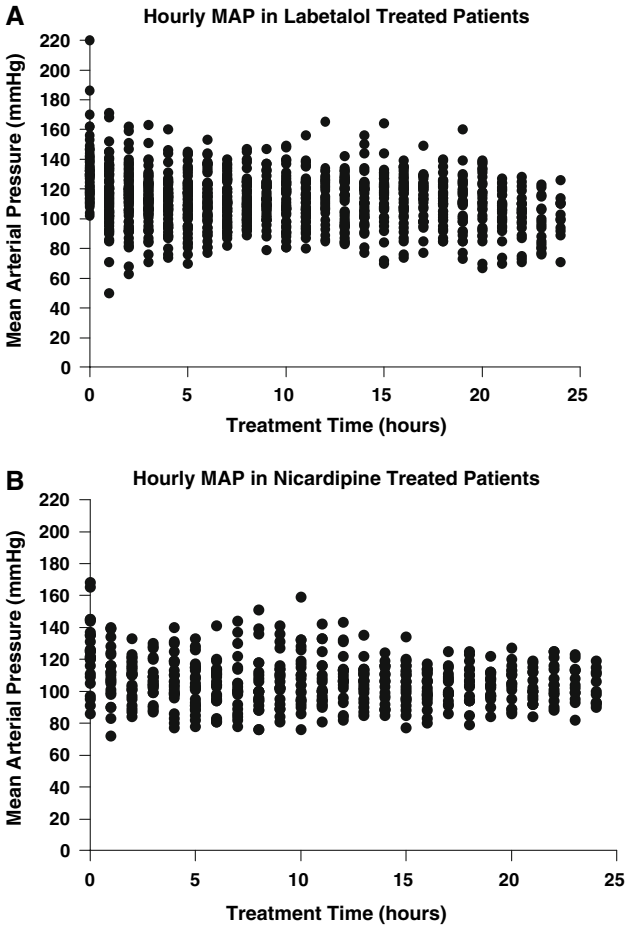

Fig. 2 Hourly MAP over 24 h. Hourly MAP for labetalol (**a**) and nicardipine (**b**) treated patients is graphed over 24 h (labetalol 64 patients; nicardipine 26 patients). MAP at hour 0 was recorded prior to the study medication

Table 3 Secondary outcomes

Variables	Labetalol ($n = 64$)	Nicardipine ($n = 26$)	p
Dosage adjustments	4 (1–17)	2 (0–5)	<0.001
Additional agents, n (%)	21 (33%)	2 (8%)	0.013
Guideline adherence rate, n (%)			NS
AIS non-rtpa[a]	3 (33%)	1 (25%)	
ICH[b]	25 (74%)	10 (67%)	
HR < 60 bpm, n (%)	13 (20.6%)	3 (12%)	NS
SBP < 90 mmHg, n (%)	2 (3%)	0 (0%)	NS

rtpa: recombinant tissue plasminogen activator; bpm: beats per minute; SBP: systolic blood pressure

[a] Patients in AIS non-rtpa: labetalol n = 9, nicardipine $n = 4$

[b] Patients in ICH: labetalol $n = 34$, nicardipine $n = 15$

Data presented as median (range) unless otherwise noted

Table 4 Clinical outcomes

Variables	Labetalol	Nicardipine
Hematoma volume expansion[a], n (%)	6 (17.6%)	2 (13.3%)
Hemorrhagic Transformation[b], n (%)	2 (13%)	1 (20%)
GOS at discharge	3 (1–5)	3 (1–5)
ICU LOS	4.5 (1–67)	8 (1–52)
Hospital LOS	7 (1–67)	8 (1–52)
Disposition, n (%)		
Home	13 (20.3%)	6 (23.1%)
Expired	15 (23.4%)	8 (30.8%)

GOS: Glasgow outcome score; ICU: Intensive care unit; LOS: Length of stay

[a] All patients with intracerebral hemorrhage: labetalol $n = 34$; nicardipine $n = 15$

[b] All patients with ischemic stroke: labetalol $n = 16$; nicardipine $n = 5$; all labetalol treated patients with hemorrhagic transformation received rtpa while the nicardipine treated patient with hemorrhagic transformation did not receive rtpa

Data presented as median (range) unless otherwise noted. There was no significant difference in any findings

The adherence rate to current practice guidelines defined as the threshold of initiation of antihypertensive therapy was assessed in each stroke subtype (Table 3). Patients with hemorrhagic stroke (ICH and SAH) were treated appropriately in more than 70% of the patient population. Patients with ischemic stroke were examined in two groups: thrombolytic ($n = 8$) and nonthrombolytic patients ($n = 13$). Blood pressure treatment was initiated appropriately in all patients who received thrombolytic therapy. The poorest adherence rate was observed in nonthrombolytic patients, where the treatment was initiated appropriately in 33% of labetalol treated patients and 25% of nicardipine treated patients. The majority of these patients received antihypertensive therapy at a lower threshold than that is recommended by the AHA/ASA Stroke Council. There was no significant difference in the incidence of adverse events between the two groups. Two patients who received labetalol experienced an episode of SBP < 90 mmHg while there was no incident of hypotension in the nicardipine group. The incidence of heart rate below 60 bpm during the study period was comparable between the two groups (L 20.6%, N 12%). Table 4 summarized clinical outcomes including intensive care and hospital length of stay, and patients' disposition at discharge.

The characteristics of patients with ICH and the hematoma volume progression following the treatment are described in Table 5. Twenty-eight patients who received labetalol and nine patients who received nicardipine had a baseline hematoma volume available. The average baseline hematoma volume was 16.5 ml and 16.0 ml, respectively. Of these patients, 19 patients in the labetalol group and five patients in the nicardipine group had a repeated CT scan of the brain. Six patients in the labetalol arm and two patients in the nicardipine arm experienced hematoma expansion (>33% increase in volume compared to the baseline). The presence of intraventricular hemorrhage and disposition of these patients are detailed in Table 5.

Discussion

This naturalistic evaluation is the first study to describe blood pressure effect of two commonly used antihypertensive agents, nicardipine, and labetalol, in patients with acute stroke in the clinical setting. There was no difference in overall blood pressure response following treatment, however, significantly less variability in blood pressure response was observed in nicardipine treated patients. In addition, patients who received nicardipine required less dosage adjustments and additional antihypertensive agents compared with labetalol-treated patients. Both treatments were well tolerated and no significant adverse effects were observed with either agent. The results suggest that nicardipine is as effective and safe as labetalol for acute blood pressure control immediately following a stroke but may be associated with easier administration.

Blood Pressure Management following Acute Stroke

Previous studies demonstrated that nicardipine was more effective compared to nitroprusside and as effective as labetalol in controlling postoperative hypertension [12, 13,

Table 5 Hematoma expansion in ICH patients

Pt ID	Drug	Baseline MAP (mmHg)	Baseline GCS	Vol. 1 (ml)	Presence of IVH	Day(s) of f/u[a]	Vol. 2 (ml)	HE	GOS[b]
1	L	129	3	7.6	No	1	7.4	No	1
4	L	117	14	29	No	1	34.4	No	3
9	L	113	7	20.5	No	1	67.3	Yes	1
13	L	111	13	3.1	Yes	5	3.6	No	3
16	L	134	10	7.9	Yes	10	8.5	No	3
21	L	114	14	9.5	No	1	11.4	Yes	4
30	L	122	15	8.8	Yes	7	9.5	No	3
37	L	116	15	0.3	No	1	1.5	Yes	3
39	L	132	15	8.3	No	2	5.1	No	4
47	L	170	11	4.1	Yes	7	4.4	No	3
61	L	129	12	3.5	No	<1	4.5	No	3
62	L	134	10	22	Yes	9	45	Yes	3
74	L	146	15	6.6	No	2	11.3	Yes	2
76	L	140	6	46.8	No	2	40.5	No	2
80	L	162	4	44.4	Yes	4	39.7	No	3
93	L	186	15	16.3	No	13	15.8	No	5
96	L	125	13	2.0	Yes	8	16.9	Yes	3
100	L	119	15	3.7	No	3	4.7	No	4
101	L	147	15	5.5	Yes	3	4.5	No	4
28	N	145	3	27	Yes	1	50.9	Yes	1
34	N	97	12	24.8	No	1	23.3	No	3
38	N	105	15	9.8	No	2	8.4	No	3
84	N	168	14	3.2	Yes	<1	21	Yes	1
95	N	121	5	29	Yes	2	15.0	No	3

ICH: intracerebral hemorrhage; MAP: mean arterial pressure; GCS: Glasgow coma scale; Vol: volume; IVH: intraventricular hemorrhage; f/u: follow up; HE: hematoma expansion; GOS: Glasgow outcome scale; L: labetalol; N: nicardipine

[a] Time interval in days between the first and second computed tomographic scan

[b] Glasgow outcome scale score determined at discharge

21]. Halpern et al. reported that postoperative hypertension was controlled more rapidly with nicardipine compared to nitroprusside (14 ± 1 vs. 30.4 ± 3.5 min; $p = .0029$, respectively) [12]. In addition, nicardipine-treated patients required significantly less dosage adjustments to achieve the target blood pressure than nitroprusside treated patients. Similarly, Dorman et al. demonstrated that nicardipine was associated with rapid blood pressure control (within the first 10 min), less variability in blood pressure, and less additional hypertensive agents compared to nitroprusside postoperatively following carotid endarterectomy [13].

Findings from our study are similar to others in that nicardipine provided less variability in blood pressure over time ($p = 0.003$) and a more consistent blood pressure control by requiring less dosage adjustments and the need for additional antihypertensive agents (Tables 2 and 3, and Fig. 2). This may be clinically significant in patients with acute stroke because large fluctuations in blood pressure can negatively affect cerebral perfusion. Current guidelines support a narrow therapeutic target of blood pressure reduction during the acute phase of stroke [16–18], therefore, an agent which can provide a controlled blood pressure lowering effect is desirable. In addition, a predictable dose response with few dosage adjustments may result in less monitoring and nursing time. Although there may be confounding factors contributing to the frequency of titration and other antihypertensive agents given (i.e., route of administration), this study is a naturalistic study representing daily clinical practice.

Blood Pressure and Clinical Outcomes

Since over half of our cohort consisted of ICH patients, we evaluated the blood pressure response and clinical outcomes specific to this population (data not shown). Similar to a recently reported tolerability study by Qureshi and colleagues, the variability in blood pressure following

nicardipine treatment was small [27]. In the tolerability study, authors also observed a high success rate (86%) in achieving target blood pressure for patients with primary ICH without any complications [27]. Only two patients required withdrawal of therapy because of hypotension and excessive tachycardia. In our cohort, 60% of nicardipine-treated ICH patients achieved the goal blood pressure within 24 h compared to 59% of labetalol-treated patients. However, significantly more patients who received nicardipine (33%) achieved targeted blood pressure within the first 60 min after initiation of the therapy compared to labetalol treated patients (6%) ($p = 0.02$).

Data from our study along with postoperative data and results presented by Qureshi et al. collectively suggest that nicardipine may provide a rapid blood pressure control with low variability, which may be important in slowing disease progression in ICH patients [27]. Radiologic studies have demonstrated that hematoma expansion most frequently occurs 1–6 h following the initial ictus [28, 29]. Of those, 26% of patients rebled within the first 1 h and 36% of patients rebled within the first 3 h [28, 29]. Early hematoma growth is an independent risk factor for neurologic deterioration and high mortality, and is directly associated with an elevated admission SBP [2–5]. Therefore, early control of elevated blood pressure may reduce the incidence of hematoma growth and improve clinical outcomes. In previous postoperative studies, target blood pressure was achieved within 15 min of nicardipine administration [12, 13]. In the current study, 33% nicardipine patients vs. 6% labetalol patients achieved target blood pressure within the first 60 min. Hematoma expansion on repeated CT scan was observed in 17.6% labetalol group and 13.3% nicardipine group. Our sample size is too small to perform meaningful comparison between the two groups, however, the incidence of hematoma expansion observed in our study is similar to what was reported by Qureshi et al. Due to the retrospective nature of the study, we were not able to determine any relationship between blood pressure and hematoma expansion.

Tolerability of Antihypertensive Therapy

During the study period, both labetalol and nicardipine were well tolerated by patients with acute stroke. There was no significant difference in the incidence of bradycardia or hypotension. A poor adherence rate to AHA/ASA guidelines was described in our study particularly in patients with ischemic stroke who did not qualify for intravenous thrombolytic therapy. Our physicians tend to treat these patients at a lower threshold than suggested by the AHA Stroke Council. This observation further suggested the lack of consistency in managing blood pressure in patients with acute stroke and the need for further institutional educational programs. While hemorrhagic transformation, length of stay, and disposition are important outcome indicators, a large sample size is needed to determine any statistical significance because there are many confounding variables that affect these outcomes.

Limitations of the Study

There are limitations to the interpretation of these results because of the nature of the retrospective design. One of the significant findings from our study is that there was less variability in blood pressure in the nicardipine group compared to the labetalol group. One possible contributing factor to this variability may be the method of drug administration (bolus for labetalol and infusion for nicardipine) rather than the pharmacology of the drug itself. This is an important consideration for agent selection as many institutions do not use labetalol infusion routinely, and available guidelines for practice suggest using one or two pulse doses of labetalol in this setting [17, 18]. Clearly, drug choice and administration are individual decisions often additionally influenced by local institutional treatment paradigms, and dosing strategy aggressiveness may be affected by experience with a given drug. These issues need to be addressed in prospective studies.

Another limitation of this retrospective study is assessing the precise time to achieve therapeutic goal (as we used time blocks for this non-continuously available variable,) but this should not affect the absolute number of patients who achieved target blood pressure. Other limitations include small sample size and heterogeneity of the patient population. As an example of the sample size issue, likely rare events, such as the lack of difference in proportions of patients having symptomatic hypotension may be different in a prospective larger study. Regarding the issue of heterogeneity of the population: Stroke is a clinical diagnosis with a common threshold in all-available published guidelines for the consideration of pharmacological blood pressure management (SBP > 220, MAP > 130 mmHg). The issue of reactive hypertension, while variable in its penetration of the population of patients with stroke, in general, likely has a common cerebral mechanism; therefore, it is reasonable to group these patients together. The subgroup analysis of an enriched population of ICH patients was planned a priori.

Lastly, this study assessed short-term outcomes related to practice variation within the framework of currently published guidelines; it was not the intent of this investigation to assess long-term outcomes with blood pressure lowering, which is best left for future prospective evaluation. When evaluating ICU length of stay, patients who were treated

with nicardipine appeared to have a longer length of stay in our cohort. This finding will need to be further assessed in a prospective study that has balanced treatment groups and that will assess when the patients actually qualify for discharge compared to actual discharge date. Since this study was retrospective we could not accurately assess the time the patient qualified for ICU discharge and the difference we observed may be related to unequal numbers in the treatment groups. However this study does represent the application of these agents in clinical practice and provides an evaluation of expected outcomes when used outside the rigors of a randomized controlled trial.

Conclusion

The findings from this study suggest that nicardipine appears to be a viable alternative to labetalol in patients with acute stroke. There is a trend toward less variability in blood pressure response following nicardipine compared to labetalol with similar tolerability. However, we do recognize that differences in administration methods (labetalol bolus and nicardipine infusion) may have contributed to these results. A prospective study is warranted to further delineate the effects of these agents on definite clinical endpoints such as hematoma expansion and neurologic deterioration.

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