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ORIGINAL ARTICLE

Nicardipine Reduces Blood Pressure Variability After Spontaneous Intracerebral Hemorrhage

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Abstract

Background: Blood pressure variability (BPV) is an independent predictor for early hematoma expansion, neurologic deterioration, and mortality. There are no studies on the effect of intravenous (IV) antihypertensive drugs on BPV. We sought to determine whether patients have more BPV with certain antihypertensive agents, in particular the effect of IV nicardipine.

Methods: We conducted a single-center, retrospective chart review of individuals diagnosed with spontaneous intracerebral hemorrhage (ICH) receiving labetalol, hydralazine, and/or nicardipine within 24 h of hospital admission to assess the primary endpoint of BPV, defined as the standard deviation of systolic BP, with labetalol and/or hydralazine compared to nicardipine ± labetalol and/or hydralazine. Repeated measures linear regression was performed to compare BPV over 24 h between regimens, and Cox proportional hazards regression was used to compare the time to goal SBP between regimens.

Results: Of the 1330 patients screened, 272 were included in our analysis; those included had a mean age of 69 years with 87.9% of Caucasian race. A total of 164 patients received IV bolus antihypertensives alone (labetalol, hydralazine or both), and 108 patients received IV nicardipine with or without additional IV boluses (labetalol, hydralazine, or both). Those who had IV nicardipine had significantly less BPV ($p = 0.04$) and was more likely to attain an SBP goal < 140 mmHg ($p < 0.01$).

Conclusion: Our study suggests patients with ICH who do not receive a nicardipine-based antihypertensive regimen have more BPV, which has been associated with poor clinical outcomes. Prospective, randomized, controlled trials are needed to determine the impact of specific antihypertensive regimens on clinical outcomes.

Keywords: Intracerebral hemorrhage, Blood pressure variability, Antihypertensive, Nicardipine, Labetalol, Hydralazine, Bolus, Infusion

Introduction

Elevated blood pressure (BP) is associated with significantly increased incidence of subsequent death or dependency following spontaneous intracerebral hemorrhage (ICH) [1, 2]. Even so, the optimal antihypertensive strategy and BP target in the acute and subacute phases of stroke are still up for debate. Current guidelines recommend acute lowering of systolic BP (SBP), advocating that SBP < 140 mmHg in patients presenting with SBP between 150 and 220 mmHg is safe and may be effective in improving functional outcomes; however, no one specific antihypertensive agent is endorsed to achieve these goals [3]. Certain details of BP management following

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spontaneous ICH remain unclear, including the importance of BP variability (BPV) and how medication selection may affect it. BPV is described as a standardized way of representing changes in BP over time and has been defined as the standard deviation (SD) of SBP over a sample time period [4]. Cerebral autoregulation is impaired in the acute phase of stroke, making blood flow completely dependent on systemic BP. Although there are multiple elements, including end-organ damage and other neural and environmental factors, that may affect it, BPV has been shown to be an independent predictor for early hematoma expansion and neurologic deterioration, as well as mortality. Increased BPV has also demonstrated an association with poor long-term functional outcomes [5–11]. Fluctuations in BP may be influenced by both the intensity of treatment and the type of antihypertensive being used. Therefore, further analyses of BPV are warranted.

Despite the correlation of BPV with increased morbidity and mortality, a few data exist relating BPV to specific medication regimens in the acute care setting [12–15]. Characteristics desired of an ideal agent to reduce BP following ICH include rapid onset of action, predictable dose response, minimal adverse effects, and limited BPV, aiming to both achieve and maintain the SBP goal. Labetalol, hydralazine, and nicardipine have been recommended as initial parenteral options in the setting of acute neurologic injury [16, 17]. Compared to nicardipine, labetalol and hydralazine are generally given as intravenous (IV) bolus doses and have relatively long half-lives, up to 4 and 6 h, respectively, which may result in difficult titration to desired BP [18, 19]. Nicardipine is generally administered as a continuous IV infusion; the duration of action is approximately 3 h with plasma concentrations rapidly decreasing by at least 50% within 2 h of discontinuation [20]. Based on the pharmacokinetics of nicardipine, it is hypothesized that this infusion may have a more predictable and safer response compared to bolus dosing. Nicardipine alone has shown to be superior in both the retrospective and prospective settings in regard to BPV when compared with labetalol (SD SBP: 8.19 vs. 10.78 mmHg; $p = 0.003$; 15 vs. 19 mmHg; $p < 0.001$, respectively) [14, 15]. Our study is unique in that our patient population size is larger than previous trials, is exclusive to patients with ICH, and depicts real-world practice of utilizing protocolized escalation of antihypertensive therapy. The purpose of our study was to determine whether specific antihypertensive medication regimens are associated with less BPV; we compared IV boluses of labetalol and/or hydralazine to continuously infused nicardipine ± labetalol and/or hydralazine.

Methods

Following institutional review board approval, we conducted a single-center, retrospective chart review at our 1265-bed academic medical center. All individuals with an International Classification of Diseases (ICD)-9 or ICD-10 diagnosis code of spontaneous ICH admitted directly or through the emergency department between January 2008 and June 2016 were screened for inclusion. Patients were included in our analysis if they were at least 18 years of age and received at least one dose of IV labetalol or hydralazine or an IV infusion of nicardipine for at least 1 h. Patients who had clear evidence of ICH from a secondary cause, such as an underlying aneurysm, vascular malformation, tumor, head trauma, hemorrhagic transformation of an ischemic infarction, or anticoagulant use within the prior 2 weeks, and patients who were pregnant or prisoners were excluded. Patients without authorization of their medical records for research purposes were also excluded. Only the first eligible admission per patient was used. Hemodynamic data were collected for 24 h following admission. Additional data collected included patient demographics, medical history, smoking status, and Sequential Organ Failure Assessment, Glasgow coma scale, and ICH scores on admission.

Patients were grouped according to antihypertensive medications received during the first 24 h after presentation; patients who received IV boluses of labetalol and/or hydralazine were categorized in the bolus group, whereas patients who received an IV infusion of nicardipine ± IV boluses of labetalol and/or hydralazine were categorized in the infusion ± bolus group. The primary objective of our analysis was to compare BPV, defined as the SD of SBP within each hour, for the first 24 h, between groups. Secondary clinical outcomes assessed included days of mechanical ventilation, ICU and hospital length of stay, and in-hospital mortality. Secondary safety outcomes assessed included the incidence of hypotension, defined as SBP < 90 mmHg, and tachycardia and bradycardia, defined as heart rates > 120 and < 50 beats per minute, respectively.

Summary statistics for continuous variables are reported as means with SD or medians with interquartile range (IQR) based on the distribution of the variable, or percentages for categorical variables. For continuous variables, groups were compared by Student's *t* test or Wilcoxon rank sum test. For dichotomous variables, groups were compared using Chi-square or Fisher's exact tests as appropriate. Repeated measures linear regression was performed to compare groups for the outcomes of BPV (with a linear term for hour), hypotension defined as SBP < 90 mmHg, bradycardia defined as heart rate < 50 beats per minute, and tachycardia defined as heart

rate > 120 beats per minute. Time to goal SBP was compared between regimens using Cox proportional hazards regression. For the repeated measures and Cox proportional hazards analyses, the regimen group was treated as a time-dependent covariate based on what regimen(s) a patient (1) was receiving in a given hour and (2) had received up to a given hour. We calculated intensive care unit (ICU) and hospital lengths of stay using the Kaplan–Meier method with time from admission to discharge, censoring those with an in-hospital mortality at time of death. All p values were two-sided and determined to be statistically significant at $p \leq 0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R version 3.2.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Results

Of the 1330 patients screened for inclusion, 272 patients were included in our analysis. Patient enrollment is further detailed in Fig. 1. Of the included patients, there were 164 patients in the bolus group who did not receive nicardipine at all and 108 patients in the infusion group who had received nicardipine at some point during the 24-h study period. Patient characteristics are displayed in Table 1. Included patients were primarily Caucasian (87.9%) with an average age of 69 years. Notably, 88.9% had a diagnosis of hypertension preceding their ICH admission. The predicted 30-day mortality of our patient sample was 26% based on ICH score [21]. The vast majority of our patients (95.2%) were admitted to the neurosciences ICU. There were no statistically significant differences identified between groups, with the exceptions of age and SBP goal. Patients in the infusion ± bolus group were younger (66 years vs. 71 years; $p < 0.01$). Glasgow coma scale scores on admission were fairly evenly split with approximately one-third ranging from 3 to 11, 12 to 14, and 15. Although not statistically different, patients in the bolus group had a lower median ICH score than those in the infusion ± bolus group (1[0–3] vs. 2[1–3]; $p = 0.28$), indicating a somewhat higher likelihood of mortality in patients receiving infusion ± bolus therapy. An SBP goal < 140 mmHg was targeted for more patients in the infusion ± bolus group (37 vs. 13.5%; $p < 0.01$). All patients in the infusion ± bolus group were admitted to the ICU, in line with our institutional protocol requiring ICU admission for nicardipine administration (100.0 vs. 92.1%).

Antihypertensive medication regimens are depicted in Table 2. When a dose was administered, the median (IQR) hourly doses while receiving each study drug are as follows: labetalol 10 mg (10–20), hydralazine 10 mg (10–10), and nicardipine 5 mg/h (5–10), with a median total dose (IQR) administered in 24 h of 20, 20, and 42.5 mg, respectively. Only 7.7% of patients received any additional IV antihypertensive agents (esmolol, nitroprusside, nitroglycerin, metoprolol, labetalol infusion or diltiazem) during the study timeframe, and 53.3% of patients were initiated on an oral antihypertensive within 24 h. In comparing antihypertensive regimens between groups, significantly fewer patients received hydralazine in the

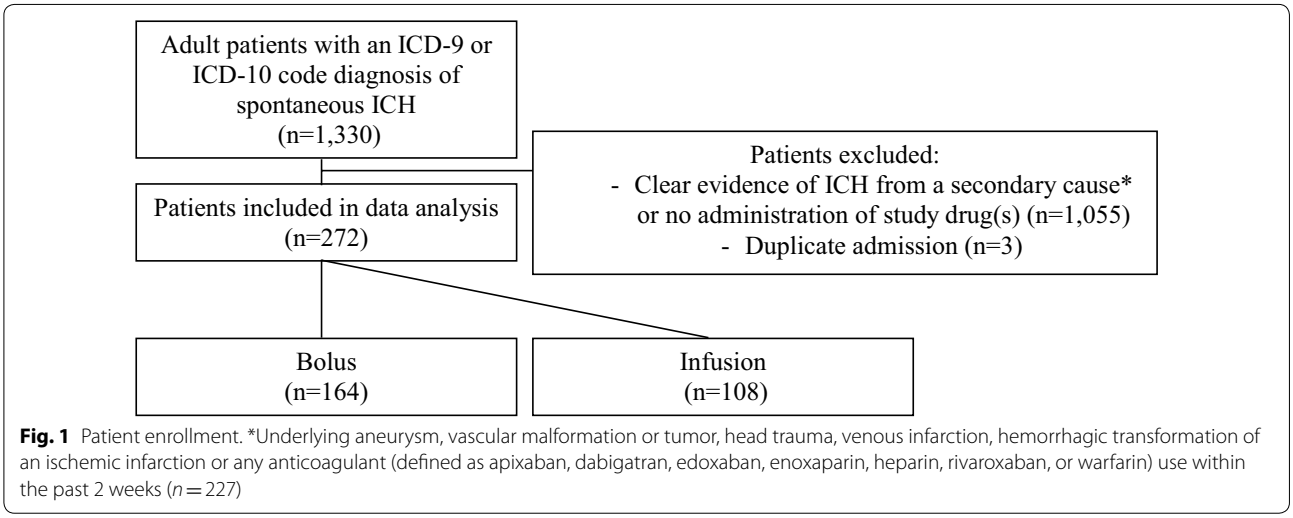

Fig. 1 Patient enrollment. *Underlying aneurysm, vascular malformation or tumor, head trauma, venous infarction, hemorrhagic transformation of an ischemic infarction or any anticoagulant (defined as apixaban, dabigatran, edoxaban, enoxaparin, heparin, rivaroxaban, or warfarin) use within the past 2 weeks ($n = 227$)

Table 1 Patient characteristics

Variable	Total sample ($N=272$)	Bolus ($n=164$)	Infusion ± bolus ($n=108$)	p value
Age, years*	69 ± 15	71 ± 15	66 ± 15	< 0.01
Male	147 (54)	81 (49.4)	66 (61.1)	0.06
Caucasian	239 (87.9)	145 (88.4)	94 (87)	0.71
Comorbidities				
Hypertension	242 (88.9)	147 (89.6)	95 (88)	0.69
Hyperlipidemia	64 (23.5)	45 (27.4)	19 (17.6)	0.08
Diabetes	29 (10.7)	20 (12.2)	9 (8.3)	0.42
History of ischemic stroke	22 (8.1)	17 (10.4)	5 (4.6)	0.11
Atrial fibrillation	18 (6.6)	11 (6.7)	7 (6.5)	1.00
Dementia	12 (4.4)	8 (4.9)	4 (3.7)	0.77
One-year smoking history	7 (2.6)	4 (2.4)	3 (2.8)	1.00
Sequential organ failure assessment score*	3.7 ± 3.0	3.7 ± 3.0	3.8 ± 2.9	0.79
Glasgow coma scale score*[a]	11 ± 5	11 ± 5	11 ± 4	
Glasgow coma scale score[a]				
3–11	102 (38.2)	60 (37.7)	42 (38.9)	0.86
12–14	64 (24.0)	36 (22.6)	28 (25.9)	0.72
15	101 (37.8)	63 (39.6)	38 (35.2)	0.46
ICH score[#]	2 (0.25–3)	1 (0–3)	2 (1–3)	0.28
Baseline SBP, mmHg*	170 ± 28.6	167 ± 29.8	176 ± 25.8	0.01
Goal SBP				
< 140 mmHg	62 (22.8)	22 (13.5)	40 (37.0)	< 0.01
< 160 mmHg	146 (53.7)	94 (57.7)	52 (48.1)	
< 180 mmHg	64 (23.5)	48 (29.3)	16 (14.8)	
ICU admission	259 (95.2)	151 (92.1)	108 (100)	

Data presented as *n* (%) unless denoted *for mean ± standard deviation or [#]for median (IQR)

ICH intracerebral hemorrhage, *ICU* intensive care unit, *SBP* systolic BP

[a] $N=267$; bolus $n=159$; infusion $n=108$

Table 2 Description of antihypertensive regimens

Variable	Total sample ($N=272$)	Bolus ($n=164$)	Infusion ± bolus ($n=108$)	p value
Patients who had labetalol, *n* (%)	211 (77.6)	129 (78.7)	82 (75.9)	0.66
Dose per 24 h, mg	20 (10–45)	20 (10–50)	20 (10–40)	0.37
Patients who had hydralazine, *n* (%)	136 (50.0)	91 (55.5)	45 (41.7)	0.03
Dose per 24 h, mg	20 (10–30)	20 (10–25)	20 (10–30)	0.12
Patients who had nicardipine, *n* (%)	108 (39.7)			
Dose per 24 h, mg	42.5 (13.8–86.8)			
Patients with additional IV antihypertensive use, *n* (%)[a]	21 (7.7)	13 (7.9)	8 (7.4)	1.00
Oral antihypertensive[b]	145 (53.3)	83 (50.6)	62 (57.4)	0.32

Data shown as median (IQR) unless otherwise noted

[a] Esmolol, nitroprusside, nitroglycerin, metoprolol, labetalol infusion, diltiazem

[b] Initiation within 24 h of admission

infusion group (41.7 vs. 55.5%, $p=0.03$). Time to first dose of any antihypertensive agent administered (from admission to the emergency department) was significantly shorter in patients who received nicardipine (1.63 vs. 3.53 h; $p<0.01$).

Attainment of SBP goal within the first 24 h was assessed for all patients by antihypertensive regimen. Patients in the infusion ± bolus group were more likely to attain a SBP goal < 140 mmHg than patients in the bolus group ($p<0.01$). However, there were no differences

noted between groups in regard to achieving SBP goals of < 160 mmHg or < 180 mmHg.

Patients in the infusion ± bolus group had significantly less BPV compared to patients in the bolus group, despite aiming for a lower SBP goal. Additionally, as anticipated due to medications reaching steady state and patients approaching goal SBP, needing less medication titration, there was less BPV within the 24-h study period as time went on. BPV over time comparing the bolus and infusion ± bolus groups is further depicted in Table 3 and Fig. 2.

Patients in the infusion ± bolus group were less likely to have hypotension than patients in the bolus group, although this difference was not statistically significant ($p = 0.052$). There were no significant differences between regimen groups for bradycardia and tachycardia ($p = 0.13$ and $p = 0.62$, respectively). Clinical and safety outcomes are shown in Table 4. There was no significant difference between groups regarding patients necessitating use of an IV vasopressor post-administration of an IV antihypertensive.

Table 3 Blood pressure variability[a]

Variable	Estimate (95% CI)	*p* value
Infusion ± bolus[b]	−0.77 (−1.51, −0.04)	0.04
Bolus[b]	Reference	
Hour	−0.15 (−0.20, −0.10)	< 0.01

[a] BPV shown as SD of SBP

[b] Time dependent, based on what regimen(s) a patient had received up until that point

Discussion

In this single-center, retrospective, explorative analysis, we observed less BPV, despite aiming for a lower SBP goal, in patients receiving infusion ± bolus therapy as compared to patients receiving bolus therapy alone for BP management following spontaneous ICH. As shown previously in a prospective study including patients with either ischemic or ICH stroke, nicardipine demonstrated a superior therapeutic response with a higher achievement of goal SBP and less BPV as compared to labetalol; however, this did not result in differences in clinical outcomes [15]. Given the poor outcomes associated with BPV, including early hematoma expansion and neurologic deterioration, poor long-term functional outcomes, and death in patients with ICH, it is critical that current antihypertensive therapies are analyzed with appropriate measures taken to decrease the occurrence of BPV [5–11, 21–24].

A multicenter trial randomizing patients in the emergency department to either continuous infusion nicardipine or labetalol boluses noted more patients in the

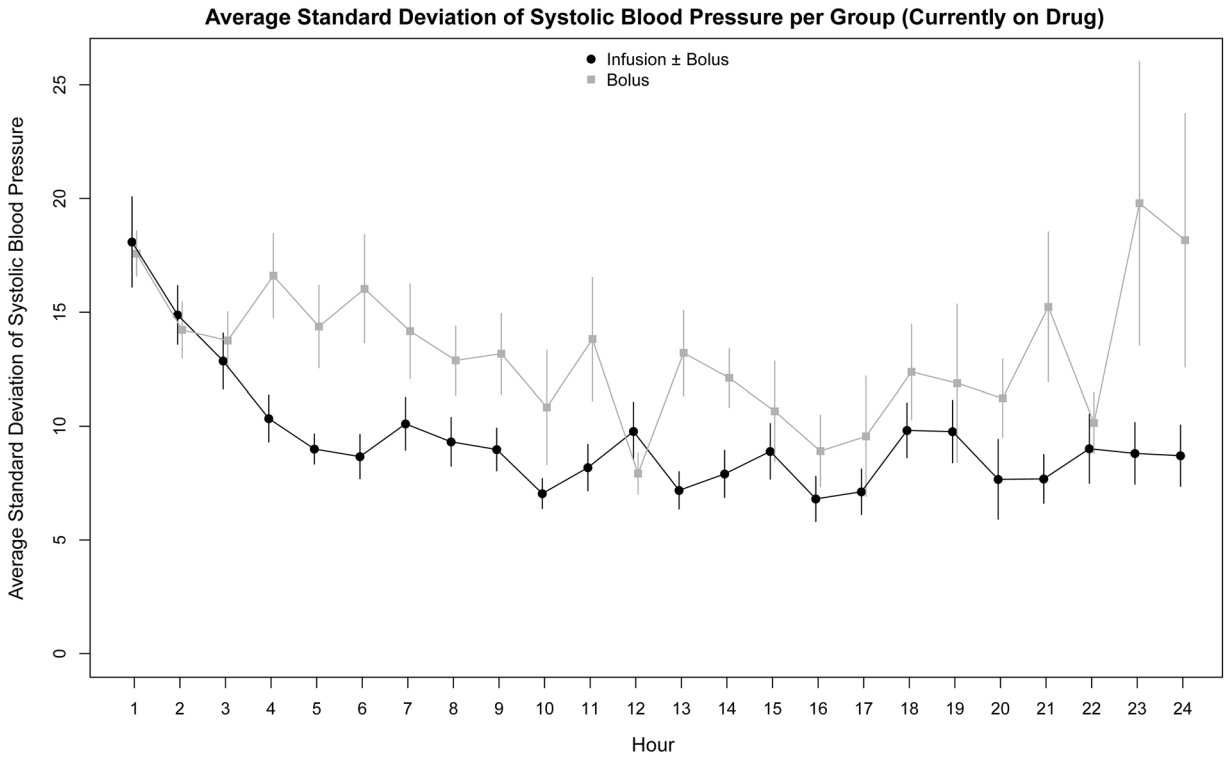

Fig. 2 Average BPV by regimen

Table 4 Safety and clinical outcomes

Variable	Total population ($N=272$)	Bolus ($n=164$)	Infusion ± bolus ($n=108$)	p value
Care withdrawn within 24 h	54 (20.0)	36 (22.0)	18 (16.7)	0.35
Patients with IV vasopressor use[a]	23 (8.5)	14 (8.5)	9 (8.3)	1.00
Invasive ventilator use	91 (33.3)	51 (31.1)	40 (37.0)	0.30
Invasive ventilator use, days[b]	1.1 (0.5–3.2)	1.0 (0.5–2.8)	1.3 (0.5–4.8)	0.41
ICU length of stay, days[c]	1.8 (1.0–5.0)	1.6 (1.0–3.6)	2.7 (1.0–6.2)	< 0.01
Hospital length of stay, days[d]	7.1 (3.9–13.6)	5.6 (3.4–13.1)	8.2 (4.6–17.3)	0.053
24-h mortality	30 (11.0)	22 (13.4)	8 (7.4)	0.16
In-hospital mortality	66 (24.3)	41 (25.0)	25 (23.1)	0.77

Data shown as *n* (%) unless otherwise noted

ICU intensive care unit

[a] Norepinephrine, epinephrine, phenylephrine, vasopressin or ephedrine

[b] Data shown as median (IQR) in those who used invasive ventilator

[c] Median and interquartile range from time-to-ICU discharge analysis in those who were admitted to the ICU

[d] Median and interquartile range from time-to-discharge analysis

nicardipine group achieved their individualized target BP range (91.7 vs. 82.5%, $p < 0.01$) within 30 min. However, there was no difference in BPV, defined as the median area under the curve for time and depth of measures outside the SBP target range, in patients receiving nicardipine and labetalol (96.4 vs. 104.9 mmHg/min, $p = 0.558$) [25]. Yet, this trial was not focused on ICH patients who may have different susceptibility to develop greater BPV. Our results suggest that careful use of an infusion may reduce BPV in patients with ICH.

The optimal management of acute hypertension after ICH remains undefined. Current guidelines state that acute lowering of SBP to 140 mmHg is safe in patients presenting with SBP between 150 and 220 mmHg and without contraindication to acute BP treatment, based on information from INTERACT and INTERACT-2 [3, 26, 27]. The ATACH-II trial, published after guideline publication, randomized patients to a target SBP of < 140 or < 180 mmHg using nicardipine. This trial was terminated early due to futility, showing an increase in renal adverse events within 7 days for SBP < 140 mmHg, which may have been caused by excessive BP lowering to the study group's average minimum SBP of 120–130 mmHg within the first 24 h [28, 29]. More intensive BP lowering was not associated with significant benefit in hematoma expansion in either INTERACT-2 or ATACH-II; however, a systematic review and meta-analysis evaluating the safety and efficacy of early intensive versus conservative BP-lowering treatment in patients with ICH found the weighted mean difference in absolute hematoma growth, a strong predictor of poor outcome, to be −1.53 (95% CI −2.94 to −0.12 mL) in the intensive treatment group [27, 28, 30]. Our results demonstrated that patients receiving a nicardipine infusion ± labetalol and/or hydralazine boluses were significantly more likely to attain SBP < 140 mmHg (though this was the therapeutic target in only 22.8% of patients treated with labetalol and/or hydralazine boluses).

Our institutional practice is to bolus with either IV labetalol 10–20 mg or hydralazine 10–20 mg with subsequent administration of an IV nicardipine infusion initiated at 5 mg/h and titrated to response after two bolus doses have been given. The use of bolus and/or infusion antihypertensives is in line with current guideline recommendations for patients with elevated BP following spontaneous ICH, while taking into consideration the predictability, pharmacological profile, potential side effects, and cost of each medication [3]. It is important to note that during the data collection period and at the time of this writing, nicardipine was not stocked in our institution's emergency department medication dispensing machines, due to cost and timeliness of delivery from central pharmacy, and patients must be admitted to an ICU in order to receive nicardipine.

Despite one of the largest studies describing BPV in the literature to date, there are limitations to the interpretation of our results due to the retrospective study design and focus on a single center of practice with a relatively small sample size. We were unable to collect medication administration prior to arrival at our institution or long-term functional outcomes, as that information was not readily accessible. Additionally, our study does not include computerized tomography measurements of ICH enlargement as this would only be feasible with prescheduled imaging. BP targets were variable across patients and sometimes within patients during the course of their

acute care; we were unable to evaluate the influence of different BP targets on BPV. Our study did not address the use of clevidipine, a dihydropyridine calcium channel blocker, recently compared to nicardipine in a retrospective review, as this medication is not readily used at our institution at this time. The study showed similar acute BP management in neurosurgical ICU patients with time to target SBP 30 versus 46 min ($p = 0.13$) and percentage of time spent within target BP 79 versus 78% ($p = 0.64$) [31]. We believe BP management at our center may be reflective of the practice at many other North American centers and adds information to the existing literature about BPV and antihypertensive medication regimens used in ICH.

Conclusion

Patients who received labetalol and/or hydralazine without nicardipine for acute BP management following ICH had more BPV within the first 24 h of admission compared to patients who received nicardipine ± labetalol and/or hydralazine. This study indicates that a nicardipine infusion may allow more consistent and stable BP lowering after spontaneous ICH than relying on boluses of labetalol or hydralazine and could avoid the deleterious effect of excessive BPV in these patients. While the use of nicardipine infusion has not been shown beneficial for ICH in a randomized clinical trial, BPV has been shown deleterious in ICH and thus reducing rapid and profound BP fluctuations through the careful use of a titratable infusion is advisable regardless of the targeted BP.

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Authors' Contributions
JOP designed and directed this study and drafted the manuscript; BMR, AAR, EFMW and PJ participated in the conceptual framing of the study, data analysis, and revision of the manuscript; RAD and KCM completed the statically analysis of the manuscript.

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Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

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