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ORIGINAL WORK

Early Initiation of Oral Antihypertensives Reduces Intensive Care Unit Stay and Hospital Cost for Patients with Hypertensive Intracerebral Hemorrhage

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Abstract

Background/Objective: Intravenous nicardipine infusion is effective for rapid blood pressure control. However, its use requires hemodynamic monitoring in the intensive care unit (ICU) and is associated with high hospital cost. This study aimed to examine the effect of early versus late initiation of oral antihypertensives on ICU length of stay (LOS) and cost of hospitalization in patients with hypertensive intracerebral hemorrhage (ICH).

Methods: This is a single-center retrospective study of patients with hypertensive ICH treated with nicardipine infusion from January 1, 2013, to December 31, 2017. Patients were dichotomized into study and control groups, based on receiving oral antihypertensives within 24 h versus after 24 h of emergency department arrival. Baseline characteristics, duration of nicardipine infusion, LOS in the ICU and hospital, functional outcome at discharge, and hospital cost were compared between the two groups using univariate and multivariate analysis.

Results: A total of 90 patients in the study group and 76 in the control group were identified. There was no significant difference in demographics, past medical history, and initial SBP between the two groups. After adjusting for confounding factors with multivariate regression models, early initiation of oral antihypertensives was associated with significant reductions in duration of nicardipine infusion (55.5 ± 60.1 vs 121.6 ± 141.3 h, $p < 0.005$), nicardipine cost ($14,207 vs $29,299, $p < 0.01$), ICU LOS (2 vs 5 days, $p < 0.005$), and cost of hospitalization ($24,564 vs $47,366, $p < 0.01$). There was no significant difference in adversary renal events, favorable outcomes, and mortality between the two groups.

Conclusions: Early initiation of oral antihypertensives is safe and may have a significant financial impact on patients with hypertensive ICH.

Keywords: Intracerebral hemorrhage, Hypertension, Nicardipine, Length of stay, Cost, Functional outcome

Introduction

Spontaneous intracerebral hemorrhage (ICH) is one of the most devastating types of stroke, with an incidence of about 10 per 100,000 person-years in the USA and a higher rate in developing countries [1–3]. It portends a high mortality rate and imposes significant financial stress on the patient and family. The mean hospital cost for patients with ICH increased from $18,300 to $28,800 between 1990 and 2001 [4]. The hospital cost continues to rise in recent years [5]. It is therefore imperative to investigate cost reduction strategies for patients with ICH.

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Hypertension is the most common risk factor for spontaneous ICH [6, 7]. Uncontrolled hypertension is an independent predictor of hematoma expansion, brain edema, neurological deterioration, longer length of stay (LOS) in the intensive care unit (ICU) and hospital, and cost of hospitalization [8–11]. Intravenous (IV) nicardipine infusion has been shown to be safe and effective for rapid lowering of systolic blood pressure (SBP) to less than 140 mmHg [9, 10, 12, 13]. Although IV nicardipine can be administered in a stroke unit that is staffed with experienced nurses 24/7, it usually requires close hemodynamic monitoring in the ICU and is associated with high cost [14]. During an internal resource utilization analysis at our medical center, IV nicardipine was identified as one of the costliest drugs used in the neurological ICU. In addition, our previous study showed that resistant hypertension in patients with ICH is associated with more medical interventions and longer LOS [10]. We therefore hypothesized that early initiation of oral antihypertensives may reduce the use of intravenous nicardipine infusion, ICU LOS, and cost of hospitalization. The aim of this study was to investigate whether early initiation of oral antihypertensives is cost-effective for patients with hypertensive ICH.

Methods

Patients Selection

This is a retrospective study of all consecutive patients with spontaneous hypertensive ICH hospitalized at University of California Irvine Medical Center between January 1, 2013, and December 31, 2017. Patients with ICH secondary to arteriovenous malformation, ruptured aneurysm, tumor, trauma, cerebral amyloid angiopathy, and coagulopathy were excluded. In addition, patients with do-not-intubate (DNI)/do-not-resuscitate (DNR) orders within 72 h of admission, initial SBP < 180 mmHg, or duration of nicardipine infusion < 2 h were also excluded. Eligible patients were divided into study and control groups based on the timing of receiving oral antihypertensives within or after 24 h of emergency department (ED) arrival. The patient list was obtained by searching the prospectively maintained stroke center data for American Heart Association-*Get With-The Guidelines-Stroke Registry*.

Study Design and Protocol

In 2013 and 2014, the initiation and titration of oral antihypertensives were at the discretion of Neuro ICU team. In January 2015, we implemented an ICU protocol for early initiation of oral antihypertensives on day 1 and rapid titrations in the next 5 days as described in our previous study [10]. This titration protocol led to early transition from iv nicardipine to oral antihypertensives. However, 12.2% (11/90) patients admitted between 2015 and 2017 did not receive oral antihypertensives within 24 h of ED arrival due to dysphagia and delayed feeding tube placement. We therefore defined control and study groups based on the timing of receiving oral antihypertensives within or after 24 h of ED arrival. The study was approved by the Institutional Review Board of the University of California, Irvine.

Data on demographics (age, sex, and race), past medical history, initial highest SBP in ED, National Institutes of Health Stroke Scale (NIHSS) score, Glasgow Coma Scale (GCS) score, ICH features, mechanical ventilation, duration of nicardipine infusion and cost, timing of oral antihypertensives, creatinine levels at admission, peak and discharge, LOS in the ICU and the hospital, total cost of hospitalization, and modified Rankin Scale (mRS) score at discharge were collected.

The cost data were provided by the Department of Decision Support. Nicardipine infusion cost includes drug acquisition expenses and indirect cost associated with monitored drug infusion (preparation, administration, and ICU monitoring). The cost of hospitalization includes expenses incurred by the hospital in providing patient care, such as nursing, room and board, medicines and supplies, as well as, indirect costs such as overhead for administrative expenses including complying with federal and state regulatory requirements, infection control, medical records, building maintenance, and equipment.

The ICH score was estimated as previously described [15]. ICH location was classified as deep (basal ganglia or thalamus), lobar, brain stem, or cerebellar [10, 16]. The outcome at hospital discharge was divided into favorable outcomes (mRS scores 0–2), unfavorable functional recovery (mRS scores 3–5), and death (mRS 6).

Initiation and Titration of Oral Antihypertensives

Our SBP goal for patients with hypertensive ICH was < 140 mmHg throughout the entire study period based on the results of Interact and Interact 2 trial [12, 17]. Patients with SBP > 140 mmHg were initially treated with labetalol or hydralazine 10 mg IV *pro re nata* and IV nicardipine infusion at 2.5–15 mg/h rate as described previously [10]. The IV nicardipine was then transitioned to oral antihypertensives gradually. The commonly used oral antihypertensives were calcium channel blocker amlodipine, angiotensin-converting enzyme inhibitor lisinopril or benazepril, angiotensin II receptor blocker losartan, diuretics spironolactone, β-blocker metoprolol,

α/β-blocker labetalol or carvedilol, central α agonist clonidine, and vasodilator hydralazine. Hydrochlorothiazide was rarely used for patients for hypertensive ICH due to risk of hyponatremia and worsening cerebral edema.

Statistical Analysis

Continuous variables were described by mean ± standard deviation (SD) or median with interquartile range (IQR) based on the results of normality testing. Categorical variables were expressed by counts with percentages. Baseline characteristics, duration and cost of nicardipine infusion, and outcomes at discharge were compared between study and control groups by student *t* or Wilcoxon rank-sum test for continuous variables and Chi-square test for categorical variables.

To investigate the independent effect of early initiation of oral antihypertensives, we first performed univariate analyses to detect possible effect of early versus late oral antihypertensives on duration of nicardipine infusion, nicardipine cost, renal function, ventilation support, LOS in the ICU and hospital, outcomes, numbers of oral antihypertensives at discharge, and cost of hospitalization. Then, we conducted multivariate logistic regression models to determine which variables were independently associated with early initiation of oral antihypertensives after adjustment for initial SBP, NIHSS, GCS, and ICH scores.

Sensitivity analysis was further performed by dividing patients by admission time into control (prior to January 2015) and study (after January 2015) groups to evaluate the effect of early oral antihypertensive protocol on duration of IV nicardipine infusion, hospital cost, and functional outcomes of the patients with ICH.

Statistical analyses were performed using SPSS software (version 23.0). A two-tailed value of $p < 0.05$ was considered statistically significant.

Results

A total of 604 patients with spontaneous ICH were admitted to our medical center during the study period. As shown in Fig. 1, 438 patients were excluded from the study (160 ICH from non-hypertensive etiology, 45 DNR/DNI within 72 h, 226 initial SBP < 180 mmHg, 2 nicardipine duration < 2 h, 5 no IV nicardipine use). Only 166 patients with hypertensive ICH and IV nicardipine use for more than 2 h were included in the analysis. All 90 patients in study group received one or two oral antihypertensives within 24 h of ED arrival. Of the 76 patients in control group, 50 (66%), 14 (18%), and 6 (8%) received oral antihypertensives on day 2, 3, or 4, respectively. Oral antihypertensives were initiated in 6 patients (8%) on day 5 or later.

The characteristics of patients with early versus late initiation of oral antihypertensives are summarized in Table 1. There was no significant difference in demographics, race, past medical history, and initial SBP between the 2 groups. Compared with control group, patients in study group had lower median NIHSS score (7.5 vs 15.5, $p < 0.001$) and ICH score (1 vs 1.5, $p < 0.001$) but higher GCS score (15 vs 13, $p < 0.001$), suggestive of less severe ICH. In contrast, there was a significantly higher proportion of dysphagia and feeding tube placement in control group (56.6% vs 28.9%, $p < 0.001$), which may have caused the delay in initiation of oral antihypertensives.

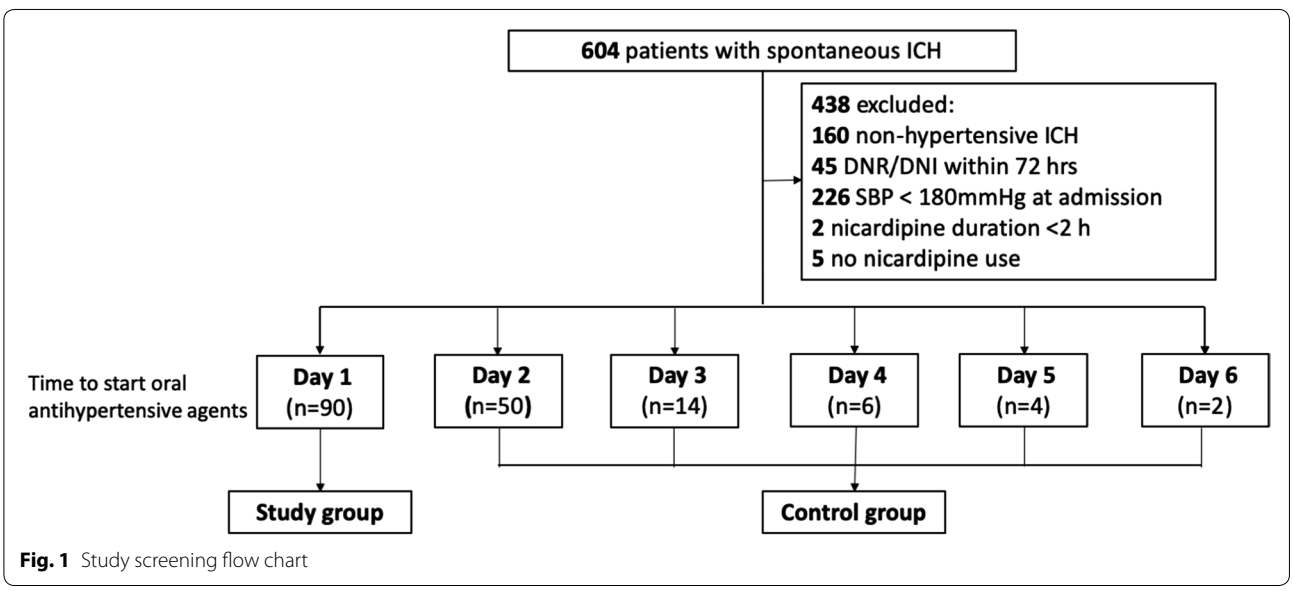

Fig. 1 Study screening flow chart

Table 1 Demographics and clinical features of study and control groups

Characteristics	Study group ($n=90$)	Control group ($n=76$)	p value
Age	64.3 ± 15.4	62.8 ± 13.4)	0.067
Male	48 (53.3)	38 (50.0)	0.668
Race			0.942
White	35 (38.9)	30 (39.5)	
Hispanic	29 (32.2)	27 (35.5)	
African-American	6 (6.7)	4 (5.3)	
Asian	20 (22.2)	15 (19.7)	
PMH			
HTN	90 (100)	76 (100)	1.000
Diabetes	29 (32.2)	22 (28.9)	0.649
Hyperlipidemia	24 (26.7)	13 (17.1)	0.140
Initial SBP (mm Hg) in ED	209 ± 23.4	215.8 ± 27.3	0.103
Initial NIHSS score	7.5 (2, 14)	15.5 (6, 25)	**< 0.001**
Initial GCS score	15 (13, 15)	13 (7, 15)	**< 0.001**
ICH score	1 (0, 2)	1.5 (1, 3)	**< 0.001**
Dysphagia/feeding tube placement	26 (28.9)	43 (56.6)	**< 0.001**

Statistically significant values are given in bold

Variables are presented as *n* (%) in nominal data; mean ± SD or median (IQR) in continuous data

ED emergency department, *GCS* Glasgow coma scale, *HTN* hypertension, *ICH* intracerebral hemorrhage, *IQR* interquartile range, *NIHSS* National Institutes of Health Stroke Scale, *PMH* past medical history, *SBP* systolic blood pressure

Table 2 Cost and outcomes of the study and control groups

Cost and outcomes	Study group ($n=90$)	Control group ($n=76$)	p value	p value*
Duration of nicardipine infusion (h)	55.5 ± 60.1	121.6 ± 141.3	**< 0.001**	**0.002**
Nicardipine cost ($)	14,207 (8690, 31,014)	29,299 (14,475, 55,772)	**< 0.001**	**0.007**
Creatinine levels				
At admission	1.5 ± 1.8	1.2 ± 0.9	0.042	–
Peak	1.7 ± 2.1	1.5 ± 1.3	0.154	–
At discharge	1.4 ± 1.6	1.2 ± 1.0	0.108	–
Rate of AKI	19 (21%)	16 (21%)	1.0	0.993
Ventilation support	24 (26.7)	38 (50.0)	**0.002**	0.986
ICU LOS	2 (1, 5)	5 (3, 10)	**< 0.001**	**0.004**
Hospital LOS	6 (4, 10)	9 (6, 16)	**< 0.001**	0.125
Favorable outcomes	38 (42.2)	13 (17.1)	**< 0.001**	0.112
Mortality	6 (6.7)	10 (13.2)	0.158	0.789
SBP at discharge	136 ± 16	129 ± 20	0.089	0.068
DBP at discharge	68 ± 13	67 ± 14	0.518	0.671
# of antihypertensives used at discharge	3 (2, 4)	3 (2, 3.5)	0.171	0.804
Cost of hospitalization ($)/patient	24,564 (15,108, 52,646)	47,366 (24,265, 89,843)	**< 0.001**	**0.007**

Statistically significant values are given in bold

Variables are presented as *n* (%) in nominal data; mean ± SD or median (IQR) in continuous data

AKI acute kidney disease, *DBP* diastolic blood pressure, *GCS* Glasgow coma scale, *ICH* intracerebral hemorrhage, *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay, *NIHSS* National Institutes of Health Stroke Scale, *SBP* systolic blood pressure

*Multivariate regression models after adjustment for initial SBP, NIHSS, GCS, and ICH scores

Table 2 shows the comparison of nicardipine use, cost, and outcomes between the study and control groups. In univariate analysis, early initiation of oral antihypertensive agents was associated with significant reductions in the duration of nicardipine infusion (55.5 ± 60.1 vs 121.6 ± 141.3 h, $p < 0.001$), median nicardipine cost ($14,207 vs $29,299, $p < 0.001$), ventilation support (26.7% vs 50.0%, $p = 0.002$), LOS in the ICU (median 2 vs 5 days, $p < 0.001$) and hospital (6 vs 9 days, $p < 0.001$), and total cost of hospitalization ($24,564 vs $47,366, $p < 0.001$). It was associated with higher rate of favorable outcomes at discharge (42.2% vs 17.1%, $p < 0.001$). Since rapid blood pressure (BP) control may cause higher incidence of adverse renal events [13], we compared the creatinine levels at admission, peak, and discharge, and rate of acute kidney injury (AKI) [18] between the study and control groups. Despite significantly higher creatinine level in the study group at admission, there was no significant difference in creatine levels at peak and hospital discharge, and rate of AKI between the 2 groups (Table 2). There was also no significant difference in SBP, DBP, and median numbers of oral antihypertensives that patients were taking at hospital discharge between the 2 groups. There was no hypotensive event in the study group. Only one incident of hypotension (86/52 mmHg) was observed in the control group (1/76, 1.3%).

In stepwise regression analysis of variables independently associated with dependent variables, the timing of the oral antihypertensive initiation was independently associated with duration of nicardipine infusion, nicardipine cost, ICU LOS, and hospital cost. In addition, initial NIHSS score was also independently associated with the duration of nicardipine infusion, hospital and ICU LOS, and functional independence, while GCS score was predictive of nicardipine and hospital cost. ICH score appears to be significantly associated with hospital LOS and mortality.

To address the imbalance issue in initial NIHSS, GCS, and ICH score between the 2 groups, we performed multivariate regression analysis of the data. After adjusting for any potential confounding factors (i.e., initial SBP, NIHSS, GCS, and ICH score), early initiation of oral antihypertensives was independently associated with significant reductions in duration of nicardipine infusion ($p = 0.002$), nicardipine cost ($p = 0.007$), ICU LOS ($p = 0.004$), and cost of hospitalization ($p = 0.007$) (Table 2). There was no significant difference in requirement for ventilation support, functional independence (42.2% vs 17.1%, $p = 0.112$), and mortality (6.7% vs 13.2%, $p = 0.789$) between the 2 groups.

The imbalance in the severity of ICH between the two treatment groups likely affected the association between the timing of oral antihypertensive administration and outcome variables as well as the magnitude of differences between the two groups. We therefore performed a sensitivity analysis by dividing patients by admission time into control (prior to January 2015) and study (after January 2015) groups. As shown in Table 3, there was no statistically significant difference in baseline characteristics and severity of ICH between the two groups. However, the study group showed significantly lower nicardipine cost, shorter ICU LOS, and lower cost of hospitalization than control group, confirming the benefit of early oral antihypertensive protocol.

Discussion

ICH imposes a substantial economic burden on patients and society [19]. Although medical complications were shown to increase LOS after ICH [20], hypertension was found to be the strongest predictor of long hospital stay and high cost per visit in patients with ICH [10, 11, 19]. Paradoxically, the most effective antihypertensive medication nicardipine has the highest drug acquisition cost [14, 21]. In addition, the need for ICU monitoring during IV nicardipine infusion increases ICU LOS, risk of medical complications, and hospital cost [10, 11, 14, 20].

A previous study with 44 and 35 patients in intervention and control groups, respectively, showed that earlier initiation of oral antihypertensive medications reduces the duration of nicardipine infusion with substantial cost saving [14]. Despite a trend toward reduction, the ICU LOS in the intervention group was similar to that in the control group possibly due to small sample size. In our current study, we have demonstrated that early initiation of oral antihypertensives has not only decreased the duration and cost of nicardipine infusion, but also reduced median ICU LOS and cost of hospitalization. The decreased ICU LOS in the early oral antihypertensive group is clinically important, as extended ICU LOS not only significantly increases the cost of care but also the risk of medical complications [20].

There are concerns about adverse effects of early initiation of oral antihypertensives while on IV nicardipine infusion. One of the concerns is AKI from rapid BP reduction and side effects of multiple drugs [22, 23]. INTERACT2 and ATACH-2 trials demonstrated that it is safe to have rapid lowering of SBP to less than 140 [12, 13]. There was no significant difference in serious adverse events between Intensive-treatment and Standard-treatment groups in the 2 landmark trials. The rate of hypotension was very low in both studies (0.5% vs 0.6% in INTERACT2 and 1.2% vs 0.6% in ATACH-2 trial). However, the rate of renal adverse events within 7 days after randomization was significantly higher in the Intensive-treatment group than in the Standard-treatment group (9.0% vs 4.0%, $p = 0.002$) in the ATACH-2 trial, likely due

Table 3 Sensitivity analysis of the 2 groups according to the time of admission

Characteristics	Study group ($n=126$)	Control group ($n=40$)	p value
Age	63.2 ± 15.0	65.0 ± 13.1	0.508
Male	64 (50.8)	22 (55.0)	0.643
Race			0.755
White	48 (38.1)	17 (42.5)	
Hispanic	41 (32.5)	15 (37.5)	
African-American	8 (6.3)	2 (5.0)	
Asian	29 (23.0)	6 (15.0)	
PMH			
HTN	126 (100)	40 (100)	1.000
Diabetes	39 (31.0)	12 (30.0)	0.909
Hyperlipidemia	31 (24.6)	6 (15.0)	0.276
Initial SBP (mm Hg) in ED	211.7 ± 23.8	215.2 ± 25.7	0.449
Initial NIHSS score	8.5 (2, 18)	10 (4, 21)	0.338
Initial GCS score	15 (12, 15)	15 (11, 15)	0.948
ICH score	1 (0, 2)	1 (0, 2)	0.534
Dysphagia/Feeding tube placement	49 (38.9)	20 (50.0)	0.214
Duration of nicardipine infusion (h)	71.6 ± 102.0	130.5 ± 123.5	**0.003**
Nicardipine cost ($)	17,080 (9413, 35,850)	29,009 (13,924, 56,237)	**0.006**
Creatinine levels			
At admission	1.4 ± 1.6	1.3 ± 0.9	0.812
Peak	1.6 ± 1.9	1.7 ± 1.4	0.821
At discharge	1.3 ± 1.4	1.4 ± 1.2	0.898
Rate of AKI	28 (22.2)	7 (17.5)	0.524
Ventilation support	44 (34.9)	18 (45.0)	0.251
ICU LOS	2 (2, 5)	5 (3, 10)	**0.003**
Hospital LOS	7 (4, 12)	10 (5, 16)	0.066
Favorable outcomes	44 (34.9)	7 (17.5)	**0.037**
Mortality	12 (9.5)	4 (10.0)	1.000
SBP at discharge	132.5 ± 17.8	136.0 ± 19.4	0.317
# of antihypertensives used at discharge	3 (2, 4)	3 (2, 3)	0.580
Cost of hospitalization ($)/patient	28,508 (16,271, 59,952)	47,269 (22,433, 91,774)	**0.013**

Statistically significant values are given in bold

Variables are presented as *n* (%) in nominal data; mean ± SD or median (IQR) in continuous data

AKI acute kidney disease, *ED* emergency department, *GCS* Glasgow coma scale, *HTN* hypertension, *ICH* intracerebral hemorrhage, *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay, *NIHSS* National Institutes of Health Stroke Scale, *PMH* past medical history, and *SBP* systolic blood pressure

to much lower SBPs (128.9 ± 16) during the first 2 h in the Intensive-treatment group [13]. We therefore examined the renal function between the 2 groups in our study. There was no significant difference in the rate of AKI between early and late oral antihypertensive groups (Table 2). We had excellent BP control at discharge in both groups. The rate of hypotension was very low (0% vs 1.3%), with only 1 incident of hypotension (86/52 mmHg) in the control group.

Of note, patients in the study group had less severe ICH scores (lower NIHSS and ICH scores and higher GCS scores) than the control group. However, after adjusting for NIHSS, GCS, and ICH scores in multivariate regression model, multivariate regression models demonstrated that early initiation of oral antihypertensives was independently associated with reduced nicardipine cost, ICU LOS, and cost of the hospitalization. In addition, the initial SBP, arguably one of the most important factors influencing the duration of nicardipine infusion and subsequently ICU LOS and cost, was similar between the 2 groups.

However, there was significant selection bias introduced by the "by treatment" group definition. We therefore performed a sensitivity analysis by dividing patients by admission time into control (prior to January 2015) and study (after January 2015) groups. We showed that

"by time" group definition was able to eliminate the imbalance in severity of ICH between the two groups and the significant effect of the early administration of oral antihypertensives on cost and ICU length of stay was maintained in the multivariate model (Table 3).

Our study has a few limitations. First, it is a single-center retrospective study. Second, only patients with initial SBP > 180 mmHg were included. Our results may only apply to patients with severe hypertension (i.e., SBP > 180 mmHg). Third, our sample sizes were relatively small and likely underpowered to identify all potential confounding factors. We also do not have 90-day outcome data. Further studies with long-term follow-up are warranted to investigate the financial impact and long-term outcome benefit of early oral antihypertensives. Lastly, our study and control groups were substantially imbalanced in terms of severity of illness. Although the multivariate models demonstrate independent association of early initiation of oral antihypertensives with reduced nicardipine cost, ICU LOS, and cost of hospitalization, the true magnitude of this difference was smaller per "by time" group assignment sensitivity analysis. The cost-effectiveness of early oral antihypertensives needs to be further investigated with well-designed randomized control trial.

Conclusion

In summary, early initiation of oral antihypertensives may significantly reduce nicardipine infusion, ICU LOS and total cost of hospitalization. Our study demonstrates significant financial impact of early initiation of oral antihypertensives in patients with hypertensive ICH that is safe and independent of baseline clinical characteristics.

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Authors Contributions
Dr. Yu and Dr. Zhu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Yu and Zhu contributed to concept and design. Acquisition, analysis, or interpretation of data was done by Zhu, Bower, Atallah, and Stradling. Zhu and Yu drafted the manuscript. Critical revision of the manuscript for important intellectual content was done by all authors. Statistical analysis was performed by Zhu. Administrative, technical, or material support was done by Atallah and Stradling. Yu supervised the study and finalized the manuscript.

Source of Support
None.

Conflicts of interest
WY is a scientific consultant at Stryker Neurovascular and Amgen. Other authors have nothing to disclose.

Ethical Approval
This study was approved by University of California Irvine Institutional Review Board.

Informed Consent
Informed consents were waived due to minimal risk of harm to the patients.

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