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A Multicenter Comparison of Outcomes Associated with Intravenous Nitroprusside and Nicardipine Treatment Among Patients with Intracerebral Hemorrhage

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Abstract

Introduction—No clinical data exist to compare outcomes between patients with intracerebral hemorrhage (ICH) treated with different intravenous antihypertensive agents. This study was performed to compare outcomes among patients with ICH who were treated with intravenous infusion of different antihypertensive medications during the first 24 hours after admission.

Methods—We analyzed one-year data (2005–2006) from the Premier database which is a nationally representative hospital discharge database containing data pertaining to admissions in the United States. We compared discharge outcomes, length of stay, and cost of hospitalization between groups of patients who were treated using either intravenous nicardipine or nitroprusside infusion. Chi-square and ANOVA were used for univariate analysis. Logistic and linear regression analyses were performed to adjust for baseline risk of mortality between the two groups.

Results—A total of 12,767 admissions with primary diagnosis of ICH were identified. Nicardipine was administered in 926 patients (7.3%) and nitroprusside was administered in 530 (4.3%) patients. There was no difference in baseline disease severity or risk of mortality among patients who were administered nicardipine or nitroprusside. After adjustment for baseline risk of mortality, the risk of in-hospital mortality (odds ratio [OR] 1.7, 95% confidence interval [95% CI] 1.3–2.2) was higher among patients treated with nitroprusside compared with nicardipine. The risk of in-hospital mortality was also higher after adjustment for baseline risk of mortality and hospital characteristics in patients treated with nitroprusside (OR 1.6, 95% CI 1.2–2.1). After exclusion of patients who died during hospitalization, there was no difference in length of stay and total hospital cost in the multivariate analysis.

Conclusion—Use of nicardipine compared with nitroprus-side infusion during the first 24 h after ICH may be associated with reduced risk of in-hospital mortality without any increase in the hospitalization cost or length of stay.

Keywords

Intracerebral hemorrhage; Nicardipine; Nitroprusside; National database; In-hospital mortality

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Introduction

Acute hypertensive response among patients with intrace-rebral hemorrhage (ICH) represents a major health problem [1]. In a study of 45,330 patients with ICH in 2004, derived from the National Hospital Ambulatory Medical Care Survey (NHAMCS), 33,992 (75.0%) had an initial systolic blood pressure (SBP) of 140 mmHg or greater [2]. Blood pressure (BP) treatment is a strategy that can be made widely available without a need of a specialized equipment and personnel. However, the management of high BP in acute ICH is controversial both in treatment targets and the pharmaceutical agent to be used. On one hand there is concern for provoking or worsening of perihematomal ischemia with significant reduction of BP [3]; and on the other, there is an increased risk for hematoma expansion associated with elevated BP [4, 5]. To date, no clinical trial has studied the differential safety or efficacy of treatment strategies for acute hypertension in patients with ICH. The American Heart Association guidelines recommend anti-hypertensive medications if SBP is more than 180 mmHg or if mean arterial pressure is more than 130 mmHg [6].

A variety of intravenous medications are commonly used for immediate BP control, as there is no proven benefit of one medication over other in ICH. Sodium nitroprusside has a short half life of 3–4 min [7, 8] but because of arterial and venous vasodilatory properties it can increase intracranial pressure (ICP). Other medications such as nicardipine and labetalol may have limited effect on ICP [9, 10]. However, it remains unclear whether there is any effect on clinical outcome with differential properties of various intravenous antihypertensive medications. The current American Heart Association guidelines include nitroprusside, nicardipine, and labetalol as treatment options [6]. We hypothesized that due to differential effect on intracranial hemodynamics, the in-hospital mortality in patients with ICH may be different between intravenous antihypertensive medication used within the first 24 h. We explored the hypothesis by comparing in-hospital outcomes among the most frequently used intravenous antihypertensive agents among patients with ICH.

Methods

We used the Premier database which is a national hospital discharge database for all payer in-hospital admissions in the United States. The database contains basic demographic information, hospital diagnoses, risk of mortality (categorized as mild, moderate, severe and extreme), pharmacy billing information, and discharge status. It contains data for one out of every six inpatient discharges from over 450 participating hospitals across 46 states in the United States. We used the data from hospital admissions that occurred from July 2005 through June 2006.

Inclusion Criteria

Patients were included in the study if the primary International Classification of Disease, 9th revision (ICD-9 CM) code was either 431 (ICH) or 432 (other and unspecified ICH) and they received either sodium nitroprusside or nicardipine intravenously during the first 24 h of admission. These two medications were selected as they were some of the most frequently used intravenous medications in this database. The frequency of other intravenous anti-hypertensive medications was considered too low for any meaningful analysis. It was

hypothesized that if aggressive BP management were required, then continuous infusion rather than bolus administration would have been used. From the description available in the database it was not possible to determine if labetalol was administered as bolus doses or continuous infusion, and so comparison with labetalol was not performed and patients receiving labetalol only (without sodium nitroprusside or nicardipine) were excluded from the analysis.

Risk of Mortality

The Premier database includes the 3M Health Information Systems All Patient Refined Diagnosis Related Group (3M APR-DRG) mortality risk algorithm. The 4-point ordinal variable for risk-for-mortality of disease is based on patient's age, and primary and secondary diagnoses; and is adjusted for in-hospital procedures. This algorithm has been demonstrated to be a reliable and valid risk of mortality adjustment system [11].

Statistical Analyses

We performed chi-square tests for comparison of categorical variables and ANOVA test for univariate comparison of continuous variables. In-hospital mortality (yes/no) was analyzed using generalized estimating equation (GEE) with a logit link function to obtain adjusted odds ratio (OR) estimates and 95% confidence intervals (CI). GEE method allows accounting for the nesting structure of the data (patients within hospitals). Similarly, to compare differences in length of stay and cost of hospitalization, we used linear mixed models on natural log scale outcomes. Values were retransformed to original scale and thus are presented as geometric means with their 95% CI. In both multivariate analyses, we adjusted for baseline risk of mortality scores and hospital characteristics (number of beds, teaching versus non-teaching, urban versus rural). Statistical significance was set at P-value < 0.05. We used SAS version 9.13 software (SAS Institute Inc. 2004, Cary, NC) for all the statistical analyses.

Results

A total of 12,767 patients (mean age 64.3 years ± 14.8; 54% male) were admitted with primary diagnosis of ICH. Nicardipine was administered in 926 (7.3%), sodium nitroprusside was administered in 530 (4.3%), and both medications were used in 53 (0.4%) patients within the first day of admission. Due to the small number of patients who received both medications, we excluded them from further analyses. There was no significant difference in age, gender, use of labetalol, baseline risk of mortality, and severity of disease among patients who received either nicardipine or sodium nitroprusside (Table 1). The hospitals using nicardipine are more likely to be large, urban, and teaching hospitals. The median duration for nicardipine treatment (2 days) was significantly longer ($P < 0.0001$) than for sodium nitroprusside infusion (1 day).

The risk of mortality, after adjustment for baseline mortality risk, (OR 1.7, 95% CI 1.3–2.2) was higher in patients treated with intravenous nitroprusside when compared with those treated with nicardipine (Table 2). The risk of mortality, after adjustment for baseline risk of mortality and hospital characteristics, was again higher in patients treated with nitroprusside

(OR 1.6, 95% CI 1.2–2.1) when compared to those treated with nicardipine (Table 2). Mortality and hospital characteristics adjusted length of stay was significantly higher in patients who were treated with nicardipine when compared with those treated with nitroprusside (Table 3). However, this difference was no longer significant when the patients who expired during hospitalization were excluded from the analysis. Similarly, the cost of hospitalization was higher for the patients who were treated with nicardipine when compared with patients who were treated with nitroprusside. However, the difference was no longer significant after excluding patients who expired during hospitalization (Table 3).

Discussion

This study demonstrates that the risk of mortality is higher (OR 1.6) without any difference in cost of hospitalization in patients with ICH who were treated with intravenous nitroprusside in the first 24 h when compared to patients treated with nicardipine. The cost of hospitalization was higher and length of stay was longer in patients treated with nicardipine than in patients treated with sodium nitroprusside. The difference was no longer observed after exclusion of patients who expired during hospitalization. These results suggest that increased survival observed in patients who received nicardipine may have contributed to increased length of stay and increased cost of hospitalization.

Patients treated with nicardipine were more likely to be admitted to a teaching hospital. A previous study had demonstrated that mortality rates among stroke patients were lower in urban teaching hospitals than in rural and urban nonteaching hospitals [12]. Although it is possible that lower mortality rates associated with nicardipine may be related to ICH admission to teaching hospitals, the results remained unchanged after adjusting for hospital characteristics in the analysis.

The reason for the differences in mortality between nitroprusside and nicardipine is unclear. Although there is evidence that nitroprusside may increase ICP in patients with mass lesions due to venodilation [13–16], comparative superiority of nicardipine in this regard is not demonstrated. The increase in ICP concomitant with reduction in systemic BP may reduce cerebral perfusion pressure and increase the risk of secondary ischemia. Nicardipine, on the other hand, is a dihydropyridine type calcium channel blocker that can be administered intravenously with limited effect on ICP because of predominant arterial vasodilatory properties [17]. Nishiyama et al. [10] determined the effect of intravenous nicardipine infusion on ICP, middle cerebral artery (MCA) velocity, and CT findings of rebleeding and edema in 22 subjects with putaminal ICH. Each subject underwent surgical drainage of the hematoma and received intravenous infusion of nicardipine initiated at 1 μg/kg/min and titrated to maintain SBP between 120 and 160 mmHg. The mean MCA velocity as measured by transcranial Doppler ultrasound was not affected by the nicardipine infusion. ICP decreased during the infusion and serial computerized tomographic (CT) scans did not demonstrate any evidence of rebleeding or exacerbation of edema. A recent clinical trial comparing nicardipine and nitroprusside in 163 neurosurgical intensive care patients noted no clinically serious elevated ICP in either group [18]. However, this study reported only serious adverse events secondary to raised ICP and prospective recording of ICP was not included.

The differences may also be attributable to adequacy of BP control during the infusion. A randomized trial in patients with severe hypertension demonstrated that goal BP was achieved in 98% of the patients treated with nicardipine compared with 93% of patients treated with sodium nitroprusside [7]. Another trial demonstrated that BP goals were achieved in 14 min with nicardipine compared with 30 min with sodium nitroprusside [8]. Both trials reported lower frequency of dosage adjustments with nicardipine compared with sodium nitroprusside. Maruishi et al. [5] investigated the effect of serial changes in BP in 57 subjects admitted within 6 h of ictus whose BPs were monitored every hour from admission. Subjects with hematoma enlargement were significantly more likely to have increased BP and fluctuations. Since hematoma enlargement is an independent predictor of mortality [19], achieving BP control faster and limiting fluctuations may result in reduced mortality. This concept is further supported by a single-center prospective registry [20] in which patients were treated with intravenous nicardipine within 24 h of symptom onset to reduce and maintain MAP of <130 mmHg. The primary outcome was the tolerability of the treatment as assessed by achieving and maintaining the MAP goals for 24 h after initiation of nicardipine infusion. The primary outcome of tolerability was achieved in 25 of the 29 treated patients (86%) with a low rate of neurologic deterioration ($n = 4$) and hematoma enlargement ($n = 5$). Favorable outcome (defined as modified Rankin Scale of ≥2) and death at 1-month was observed in 11 (38%) and nine (31%) of the patients, respectively. In addition to the low risk of elevated ICP, there is also some evidence to suggest a neuroprotective role of nicardipine [21]. It is possible that such effect could have contributed to the differential risk of mortality found in this study.

This study has several limitations: First, we used the Premier database, which includes the pharmacy billing information. Although this information can be used to determine the use of medication on a particular hospital day, the administered dose and the time of administration are not available. Therefore, the analysis can only provide time intervals in the order of days rather than hours. Second, we were unable to compare the outcomes with intravenous labetalol, a commonly used antihypertensive in neurological emergencies. The Premier database provides comprehensive information on a nationally representative sample of ICH admissions. The information includes information about medication utilization in contrast to other national databases such as Nationwide Inpatient Survey and National Hospital Discharge Survey [22, 23]. However, similar to other national databases, no specific information about the severity of ICH and other prognostically important clinical variables including Glasgow Coma Score, baseline BP, target BP, intraventricular hemorrhage, or hematoma characteristics is available. The calculation of the 3M proprietary mortality risk severity scale used for multivariate adjustment has not been specifically tested for patients with ICH. It also incorporates some elements of hospital course. As these elements may be related to the treatment rather than the baseline disease severity, the use of such a scale for severity adjustment is not ideal. Fourth, the outcomes in this study (discharge destination, length of hospitalization, and cost of hospitalization) are not directly interpretable as neurological functional outcomes and may be confounded by multiple unknown variables. Also, the threshold for withdrawal of life sustaining therapies may be different among hospitals which may influence the rate of ICU utilization and subsequently intravenous antihypertensive agent infusions requiring intensive monitoring. However, it is unlikely that

the use of specific antihypertensive agents such as nitro-prusside or nicardipine may vary according to the decision for withdrawal of care. Another potential limitation is the use of ICD-9 codes from discharge abstracts to identify ICH admissions. Broderick et al. [24] reported a positive predictive value of 83% for ICD-9 diagnoses of ICH, and Leibson et al. [25] reported a positive predictive value of 87% in the Rochester Stroke Registry. Tirschwell et al. [26] reported ICD-9 431 to be 96% specific and 85% sensitive for ICH. ICD-9 432 is coded for intracranial hemorrhage and is commonly used in addition to ICD-9 431 for identification of ICH admissions [27, 28]. ICD-9 430, which is very specific (97%) and sensitive (90%) for subarachnoid hemorrhage, was not included in our study [26]. Probably most important, the validity of ICD-9 diagnoses codes does not differ by utilization of a specific antihypertensive agent.

Compared to sodium nitroprusside, nicardipine is an expensive medication, and use of such medication is expected to raise the cost of hospitalization. If there is no clinical benefit, such practice is not cost-effective. Our study suggests that use of nicardipine compared with nitroprusside infusion during the first 24 h after ICH may be associated with reduced risk of mortality without any increase in the hospitalization cost or length of stay. In the absence of randomized controlled design, the analysis cannot exclude imbalances between the two groups of patients treated with either nicardipine or nitroprusside that may account for a differential outcome. However, the study provides a perspective of current patterns of utilization of intravenous antihypertensive medications and associated outcomes in patients with ICH in the United States.

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Table 1

Baseline demographic and clinical variables in patients with intracerebral hemorrhage treated with either intravenous nicardipine or nitroprusside (Premier data set, 2005–2006)

	Nicardipine (*n* = 926)	Sodium nitroprusside (*n* = 530)	*P*-value*
Mean age (standard deviation)	64.6 (14.7)	64.3 (15.1)	0.78
Sex (men)	511 (55%)	278 (52%)	0.31
Risk of mortality			0.33
Mild	38 (4%)	21 (4%)	
Moderate	448 (48%)	238 (45%)	
Severe	165 (18%)	89 (17%)	
Extreme	275 (30%)	182 (34%)	
Severity of disease			0.98
Mild	121 (13%)	67 (13%)	
Moderate	288 (31%)	161 (30%)	
Severe	304 (33%)	177 (33%)	
Extreme	213 (23%)	125 (24%)	
Labetalol	288 (31%)	187 (35%)	0.10
Hospital characteristics			
Median number of beds (min–max)	620 (100–1836)	442 (60–962)	<0.0001
Teaching hospital	597 (64%)	302 (57%)	0.005
Urban hospital	907 (98%)	472 (89%)	<0.0001
Median length of treatment, days (range)	2 (1–8)	1 (1–8)	<0.0001
Hospital transfer	62 (7%)	34 (6%)	0.84

Chi-square for categorical variables, *F*-test for age, Kruskal-Wallis test for number of beds

Table 2

Multivariate-adjusted risk of mortality among patients with intracerebral hemorrhage treated with either intravenous nicardipine or nitroprusside (Premier data set, 2005–2006)

	Total patients	Events N (%)	Odds ratio (95% confidence interval)		
			Crude	Baseline risk mortality algorithm adjusted	Baseline risk mortality algorithm and hospital characteristics adjusted
Nicardipine	926	261 (28%)	Reference	Reference	Reference
Nitroprusside	530	202 (38%)	1.6 (1.3–2.0)	1.7 (1.3–2.2)	1.6 (1.2–2.1)
			$P < 0.0001$	$P = 0.0003$	$P = 0.001$

Table 3

Multivariate-adjusted length of stay and cost of hospitalization among patients with intracerebral hemorrhage treated with either intravenous nicardipine or nitroprusside (Premier data set, 2005–2006)

	Age-baseline mortality risk algorithm adjusted Geometric means (95% CI)		Age-baseline mortality risk algorithm and hospital characteristics adjusted geometric means (95% CI)	
	All patients	**Patients who survived hospitalization**	**All patients**	**Patients who survived hospitalization**
Length of stay (days)				
Nicardipine	5.8 (5.4–6.2) Reference	7.8 (7.2–8.4) Reference	5.8 (5.4–6.2) Reference	7.8 (7.3–8.4) Reference
Sodium nitroprusside	5.0 (4.5–5.4) Diff = −0.8, $P = 0.006$	8.1 (7.4–8.8) Diff = 0.2, $P = 0.50$	5.0 (4.6–5.4) Diff = −0.8, $P = 0.006$	8.0 (7.3–8.8) Diff = 0.2, $P = 0.50$
Cost of hospitalization (US dollars)				
Nicardipine	12,630 (11,991–13,303) Reference	14,472 (13,239–15,821) reference	12,642 (11,632–13,740) Reference	14,536 (13,274–15,918) Reference
Sodium nitroprusside	10,986 (10,030–12,034) 12% decrease, $P = 0.03$	14,968 (13,543–16,543) 3% increase, $P = 0.57$	11,173 (10,135–12,317) 12% decrease, $P = 0.04$	14,974 (13,433–16,692) 3%, $P = 0.63$

Abbreviations used CI confidence interval, Diff difference