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Original Contributions

IS EMERGENT ANTI-HYPERTENSIVE TREATMENT BENEFICIAL IN INTRACRANIAL HEMORRHAGE?

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□ **Abstract—A retrospective chart review of adult patients with primary intracranial hemorrhage (ICH) was conducted to determine the effects of emergent anti-hypertensives on mortality. Data included mean arterial pressure (MAP), Glascow Coma Scale score (GCS), ICH size, and anti-hypertensive treatment. Multi-variable logistic regression determined the effect of anti-hypertensives on ICH mortality. Of 66 patients studied, the overall mortality was 30.3%. Mortality was 34.5% for patients initially treated with anti-hypertensives vs. 25.8% for patients not treated. After controlling for age, MAP, GCS, and ICH size, anti-hypertensives given within the first 6 h of presentation were associated with a reduction in mortality with a *p* value of 0.0375 and an odds ratio of 140 (95% confidence interval [CI] 1.332 to >999). However, this effect may not occur in patients presenting with a systolic blood pressure (SBP) < 200 mm Hg. In conclusion, in patients with primary intracranial hemorrhage, there was a significant decrease in mortality associated with emergent anti-hypertensive therapy. A larger prospective study is needed to confirm these findings, define the subgroups that may benefit, and better determine the effect size. © 2005 Elsevier Inc.**

□ **Keywords—intracranial hemorrhage; cerebral hemorrhage; hypertension; therapy; mortality; retrospective studies**

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INTRODUCTION

Intracranial hemorrhage (ICH) accounts for approximately 10% of all strokes and carries a high mortality rate, with a case fatality rate of 30% in the first month and almost 40% at one year (1–4). Among these hemorrhages, hypertension remains a frequent cause (3,5,6). Scientific investigation into the medical and surgical management of ICH is lacking, making it difficult to impossible to determine efficacy of treatment or make specific treatment recommendations (7,8).

Specific recommendations regarding the degree of treatment and preferred agent are sparse, but most recommend short-acting, easily titratable agents to adjust quickly to the patient's condition (3,6,7,9,10). Some advocate a goal blood pressure within 10–20% of the patient's baseline pressure in known hypertensives or the upper limit of normal in others (5,10,11).

Conversely, lowering blood pressure too aggressively is thought to possibly increase brain injury by reducing cerebral perfusion pressure (6,8–10,12). Some preliminary studies suggest that inflammation is more likely the cause of further neuronal injury, as opposed to ischemia (13). One study found that regardless of initial mental status or hematoma size, a rapid decline in mean arterial pressure (MAP) in the first 24 h after ICH is associated with increased mortality (14). However, a prospective animal research laboratory trial showed no evidence of deleterious

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Table 1. Comparison of ICH Patients

	Patients Died	Patients Survived	All Patients
Number	20	46	66
Age (SD) in years	80.2 (7.5)	72.4 (13.9)	74.8 (12.8)
Gender (% females)	70.0% (14/20)	61.0% (28/46)	63.6% (42/66)
Systolic BP mm Hg (SD)	191.4 (37.1)	167.4 (31.0)	174.7 (34.5)
Diastolic BP mm Hg (SD)	104.3 (26.8)	92.8 (21.3)	96.3 (23.5)
MAP (SD)	133.3 (29.0)	117.7 (22.6)	122.4 (25.5)
Glascow scale (SD)	7.8 (4.4)	13.8 (1.8)	12.0 (4.0)
History of HTN	77.8% (14/18)	71.1% (32/45)	73.0% (46/63)
ICH size $<$3 cm	5.0% (1/20)	40.0% (18/45)	29.2% (19/65)
ICH size 3–6 cm	50.0% (10/20)	55.6% (25/45)	53.8% (35/65)
ICH size $>$ 6 cm	45.0% (9/20)	4.4% (2/45)	16.9% (11/65)
HTN med $<$6 h	60.0% (12/20)	50.0% (23/46)	53.0% (35/66)
Mannitol	70.0% (14/20)	43.5% (20/46)	51.5% (34/66)
Dexamethasone	70.0% (14/20)	60.9% (28/46)	63.6% (42/66)
Intubated	60.0% (12/20)	6.5% (3/46)	22.7% (15/66)

effect on regional cerebral blood flow with careful reduction in blood pressure (12).

The primary study objective was to determine the effect on mortality of emergent anti-hypertensive treatment in primary ICH patients, controlling for severity of initial blood pressure and other markers of disease severity.

METHODS

Study Design

A retrospective chart review was performed on consecutive patients diagnosed with ICH between January 1999 and July 2001.

Study Setting and Population

After IRB approval, the study was conducted at a 434-bed community teaching hospital with an Emergency Medicine Residency Program and annual Emergency Department (ED) volume of 34,000.

Study Protocol

Patients were included if they were at least 18 years of age and were diagnosed with ICH. Patients were excluded if they had evidence of head trauma (by history or physical findings), subdural hematoma, subarachnoid hemorrhage, arterial venous malformation, cerebral aneurysm, intracranial tumor, coagulopathy (by history, INR $>$ 2, platelets $<$100K, or warfarin use) or had undergone surgical intervention. The ICH patients not excluded by these criteria were felt to have medically managed primary hypertensive ICH and formed the study cohort.

Measurements

Data collection included initial systolic blood pressure (SBP), initial diastolic blood pressure (DBP), initial Glascow Coma Scale score (GCS), underlying history of hypertension (HTN), ICH size and location, emergent interventions (intubation, mannitol and dexamethasone), and anti-hypertensive medication administration within 6 h of initial presentation. Mean arterial blood pressure (MAP) was calculated using the standard formula, MAP $= (SBP + 2DBP)/3$. The outcome measure investigated was mortality.

Data Analysis

Descriptive comparisons were made between patients who survived and patients who died from ICH. Statistical

Table 2. Differences Between ICH Deaths and Survivors

	Difference	(95% CI)	*p* Value
Age, years	7.8	1.2 to 14.4	0.0047
Gender (female)	9.1%	–15.4% to 33.7%	0.4785
Systolic BP mm Hg	24.0	6.4 to 41.6	0.0083
Diastolic BP mm Hg	11.5	–0.8 to 23.8	0.0671
MAP	15.7	2.5 to 28.9	0.0208
Glascow scale	–6.0	–4.5 to –7.6	$<$0.0001
History of HTN	6.7%	–16.7% to 30.0%	0.5902
ICH size $<$3 cm	–35.0%	–52.2% to –17.8%	0.0065
ICH size $>$6 cm	40.6%	17.9% to 63.2%	0.0002
HTN med $<$6 h	10.0%	–15.9% to 35.9%	0.4544
Mannitol	26.5%	1.8% to 51.2%	0.0476
Dexamethasone	9.1%	–15.4% to 33.7%	0.4785
Intubated	53.5%	30.8% to 76.1%	$<$0.0001

significance was determined using Student's *t*-test for continuous variables and chi-square (or Fisher's) test for categorical variables. Using a logistic regression model to control for significant confounders identified during univariate analysis, the independent effect of emergent anti-hypertensive treatment on mortality was determined. Significance was set at a two-tailed p of < 0.05 and all computations were performed using SAS Version 8 (SAS Institute, Inc., Cary, NC).

RESULTS

This study reviewed 141 patients, 75 of whom were excluded. Those excluded included 28 due to coagulopathy, 14 due to trauma, 13 for surgical interventions, 12 due to intracranial tumor, and 5 due to subarachnoid hemorrhage (SAH), arterial-venous malformation (AVM), or aneurysm. An additional three excluded cases were transfer patients with insufficient records. The sample consisted of 66 patients (Table 1) with a mean age of 74.8 years (SD 12.8); 63.3% were females. A history of hypertension was noted in 73.0% of the patients and the mean initial MAP was 122.4 mm Hg (SD 25.5). In 53.9% of the cases, the ICH size was between 3 and 6 cm, whereas 29.2% had ICH < 3 cm and 16.9% had ICH > 6 cm.

The overall mortality was 30.3% and the differences between those who lived and died are shown in Table 2. Patients presenting with lower GCS and larger ICH lesions had significantly greater relative risk (RR) of death. Also, patients needing emergent intubation were significantly more likely to die. Patients who expired were older by 7.8 years (95% confidence interval [CI] 1.2–14.4) and had higher initial mean arterial blood pressure of 15.7 mm Hg (95% CI 2.5–28.9)

Patients were treated with anti-hypertensive medication in 46 cases (69.7%): 35 cases (53.0%) received anti-hypertensives within 6 h, 6 cases (9.1%) between 6 to 24 h, and 5 cases (7.6%) after 24 h. Patients receiving anti-hypertensive therapy within the first 6 h had initial MAP 28.4 mm Hg higher than patients not initially treated (Table 3). Without controlling for age, initial MAP, initial GCS, and ICH size, patients not initially treated with anti-hypertensives had a mortality rate of 25.8% (8/31), whereas patients treated had a mortality rate of 34.3% (12/35). However, when stratified by initial systolic blood pressure (Table 4), patients with initial SBP between 140 and 200 mm Hg had improved mortality when treated with anti-hypertensives in the first 6 h (29.6% vs. 11.1%, respectively; RR = 0.38, 95% CI 0.09–1.57), although this effect was not statistically significant ($p = 0.11$).

A multi-variable logistic regression model was used to control for age, MAP, GCS, and ICH size. Four emergent interventions (intubation, mannitol, dexamethasone, and anti-hypertensives in the first 6 h) were placed in the logistic model. (Table 5) The resulting regression had an adjusted R-squared of 84.1% and passed the Hosmer and Lemeshow goodness-of-fit test with a p value of 0.7207, both values indicating a good logistic model. After controlling for age, MAP, GCS, and ICH size, emergent treatment of blood pressure within the first 6 h of presentation was associated with a significant reduction in mortality, with a p value of 0.0375 and an odds ratio of 140 (95% CI 1.332 to >999).

Table 3. Differences between Patients Receiving Anti-hypertensive Medication in First 6 Hours and Patients not Treated

	Difference	(95% CI)	*p* Value
Age, years	4.2	–2.0 to 10.5	0.1788
Gender (female)	16.6%	–6.4% to 39.6%	0.1620
Systolic BP mm Hg	37.9	23.6 to 52.2	<0.0001
Diastolic BP mm Hg	23.6	13.5 to 33.6	<0.0001
MAP	28.4	17.8 to 38.8	<0.0001
Glascow scale	–0.52	–2.50 to 1.46	0.6019
History of HTN	24.8%	3.5% to 46.2%	0.0265
ICH Size<3 cm	–18.7%	–40.4% to 29.6%	0.0938
ICH Size >6 cm	1.0%	–17.0% to 19%	0.9122
Mannitol	5.9%	–18.2% to 30.0%	0.6323
Dexamethasone	–1.6%	–24.9% to 21.6%	0.8888
Intubated	6.4%	–13.7% to 26.4%	0.5384

DISCUSSION

Blood pressure management in ICH remains highly controversial. Many patients have elevated blood pressure acutely after ICH, which may resolve spontaneously without intervention (9,10,15). Generally accepted recommendations advocate cautious blood pressure reduction if the systolic blood pressure (SBP) remains > 200 mm Hg or diastolic blood pressure (DBP) remains >110 mm Hg (3,6,9–11). It is unclear from the Emergency Medicine literature whether or not SBP in the 140 to 200 mm Hg range should be lowered initially.

Approximately 25% of patients with ICH develop hematoma enlargement in the first hour and up to 40% in the first 24 h, many of whom develop neurologic deterioration (11,16). In those patients with hemorrhage increase there is a slight trend towards higher morbidity and mortality at 4 to 6 weeks (16). Neither marked elevations in presenting blood pressure nor initial hemorrhage size predicted hemorrhage growth in these patients (16). Although the reduction of blood pressure in the acute phase of ICH theoretically is thought to reduce continued bleeding from leaking arterioles, a definitive relationship between blood pressure elevation and in-

Table 4. Mortality with Anti-hypertensive Treatment within 6 Hours When Stratified by Severity of Initial Systolic Blood Pressure (mm Hg)

Systolic BP	Not Treated	Treated	Relative Risk (95% CI)	*p* Value
≤140	0 (0/4)	33.3% (1/3)	N/C	0.4286
140 < SBP < 200	29.6% (8/27)	11.1% (2/18)	0.38 (0.09–1.57)	0.1065
≥200	0 (0/0)	64.3% (9/14)	N/C	N/C

creasing hematoma size has not been demonstrated (2,8,9,11,12,17). Regardless, some have shown a more favorable outcome in those ICH patients with blood pressure reductions (15).

Our primary study objective was to determine the independent effect on mortality of initial anti-hypertensive treatment in primary ICH patients. The univariate analysis shows that advanced age and increased initial blood pressures are associated with increased ICH mortality. Therefore, without controlling for the initial blood pressure, any effect seen with initial anti-hypertensive treatment may be masked by the effect of the initial blood pressure itself. A similar argument is made for controlling severity of disease. ICH patients with very severe disease may have such high mortality probabilities that any effect of treatment is again hidden. It is no surprise that on the univariate analysis, all three markers of ICH severity (Glascow Coma score, hemorrhage size, and emergent intubation) are significantly associated with increased mortality. These univariate results clearly suggest that a multi-variable regression approach is necessary to define the effect of early anti-hypertensive treatment.

The logistic regression model shows that after controlling for initial severity of illness and initial MAP, early anti-hypertensive treatment has a beneficial effect on patient mortality. Although the size of this beneficial effect is imprecise with a wide 95% confidence interval, the lower confidence limit of the odds ratio suggests that, at minimum, there will be a 33% increase in survival with early anti-hypertensive treatment.

Because there are already generally accepted recommendations regarding systolic blood pressures >200 mm Hg, our findings will have greatest applicability for patients presenting with SBP < 200 mm Hg (3,6,9–11). In our study, 68% of ICH patients had 140 < SBP < 200 mm Hg, and it was in this group that initial anti-hypertensive treatment demonstrated a difference in mortality, although this was not statistically significant.

These findings also confirm a similar association found in a prior study that persistent inadequate blood pressure control in the first 6 h adversely affected prognosis (15). Although there have been arguments made that lowering initial blood pressure may lower cerebral blood flow leading to poor results, our results suggest otherwise. It has been shown that autoregulation of blood pressure is maintained despite pressure reduction in the small and medium-sized ICH (12).

Study Limitations and Future Questions

A major limitation is the retrospective nature of this study. Without a prospective protocol, it is not possible to control for the individual physician's decision to initiate different therapies. Perhaps patients given anti-hypertensives were more clinically stable and treating physicians were more inclined to treat. Or, perhaps, patients not given treatments had major co-morbidities and this selection process influenced the effect on mortality. By its retrospective nature, this study can show only association between treatments and outcome and not causality.

The power and sample size is a limitation of our study. It is too small to allow precise estimates of the magnitude of the effect seen with early anti-hypertensive treatment of ICH patients. Another limitation of our study is the likelihood of additional confounding factors.

Table 5. Multi-variable Logistic Regression Predicting Probability of Survival after ICH

Effect	Wald *p* Value	Odds Ratio	(95% CI)
Anti-hypertensive in first 6 h	0.0375	140.4	1.332–>999
Age, years	0.0145	0.707	0.535–0.934
MAP	0.0317	0.887	0.796–0.990
GCS	0.0546	2.131	0.985–4.610
ICH size > 6cm	0.7676	0.521	0.007–38.59
Intubation	0.9749	0.909	0.002–355.2
Mannitol	0.9470	<0.001	<0.001 ≥ 999
Dexamethasone	0.9561	>999	<0.001 ≥ 999

The effect of treatment may be confounded by factors not included in our logistic model.

Further studies with a prospective protocol and larger sample size will clarify and better estimate the independent effect of anti-hypertensive therapy in ICH patients. Such studies should include other factors not included in our study and also look at outcomes between different specific hypertensive medications.

CONCLUSIONS

In this study of patients with intracranial hemorrhage, there was a significant decrease in mortality associated with initial anti-hypertensive treatment for the whole group. This improvement in mortality was found after controlling for age, initial blood pressure, and markers of severity such as Glascow score, hemorrhage size, and intubation. A larger prospective study is needed to confirm these findings and better determine the effect size. A prospective study will also be important to determine whether anti-hypertensive treatment will decrease mortality in the subgroup of patients in whom initial SBP is 140–200 mm Hg.

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