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ORIGINAL RESEARCH

Usage of Angiotensin-Converting Enzyme Inhibitor or Angiotensin II Receptor Blocker in Hypertension Intracerebral Hemorrhage

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Background: Inflammation plays an essential role in secondary brain injury after intracerebral hemorrhage (ICH). Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) have been suggested to suppress neuroinflammation after central nervous system (CNS) damage in animal models. However, the role of ACEIs and ARBs in ICH patients with hypertension remains unresolved in clinic. The aim of the present study is to evaluate the effect of ACEIs/ARBs on ICH patients with hypertension using a retrospective, single-center data analysis.

Methods: ICH patients diagnosed by computerized tomographic (CT) at Southwest Hospital, Third Military Medical University were included in the present research from January 2015 to December 2019. According to the medical history for the usage of antihypertensive drugs, patients were assigned into either ACEIs/ARBs group or non-ACEIs/ARBs group. Demographics, clinical baseline, radiological documents and treatments were collected and these data were statistically analyzed between the two groups.

Results: A total of 635 ICH patients with hypertension were included and allocated into 2 groups according to the usage of antihypertensive drugs: 281 in the ACEIs/ARBs group and 354 in the non-ACEIs/ARBs group. The results presented that the 3-months mortality and prevalence of ICH-associated pneumonia were lower in ACEIs/ARBs group than that in non-ACEIs/ARBs group (5.0% vs 11.9%, p=0.002; 58.4% vs 66.7%, p=0.031). While, there was no significant difference in favorable outcome (40.2% vs 33.9%, p=0.101) between the two groups. Furthermore, patients in ACEIs/ARBs group exhibited significantly less perihematomal edema volume on days 3 (23.5 ± 14.4 versus 28.7 ± 20.1 mL, p=0.045) and 7 (21.0 ± 13.7 versus 25.7 ± 17.6 mL, p=0.044), compared to that in non- ACEIs/ARBs group.

Conclusion: The usage of ACEIs/ARBs helps decrease mortality, perihematomal edema volume, and prevalence of ICH-associated pneumonia in ICH patients with hypertension.

Keywords: angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, inflammation, intracerebral hemorrhage, ICH-associated pneumonia

Introduction

Hypertension intracerebral hemorrhage (ICH) is associated with high mortality and disability.[1–4] Few effective treatments are available in the several prospective, randomized, controlled, multicenter trials, except for rapid blood-pressure lowering.[5–8] Primary brain injury is mainly caused by mechanical damage to the surrounding tissues inducing by dissection and compression of the hematoma formation within the first few hours after ICH onset.[9] Secondary brain injury caused

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by the physiologic response to the primary brain injury could lead more serious and fatal injury, which plays a key role in the overall prognosis of ICH.[9] The preclinical studies have suggested that inhibition of neuroinflammation holds beneficial effect on ICH animals after central nervous system (CNS) injury.[2,9–13]

The renin-angiotensin-aldosterone system (RAAS), existing in the cardiovascular system, kidneys and CNS, can influence the outcome of ischemic stroke.[14–16] Angiotensin (Ang) Ⅱ is a product of the proteolytic cleavage of Ang I by Angiotensin-converting enzyme (ACE) and is the pivotal protein of the RAAS for the regulation of blood pressure.[14] Ang Ⅱ can also produce an inflammatory response by binding to type-1 Ang Ⅱ receptors.[17] Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are two critical suppressors of the RAAS and widely used as the first-line anti-hypertensive drugs.[18] Previous researches have shown that ACEIs/ARBs have multiple neuroprotective effects, such as slowing inflammatory processes, inhibition of fibrinoid necrosis, anti-apoptotic and anti-oxidant effects by the reduction of Ang Ⅱ in the animal models after CNS injury.[2,17,19–24] However, the role of ACEIs and ARBs in ICH patients with hypertension remains elusive in clinic.[25] Herein, the aim of the present study is to evaluate the effect of ACEIs/ARBs on ICH patients with hypertension using a retrospective, single-center data analysis.

Methods

Study Design and Patient Selection

This retrospective study was approved by the Ethics Committee of the Southwest Hospital, Third Military Medical University (approval no. KY2020114) and the informed consent for patients was waived.

ICH patients diagnosed by initial computerized tomographic (CT) at Southwest Hospital, Third Military Medical University were included in the present research from January 2015 to December 2019. Patients with a history of hypertension and taking at least one of anti-hypertensive ACEIs/ARBs drugs was assigned into ACEIs/ARBs group, and without any anti-hypertensive ACEIs/ARBs drugs into non- ACEIs/ARBs group.

Eligibility patients were aged 18 years or older with a spontaneous, non-traumatic ICH with a history of hypertension and taking at least one of anti-hypertensive drugs. Exclusion criteria was as follows: (1) ICH from secondary causes, such as head trauma, aneurysm, vascular malformation, tumor or hemorrhagic transformation of ischemic infarcts; (2) the time from symptom onset to admission more than 3 days; (3) unavailable information of anti-hypertensive medication. Modified Rankin Scale (mRS) score was measured at 90 days, and an mRS score of 4–6 was defined as unfavorable outcome.[7]

Demographics and ICH Characteristics

The usage of antihypertensive drugs before admission and during hospital stay were collected. Demographic data included sex, age, smoking (currently smoking one or more cigarettes per day on a regular basis),[26] alcohol use (≥1 drink per week for 1 year),[26] previous medical history (diabetes mellitus, coronary artery disease, history of stroke [ischemic stroke and intracerebral hemorrhage], anticoagulant therapy, anti-platelet therapy, and sulfonylureas therapy). Home blood pressure (self-measurement at home or nearby clinic) and blood pressure on admission and Glasgow Coma Score Scale (GCS) on admission also were obtained. Laboratory parameters, including neutrophil count, lymphocyte count, C-reactive protein (CRP), procalcitonin, interleukin-6, blood glucose, were measured. ICH volumes and edema volumes (baseline, 3 days and 7 days) were calculated using a semi-automated threshold-based approach by an experienced investigator who was blinded to clinical and biochemical data.[7,27] Hematoma location and expansion (more than 6 mL or 33% growth compared to the initial ICH volume) were centrally evaluated.[28] Treatment-related data (surgery and statins therapy) and complications (hydrocephalus, pneumonia, mechanical ventilation, gastrointestinal bleeding and seizures) were also collected.

Statistical Analysis

Data analyses was performed using SPSS software for Windows (version 18.0, Inc., Chicago, IL). Continuous data were presented as mean ± Standard Deviation (SD) or median (interquartile ranges [IQRs]) and analyzed by independent group using Student's *t*-test or Mann–Whitney *U*-test, respectively. Categorical data were presented as counts (percentages) and analyzed by chi-square test or continuity correction test. Significant variables ($p < 0.2$) were entered into the multivariable analysis via the binary logistic regression model to see whether the use of ACEIs/ARBs was associated with beneficial outcome. General linear models (repeated measures) were performed to analyze the within-subjects' effects of perihematomal edema volume at different time points between

ACEIs/ARBs group and non-ACEIs/ARBs group. A P <0.05 was considered statistically significant.

Results

A total of 1049 ICH patients were included for initial screening, and 635 patients met the inclusion/exclusion criteria who were analyzed in this study (Figure 1). The remaining patients were allocated into 2 groups based on the usage of ACEIs/ARBs: 281 in the ACEIs/ARBs group and 354 in the non-ACEIs/ARBs group. Baseline characteristics of ICH patients with hypertension were shown in Table 1. The mean age was 56 ± 12 years with males (71.7%). The time of usage of ACEIs/ARBs was 3 (0.1–8) years. The data of anti-hypertension drugs for the ICH patients are shown in Table 2. There was no difference between the 2 groups in age, sex, previous diseases, lifestyle factors, and radiological data. Blood pressure was higher in the ACEIs/ARBs group than that in the non-ACEIs/ARBs group (Table 1).

At 3 months, 56 (8.8%) patients died, 402 (63.3%) patients had unfavorable outcome and 233 (36.7%) patients had favorable outcome (Table 3). The mortality and ICH-associated pneumonia in ACEIs/ARBs group were obviously lower than that in non-ACEIs/ARBs group (5.0% vs 11.9%, p=0.002; 58.4% vs 66.7%, p = 0.031). Non-ACEIs/ARBs (OR 1.282, 95% CI 0.883 to 1.863, p = 0.192) was found to be a significant predictor for mortality after ICH, but not for ICH-associated pneumonia (OR 2.299, 95% CI 1.124 to 4.700, p = 0.023) in the multivariable analysis. The distribution of mRS at 3-months was different between patients with or without ACEIs/ARBs treatment (p = 0.007) (Figure 2). Nevertheless, there were no significant difference in favorable outcome (40.2% vs 33.9%, p=0.101) between patients with or without ACEIs/ARBs treatment.

Perihematomal edema was determined using CT scan, calculated and analyzed in patients with supratentorial ICH, without intraventricular hemorrhage (IVH) and surgical treatments, on days 1, 3 and 7 in the two groups (93 cases in the ACEIs/ARBs group and 93 cases in the non-ACEIs /ARBs group). The results delineated that patients in ACEIs/ARBs group exhibited significantly less perihematomal edema volume on days 3 (23.5 ± 14.4 versus 28.7 ± 20.1 mL, p = 0.045) and 7 (21.0 ± 13.7 versus 25.7 ± 17.6 mL, p = 0.044), compared to that in non- ACEIs/ARBs group (Figure 3). However, the hematoma volume at different time points showed no evident difference between

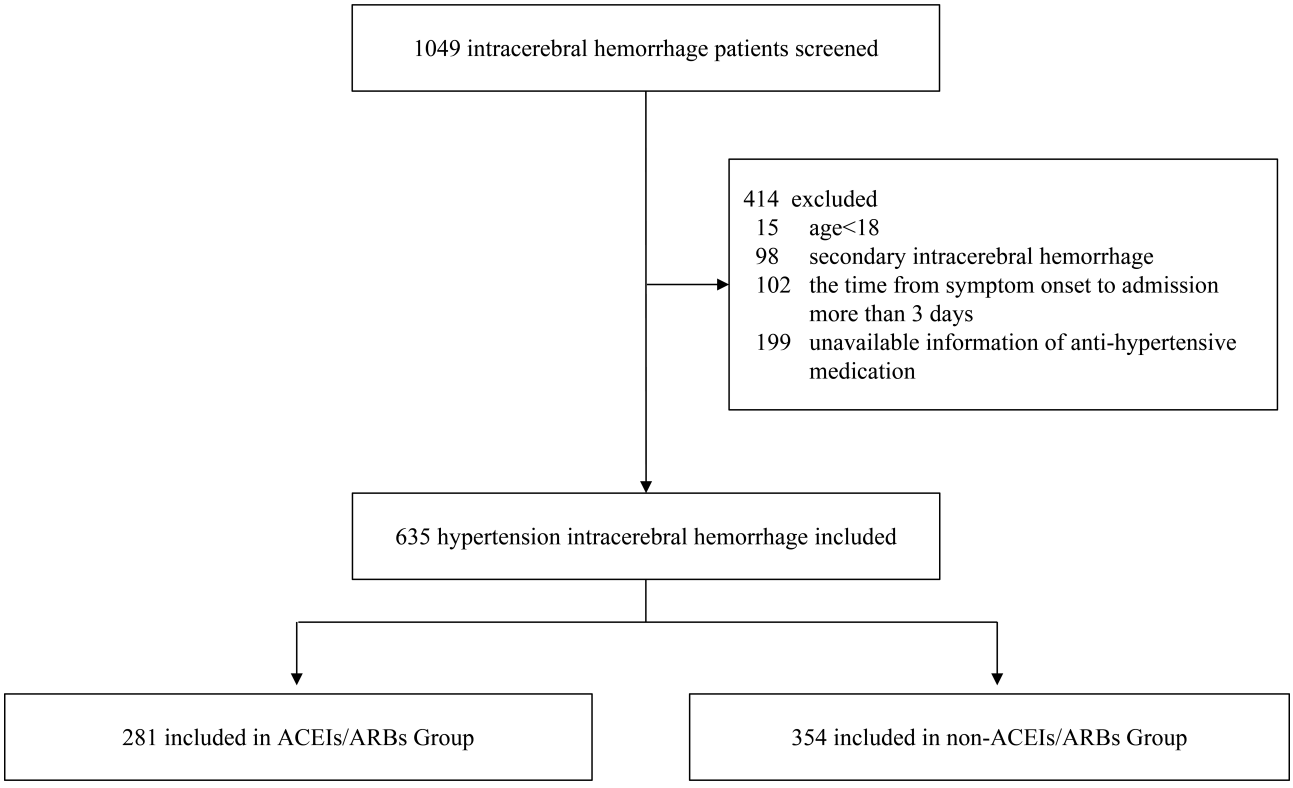

Figure 1 Flowchart of the selection for study subjects.
Abbreviations: ICH, intracerebral hemorrhage; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

Table 1 Baseline Characteristics of ICH Patients with Hypertension

Variables	ACEIs/ARBs (n=281)	Non-ACEIs/ARBs (n=354)	p value
Age, y, mean ± SD	56 ± 13	57 ± 12	0.131
Male, n (%)	194 (69.0)	261 (73.7)	0.193
Medical history, n (%)			
Diabetes mellitus	19 (6.8)	31 (8.8)	0.354
Coronary artery disease	21 (7.5)	15 (4.2)	0.080
History of stroke	50 (17.8)	62 (17.5)	0.927
Lifestyle factors, n (%)			
Smoking	62 (22.1)	88 (24.9)	0.41
Alcohol use	100 (35.6)	120 (33.9)	0.657
Clinical features			
Home SBP, mmHg, mean ± SD	166 ± 29	160 ± 29	0.025
Home DBP, mmHg, median (IQR)	92 (80–106)	90 (80–100)	0.008
SBP on admission, mmHg, mean ± SD	172 ± 31	167 ± 29	0.019
DBP on admission, mmHg, median (IQR)	97 (85–110)	94 (83–101)	0.002
Neutrophil count, 10^9/L, mean ± SD	9.3 ± 4.2	9.3 ±4.5	0.979
Lymphocyte count, 10^9/L, mean ± SD	1.2 ± 0.6	1.1 ± 0.6	0.352
C-reactive protein, mg/L, mean ± SD	55.6 ± 74.1	62.3 ± 66.2	0.522
Procalcitonin, ng/mL, median (IQR)	0.1 (0.1–0.4)	0.1 (0.1–0.6)	0.026
Interleukin-6, ng/L, mean ± SD	41.7 ± 52.1	51.5 ± 88.1	0.485
Blood glucose, mmol/L, median (IQR)	7.2 (6.1–8.4)	7.2 (6.0–9.0)	0.302
GCS score, n (%)			
3–8	55 (19.6)	121 (34.2)	0.000
9–12	74 (26.3)	79 (22.3)	
13–15	152 (54.1)	154 (43.5)	
Radiological data			
Left, n (%)	132 (47.0)	172 (48.6)	0.686
Location, n (%)			
Supratentorial	250 (89.0)	300 (84.7)	0.121
Infratentorial	31 (11.0)	54 (15.3)	
ICH volume, mL, median (IQR)	25 (15–40)	25 (15–45)	0.289
Extension to ventricles, n (%)	89 (31.7)	142 (40.1)	0.028
Hematoma expansion, n (%)	45 (16.0)	49 (13.8)	0.444

Abbreviations: ICH, intracerebral hemorrhage; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale.

ACEIs/ARBs group and non-ACEIs/ARBs group (p = 0.533).

Additionally, the relationship between perihematomal edema and hematoma volume was further investigated. The results presented that the perihematomal edema reached to the peak at 3 days (24 hours [16.0 ± 10.0 mL]; 3 days [26.1 ± 17.6 mL]; 7 days [23.4 ± 16.0 mL]; p=0.000 [24 hours versus 3 days]; p=0.116 [3 days versus 7 days]). Then, Pearson correlation coefficient was used to determine the relationship between baseline hematoma and perihematomal edema. The results demonstrated that it exhibited a positive correlation at 24 hours (r=0.639, P=0.000), perihematomal edema at 3 days (r=0.609, P=0.000), and perihematomal edema at 7 days (r=0.671, P=0.000).

Discussion

ICH is associated with higher mortality and disability than other types of strokes.[4] Currently, the efficacy of treatments for ICH is still controversial.[4] Increasing evidence have suggested that inflammation plays a key role in ICH-induced secondary brain injury.[2,21] Hemoglobin, heme,

Table 2 Anti-Hypertension Drugs of ICH Patients

Variables	Total (n=635)	ACEIs/ARBs (n=281)	Non-ACEIs/ARBs (n=354)	p value
ACEIs, n (%)	215 (35.5)	215 (76.5)	0 (0.0)	0.000
ARB, n (%)	83 (13.7)	83 (29.5)	0 (0.0)	0.000
CCB, n (%)	537 (88.8)	226 (80.4)	311 (87.9)	0.010
α-blocker, n (%)	27 (4.5)	0 (0.0)	27 (7.6)	0.000
β-blocker, n (%)	41 (6.8)	21 (7.5)	20 (5.6)	0.353
Diuretics, n (%)	47 (7.8)	45 (16.0)	2 (0.6)	0.000

Abbreviations: ICH, intracerebral hemorrhage; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCB, calcium channel blocker.

iron and thrombin released from the hematoma trigger inflammation via activation of microglia, and subsequently facilitate the infiltration of various circulating immune cells, especially macrophages and T cells.[29] The activation of M1 microglia upregulates inflammatory cytokines, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and other inflammatory products via coordinating the transcription factor nuclear factor-κB (NF-κB).[2,21,30] The upregulating of inflammatory cytokines lead to potentiating cellular damage, and increasing of permeability of blood brain barrier (BBB), which contributes to exaggeration of edema and further secondary ischemia by cell death.[13,31] The process of brain edema and secondary ischemia further exert inflammatory response to the surrounding brain tissue.[2]

Table 3 Clinical Courses and Outcomes of ICH Patients

Variables	ACEIs/ARBs (n=281)	Non-ACEIs /ARBs (n=354)	p value
Treatment-related data, n (%)			
Surgery	119 (42.3)	170 (48.0)	0.154
Antiplatelet therapy	22 (7.8)	18 (5.1)	0.157
Anticoagulant therapy	6 (2.1)	4 (1.1)	0.49
Statins	53 (18.9)	35 (9.9)	0.001
Sulfonylureas	12 (4.3)	17 (4.8)	0.75
Complications, n (%)			
Hydrocephalus	17 (6.0)	44 (12.4)	0.007
Pneumonia	164 (58.4)	236 (66.7)	0.031
Mechanical ventilation	52 (18.5)	84 (23.7)	0.111
Gastrointestinal bleeding	20 (7.1)	28 (7.9)	0.708
Seizures	7 (2.5)	10 (2.8)	0.796
Day, mean ± SD			
Stay in NICU	7.7 ± 7.2	7.9 ± 7.8	0.697
Stay in hospital	24.3 ± 15.9	20.7 ± 16.9	0.006
Outcomes, n (%)			
Favorable outcome	113 (40.2)	120 (33.9)	0.101
Unfavorable outcome	168 (59.8)	234 (66.1)	
Death	14 (5.0)	42 (11.9)	0.002
Alive	267 (95.0)	312 (88.1)	

Abbreviations: ICH, intracerebral hemorrhage; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; NICU, neurological intensive care unit.

The renin-angiotensin-aldosterone system (RAAS), which exists in the CNS, can influence the outcome of stroke.[14,15] Angiotensin-converting enzyme inhibitor (ACEIs) and angiotensin II receptor blocker (ARBs) are two critical inhibitors of the RAAS and usually used as the first-line anti-hypertensive drugs.[18] Meanwhile, previous studies have proven that ACEIs/ARBs can inhibit atherosclerosis processes and further reduce the risk of stroke recurrence.[17,19,20,32,33] Moreover, previous studies have also revealed that ACEIs/ARBs may protect neural tissue, prevent secondary neuronal death after ICH including anti-oxidant, anti-apoptotic effects, and inhibit fibrinoid necrosis by a reduction of the generation of Ang II through the activation of the ACE2/Ang-(1-7)/Mas pathway.[20,22–24] However, these results are not thoroughly attested by the clinical data.[25]

In the present study, our results illustrated that the usage of ACEIs/ARBs was associated with lower mortality in ICH sufferers with hypertension, compared with non-usage of ACEIs/ARBs (5.0% [14 of 281] vs 11.9% [42 of 354], p = 0.002), which is in consistent with that the use of ACEIs/ARBs are associated with lower risk of all-cause mortality compared with non-ACEI/ARB users in patients with COVID-19 and hypertension.[34–37] Meanwhile, our results also demonstrated that the use of ACEIs/ARBs markedly lower the prevalence of ICH-associated pneumonia but without improvement in independent ability in ICH patients (40.2% vs 33.9%, p=0.101), implying that some other significant co-morbidities (eg, diabetes, previous stroke, and ischemic heart disease), the severity on admission, the white matter bundle injury, which needs long time to regenerate, might contribute to the equal outcome between two groups.[25,38] These complicated pathophysiological effectors reduce the beneficial effect induced by ACEIs/ARBs, in some degree.

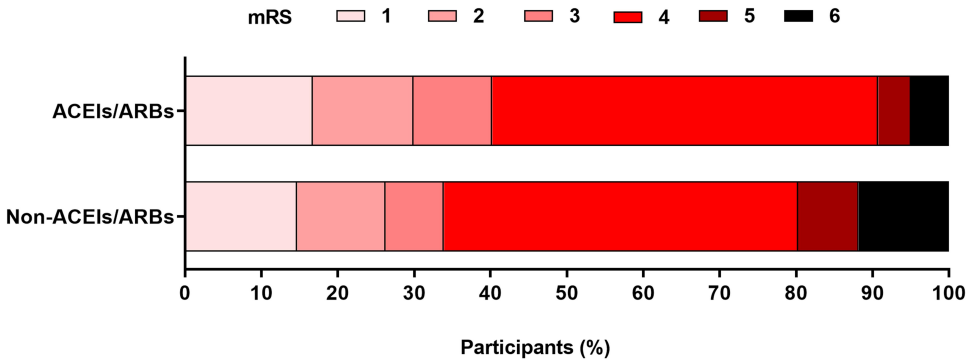

Figure 2 Modified Rankin Scale (mRS) of ICH patients at 3 months. Proportional odds model p=0.007.
Abbreviations: ICH, intracerebral hemorrhage; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

The use of ACEIs/ARBs reduces perihematomal edema volume over 7 days after the occurrence of ICH with hypertension. Perihematomal edema, which ubiquitously occurs in ICH patients, is associated with mass effect and is a predictor of poor outcome.[3,39–41] The mechanisms of brain edema formation after ICH are complex, and several potential mechanisms contribute to the formation and progression of brain edema after ICH.[3] The brain edema formation is rapid and follows three stages after ICH.[3,10,42] In the first stage (a few hours after ICH), retraction of the clot contributes to vasogenic edema formation. In the second stage (24 to 48 hours after ICH), the activation of the coagulation cascade promotes edema formation and further disruption of the blood–brain barrier by the inflammatory cascade and overexpression of matrix metalloproteinase. In the third stage (days to weeks after ICH), erythrocyte lysis and hemoglobin/hemoglobin degradation products initiate a potent inflammatory reaction by the iron-catalyzed production of reactive oxygen species. Previous studies have represented that ACEIs/ARBs could reduce the inflammatory cascade of reactive oxygen species, then relieve brain edema and improve neurological function.[15,20,32,33,43] The reason why patients with supratentorial ICH, without intraventricular hemorrhage (IVH) and surgical treatments were screened and analyzed was due to avoiding technical flaws regarding accurate edema volume measurements, and exhibiting excellent repeat scans for perihematomal edema examination on day 3 to 4 and 7 to 8 of hospitalization, which is in line with previous report.[27] Here, our results represented a positive correlation between hematoma volume and the perihematomal edema, which is supported by previous studies.[44,45]

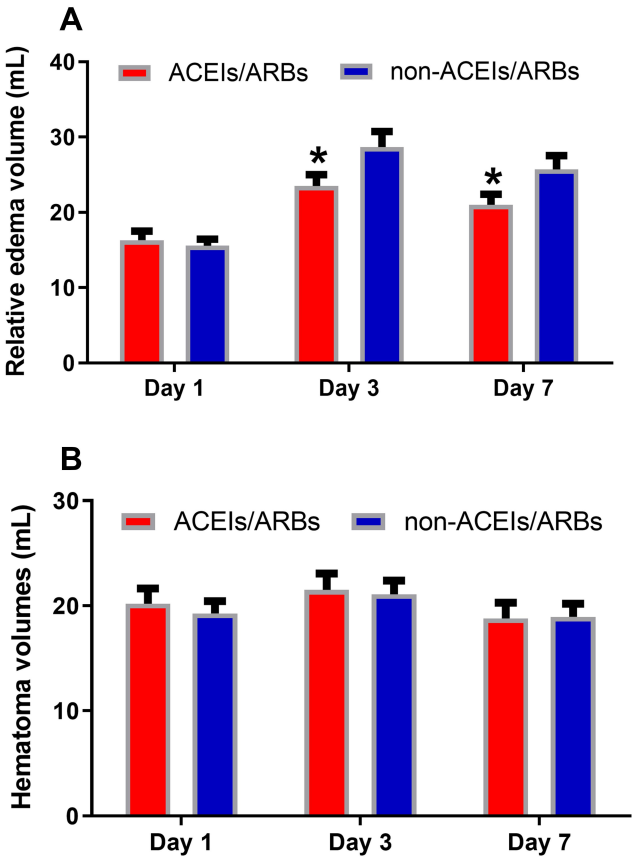

Figure 3 The lower perihematomal edema volume at day 3 and day 7 in ICH and hypertension patients with the usage of ACEIs/ARBs. (**A**) The perihematomal edema volumes at baseline, day 3 and day 7 in ICH patients with or without the usage of ACEIs/ARBs. (**B**) The hematoma volumes at baseline, day 3 and day 7 in ICH and hypertension patients with or without the usage of ACEIs/ARBs. Data were presented as Mean ± SEM, n=93 for each group. *P < 0.05 vs non-ACEIs/ARBs group.
Abbreviations: ICH, intracerebral hemorrhage; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

In addition, our results indicated that the occurrence of ICH-associated pneumonia was reduced with the use of ACEIs/ARBs (p=0.031). The underlying mechanisms may be that the treatment of ACEIs/ARBs was associated with a reduction in myeloperoxidase activity and decreased

cytokine and high-mobility group box 1 levels by an inhibition of NF-κB activity.[46,47] This neuroprotective effect needs to be elucidated through further animal experiments in our future research.

Some limitations still exist in the present study. First, due to the retrospective nature of this study, some data were not available in ICH patients. For instance, the laboratory data about inflammatory factors and the expression of ACE2 were failed to test. The dosage of antihypertensive drugs for patients was not recorded accurately. Second, many patients were excluded because of unavailable information of anti-hypertensive treatments, thereafter the selection bias might exist. Third, a multicentre, open, randomised trial needs to be carried out to attest the effectiveness of ACEIs/ARBs in ICH patients with hypertension. In addition, the underlying mechanisms that ACEIs/ARBs reduce the inflammatory response and ICH-related pneumonia post-ICH need to be explored using animal model studies.

Conclusions

Though the usage of ACEIs/ARBs cannot reduce the proportion of unfavorable outcome, it helps decrease mortality, perihematomal edema volume, and prevalence of ICH-associated pneumonia in ICH patients with hypertension, which enlarges the therapeutic application of ACEIs/ARBs, except for hypertension.

Ethics and Consent Statements

This study adheres to the principles of the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the Southwest Hospital of Third Military Medical University, China (Ethical Approval no. KY2020114). Because it is a retrospective study that contained no identifiable data, informed consent was waived. Patients' privacy and personal identity information were well protected.

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Disclosure

The authors report no conflicts of interest in this work.

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