MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2020; 26: e924593
DOI: 10.12659/MSM.924593

Received: 2020.03.26
Accepted: 2020.05.04
Available online: 2020.05.19
Published: 2020.07.15

Argatroban Increased the Basal Vein Drainage and Improved Outcomes in Acute Paraventricular Ischemic Stroke Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AE 1,2 Shoufeng Liu*
BCDEF 2 Peipei Liu*
BC 3 Po Wang
BD 4 Fang Zhang
BD 5 Lijun Wang
BD 6 Yu Wang
B 7 Hao Lu
AG 4 Xiaofeng Ma

1 The Graduate School, Tianjin Medical University, Tianjin, P.R. China
2 Department of Neurology, Tianjin Huanhu Hospital, Tianjin, P.R. China
3 Department of Neurology, Baotou Central Hospital, Baotou, Inner Mongolia, P.R. China
4 Department of Neurology, Tianjin Neurological Institute, Tianjin Medical University General Hospital, Tianjin, P.R. China
5 Department of Neurology, Tianjin Fourth Central Hospital, Tianjin, P.R. China
6 Department of Ultrasonography, Tianjin Huanhu Hospital, Tianjin, P.R. China
7 Department of Radiology, Tianjin Huanhu Hospital, Tianjin, P.R. China

* Shoufeng Liu and Peipei Liu contributed equally to this work

Corresponding Author: Xiaofeng Ma, e-mail: xfengma@126.com

Source of support: This work was supported by the National Natural Science Foundation of China (Grant Nos: 81401361 and 81870954)

Background: Since venous drainage in acute arterial ischemic stroke has not been thoroughly researched, we evaluate the effect of argatroban, a selective direct thrombin inhibitor, as a therapy to increase the rate of basal vein Rosenthal (BVR) drainage and improve patients' post-stroke outcomes.

Material/Methods: In this multicenter clinical trial, 60 eligible patients at 4.5 to 48 hours after the stroke onset were recruited. After being randomly allocated into 2 groups, they were treated with standard therapy either alone or with argatroban.

Results: Compared to the contralateral brain hemisphere, the mean flow velocity (MFV) in BVR drainage was significantly reduced in the stroke-afflicted ipsilateral hemisphere. After treatment with argatroban for 7 days, the MFV from BVR of the ipsilateral hemisphere in the argatroban treated group was significantly increased when compared to the control group. At 90 days after the onset of stroke, the MFV of BVR in the ipsilateral hemisphere was similar in both groups. Compared with controls, the argatroban-treated patients had smaller lesions from baseline to 7 days. Argatroban also improved National Institutes of Health Stroke Scale (NIHSS) scores on day 7 after the onset of stroke. Furthermore, the argatroban group's neurological functions were superior to those of their untreated counterparts after 90 days. No difference was found in the incidence of adverse reactions between the 2 groups.

Conclusions: These observations indicate that vein drainage change may contribute to the acute phase of brain edema and the outcomes of ischemic stroke patients.

Clinical Trial Registration: *URL-http://www.chictr.org*
Unique identifier: ChiCTR-IPR-16008663

MeSH Keywords: Cerebral Veins • Drainage • Stroke • Ultrasonography, Doppler, Transcranial

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/924593

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Ischemic stroke is a leading cause of disability and death [1]. Past studies focused on the arterial side of cerebral circulation, either thrombolysis or blood clot retrieval, have shown significant clinical improvement in stroke patients [2]. However, some recanalized patients failed to improve due to non-reflow, futile reperfusion, or other causes [3–5].

However, the cerebral venous system's participation in acute arterial ischemic stroke has been rarely investigated, and the possibility that venous congestion aggravates brain injury remains to be explored [6]. The basal vein Rosenthal (BVR) drains large areas of the brain's ventricular walls. Indeed, Stolz et al. reported that some patients with decreased flow velocity in the BVR suffered ipsilateral herniation after ischemic lesion [7].

Argatroban, a selective direct thrombin inhibitor, has been adopted to treat acute ischemic stroke [8]. Preclinical [9,10] and clinical [11,12] studies have indicated that argatroban is effective in treating acute ischemic stroke without increasing hemorrhage in the brain. In rat models, argatroban increased blood flow to the lesion area, reduced secondary microthrombi formation, and decreased neurologic deficit [13,14]. Because of its efficacy in lessening secondary microthrombi formation, we theorized that argatroban would increase venous drainage in ischemic periventricular stroke and alleviate its aftereffects.

Material and Methods

Study population

This multicenter, open-label, randomized and evaluator-blinded study has been registered with *Chictr.org.cn* (No. ChiCTR-IPR-16008663). The approval for the trial protocol and supportive documents was obtained from the institutional review boards of all the participating centers.

From the 526 patients with acute ischemic stroke, 60 patients with matched clinical characteristics, stroke etiology, lesion location and volume were selected and enrolled into this study in Tianjin Medical University General Hospital, Tianjin Huanhu Hospital, and Baotou Central Hospital, Bao tou, China.

At enrollment, written informed consents were obtained from all patients. The inclusion and exclusion criteria were presented as follows. Inclusion criteria were as follows: 1) age >40 years; 2) large artery atherosclerosis (LAA) defined by magnetic resonance angiography (MRA) and diffusion weighted imaging (DWI) according to the Trial of Org 10172 in acute stroke treatment classification (TOAST), i.e., the ischemic stroke caused by intracranial LAA as a parent artery (plaque or thrombus) that blocks a penetrating artery); 3) magnetic resonance imaging (MRI) scan showed an ischemic lesion in the paraventricular area, which was defined as acute paraventricular ischemic stroke; 4) acute focal neurological deficit caused by acute ischemic stroke; 5) National Institutes of Health Stroke Scale (NIHSS) ≥5; and 6) patient treated 4.5 to 48 hours after symptom onset at admission. Since stroke patients within 4.5 hours after symptom onset were normally treated with alteplase, all patients recruited for this study had passed the 4.5-hour time-window for thrombolytic treatment when recruited.

Exclusion criteria were as follows: 1) hemorrhagic stroke; 2) other central nervous diseases; 3) diabetes; 4) tumor or hematological systemic diseases; 5) infection prior to stroke; and 6) antineoplastic or immune modulating therapies. Patients with diabetes were excluded, because their prothrombotic milieu with hyperreactive platelets and hypercoagulation abnormalities may contribute to a reduction in mean flow velocity (MFV) of BVR.

Study design

Sixty patients with acute paraventricular ischemic stroke were randomly divided into 2 groups: a control group (standard treatment based on guidelines of American Heart Association) and an argatroban group (standard treatment combined with argatroban, TIRP Pharmaceutical Co., Ltd., Tianjin, China). Patients in the 2 groups had similar clinical characteristics when recruited (Table 1). The control group received standard treatment (antihypertensives, antiplatelet agents, and statins) following the guidelines of American Heart Association. Meanwhile, the patients in the argatroban group were additionally given intravenous infusion of 10 mg argatroban twice a day for 7 days consecutively, starting 1 hour after the baseline MRI and no later than 48 hours after symptom onset. The patients enrolled were allocated by computer in a 1: 1 ratio to either the control or the argatroban group in a random way. A centralized web-based randomization system was used for allocation concealment, with the identifier of the participant entered before the allocation. The treatment assignment was known only to the clinicians, but not to the evaluators (Figure 1).

Clinical assessments

Each patient was clinically assessed upon enrollment (baseline) and at day 7 and day 90 after start of treatment, which was blinded to the evaluators (Figure 1). NIHSS was used to assess the neurologic deficit. The modified Rankin scale (mRS) was used to assess the 90-day outcomes. The modified Barthel index (mBI) was used to evaluate the limited ability to perform daily activities. A score of 0 to 1 represented a good outcome and a score of 2 to 5 depicted a poor outcome.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1. Characteristics of the patients at baseline.

Characteristic	Control n=30	Argatroban n=30	*p* value
Age, y	57.1±10.7	57.7±8.8	0.33
Female sex, n (%)	6 (20)	7 (23)	0.75
Previous stroke, n (%)	3 (10)	2 (6)	0.64
Risk factors, n (%)			
Hypertension	17 (57)	19 (63)	0.60
Heart disease	2 (6)	3 (10)	0.64
Hyperlipidemia	5 (17)	7 (23)	0.52
Smoking	11 (37)	13 (43)	0.60
Renal failure	0 (0)	0 (0)	1.00
Diabetes mellitus	0 (0)	0 (0)	1.00
Etiology*, n (%)			
Subtype 1: atheromatosis	30 (100)	30 (100)	1.00
Subtype 2: embolus	0 (0)	0 (0)	1.00
Subtype 3: lacunar infarct	0 (0)	0 (0)	1.00
Subtype 4: other causes	0 (0)	0 (0)	1.00
Subtype 5: undetermined	0 (0)	0 (0)	1.00
INR	1.0±0.1	1.0±0.1	0.69
Infarct volume on admission, mL	21.1±2.9	20.7±3.1	0.85
NIHSS score at baseline, median(range)	8 (5~12)	8 (5~13)	0.58
Time to treatment, h	26±8	25±10	0.36

Plus-minus values are mean±SE. a Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. INR – international normalized ratio; NIHSS – National Institutes of Health Stroke Scale.

Neuroimaging

At admission, MRIs (MRA, T2FLAIR, and DWI) were conducted using 3 Tesla GE and Siemens, following a comprehensive MRI protocol for acute stroke. Characteristically, ischemic stroke lesion locates in the ventricular walls of one brain hemisphere. In our study, 2 radiologists (blinded to the study design) conducted measurements independently with MIPAV software. By manual outlining and automatic calculation, the lesion area and slice thickness on each of the DWI and FLAIR slices were determined, and then lesion volume was calculated [15]. Another radiologist validated the lesion volume using the semiautomated technique (Cheshire; Perceptive Informatics, Waltham, MA, USA).

Transcranial Doppler ultrasonography (TCD)

We performed transcranial Doppler ultrasonography (TCD) measurements using the TC-2000 (Nicolet EME, Kleinostheim, Germany) with a handheld transducer in a range-gated, pulsed-wave mode with a frequency of 2 MHz [16]. TCD insonated the BVR in the ambient cistern, then the posterior cerebral artery cranially and medially. The Doppler gate depth was about 62 mm [17], and the probe was steered clear of the blood flowing direction in the vessel. Bilateral BVR were examined with a TCD device at admission, day 7 and day 90 after stroke onset. MFV in the BVR was calculated and displayed automatically by the TCD device in the ipsilateral and contralateral hemispheres.

Statistical analyses

Data analyses were performed by SPSS for Windows version 17.0 software (SPSS, Inc., Chicago, IL, USA). Continuous variables (e.g., MFV) were calculated and presented as means±standard error (SE). Discontinuous or abnormally distributed variables were presented as a median (range) and compared by a Mann-Whitney U test. All continuous variables were compared with the *t*-test used for independent samples. A chi-square test was adopted to compare the categorical variables. A $P<0.05$ was considered statistically significant.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

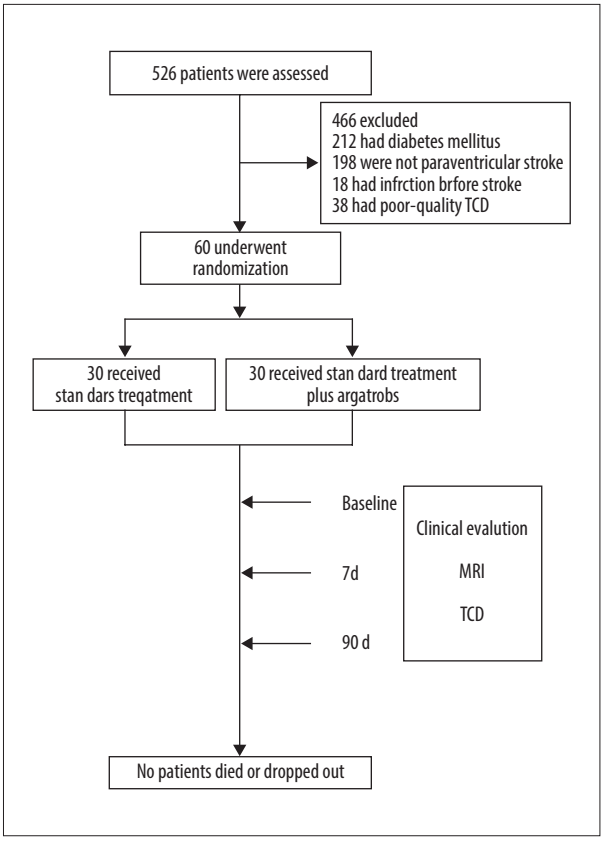

Figure 1. Effect of argatroban on BVR drainage in acute ischemic stroke: trial profile. Sixty patients with acute paraventricular ischemic stroke and matched clinical characteristics, who were beyond the 4.5-hour window for alteplase when recruited, were randomized into 2 groups. Both groups received standard stroke therapy, and one group (n=30) also received 10 mg intravenous argatroban (twice daily for 7 days consecutively). Treatment began between 1 hour after a baseline MRI and 48 hours after symptom onset. NIHSS, mBI, and mRS were conducted. Lesion volume was measured by MRI on admission. MFV in the BVR was measured by TCD at baseline and on day 7 and day 90. BVR – basal vein Rosenthal; MRI – magnetic resonance imaging; NIHSS – National Institutes of Health Stroke Scale; MFV – mean flow velocity; TCD – transcranial Doppler ultrasonography.

Results

Baseline characteristics

Sixty acute ischemic paraventricular stroke patients at 4.5 hours to 48 hours after symptom onset were enrolled in the present study (Figure 1). They were randomly placed in a treatment group or a control group. During the 90-day study, there were no losses to follow-up, dropouts, or fatalities. At the pretreatment baseline, no differences in age, stroke etiology, NIHSS score, or lesion volume were identified (Table 1). Similarly, at that time, no differences of MFV were found in ipsilateral or contralateral BVR between the 2 groups (9.76±1.95 versus 9.50±2.12, *P*=0.616, 11.26±1.79 versus 11.03±2.29, *P*=0.663) (Figure 2A). Standard treatment, with or without argatroban, ensued within 48 hours of diagnosis. Compared to these patients' contralateral hemispheres, BVRs in their ipsilateral hemispheres manifested significant reductions in MFV in both control and argatroban-treated patients (9.50±2.12 versus 11.03±2.29, *P*=0.010, 9.76±1.95 versus 11.26±1.79, *P*=0.003) (Figure 2A).

Argatroban increased the BVR drainage

At day 7 after treatment, the argatroban group had a significantly higher MFV in BVR of the ipsilateral hemispheres than the control group (11.80±2.18 versus 10.46±2.14, *P*=0.020). However, at day 90, the MFV in BVR of the ipsilateral hemispheres no longer reached the level of statistical significance in comparisons between the two groups (11.60±1.79 versus 11.00±2.15, *P*=0.245) (Figure 2B). In contrast, despite the administration of argatroban, the MFV in the BVR of the contralateral hemisphere did not change at day 7 or day 90 after stroke onset (12.03±2.10 versus 12.13±2.45, *P*=0.866; 12.23±2.02 versus 11.96±2.09, *P*=0.618) (Figure 2C). However, the representative TCD in Figure 2D shows that argatroban improved venous drainage from day 1 to day 7 (Figure 2D).

Argatroban reduced infarction enlargement

Prior to the treatment, no significant difference was found in lesion volumes between the 2 groups (Table 1). At day 7 after treatment, the argatroban recipients had a significantly smaller lesion volume (day 7 volume versus baseline volume) than the controls (1.51±0.71 versus 4.67±1.29, *P*=0.002) (Figure 3A, 3B). Though, in the T2FLAIR image, the argatroban group had a smaller lesion volume at day 7 (*P*=0.87).

Argatroban improved clinical outcomes

As shown by the baseline and subsequent clinical evaluations (Figure 4), the argatroban group had only moderate neurological deficits, and most diminished in 7 days after treatment. Compared with the control group, patients who received argatroban exhibited lower NIHSS scores [0.75 (range, –3 to 4) versus 1.5 (range, 0 to 6); *P*=0.015] from baseline to day 7. The difference in NIHSS scores reached the level of statistical significance at 90 days after symptom onset [3.0 (range, 1 to 7) versus 5.0 (range, 2 to 10); *P*<0.01] (Figure 4A, 4B). Additionally, the argatroban group had significantly higher mBI scores (which reflected the ability to perform routine activities), than the control group at day 7 and day 90 (76.5±10.9 versus 70.5±11.6, *P*=0.045; 83.3±7.7 versus 75.3±10.1, *P*=0.001). And the mRS scores for clinical recovery of 0–1 at post-stroke day 90 were 69% in the argatroban group, compared to 51% in the control group (*P*=0.014; Figure 4C, 4D).

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

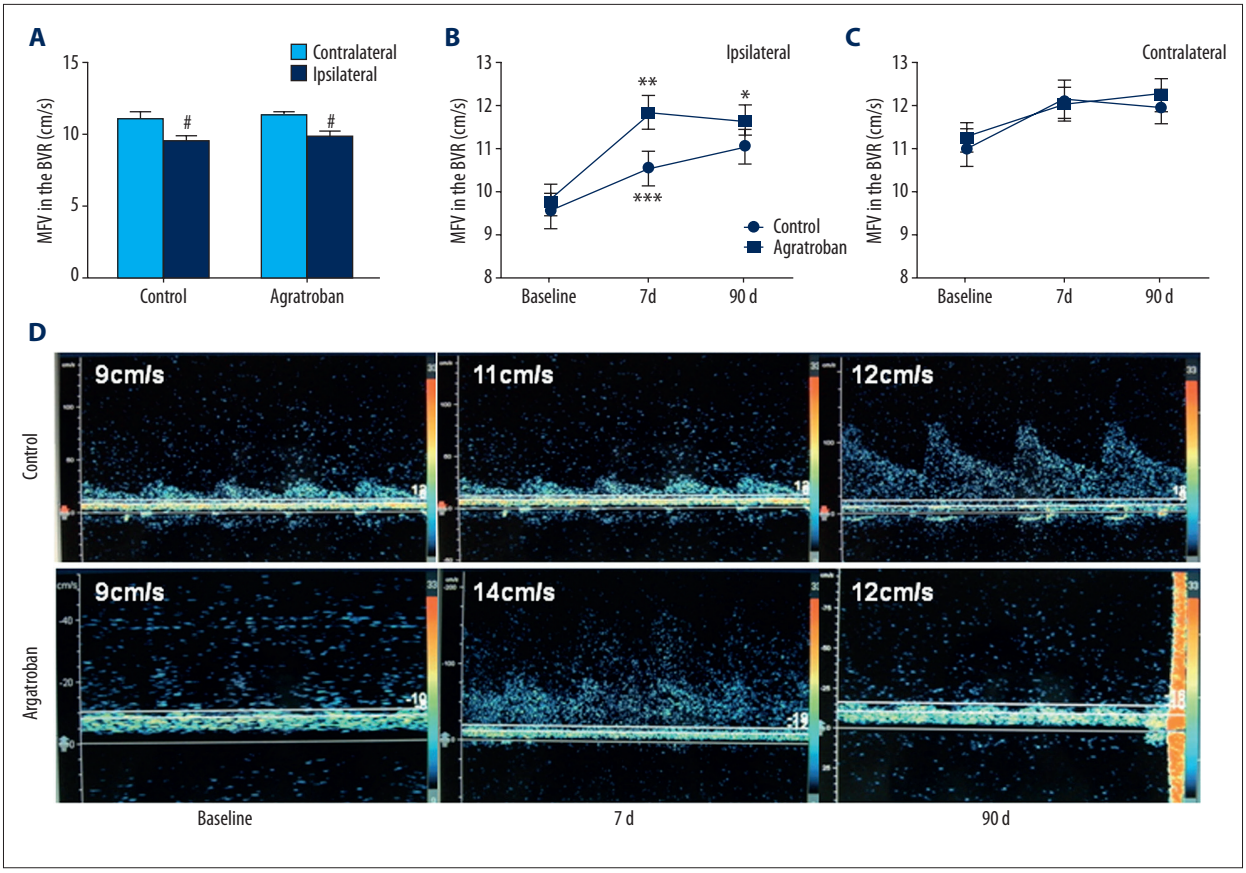

Figure 2. MFV in bilateral BVR of the patients with acute paraventricular ischemic stroke at baseline and after argatroban therapy. (**A**) Comparison of MFV in ipsilateral versus contralateral BVR between control and argatroban-treated patients. (**B**) Impact of argatroban on venous flow in the BVR of patients' ipsilateral hemisphere. (**C**) Impact of argatroban on venous flow in BVR of patients' contralateral hemisphere. (**D**) Representative TCD illustrates the MFV in BVRs of ipsilateral hemispheres in patients at the baseline and at day 7 and day 90 after argatroban treatment. # $P<0.05$ versus contralateral hemisphere at baseline, * $P<0.05$, ** $P<0.05$ compared to baseline of argatroban group, *** $P<0.05$ compared to control at the same time point. BVR – basal vein Rosenthal; MFV – mean flow velocity; TCD – transcranial Doppler ultrasonography.

Safety

None of the argatroban recipients had recurrent strokes while 3% of patients in the control group had recurrent strokes. One patient in the control group had lung infection after stroke with temperatures >38°C and was administered antibiotics. One patient in the argatroban group had an upper respiratory tract infection. None of the patients in the argatroban group were given antibiotics. One patient had mild hemorrhage of digestive tract (Table 2).

Discussion

In the present trial, we explored the impact of argatroban on BVR drainage in acute paraventricular ischemic stroke; we observed substantially better clinical outcomes in 30 recipients of standard treatment plus argatroban compared to 30 matched controls given standard treatment alone. This study focused on acute paraventricular ischemic stroke, the ischemic stroke caused by intracranial LAA [parent artery (plaque or thrombus) that occludes a penetrating artery]. In order to justify the bias, we did not include larger infarctions in this trial. Prior to the study treatment, no significant difference was found in lesion volume between the 2 groups. All the patients entered the hospital after the 4.5-hour therapeutic window for alteplase treatment but within 48 hours after the onset of stroke. We found that argatroban (10 mg) administered intravenously twice daily for 7 consecutive days improved BVR drainage in the ipsilateral hemisphere compared to drainage rates in patients randomly selected as controls. Continuous monitoring for 90 days after stroke onset showed that NIHSS, mBI, and mRS scores reached statistically significant levels for clinical recovery in the patients given argatroban.

Argatroban has been used in Japan and Korea to treat non-lacunar acute ischemic stroke within 48 hours of symptom

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

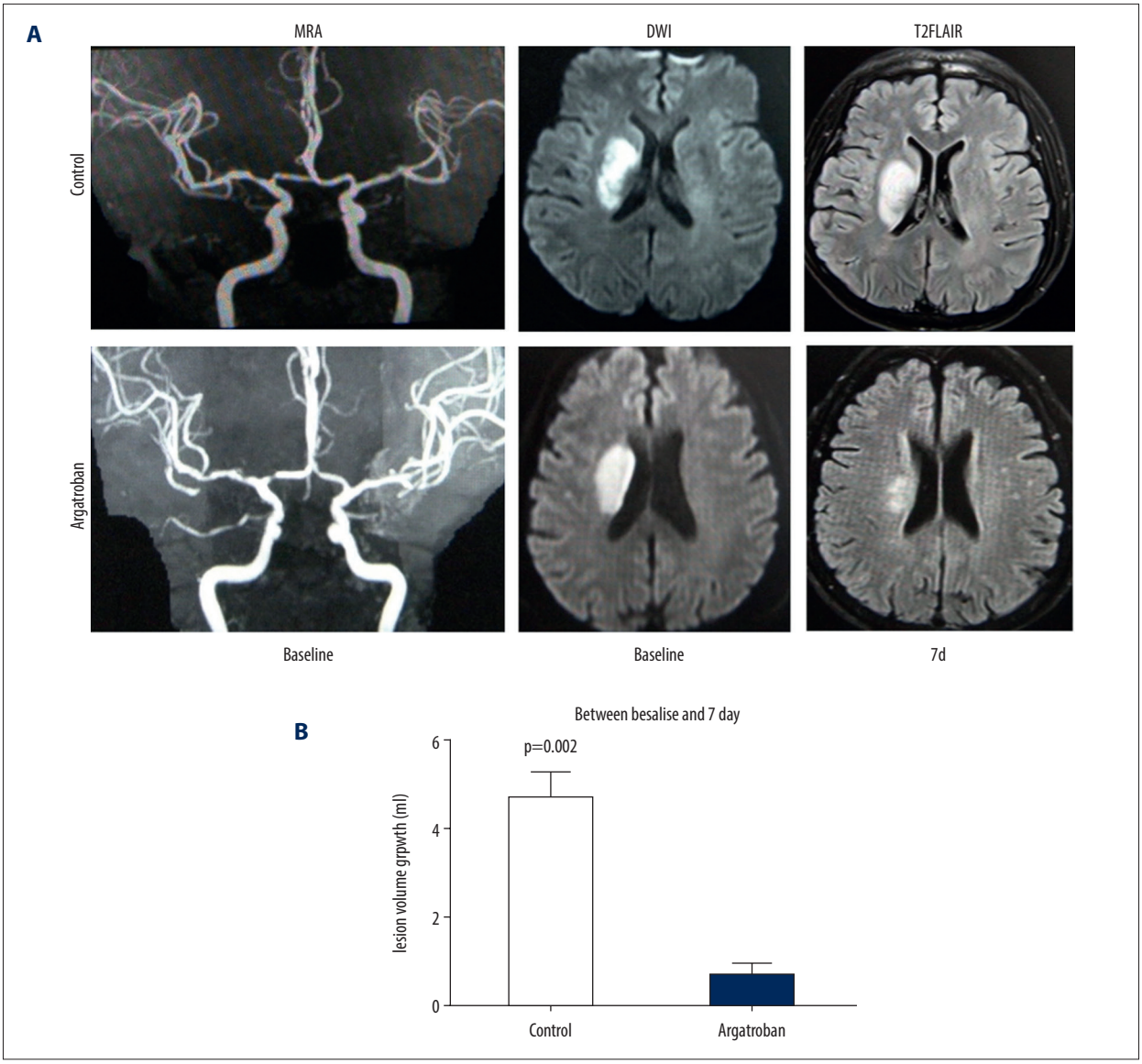

Figure 3. Impact of argatroban on lesion volume growth in patients. (**A**) MRI images show acute right hemisphere infarct with middle cerebral artery stenosis in a control patient (**top**) and acute right hemisphere infarct with middle cerebral artery stenosis in an argatroban-treated patient (**bottom**). Lesion volumes were measured on a DWI (baseline) and T2FLAIR (day 7). (**B**) Growth of lesion volume from baseline to day 7. Lesion growth equals lesion volume measured on T2FLAIR at day 7 minus that measured on DWI at baseline. Data are presented as mean±SD. An independent *t*-test was conducted for each comparison. MRI – magnetic resonance imaging; DWI – diffusion weighted imaging; SD – standard deviation.

onset [8,13]. It can increase local blood flow, improve regional blood flow, decease secondary microthrombin in the penumbra, shrink ischemic lesions, and alleviate neurological deficits through inhibiting clot-bound and circulating thrombin, platelet aggregation, and vascular contraction [18–21]. However, it has been difficult to confirm that the neurological improvement after argatroban therapy resulted solely from increased venous flow in the basal veins of these stroke patients. There are 3 subtypes of stroke: cardioembolic stroke, atherothrombotic stroke, and lacunar infarction [22]. In order to justify the bias, in the present study, we excluded patients with cardioembolic stroke or lacunar infarction, and administered argatroban to atherothrombotic infarction (LAA) patients. There have been few clinical studies concerning the impact of argatroban on vein drainage in acute ischemic stroke patients in the context described here [23,24].

TCD has been used to examine the vessels in a reliable and noninvasive manner since its first application decades ago [25]. The new Doppler devices optimize the venous system

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

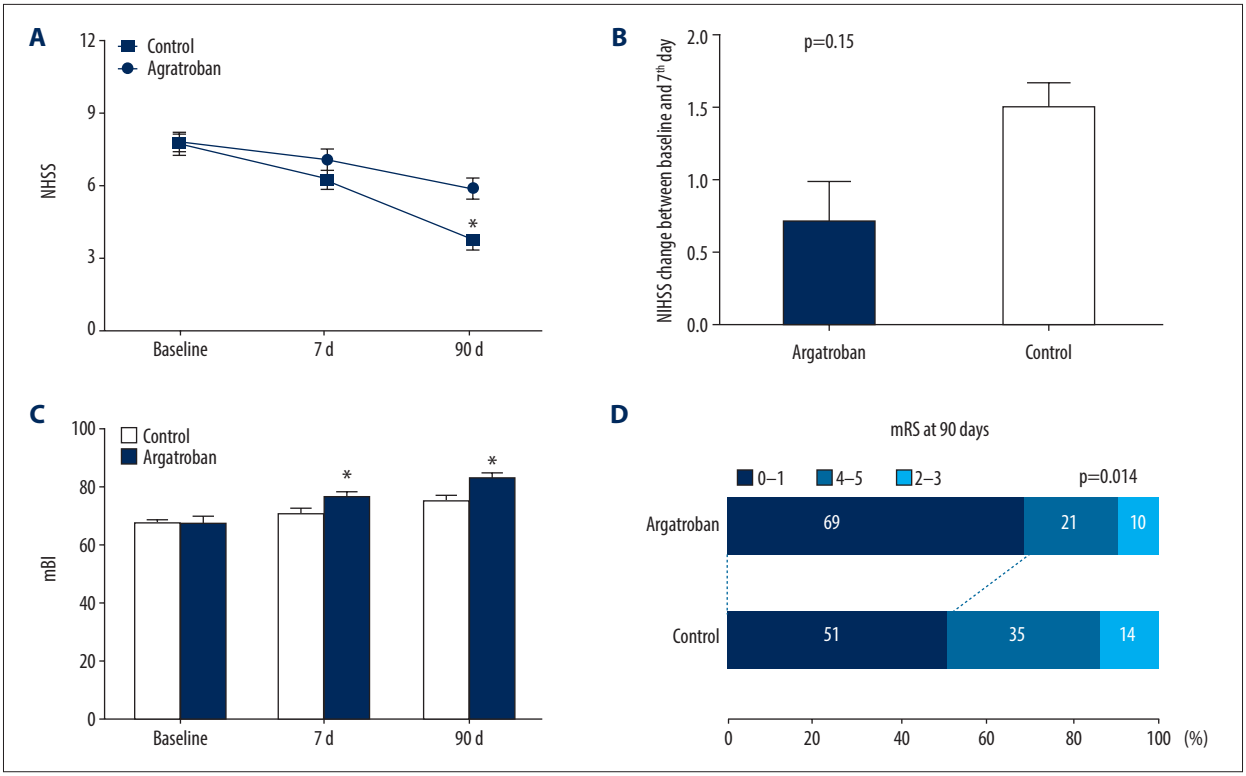

Figure 4. Impact of argatroban on clinical outcomes in the argatroban group compared to the control group. (**A**) Trends of NIHSS scores from argatroban-treated and control patients. (**B**) NIHSS values for argatroban-treated and control patients in the 7 days (NIHSS change=baseline – day 7). (**C**) Comparison of mBI between groups. (**D**) mRS difference between groups at day 90. * *P*<0.05 compared to the control at the same time point. NIHSS – National Institutes of Health Stroke Scale; mBI – modified Barthel Index; mRS – modified Rankin Scale.

examination with improved sample volume, filter setting, and power intensity. The venous signal has low-flow characteristics, and often it is drowned out by arterial signals. However, according to Valdueza et al. [26], TCD could detect and evaluate the basal cerebral veins in people of different sexes and ages. BVR, in particular, could be detected in almost all the cases [26]. Therefore, due to its accuracy and non-invasiveness, TCD has great potential in examination of venous circulation and cerebral autoregulation [27].

The basal vein, which is located in the ambient cistern medially and cranially to the posterior cerebral artery, drains large areas of ventricular walls of one hemisphere [28,29]. Because their identification rate is greater than 90% and their location is constant, BVRs are ideal targets for assessment of venous blood flow by TCD [30]. In addition, the BVR is easily found in the region adjacent to the P2-segment of the posterior cerebral artery. TCD has a fairly high detection rate (90–100%), which further proves the constant presence of the BVR in this region [31]. Some interwoven factors possibly contribute to BVR drainage abnormalities in acute ischemic stroke. Firstly, following ischemic stroke, the increased intracranial pressure caused by cerebral edema might compress or even collapse the BVR wall [32]. Since most cerebral veins are without protective smooth muscle cells, tissue edema and elevated intracranial pressure are more likely to occur in the venous system than in the arterial system [33]. Secondly, the factors frequently involved in acute ischemic stroke are hypercoagulation and microthrombi formation, both of which may contribute to the occlusion and reduction in MFV of BVR [34–36].

In the present study, we observed that argatroban improved regional BVR drainage, reduced ischemic lesions and ameliorated neurological deficits, possibly by reducing secondary microthrombi formation in the BVR or other venous systems, since argatroban has been reported to inhibit clot-bound thrombin, vascular contraction, and platelet aggregation [37].

We chose to administer argatroban in this study because its past record predicted the likelihood of preventing the formation of secondary microthrombi in the veins, reducing ischemic stroke lesions and acting safely in terms of avoiding intracranial hemorrhage. In a previous study, La Monte et al. showed the anticoagulative effects of argatroban in 171 acute ischemic stroke patients within 12 hours of symptom onset without any increased hemorrhage risk [9]. Hosomi et al. demonstrated that

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 2. Complications and adverse events.

Complication or event	Control n=30	Argatroban n=30	*P* value
Complications			
Deaths	0 (0)	0 (0)	1.00
Myocardial infarctions	0 (0)	0 (0)	1.00
Recurrent strokes	1 (3)	0 (0)	0.31
Cerebral hemorrhage	0 (0)	0 (0)	1.00
Hemorrhage of digestive tract	0 (0)	1 (3)	0.31
Fever (>38°C)	1 (3)	1 (3)	1.00
Event			
All events			
At least one adverse event	1 (3)	1 (3)	1.00
Any adverse event leading to discontinuation	0 (0)	0 (0)	1.00
Any serious adverse event	0 (0)	0 (0)	1.00
Infection after stroke	1 (3)	1 (3)	1.00
Suspected lung infection	1 (3)	0 (0)	0.31
Urinary tract infection	0 (0)	0 (0)	1.00
Upper respiratory tract infection	0 (0)	1 (3)	0.31
Digestive system infection	0 (0)	0 (0)	1.00
Herpes virus infection	0 (0)	0 (0)	1.00
Antibiotic therapy	1 (3)	0 (0)	0.31

Data are n (%).

argatroban was safe and effective in acute ischemic stroke patients, increasing clinical improvement without increasing intracranial hematoma [38]. Urabe et al. stated that argatroban could reduce ischemic lesions and inhibit clot-bound thrombin [22].

Japanese researchers reported in a clinical study that argatroban inhibited microthrombi activity and ameliorated regional blood flow in the brain [39]. The results of another similar study indicated that argatroban treatment could decrease secondary microthrombi in the infarct area, improve regional blood flow in the brain, downsize ischemic lesions, and therefore, produce better clinical outcomes [40]. Similarly, we observed that after argatroban treatment, the acute ischemic paraventricular stroke patients had improved outcomes.

Limitations

There were 2 limitations to our present study: First, the sample size of the present study was too small to draw a solid conclusion. Studies of larger scales are needed in the future to confirm the results of the present study. Second, there still exists a possibility that infarction reduction and neurological improvement might be directly related to improved BVR outflow in acute ischemic stroke after argatroban treatment. Although our observations in this study precluded us from drawing such a conclusion, this study is a first observation to show that argatroban increased flow velocity of the basal vein after acute ischemic paraventricular stroke for up to 7 days. This effect of argatroban on expanding venous blood flow was accompanied by a reduced infarction volume and improved clinical outcomes at day 7 and day 90 from the onset of stroke. Future confirmation directly linking argatroban to the reduction of venous microthrombi formation is well-warranted.

Conclusions

Vein drainage change may contribute to the acute phase of brain edema and the outcomes of ischemic stroke patients.

Acknowledgments

We wish to thank all participants in this study. We thank Changshen Yu, Wanjun Wang, Yajing Wang, and Chunlin Gao for the recruitment of study participants.

Conflict of interest

None.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

References:

1. Chwojnicki K, Ryglewicz D, Wojtyniak B et al: Acute ischemic stroke hospital admissions, treatment, and outcomes in Poland in 2009–2013. Front Neurol, 2018; 9: 134
2. Zhang JH, Obenaus A, Liebeskind DS et al: Recanalization, reperfusion, and recirculation in stroke. J Cereb Blood Flow Metab, 2017; 37(12): 3818–23
3. Manning NW, Warne CD, Meyers PM: Reperfusion and clinical outcomes in acute ischemic stroke: systematic review and meta-analysis of the Stent-Retriever-Based, Early Window Endovascular Stroke Trials. Front Neurol, 2018; 9: 301
4. Iglesias-Rey R, Rodríguez-Yáñez M, Rodríguez-Castro E et al: Worse outcome in stroke patients treated with rt-PA without early reperfusion: Associated factors. Transl Stroke Res, 2018; 9(4): 347–55
5. Puetz V, Gerber JC, Krüger P et al: Cerebral venous drainage in patients with space-occupying middle cerebral artery infarction: Effects on functional outcome after hemicraniectomy. Front Neurol, 2018; 9: 876
6. Li Q, Khatibi N, Zhang JH: Vascular neural network: The importance of vein drainage in stroke. Transl Stroke Res, 2014; 5(2): 163–66
7. Stolz E, Gerriets T, Babacan SS et al: Intracranial venous hemodynamics in patients with midline dislocation due to postischemic brain edema. Stroke, 2002; 33(2): 479–85
8. Escolar G, Bozzo J, Maragall S: Argatroban: A direct thrombin inhibitor with reliable and predictable anticoagulant actions. Drugs Today (Barc), 2006; 42(4): 223–36
9. LaMonte MP, Nash ML, Wang DZ et al: Argatroban anticoagulation in patients with acute ischemic stroke (ARGIS-1): A randomized, placebo-controlled safety study. Stroke, 2004; 35(7): 1677–82
10. Sugg RM, Pary JK, Uchino K et al: Argatroban tPA stroke study: Study design and results in the first treated cohort. Arch Neurol, 2006; 63(8): 1057–62
11. Fujimori Y, Wakui M, Katagiri H et al: Evaluation of anticoagulant effects of direct thrombin inhibitors, dabigatran and argatroban, based on the Lineweaver-Burk plot applied to the Clauss assay. J Clin Pathol, 2016; 69(4): 370–72
12. Park JS, Park SS, Koh EJ et al: Treatment for patients with acute ischemic stroke presenting beyond six hours of ischemic symptom onset: Effectiveness of intravenous direct thrombin inhibitor, argatroban. J Korean Neurosurg Soc, 2010; 47(4): 258–64
13. LaMonte MP, Brown PM, Hursting MJ: Alternative parenteral anticoagulation with argatroban, a direct thrombin inhibitor. Expert Rev Cardiovasc Ther, 2005; 3(1): 31–41
14. Kawai H, Umemura K, Nakashima M: Effect of argatroban on microthrombi formation and brain damage in the rat middle cerebral artery thrombosis model. Jap J Pharmacol, 1995; 69(2): 143–48
15. Zhang F, Yan C, Wei C et al: Vinpocetine inhibits NF-κB-dependent inflammation in acute ischemic stroke patients. Transl Stroke Res, 2018; 9(2): 174–84
16. Gao S, Lam WW, Chan YL et al: Optimal values of flow velocity on transcranial Doppler in grading middle cerebral artery stenosis in comparison with magnetic resonance angiography. J Neuroimaging, 2002; 12(3): 213–18
17. Stolz E, Kaps M, Kern A et al: Transcranial color-coded duplex sonography of intracranial veins and sinuses in adults. Reference data from 130 volunteers. Stroke, 1999; 30(5): 1070–75
18. Ahnstedt H, Sweet J, Cruden P et al: Effects of early post-ischemic reperfusion and tPA on cerebrovascular function and nitrosative stress in female rats. Transl Stroke Res, 2016; 7(3): 228–38
19. Lu Y, Wang J, Huang R et al: Microbubble-mediated sonothrombolysis improves outcome after thrombotic microembolism-induced acute ischemic stroke. Stroke, 2016; 47(5): 1344–53
20. Nagai N, Zhao BQ, Suzuki Y et al: Tissue-type plasminogen activator has paradoxical roles in focal cerebral ischemic injury by thrombotic middle cerebral artery occlusion with mild or severe photochemical damage in mice. J Cereb Blood Flow Metab, 2002; 22(6): 648–51
21. Siler DA, Gonzalez JA, Wang RK et al: Intracisternal administration of tissue plasminogen activator improves cerebrospinal fluid flow and cortical perfusion after subarachnoid hemorrhage in mice. Transl Stroke Res, 2014; 5(2): 227–37
22. Mandava P, Martini SR, Munoz M et al: Hyperglycemia worsens outcome after rt-PA primarily in the large-vessel occlusive stroke subtype. Transl Stroke Res, 2014; 5(4): 519–25
23. Paris C, Derex L: Intravenous thrombolysis in ischemic stroke: Therapeutic perspectives. Rev Neurol, 2015; 171(12): 866–75
24. Asadi H, Yan B, Dowling R et al: Advances in medical revascularisation treatments in acute ischemic stroke. Thrombosis, 2014; 2014: 714218
25. Aaslid R, Markwalder TM, Nornes H: Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg, 1982; 57(6): 769–74
26. Valdueza JM, Schmierer K, Mehraein S et al: Assessment of normal flow velocity in basal cerebral veins. A transcranial doppler ultrasound study. Stroke, 1996; 27(7): 1221–25
27. Aaslid R, Newell DW, Stooss R et al: Assessment of cerebral autoregulation dynamics from simultaneous arterial and venous transcranial Doppler recordings in humans. Stroke, 1991; 22(9): 1148–54
28. Ono M, Rhoton AL Jr., Peace D et al: Microsurgical anatomy of the deep venous system of the brain. Neurosurgery, 1984; 15(5): 621–57
29. Karatas A, Cakir V, Sevin E et al: Angiographic assessment of variants of basal vein of Rosenthal in idiopathic subarachnoid hemorrhage. Neurol Neurochir Pol, 2015; 49(4): 207–11
30. Baumgartner RW, Nirkko AC, Muri RM et al: Transoccipital power-based color-coded duplex sonography of cerebral sinuses and veins. Stroke, 1997; 28(7): 1319–23
31. Schreiber SJ, Stolz E, Valdueza JM: Transcranial ultrasonography of cerebral veins and sinuses. Eur J Ultrasound, 2002; 16(1–2): 59–72
32. Ostergaard L, Aamand R, Karabegovic S et al: The role of the microcirculation in delayed cerebral ischemia and chronic degenerative changes after subarachnoid hemorrhage. J Cereb Blood Flow Metab, 2013; 33(12): 1825–37
33. Chen S, Chen Y, Xu L et al: Venous system in acute brain injury: Mechanisms of pathophysiological change and function. Exp Neurol, 2015; 272: 4–10
34. Desilles JP, Loyau S, Syvannarath V et al: Alteplase reduces downstream microvascular thrombosis and improves the benefit of large artery recanalization in stroke. Stroke, 2015; 46(11): 3241–48
35. Wong KS: Is the measurement of cerebral microembolic signals a good surrogate marker for evaluating the efficacy of antiplatelet agents in the prevention of stroke? Eur Neurol, 2005; 53(3): 132–39
36. Gao S, Wong KS: Characteristics of microembolic signals detected near their origins in middle cerebral artery stenoses. J Neuroimaging, 2003; 13(2): 124–32
37. Lyden P, Pereira B, Chen B et al: Direct thrombin inhibitor argatroban reduces stroke damage in 2 different models. Stroke, 2014; 45(3): 896–99
38. Hosomi N, Naya T, Kohno M et al: Efficacy of anti-coagulant treatment with argatroban on cardioembolic stroke. J Neurol, 2007; 254(5): 605–12
39. Kobayashi S, Tazaki Y: Effect of the thrombin inhibitor argatroban in acute cerebral thrombosis. Semin Thromb Hemost, 1997; 23(6): 531–34
40. Barreto AD, Alexandrov AV, Lyden P et al: The argatroban and tissue-type plasminogen activator stroke study: Final results of a pilot safety study. Stroke, 2012; 43(3): 770–75

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]