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Original Article

Two weeks administration of tranexamic acid for acute intracerebral hemorrhage: A hospital-based pilot study

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ABSTRACT

Background: A previous report suggested that functional status does not differ between patients who received tranexamic acid and those who received placebo within the early hours of intracerebral hemorrhage (ICH). Our pilot study tested the hypothesis that 2 weeks administration of tranexamic acid would contribute to functional improvement.

Methods: Consecutive patients with ICH were administered 250 mg tranexamic acid 3 times a day continuously for 2 weeks. We also enrolled historical control consecutive patients. We collected clinical data that involved hematoma size, level of consciousness, and Modified Rankin Scale (mRS) scores.

Results: Univariate analysis showed that the mRS score on day 90 was better in the administration group (P = 0.0095). The mRS scores on the day of death or discharge suggested a favorable effect of the treatment (P = 0.0678). Multivariable logistic regression analysis also showed that the treatment was associated with good mRS scores on day 90 (odds ratio [OR] = 2.81, 95% confidence interval [CI]: 1.10–7.21, P = 0.0312). In contrast, ICH size was associated with poor mRS scores on day 90 (OR = 0.92, 95% CI: 0.88–0.97, P = 0.0005). After propensity score matching, there was no difference in the outcomes between the two groups. We did not detect mild and serious adverse events.

Conclusion: The study could not show the significant effect of 2 weeks administration of tranexamic acid on functional outcomes of ICH patients after the matching; however, suggested that this treatment is at least safe and feasible. A larger and adequately powered trial is needed.

Keywords: Antifibrinolytic effect, Anti-inflammatory effect, Intracerebral hemorrhage, Kallikrein-Kinin system, Tranexamic acid

INTRODUCTION

The survival rate after spontaneous acute intracerebral hemorrhage (ICH) has not changed for several decades, and it is well known that the only treatment possibility for functional improvement on day 90 is early intensive blood pressure control.[1] The role of surgical treatment

remains controversial, and no significant advantage of surgery, especially in older patients, has been identified.[10]

Tranexamic acid, an antifibrinolytic drug, is often used for hemostasis. The CRASH-3 trial showed that administration of tranexamic acid within 3 h reduced head injury-related death in patients with traumatic brain injury.[5] Conversely, the tranexamic acid for hyperacute primary ICH (TICH-2) trial surveyed the role of tranexamic acid in patients with ICH and showed that functional status on day 90 after ICH did not differ significantly between patients who received tranexamic acid and those who received placebo.[15] The study aimed to determine whether 1 g intravenous tranexamic acid bolus followed by an 8 h infusion of 1 g tranexamic acid reduced hematoma expansion when administered within 8 h of symptom onset. Moreover, this trial did not include Japanese patients, in whom the incidence of ICH is higher than in Western patients.[16]

Tranexamic acid, which inhibits plasmin activity, has both antifibrinolytic and anti-inflammatory effects.[11] Plasmin is a known activator of the Kallikrein-Kinin system (KKS).[7] The KKS plays a role in inflammation and cerebral edema following ICH.[9] Cerebral edema increases until 9–14 days after ICH[20] and is associated with poor outcomes.[12] Recently, potential therapeutic targets for ICH-associated inflammation have received a lot of attention.[14]

Therefore, we considered a different method of tranexamic acid administration from the TICH-2 trial. Our pilot study tested the hypothesis that 2 weeks administration of tranexamic acid inhibits fibrinolytic and inflammatory activity in acute spontaneous ICH and is associated with functional improvement.

MATERIALS AND METHODS

Patient population

Our pilot study was a single-center study. All consecutive patients with acute ICH were eligible for inclusion if they were admitted to our hospital within 8 h of symptom onset. Recruitment started on August 9, 2018, and ended on September 30, 2019. ICH was defined as hemorrhage due to hypertension and included putaminal, thalamic, brainstem (pontine), and cerebellar hemorrhage. The exclusion criteria were a Glasgow Coma Scale (GCS) score of ≤8; ICH secondary to thrombolysis, trauma, or a known underlying structural abnormality; patients for whom tranexamic acid was contraindicated; patients with a Modified Rankin Scale (mRS) score >4; patients undergoing surgical treatment; and multiple ICHs. The treatment window and exclusion criteria were based on the TICH-2 trial.[15] Written informed consent was obtained from each patient or their family. We identified patients belonging to the non-administration group by retrospective analysis. Historical control patients were collected to avoid differences in medical treatment, other than tranexamic acid, that might influence patients' outcomes. We used historical control consecutive patients who had presented during the 30 months before the recruitment but otherwise would have been included in the study.

As this study involved human subjects, it was approved by the Local Institutional Review Board (Hitoyoshi Medical Center, Approval No. 2018-12). The study was performed in accordance with the principles of good clinical practice and the Declaration of Helsinki. Clinical trial registration number of the study was UMIN000035584 (18/01/2019).

Treatment

The target patients were administered 250 mg tranexamic acid intravenously or orally 3 times a day. The initial intervention, tranexamic acid, was administered as quickly as possible after diagnosis. Tranexamic acid was continuously administered for 2 weeks from the time of admission. This was discontinued if a serious complication occurred from drug administration, if another stroke occurred, or if the patient died. The dose of tranexamic acid was based on a previous report of its daily administration for a chronic subdural hematoma.[11] This report also focused on the effect of tranexamic acid on KKS and also reported the safety of the dose of tranexamic acid. The medical treatments, other than tranexamic acid, mainly blood pressure control, were same with the historical control patients. For blood pressure control, we used calcium channel blockers and other medications to keep systolic blood pressure below 140 mmHg for the 1st week.

Clinical evaluations

Baseline characteristic data were extracted at the time of admission from the patients' medical records and their computed tomography (CT) scans. This data included the following: age, sex, ICH location, ICH size, intraventricular hemorrhage (IVH), pre-onset mRS score, GCS score at admission, and antithrombotic drug history. The target patients were reviewed on the day after admission, day 7, on the day of death or hospital discharge, and on day 90 to gather information on changes in ICH size, GCS score, and mRS score. This information was obtained through the transferred hospital report, on the outpatient visit, or through a direct phone interview.

Imaging evaluations

For all target patients, CT was conducted at admission. A second CT was conducted on the day after admission to assess hematoma expansion. The first author evaluated all CT images. ICH location and size and IVH severity were

also examined. The formula ABC/2 was used to measure ICH size.[13] Hematoma expansion was defined as an absolute increase of >6 mL or relative growth of >33%.

Outcomes

The primary outcome was mRS score on day 90. The secondary outcomes included hematoma expansion on the day after admission, GCS score on day 7, and mRS score on the day of death or hospital discharge (whichever came first). We hypothesized that 2 weeks administration of tranexamic acid would improve these outcomes. Whether tranexamic acid inhibited fibrinolytic and inflammatory activity in ICH was difficult to evaluate using CT. Therefore, we focused on clinical improvement, not imaging improvement.

Safety outcomes were thromboembolic complications (myocardial infarction, stroke, pulmonary embolism). These outcomes were recorded if they occurred while the patient was still in our hospital.

Statistical analysis

Our study was a prospective and single-arm pilot study with historical controls. Since this was a pilot study, the sample size was not calculated before the start of the study. First, a univariate analysis was performed for each baseline and outcome parameter. We analyzed the mRS score as a binary outcome (dichotomized at mRS scores 0–3 vs. 4–6). Continuous data were reported as the mean and standard deviation or as the median with the corresponding interquartile range and compared using the *t*-test or Wilcoxon rank-sum test. Categorical data were reported as numbers and percentages and compared using the Chi-squared test. Because of the bias caused by potentially confounding factors, a logistic regression model was used to calculate the adjusted odds ratio (OR) with a 95% confidence interval (CI) for 2 weeks administration of tranexamic acid associated with mRS score on day 90. Furthermore, all outcomes were compared after adjusting for baseline characteristics using propensity score matching. A multivariable logistic regression model was used to predict patients' propensity scores. One-to-one nearest neighbor matching was performed (caliper width, 20%). After matching, continuous data were compared using the corresponding *t*-test, and categorical data were compared using the McNemar test. All $P < 0.05$ were considered statistically significant. No adjustment was made for testing multiplicity. There was no missing data in this trial, except in the case of one patient, for whom the mRS score on day 90 could not be obtained. The full analysis set was performed in accordance with the intention-to-treat principle. All analyses were performed using the JMP software (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 35 patients were recruited and received tranexamic acid. Furthermore, we identified 90 historical control patients who had presented between January 2016 and September 2018. Table 1 shows the results of univariate analyses. These groups were well balanced at baseline, except for ICH size ($P = 0.0354$), and antithrombotic drug history ($P = 0.0092$). The primary outcome, mRS score on day 90, was assessed in 35 patients in the administration group and 89 patients in the nonadministration group because one patient was lost to follow-up.

Univariate analysis showed that the primary outcome (mRS score on day 90) was better in the administration group ($P = 0.0095$). The secondary outcomes of hematoma expansion and GCS score on day 7 were not significantly different between the two groups ($P = 0.6762$, $P = 0.1182$). mRS score on the day of death or discharge suggested a favorable effect of tranexamic acid treatment ($P = 0.0678$) [Table 1]. However, the ICH size and antithrombotic drug history, which were collected at baseline, were different between the two groups and might be confounding factors. Therefore, multivariable logistic regression was used to control for these two potentially confounding factors. Two weeks administration of tranexamic acid was associated with good mRS scores on day 90 (OR = 2.81, 95% CI: 1.10–7.21, $P = 0.0312$). In contrast, ICH size was associated with poor mRS scores on day 90 (OR = 0.92, 95% CI: 0.88–0.97, $P = 0.0005$) [Table 2].

Table 1: Univariate analysis of patient baselines and outcomes.

Variables	Tranexamic acid (*n*=35)	Control (*n*=90)	*P*-value
Age, years	74.2 (12.28)	72.0 (13.68)	0.4154
Male	19 (54.29%)	43 (47.78%)	0.5135
ICH location (supratentorial)	24 (68.57%)	74 (82.22%)	0.0959
ICH size (mL)	8.5 (9.70)	14.9 (16.69)	0.0354*
intraventricular hemorrhage	10 (28.57%)	40 (40.0%)	0.2342
Prestroke mRS	0 (0–2)	0 (0–1)	0.1143
GCS at admission	15 (12–15)	14 (13–15)	0.5003
Previous antithrombotic therapy	16 (45.71%)	20 (22.22%)	0.0092*
Good outcome on day 90 (mRS 0–3)	24 (68.57%)	38 (42.70%)	0.0095*
Hematoma expansion on the day after admission	3 (8.57%)	10 (11.11%)	0.6762
GCS on day 7	15 (14–15)	14 (13–15)	0.1182
mRS on the day of death or discharge (=0, 1, 2, 3)	17 (48.57%)	28 (31.11%)	0.0678

Data are *n* (%), mean (SD), or median (IQR). SD: Standard deviation, IQR: Interquartile range, ICH: Intracerebral hemorrhage, mRS: Modified rankin scale, GCS: Glasgow coma scale, *$P<0.05$

Moreover, the primary outcome and other outcomes, such as hematoma expansion, GCS on day 7, and mRS score on the day of death or discharge were compared after adjusting for baseline characteristics by propensity score matching. Only two characteristics, ICH size and history of antithrombotic drugs, were selected as Matched predictor variables to reduce the risk of overfitting. Multivariate logistic analysis was performed to calculate the propensity scores, which were balanced between the two groups [Table 3]. Table 4 shows the results of the comparisons after matching. The differences in ICH size and anti-thrombotic drug history were smaller between the two groups. After propensity score matching, there was no difference in the outcomes between the two groups.

We did not detect adverse events that occurred from drug administration, such as thromboembolic complications (myocardial infarction, stroke, and pulmonary embolism) in the study.

DISCUSSION

Our study showed that 2 weeks administration of tranexamic acid might have a positive impact on the functional prognosis of patients with ICH in multivariable logistic regression. At present, the only treatment for functional improvement in patients with ICH is early intensive blood pressure control.[1] The TICH-2 trial surveyed the role of tranexamic acid within the early hours of ICH and showed that functional status 90 days after ICH did not improve significantly.[15] Therefore, this study investigated the hypothesis that 2 weeks administration of tranexamic acid would inhibit fibrinolytic and inflammatory activity and would be associated with functional improvement. This is the first study to examine the efficacy of the continuous administration of tranexamic acid in patients with ICH. Several trials have shown the efficacy of tranexamic acid for hemorrhagic diseases, such as head trauma[5] and post-partum hemorrhage.[19] In these trials, as in the TICH-2 trial, the protocol was to administer tranexamic acid on the day of injury or at the time of bleeding. However, one report found that chronic subdural hematoma could be treated with continuous administration of tranexamic acid without a drainage operation.[11]

Along with compression of the surrounding brain tissue by a hematoma, various cellular and molecular components of inflammation are associated with ICH-induced brain injury.[17] When ICH occurs, blood components, including plasma proteins (thrombin, plasmin, etc.) enter the brain.[18] Plasmin is known as an activator of the KKS,[7] which plays a role in inflammation and cerebral edema following ICH.[9] Cerebral edema increases for 9–14 days after the onset of ICH[20] and is associated with poor outcomes.[12] Tranexamic acid is a drug that inhibits plasminogen activation and plasmin activity.[6] It was developed as a hemostatic agent, but also has anti-inflammatory and anti-edema effects through inhibition of the KKS.[11]

We hypothesized that 2 weeks administration of tranexamic acid might inhibit the increase in vascular permeability seen in ICH, which would reduce cellular damage, although this was difficult to evaluate using CT. Therefore, the multivariable logistic regression showed that the treatment was associated with good mRS scores on day 90. After propensity score matching, however, there was no difference in the outcomes between the two groups. The reason for this result may be that ICH size was a much stronger prognostic factor[3] than the treatment. The study could not show the significant effect of the treatment; however, in a subanalysis after matching, there was an interesting finding regarding the introduction of rehabilitation. A Very Early Rehabilitation Trial for Stroke trial showed that the early introduction of rehabilitation had a positive impact on the functional prognosis of stroke patients. In this study, no response to voice was raised as one of the exclusion criteria, which means that the best eye response (E) score of 3 or 4 on the GCS is important for the introduction of rehabilitation.[2] Therefore, we further analyzed the GCS

Table 2: ORs and 95% CIs for modified Rankin Scale on day 90, associated with 2 weeks administration of tranexamic acid and covariates.

	OR	95% CI	*P*-value
Two weeks administration of tranexamic acid	2.81	1.10–7.21	0.0312*
ICH size	0.92	0.88–0.97	0.0005*
previous antithrombotic therapy	0.45	0.18–1.14	0.0934

OR: Odds ratio, CI: Confidence interval, ICH: Intracerebral hemorrhage. *$P<0.05$

Table 3: Patients' baselines before and after propensity score matching.

Variables	Unmatched				Matched			
	Tranexamic acid (*n*=35)	Control (*n*=90)	*P*-value	Std diff	Tranexamic acid (*n*=34)	Control (*n*=34)	*P*-value	Std. diff.
ICH size (mL)	8.5 (9.70)	14.9 (16.69)	0.0354*	46.9%	8.6 (9.83)	6.6 (7.67)	0.3671	22.7%
previous ATD	16 (45.71%)	20 (22.22%)	0.0092*	51.2%	15 (44.12%)	13 (38.24%)	0.2888	12.0%

Data are *n* (%) or mean (SD). SD: Standard deviation, Std diff: Standardized difference, ICH: Intracerebral hemorrhage, ATD: Antithrombotic therapy. *$P<0.05$

Table 4: Outcomes between patients who received tranexamic acid and those who did not in the matched cohort.

	Tranexamic acid (*n*=34)	Control (*n*=34)	*P*-value
Good outcome on day 90 (mRS 0–3)	23 (67.75%)	18 (52.94%)	0.2623
hematoma expansion on day 2	3 (8.82%)	2 (5.88%)	0.6422
GCS on day 7	15 (14–15)	15 (14–15)	0.4163
Good outcome on the day of death or discharge (mRS 0–3)	16 (47.06%)	13 (38.24%)	0.4111
E at day 7 (=4)	33 (97.06%)	31 (91.18%)	<0.001*

Data are *n* (%) or median (IQR). SD: Standard deviation, IQR: Interquartile range, mRS: Modified rankin scale, GCS: Glasgow coma scale, E: best eye response. *P<0.05

at day 7 in our data set after propensity score matching. The percentage of patients with an E score of 4 was higher in the administration group than in the nonadministration group [Table 4]. Therefore, this treatment may have positive effects on the early introduction of rehabilitation, which may improve the functional prognosis of patients with ICH.

Nausea and diarrhea are the most common adverse events associated with tranexamic acid.[6] An increased risk of ischemic events with the drug has not been found in some clinical trials.[4,6] In addition, no increase in thromboembolic complications has been detected in one trial of long-term administration of tranexamic acid 3 g/day.[8] No such serious adverse events were detected in this study, suggesting the safety of this treatment.

Our study had several limitations. First, selection bias was possible due to the nature of the study design, as this was a single center, single-arm pilot study with a small sample size. However, we used multivariable logistic regression and propensity score matching to balance the patient baselines to minimize its influence as much as possible. Second, this study included only Japanese patients. The same results cannot always be obtained when this treatment is administered to patients of other ethnicities. Third, the administration group represented mild ICH patients with a median GCS of 15 and a median ICH volume <10 mL. This limited the generalizability of this trial. Fourth, we hypothesized that this treatment might reduce cellular damage; however, we did not collect image data that supported the hypothesis such as magnetic resonance imaging. This is a subject for future research. Finally, the dose of tranexamic acid was based on a previous report of its daily administration for a chronic subdural hematoma,[11] but it is unclear whether the dose setting was appropriate for ICH. Therefore, the efficacy of tranexamic acid treatment for ICH must be confirmed in larger multicenter randomized and controlled trials.

CONCLUSION

We surveyed the effect of 2 weeks administration of tranexamic acid for acute ICH. The outcomes did not differ between the two groups after matching; however, this pilot study suggested that this treatment is at least safe and feasible. This treatment might have anti-inflammatory effects, which could reduce cellular damage. Therefore, this treatment may have positive effects, such as the early introduction of rehabilitation, which may improve the functional prognosis of patients with ICH. The study may provide future directions on the treatment of ICH; however, a larger and adequately powered trial is needed because the study had many limitations including study size.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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