J Neurosurg 119:332–337, 2013

Nonsurgical treatment of chronic subdural hematoma with tranexamic acid

Clinical article

Hiroshi Kageyama, M.D.,[1,2] Terushige Toyooka, M.D., D.M.Sc.,[1] Nobusuke Tsuzuki, M.D., D.M.Sc.,[1] and Kazunari Oka, M.D., D.M.Sc.[1]

[1]Department of Neurosurgery, Kuki General Hospital, Kuki, Saitama; and [2]Department of Neurosurgery, Juntendo University, Tokyo, Japan

Object. Chronic subdural hematoma (CSDH) is a common condition after head trauma. It can often be successfully treated surgically by inserting a bur hole and draining the liquefied hematoma. However, to the best of the authors' knowledge, for nonemergency cases not requiring surgery, no reports have indicated the best approach for preventing hematoma enlargement or resolving it completely. The authors hypothesized that hyperfibrinolysis plays a major role in liquefaction of the hematoma. Therefore, they evaluated the ability of an antifibrinolytic drug, tranexamic acid, to completely resolve CSDH compared with bur hole surgery alone.

Methods. From 2007 to 2011, a total of 21 patients with CSDH seen consecutively at Kuki General Hospital, Japan, were given 750 mg of tranexamic acid orally every day. Patients were identified by a retrospective records review, which collected data on the volume of the hematoma (based on radiographic measurements) and any complications. Follow-up for each patient consisted of CT or MRI every 21 days from diagnosis to resolution of the CSDH.

Results. Of the 21 patients, 3 with early stages of CSDH were treated by bur hole surgery before receiving medical therapy. The median duration of clinical and radiographic follow-up was 58 days (range 28–137 days). Before tranexamic acid therapy was initiated, the median hematoma volume for the 21 patients was 58.5 ml (range 7.5–223.2 ml); for the 18 patients who had not undergone surgery, the median hematoma volume was 55.6 ml (range 7.5–140.5 ml). After therapy, the median volume for all 21 patients was 3.7 ml (range 0–22.1 ml). No hematomas recurred or progressed.

Conclusions. Chronic subdural hematoma can be treated with tranexamic acid without concomitant surgery. Tranexamic acid might simultaneously inhibit the fibrinolytic and inflammatory (kinin-kallikrein) systems, which might consequently resolve CSDH. This medical therapy could prevent the early stages of CSDH that can occur after head trauma and the recurrence of CSDH after surgery.
(http://thejns.org/doi/abs/10.3171/2013.3.JNS122162)

Key Words • **chronic subdural hematoma** • **tranexamic acid** • **fibrinolysis** • **kallikrein system** • **traumatic brain injury**

Chronic subdural hematoma is a common condition after head trauma. It is often successfully treated surgically by inserting a bur hole and draining the liquefied hematoma. However, to the best of our knowledge, for nonemergency cases not requiring surgery, no reports have indicated the best approach for preventing hematoma enlargement or resolving it completely. To date, conservative treatments have not been established. The resolution of CSDH after treatment with simple observation has been reported as a relatively rare phenomenon.[5,7]

Several studies have shown that hyperfibrinolytic activities play a major role in the liquefaction and enlargement of CSDH.[4,6] We hypothesized that tranexamic acid, an antifibrinolytic agent that has fewer side effects than other agents and is widely used for hemostasis,[2] would inhibit the hyperfibrinolytic activity of CSDH. Therefore, we assessed the effects of tranexamic acid on CSDH volume.

Abbreviation used in this paper: CSDH = chronic subdural hematoma.

Methods

Patient Population

We identified patients by retrospective analysis of the medical records and neuroradiographic studies for all patients seen at the Department of Neurosurgery, Kuki General Hospital, Japan, from 2007 to 2011, in whom CSDH was diagnosed by initial head CT scans or MR images. Two neurosurgeons (H.K. and K.O.) evaluated all imaging studies and clinical symptoms of each patient. The data were extracted from medical records and follow-up CT scans and included the following: a history of head trauma, hypertension, cerebral infarction, coronary heart disease, atrial fibrillation, trauma, Alzheimer disease, cerebrovascular dementia, or other significant medical history. Also extracted was information about presence of hematoma, neuroradiological examinations, and extent of antiplatelet therapy. Patients who were taking warfarin were excluded from the study.

Treatment

Three patients were in a clinically urgent state, with

uncal herniation requiring bur hole surgery. All 21 patients (or their families) chose whether to undergo surgery. Regardless of whether surgery was performed, all patients with symptomatic or asymptomatic CSDH were given 750 mg of tranexamic acid (Transamin, Daiichi-Sankyo; 250 mg capsules) orally every day. Administration of tranexamic acid was continued for all patients until CSDH completely resolved or sufficiently decreased, according to results of imaging studies.

Clinical Evaluations

During the initial clinic visit, clinical histories were taken and neurological examinations were conducted. Each patient was followed up every 21 days. Two neurosurgeons (H.K. and K.O.) independently evaluated the patients. All signs, symptoms, and any adverse events were recorded.

Imaging Evaluations

For all patients, CT and/or MRI without contrast enhancement (slice thickness 5 mm) were conducted at the time of diagnosis. Each patient underwent CT scanning every 21 days. Final imaging studies were performed 21 days after the end of tranexamic acid administration. The volume (in milliliters) of the hematoma was calculated from the CT or MR images before, during, and after the therapy by using image analysis software (ImageJ, National Institutes of Health). The size of the hematoma was computed on the basis of imaging results and slice thicknesses.

Outcomes

Therapy and therapeutic periods for CSDH were recorded for all patients, regardless of whether they received surgical intervention. Each clinical symptom was evaluated as "improved" or "not improved." The hematoma categories were as follows: cure (defined as sufficient decrease of the CSDH according to imaging studies); recurrence (defined as a new CSDH in a new location or in the same location after confirmation of hematoma disappearance 21 days after cure); or progression (defined as expansion of the CSDH in the same location without cure or regression).

Results

Patient Characteristics

During the study period, a diagnosis of CSDH was made for 21 patients, 12 men (57%) and 9 women (43%) (Table 1), median age 79 years (range 54–93 years). Twelve patients (57%) had a history of mild or severe head trauma; 3 (14%) were taking medication for hypertension; 3 (14%) were taking antiplatelet drugs for cerebral infarc-

TABLE 1: Patient and hematoma characteristics, therapeutic period, and results*

Case No.	Age (yrs), Sex	History	Symptoms	Hematoma Laterality	Hematoma Volume (ml)†	Op	Therapy Duration (days)‡	Result
1	72, M	parkinsonism	none	rt	54.2	–	70	
2	88, F	HT, parkinsonism	gait disturbance, dementia	bilat	223.2 (61.4)	+	55	improved
3	71, M		lt hemiparesis	bilat	96.7 (16.9)	+	57	improved
4	82, F	AF	gait disturbance	bilat	87.4	–	91	improved
5	54, F	HL	none	lt	18.7	–	29	
6	91, F	cilostazol	none	lt	7.5	–	58	
7	65, M		headache	bilat	122.2 (20.6)	+	72	improved
8	82, M	aspirin	none	rt	21.8	–	58	
9	76, M		dementia	rt	31.2	–	28	improved
10	88, M	lymphoma	none	bilat	73.5	–	28	
11	88, F	lumbar fracture	none	lt	32.1	–	50	
12	75, M		none	rt	29.0	–	63	
13	92, M	ticlopidine, DM, CHF, AF, OMI	rt hemiparesis, dementia	lt	126.1	–	127	improved
14	90, M		none	lt	58.5	–	137	
15	78, F	brain contusion	none	rt	22.5	–	28	
16	93, F	dementia, HT	gait disturbance, polyuria	rt	34.4	–	56	improved
17	70, M	epilepsy	gait disturbance, headache	bilat	129.6	–	59	improved
18	69, M		headache	lt	73.4	–	70	improved
19	67, F	AEDH	headache	bilat	85.2	–	127	improved
20	79, F	breast cancer	gait disturbance, dementia	bilat	140.5	–	99	improved
21	82, M	clavicle fracture	none	rt	56.9	–	28	

* AEDH = acute epidural hematoma; AF = atrial fibrillation; CHF = chronic heart failure; DM = diabetes mellitus; HL = hyperlipidemia; HT = hypertension; OMI = old myocardial infarction; Op = operation (bur hole insertion); + = yes; – = no.

† Values inside parentheses indicate volume after surgery.

‡ Medical therapy with tranexamic acid.

tion or coronary heart disease; 2 (10%) had atrial fibrillation but were not taking any anticoagulant drugs; and 1 (5%) received a diagnosis of malignant lymphoma after chemotherapy, but platelet counts and coagulation data were within reference ranges.

Clinical Presentations

Among the 21 patients, no clinical symptoms were found for 10 patients (48%); evidence of mild head trauma was found incidentally or by follow-up CT scans. For the other 11 patients (52%), common initial symptoms were gait disturbance (24%), dementia (19%), headache (19%), and hemiparesis (10%).

Treatment

Bur hole surgery was performed for 3 patients (14%) (Cases 2, 3, and 7) in the early stages of CSDH; tranexamic acid was given concomitantly. Tranexamic acid alone (without surgery) was given to 18 patients (86%). Of these 18 patients, 8 who had apparent clinical symptoms chose tranexamic acid therapy without surgery.

Imaging Studies

Hematomas were bilateral in 8 patients (38%), on the right side of the head in 7 (33%), and on the left side in 6 (29%). Before therapy, the median hematoma volume was 58.5 ml (range 7.5–223.2 ml) (Table 1). For the 18 patients who did not receive surgical intervention, the median hematoma volume was 55.6 ml (range 7.5–140.5 ml) (Table 1). Before therapy without surgical intervention, the maximum volume on 1 side of the head was 126.1 ml (Table 2). The brain was more restorative and the residual effusion was less in patients who received tranexamic acid alone than in patients who underwent bur hole surgery alone.

Outcomes

Among all patients, clinical symptoms improved before the hematomas were fully reduced. For all patients with headache who did not undergo surgery, the headache pain rapidly disappeared by the second visit after starting therapy. Follow-up visits were performed for each patient for a median of 58 days (range 28–137 days). After therapy, the median volume of the hematomas in all patients was 3.7 ml (range 0–22.1 ml). Figure 1 shows the changes in the volumes of the hematomas in the 18 patients who did not undergo surgery. For all patients, hematomas were assigned to the category of "cure." None of the hematomas recurred or progressed. Among all study patients, no adverse events, including thromboembolic events, were observed; thus, tranexamic acid was not discontinued for reasons of death or severe adverse event.

The patient in Case 19 represents a common case from this study (Fig. 2). The patient was a 67-year-old woman who had an acute epidural hematoma on her right

TABLE 2: Volume of hematoma before and after tranexamic acid therapy

	Hematoma Volume (ml)						
	Before Treatment			After Treatment			
Case No.	Lt	Rt	Total	Lt	Rt	Total	Period (days)
1	54.2	0	54.2	2.6	0	2.6	70
2	84.0	139.2	223.2	9.5	7.4	16.9	55
3	16.9	79.8	96.7	4.3	5.0	9.3	57
4	63.9	23.6	87.5	3.9	11.5	15.4	91
5	0	18.7	18.7	0	0	0	29
6	0	7.5	7.5	0	0.7	0.7	58
7	53.2	69	122.2	1.2	0.6	1.8	72
8	21.8	0	21.8	3.5	0	3.5	58
9	17.7	13.5	31.2	20.8	1.3	22.1	28
10	32.3	41.2	73.5	7.2	5.0	12.2	28
11	0	32.1	32.1	0	0.3	0.3	50
12	29.0	0	29.0	3.7	0	3.7	63
13	0	126.1	126.1	0	17.8	17.8	127
14	0	58.5	58.5	0	9.5	9.5	137
15	22.5	0	22.5	2.5	0	2.5	28
16	34.4	0	34.4	7.1	0	7.1	56
17	48.1	81.5	129.6	1.7	8.6	10.3	59
18	0	73.4	73.4	0	0	0	70
19	9.4	75.8	85.2	0	3.8	3.8	127
20	68.3	72.1	140.4	0	0	0	99
21	56.9	0	56.9	0	0	0	28

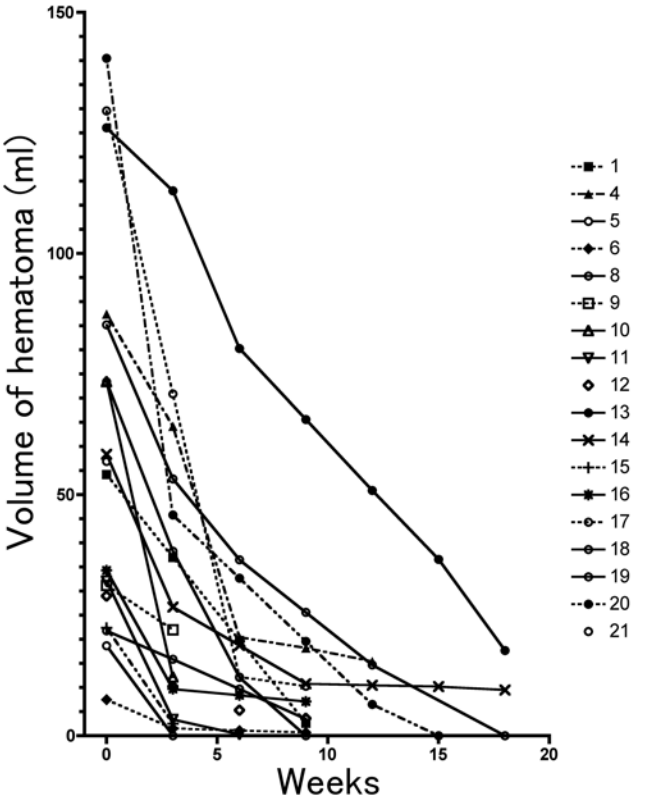

Fig. 1. Changes in the hematoma volumes in 18 patients who received tranexamic acid therapy but did not undergo surgery. Key to the right of the graph lists patients according to their case number.

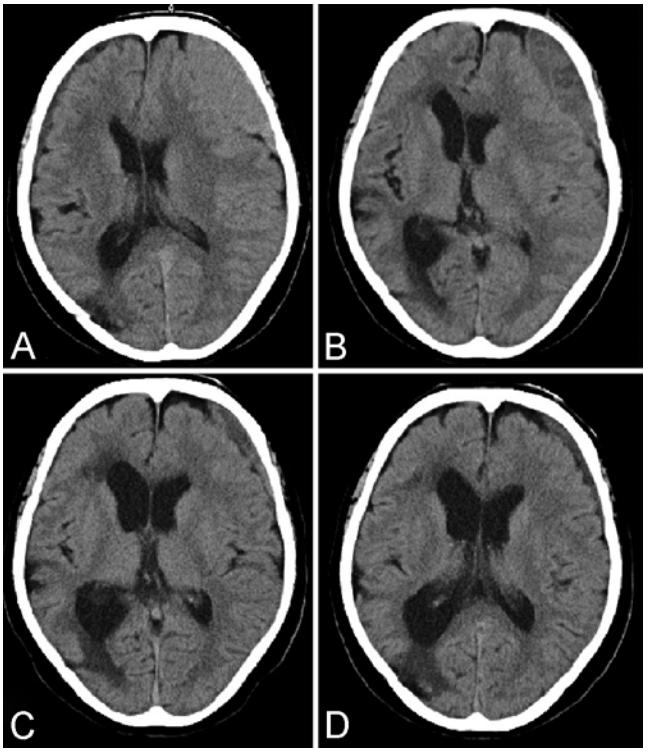

Fig. 2. Case 19. CT images obtained after starting tranexamic acid therapy. **A:** Day 1. **B:** Day 28. **C:** Day 78. **D:** Day 127.

side. The hematoma was removed through a small craniotomy, and the patient was discharged from the hospital 2 months later. One month after discharge, she complained of a headache. Computed tomography scanning showed a thin hematoma on the right side of her head and a thick hematoma on the left side. Tranexamic acid was then given, after which the neuroimaging course varied; initially the density decreased, and then the hematoma diminished. The hematoma was completely resolved 4 months later.

The patient in Case 13, a 92-year-old man who was receiving ticlopidine for an old myocardial infarction, had a CSDH of the maximum size on 1 side; he did not undergo surgical intervention (Fig. 3). After a fall, he suffered rib fractures, and 2 weeks later, right hemiparesis and dementia developed. We recommended bur hole surgery, but he rejected it. The massive hematoma was treated with tranexamic acid without surgery and completely resolved after 4 months (Fig. 4).

One patient with CSDH was not treated with tranexamic acid. This patient was an 81-year-old man who received a bruise on his head from a fall after drinking. Traumatic subarachnoid hemorrhage and a thin acute subdural hematoma developed. The hemorrhage and the hematoma did not worsen. Because he had progressing dementia, he was transferred to a psychiatric hospital. Follow-up 1 month later at Kuki General Hospital showed that his neurological symptoms had not changed; however, a CT scan showed a CSDH on his left side (Fig. 5A). He was followed up in the psychiatric hospital by a psychiatric doctor without receiving tranexamic acid treatment. After another month, he became somnolent, had severe headache, and exhibited decorticated posture of his right arm and leg. He was taken by ambulance to Kuki General Hospital, where CT scans showed enlargement of the left CSDH and brainstem compression (Fig. 5B). After emergency bur hole surgery, he fully recovered consciousness. This case provides an example of how treatment with simple observation for asymptomatic CSDH might not be without risk.

Discussion

To date, medical therapies for CSDH have not been a major focus in neurosurgery. When treating a CSDH, 2 therapeutic modes are generally chosen: observation for asymptomatic patients and hematoma drainage for symptomatic patients. However, spontaneous resolution of CSDH has rarely been reported,[5] and the reported rate of recurrence after surgery for CSDH is approximately 5%–30%.[13] A few studies have described spontaneous resolution of CSDH. Horikoshi et al.[7] reviewed a number of studies and reported that 2.4%–18.0% of cases of CSDH resolved spontaneously without surgical or medical intervention. In our series, all cases of CSDH that were treated with tranexamic acid resolved, indicating more frequent resolution with medical treatment than with no treatment.

The pathophysiology of the development of CSDH

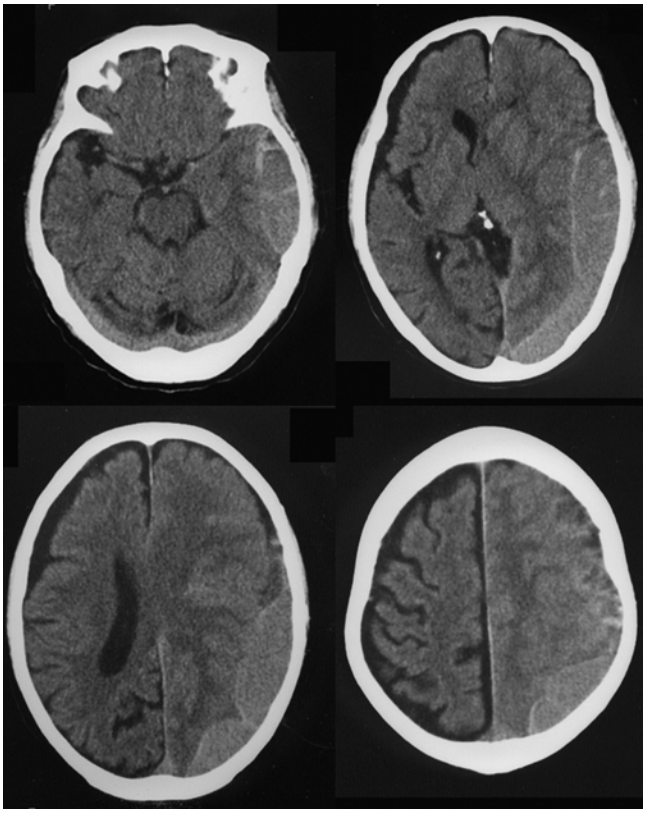

Fig. 3. Case 13. CT images on Day 1, at the initiation of tranexamic acid therapy.

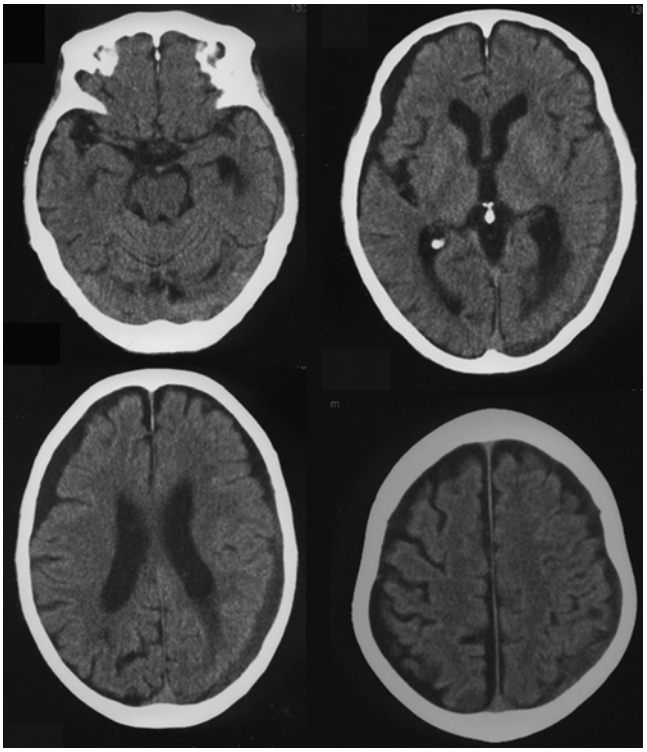

Fig. 4. Case 13. CT images at 4 months after starting tranexamic acid therapy.

has not been fully investigated; only a few studies have explored this condition. However, hyperfibrinolytic activity has been shown to be critical for liquefaction of the hematoma and progression of CSDH.[4,6] Several studies have demonstrated hyperfibrinolytic and coagulative activity in CSDH,[8,10,12,14,15] and some have shown that increased permeability of the capillaries in the hematoma outer membrane can influence the enlargement of a CSDH.[4,16] Plasmin acts simultaneously on the fibrinolytic and kallikrein systems (Fig. 6). Because the kallikrein system induces inflammation, vascular permeability increases. Fujisawa et al.[4] showed, biochemically and histologically, activation of the kallikrein system in hematomas and the outer membrane.

Tranexamic acid is a specific antifibrinolytic drug that inhibits plasminogen activation and plasmin activity. It is a derivative of the amino acid lysine and exerts antifibrinolytic effects by reversibly binding to lysine sites on plasminogen. This drug inactivates plasminogen.[3] Therefore, we hypothesized that tranexamic acid might inhibit the hyperfibrinolytic activity and the increased vascular permeability, which would consequently allow the hematoma to be gradually absorbed without expansion (Fig. 6).

Side effects of tranexamic acid are mild and uncommon; some patients experience gastrointestinal symptoms.[2] The hemostatic effect of tranexamic acid can cause ischemic events. In 1984, Kassell et al.[9] reported that the rate of ischemic deficits increases among patients receiving antifibrinolytic therapy during management of subarachnoid hemorrhage.[9] In a more recent randomized controlled clinical trial that assessed the effect of tranexamic acid on intracranial hemorrhage in patients with traumatic brain injury, thromboembolic cerebrovascular events did not occur more frequently in the group receiving tranexamic acid than in the group receiving placebo.[1] However, in a recent systematic review and cumulative meta-analysis assessing the effects of tranexamic acid on surgical bleeding, the effect of tranexamic acid on thromboembolic events and death was inconclusive.[11]

Our study had some limitations. First, it was a retrospective analysis, not a randomized controlled study. Second, this study excluded patients with CSDH who were taking anticoagulants; therefore, concurrent use of anticoagulants and tranexamic acid should be carefully assessed. Third, because all patients were Japanese, the

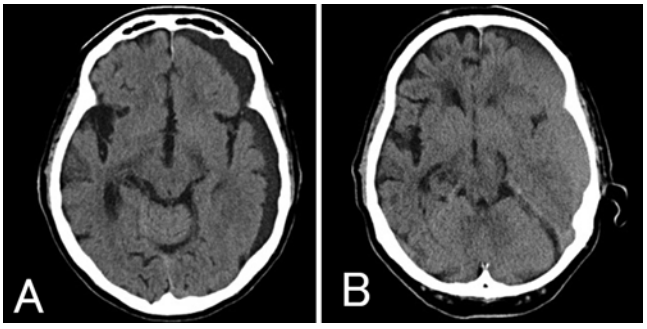

Fig. 5. CT images of a patient with CSDH treated with observation only. **A:** Day 1. **B:** At 1 month.

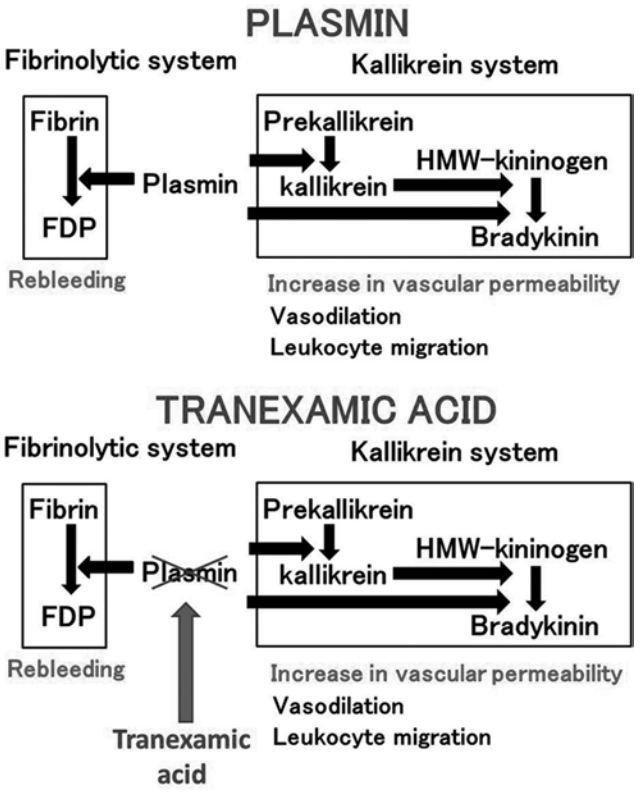

Fig. 6. Fibrinolytic system and kallikrein system. FDP = fibrin degradation products; HMW = high molecular weight.

conclusions that can be drawn from these findings are limited. In addition, few studies have assessed the effects of long-term treatment with tranexamic acid.

Conclusions

In some patients, tranexamic acid can be safely used as a primary medical therapy, without surgical intervention, to prevent the progression of CSDH. Tranexamic acid might act through the antifibrinolytic and antiinflammatory (kinin-kallikrein) systems. This medical therapy is effective; recurrence of CSDH is rare and subdural effusion is less, although long-term administration is required.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Kageyama, Oka. Acquisition of data: Kageyama, Toyooka, Oka. Analysis and interpretation of data: Kageyama, Toyooka, Oka. Drafting the article: Kageyama, Oka. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kageyama. Statistical analysis: Kageyama. Study supervision: Toyooka, Tsuzuki, Oka.

References

1. CRASH-2 Collaborators, Intracranial Bleeding Study: Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). **BMJ 343:**d3795, 2011
2. Ducloy-Bouthors AS, Jude B, Duhamel A, Broisin F, Huissoud C, Keita-Meyer H, et al: High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. **Crit Care 15:** R117, 2011
3. Dunn CJ, Goa KL: Tranexamic acid: a review of its use in surgery and other indications. **Drugs 57:**1005–1032, 1999
4. Fujisawa H, Ito H, Kashiwagi S, Nomura S, Toyosawa M: Kallikrein-kinin system in chronic subdural haematomas: its roles in vascular permeability and regulation of fibrinolysis and coagulation. **J Neurol Neurosurg Psychiatry 59:**388–394, 1995
5. Göksu E, Akyüz M, Uçar T, Kazan S: Spontaneous resolution of a large chronic subdural hematoma: a case report and review of the literature. **Ulus Travma Acil Cerrahi Derg 15:** 95–98, 2009
6. Harada K, Orita T, Abiko S, Aoki H: [Coagulation and fibrinolysis in chronic subdural hematoma. Measurement of fibrinopeptides.] **Neurol Med Chir (Tokyo) 29:**113–116, 1989 (Jpn)
7. Horikoshi T, Naganuma H, Fukasawa I, Uchida M, Nukui H: Computed tomography characteristics suggestive of spontaneous resolution of chronic subdural hematoma. **Neurol Med Chir (Tokyo) 38:**527–533, 1998
8. Ito H, Yamamoto S, Komai T, Mizukoshi H: Role of local hyperfibrinolysis in the etiology of chronic subdural hematoma. **J Neurosurg 45:**26–31, 1976
9. Kassell NF, Torner JC, Adams HP Jr: Antifibrinolytic therapy in the acute period following aneurysmal subarachnoid hemorrhage. Preliminary observations from the Cooperative Aneurysm Study. **J Neurosurg 61:**225–230, 1984
10. Kawakami Y, Chikama M, Tamiya T, Shimamura Y: Coagulation and fibrinolysis in chronic subdural hematoma. **Neurosurgery 25:**25–29, 1989
11. Ker K, Edwards P, Perel P, Shakur H, Roberts I: Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. **BMJ 344:**e3054, 2012
12. Nomura S, Kashiwagi S, Fujisawa H, Ito H, Nakamura K: Characterization of local hyperfibrinolysis in chronic subdural hematomas by SDS-PAGE and immunoblot. **J Neurosurg 81:**910–913, 1994
13. Oh HJ, Lee KS, Shim JJ, Yoon SM, Yun IG, Bae HG: Postoperative course and recurrence of chronic subdural hematoma. **J Korean Neurosurg Soc 48:**518–523, 2010
14. Saito K, Ito H, Hasegawa T, Yamamoto S: Plasmin-alpha 2-plasmin inhibitor complex and alpha 2-plasmin inhibitor in chronic subdural hematoma. **J Neurosurg 70:**68–72, 1989
15. Suzuki M, Kudo A, Kitakami A, Doi M, Kubo N, Kuroda K, et al: Local hypercoagulative activity precedes hyperfibrinolytic activity in the subdural space during development of chronic subdural haematoma from subdural effusion. **Acta Neurochir (Wien) 140:**261–266, 1998
16. Yamashima T, Yamamoto S, Friede RL: The role of endothelial gap junctions in the enlargement of chronic subdural hematomas. **J Neurosurg 59:**298–303, 1983

Manuscript submitted November 13, 2012.
Accepted March 29, 2013.
Please include this information when citing this paper: published online May 3, 2013; DOI: 10.3171/2013.3.JNS122162.

Address correspondence to: Hiroshi Kageyama, M.D., Kuki General Hospital, Kamihayami 418-1, Kuki, Saitama 346-0021, Japan. email: kageyamahiroshi29@gmail.com.