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Adjuvant oral tranexamic acid and reoperation after burr hole surgery in patients with chronic subdural hematoma: propensity score–matched analysis using a nationwide inpatient database

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OBJECTIVE Adjuvant medical treatment to reduce the recurrence rate after burr hole surgery for chronic subdural hematoma (CSDH) has not yet been established. This study aimed to investigate the association between tranexamic acid (TXA) use after burr hole surgery and the reoperation rate in patients with CSDH.

METHODS This observational study used the Japanese Diagnostic Procedure Combination inpatient database, a nationwide inpatient database in Japan, from July 1, 2010, to March 31, 2019. The authors identified patients who were hospitalized for CSDH and underwent burr hole surgery within 2 days of admission. The primary outcome measure was reoperation within 1 year after surgery. One-to-one propensity score–matched analysis was performed to compare the outcomes between patients who started oral TXA within 2 days after surgery (TXA users) and those who did not (TXA nonusers). Robustness of the analyses was assessed using the instrumental variable analysis.

RESULTS Of the 149,543 patients with CSDH treated at 1100 hospitals, 7366 (4.9%) were TXA users. Propensity score matching created 6564 matched pairs with highly balanced baseline characteristics. The reoperation rate was significantly lower in TXA users than in nonusers (1.9% vs 6.1%, $p < 0.001$) with a risk difference of −4.1% (95% CI −4.8% to −3.4%). There was no significant difference in composite adverse events (0.6% vs 0.5%, $p = 0.817$). Total hospitalization costs were also significantly lower in TXA users than in nonusers ($5229 vs $5344 [USD], $p < 0.001$). The results of the instrumental variable analysis were consistent with those of the propensity score–matched analysis.

CONCLUSIONS Findings of this study, using a nationwide inpatient database, suggest that adjuvant TXA use after burr hole surgery was associated with a reduced reoperation rate in patients with CSDH.

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KEYWORDS chronic subdural hematoma; tranexamic acid; recurrence; reoperation; adjuvant therapy; adjunctive treatment; traumatic brain injury

A CHRONIC subdural hematoma (CSDH) is an encapsulated blood collection in the subdural space. CSDHs are often encountered in older individuals, and their incidence is expected to increase in the future with the growth of the older population.[1] Burr hole irrigation is a standard treatment for CSDH, and outcomes are generally favorable; however, substantial postoperative recurrence rates of 4%–27% have been reported.[1–5]

Tranexamic acid (TXA) is a synthetic analog of the amino acid lysine that inhibits fibrinolysis and inflammation by competitively binding to the lysine receptor on plasminogen and plasmin.[6,7] As both fibrinolysis and inflammation are considered to play critical roles in CSDH development,[8] TXA is expected to promote CSDH absorption and reduce recurrence after surgery.[9] Previous studies have suggested that TXA is safe and effective for hematoma resolution and prevents the recurrence of CSDH after surgery.[9–13]

However, most evidence is from case series without a control group.[9–12] Moreover, these studies focused on conservative CSDH management with primary TXA use;[9–11] thus, the clinical effectiveness of TXA as an adjunctive treatment to surgery for CSDH remains unknown.

This study aimed to investigate the association between TXA use after burr hole surgery and the need for reoperation in patients with CSDH using a nationwide inpatient database.

ABBREVIATIONS CCI = Charlson Comorbidity Index; CSDH = chronic subdural hematoma; DPC = Diagnosis Procedure Combination; ICD-10 = *International Classification of Diseases, 10th Revision*; JCS = Japan Coma Scale; TXA = tranexamic acid.

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Methods

This observational study used the Japanese Diagnosis Procedure Combination (DPC) inpatient database. The study protocol was approved by the institutional review board of the University of Tokyo. The requirement for informed consent from patients was waived because the data were anonymized before analysis.

Data Source

The DPC database is a nationwide inpatient database that includes administrative claims data and discharge abstracts from more than 1200 participating acute care hospitals. It contains the following information: type of hospital (teaching or nonteaching, university or nonuniversity), age, sex, body weight and height, smoking history, activities of daily living scores that can be converted to the Barthel Index at admission, level of consciousness, diagnosis (primary diagnosis, comorbidities at admission, and complications arising after admission), drugs and devices used, surgical procedures, total hospitalization cost, and discharge status. Diagnoses and medical procedures were coded according to the *International Classification of Diseases*, *10th Revision* (ICD-10) and Japanese medical procedure codes, respectively. As diagnostic codes are used for treatment reimbursement, attending physicians are required to report objective evidence for diagnosis. The DPC database was previously validated; the specificity of the diagnoses exceeded 96%, while the sensitivity of the diagnoses ranged from 50%–80%. Both the specificity and sensitivity of the procedures exceeded 90%.[14] We obtained information regarding the hospital type (university hospital or not) by linking the DPC database to facility information and statistical data from the 2016 Survey of Medical Institutions.[15]

Study Population

From the DPC database between July 1, 2010, and March 31, 2019, we included patients aged 40–90 years who were hospitalized with CSDH (ICD-10 codes I620 and S650) as the main diagnosis and underwent first burr hole surgery for CSDH (Japanese procedure code K164–2) within 2 days after admission (i.e., on the day of admission or the following day). All eligible patients were followed up until reoperation of the burr hole surgery or 1 year after the first burr hole surgery.

Outcomes and Covariates

The primary outcome measure was reoperation of burr hole surgery performed during the same hospitalization or readmission to the same hospital within 1 year after surgery. The secondary outcome measures were complications during hospitalization and the total hospitalization cost for both initial admission and readmission. Complications included deep venous thrombosis (ICD-10 code I802), pulmonary embolism (ICD-10 code I26), cerebral infarction (ICD-10 code I63), myocardial infarction (ICD-10 codes I21, I22, and I252), and a composite of these complications. Hospitalization costs, recorded in Japanese yen, were converted to US dollars (¥110 = $1).

The covariates used are listed in Table 1. We categorized the patient's ages as 40–49, 50–59, 60–69, 70–79, and 80–89 years. We categorized fiscal years as 2010–2012, 2013–2015, or 2016–2019. We calculated the BMI and classified it according to the World Health Organization criteria for Asian populations: < 18.5, 18.5–24.9, 25.0–29.9, and ≥ 30 kg/m^2,[16] and missing data. The level of consciousness at admission was evaluated using the Japan Coma Scale (JCS). The JCS and Glasgow Coma Scale scores correlated well, and a JCS score of 100 was equivalent to a Glasgow Coma Scale score of 7 or 8.[17] We calculated the Charlson Comorbidity Index (CCI) based on a validated coding algorithm and categorized comorbidities as 0, 1, 2, and ≥ 3.[18,19] In addition to the comorbidities included in the CCI calculation, we collected data regarding comorbid liver cirrhosis (ICD-10 codes K703, K717, K743, K744, K745, and K746), ischemic cerebrovascular disease (ICD-10 codes G45, G46, H340, I63, I65, I66, and I672), deep venous thrombosis (ICD-10 code I802), pulmonary embolism (ICD-10 code I269), valvular heart disease (ICD-10 codes I059, I08, I091, I358, and I38), and atrial fibrillation (ICD-10 code I48). Activities of daily living were categorized based on the Barthel Index at admission as follows: independent (Barthel Index 100), moderate dependency (Barthel Index 61–99), severe dependency (Barthel Index 0–60), and missing data.[20] The hospital volume was defined as the average number of patients with CSDH who underwent burr hole surgery at each hospital per year.

Statistical Analysis

We used propensity score–matching analysis to compare outcomes between patients who started oral TXA within 2 days after surgery (TXA users) and those who did not (TXA nonusers). The propensity score was estimated using a mixed-effects multivariable logistic regression model with predetermined covariates. The mixed-effects model is a standard method that accounts for the hierarchical structure of the data. In this study, we used hospitals as a random-effects variable to consider the differences in TXA use among hospitals. The C-statistic was calculated to assess the ability of the model to differentiate between the two groups. TXA users were then matched with nonusers using one-to-one nearest-neighbor matching without replacement. The allowable caliper width was set to 20% of the pooled standard deviation of the logit of the propensity score.[21] We used the standardized mean differences of covariates to assess the performance of matching, and an absolute standardized mean difference ≥ 0.1 was considered a meaningful imbalance. After propensity score matching, we compared outcomes between the two groups using the Mann-Whitney U-test for numeric variables and the chi-square test for categorical variables. The risk difference with a 95% CI was calculated using a mixed-effects linear regression model.

Sensitivity Analysis

We tested the robustness of the results using the instrumental variable analysis, which can address potential unmeasured confounding factors.[22] In this study, we used hospital treatment preference as an instrumental variable.

TABLE 1. Baseline patient characteristics before and after propensity score matching

	Before Propensity Score Matching			After Propensity Score Matching		
	TXA Users (n = 7366)	TXA Nonusers (n = 142,177)	ASD	TXA Users (n = 6564)	TXA Nonusers (n = 6564)	ASD
University hospital, n (%)	483 (6.6)	9829 (6.9)	0.014	483 (7.4)	518 (7.9)	0.020
Teaching hospital, n (%)	6196 (84.1)	115,946 (81.6)	0.068	5559 (84.7)	5481 (83.5)	0.032
Hospital vol per yr, mean (SD)	34.3 (22.0)	32.1 (18.2)	0.109	33.7 (20.1)	34.5 (21.3)	0.037
Fiscal year, n (%)			0.494			0.015
2010–2012	988 (13.4)	41,657 (29.3)		948 (14.4)	914 (13.9)	
2013–2015	2132 (28.9)	49,496 (34.8)		2064 (31.4)	2064 (31.4)	
2016–2019	4246 (57.6)	51,024 (35.9)		3552 (54.1)	3586 (54.6)	
Season, n (%)			0.051			0.016
Spring (March–May)	1950 (26.5)	37,593 (26.4)		1737 (26.5)	1779 (27.1)	
Summer (June–August)	1794 (24.4)	35,796 (25.2)		1634 (24.9)	1625 (24.8)	
Autumn (September–November)	1671 (22.7)	34,043 (23.9)		1484 (22.6)	1455 (22.2)	
Winter (December–February)	1951 (26.5)	34,745 (24.4)		1709 (26.0)	1705 (26.0)	
Admission on weekend or at night, n (%)	224 (3.0)	4417 (3.1)	0.004	203 (3.1)	206 (3.1)	0.003
Ambulance use, n (%)	2295 (31.2)	44,892 (31.6)	0.009	2110 (32.1)	2040 (31.1)	0.023
Age in yrs, n (%)			0.052			0.021
40–49	133 (1.8)	2293 (1.6)		116 (1.8)	119 (1.8)	
50–59	325 (4.4)	6207 (4.4)		283 (4.3)	282 (4.3)	
60–69	1267 (17.2)	22,120 (15.6)		1101 (16.8)	1143 (17.4)	
70–79	2560 (34.8)	49,349 (34.7)		2291 (34.9)	2237 (34.1)	
80–89	3081 (41.8)	62,208 (43.8)		2773 (42.2)	2783 (42.4)	
Male sex, n (%)	5098 (69.2)	97,939 (68.9)	0.007	4544 (69.2)	4523 (68.9)	0.007
BMI at admission, kg/m^2, n (%)			0.030			0.037
<16.5	220 (3.0)	4866 (3.4)		202 (3.1)	213 (3.2)	
16.5–18.4	684 (9.3)	12,696 (8.9)		613 (9.3)	643 (9.8)	
18.5–22.9	2891 (39.2)	54,922 (38.6)		2572 (39.2)	2531 (38.6)	
23.0–24.9	605 (8.2)	11,865 (8.3)		552 (8.4)	512 (7.8)	
≥25.0	219 (3.0)	4140 (2.9)		194 (3.0)	220 (3.4)	
Missing	2747 (37.3)	53,688 (37.8)		2431 (37.0)	2445 (37.2)	
Smoking history, n (%)			0.011			0.006
Nonsmoker	4511 (61.2)	86,352 (60.7)		4042 (61.6)	4051 (61.7)	
Current/past smoker	1815 (24.6)	35,680 (25.1)		1618 (24.6)	1603 (24.4)	
Unknown	1040 (14.1)	20,145 (14.2)		904 (13.8)	910 (13.9)	
Barthel Index at admission, n (%)			0.097			0.006
0–60	3367 (45.7)	70,854 (49.8)		3024 (46.1)	3024 (46.1)	
61–99	718 (9.7)	14,554 (10.2)		612 (9.3)	610 (9.3)	
100	1691 (23.0)	30,246 (21.3)		1499 (22.8)	1486 (22.6)	
Missing	1590 (21.6)	26,523 (18.7)		1429 (21.8)	1444 (22.0)	
Comorbidities, n (%)						
Myocardial infarction	46 (0.6)	1443 (1.0)	0.043	44 (0.7)	44 (0.7)	<0.001
Congestive heart failure	197 (2.7)	4902 (3.4)	0.045	191 (2.9)	196 (3.0)	0.005
Peripheral vascular disease	37 (0.5)	1153 (0.8)	0.038	33 (0.5)	36 (0.5)	0.006
Cerebrovascular disease	576 (7.8)	12,877 (9.1)	0.045	539 (8.2)	538 (8.2)	0.001
Dementia	638 (8.7)	11,684 (8.2)	0.016	555 (8.5)	567 (8.6)	0.007
Chronic pulmonary disease	178 (2.4)	3681 (2.6)	0.011	159 (2.4)	161 (2.5)	0.002
Rheumatic disease	37 (0.5)	770 (0.5)	0.005	32 (0.5)	26 (0.4)	0.014
Peptic ulcer disease	422 (5.7)	6052 (4.3)	0.068	380 (5.8)	385 (5.9)	0.003
Mild liver disease	213 (2.9)	3739 (2.6)	0.016	182 (2.8)	195 (3.0)	0.012

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TABLE 1. Baseline patient characteristics before and after propensity score matching

	Before Propensity Score Matching			After Propensity Score Matching		
	TXA Users (n = 7366)	TXA Nonusers (n = 142,177)	ASD	TXA Users (n = 6564)	TXA Nonusers (n = 6564)	ASD
Comorbidities, n (%) (*continued*)						
Diabetes	1189 (16.1)	24,051 (16.9)	0.021	1066 (16.2)	1066 (16.2)	<0.001
Hemiplegia/paraplegia	379 (5.1)	9747 (6.9)	0.072	366 (5.6)	348 (5.3)	0.012
Renal disease	97 (1.3)	2606 (1.8)	0.041	95 (1.4)	86 (1.3)	0.012
Malignancy/lymphoma/leukemia	265 (3.6)	5824 (4.1)	0.026	248 (3.8)	239 (3.6)	0.007
Moderate or severe liver disease	15 (0.2)	217 (0.2)	0.012	13 (0.2)	20 (0.3)	0.021
Metastatic solid tumor	23 (0.3)	410 (0.3)	0.004	20 (0.3)	19 (0.3)	0.003
AIDS/HIV	<5 (0.0)	14 (0.0)	0.013	<5 (0.0)	<5 (0.0)	0.010
Liver cirrhosis	44 (0.6)	753 (0.5)	0.009	38 (0.6)	42 (0.6)	0.008
Ischemic cerebrovascular disease	146 (2.0)	3791 (2.7)	0.045	138 (2.1)	139 (2.1)	0.001
Deep venous thrombosis	18 (0.2)	360 (0.3)	0.002	18 (0.3)	14 (0.2)	0.012
Pulmonary embolism	7 (0.1)	90 (0.1)	0.011	7 (0.1)	7 (0.1)	<0.001
Valvular heart disease	3 (0.0)	203 (0.1)	0.034	<5 (0.0)	<5 (0.0)	0.008
Atrial fibrillation	66 (0.9)	949 (0.7)	0.026	59 (0.9)	65 (1.0)	0.009
CCI, n (%)			0.074			0.021
0	4144 (56.3)	76,254 (53.6)		3645 (55.5)	3622 (55.2)	
1	1880 (25.5)	35,939 (25.3)		1668 (25.4)	1721 (26.2)	
2	873 (11.9)	19,289 (13.6)		815 (12.4)	785 (12.0)	
≥3	469 (6.4)	10,695 (7.5)		436 (6.6)	436 (6.6)	
JCS score at admission, n (%)			0.123			0.040
0	3425 (46.5)	61,623 (43.3)		2989 (45.5)	2940 (44.8)	
1	1604 (21.8)	30,553 (21.5)		1441 (22.0)	1497 (22.8)	
2	1097 (14.9)	21,413 (15.1)		1017 (15.5)	1000 (15.2)	
3	774 (10.5)	17,133 (12.1)		695 (10.6)	697 (10.6)	
10	265 (3.6)	5305 (3.7)		234 (3.6)	243 (3.7)	
20	61 (0.8)	1559 (1.1)		55 (0.8)	61 (0.9)	
30	53 (0.7)	1348 (0.9)		48 (0.7)	45 (0.7)	
100	56 (0.8)	1439 (1.0)		55 (0.8)	45 (0.7)	
200	25 (0.3)	1370 (1.0)		24 (0.4)	24 (0.4)	
300	6 (0.1)	433 (0.3)		6 (0.1)	12 (0.2)	
Missing	0 (0.0)	<5 (0.0)		0 (0.0)	0 (0.0)	
Surgical site, n (%)			0.032			0.012
Rt	1964 (26.7)	38,426 (27.0)		1750 (26.7)	1769 (27.0)	
Lt	2425 (32.9)	48,149 (33.9)		2169 (33.0)	2143 (32.6)	
Bilat	874 (11.9)	15,697 (11.0)		789 (12.0)	806 (12.3)	
Not specified	2103 (28.6)	39,905 (28.1)		1856 (28.3)	1846 (28.1)	
Admission-surgery interval, n (%)			0.088			0.018
1 day (surgery on admission day)	5827 (79.1)	107,249 (75.4)		5181 (78.9)	5230 (79.7)	
2 days (surgery on the following day)	1539 (20.9)	34,928 (24.6)		1383 (21.1)	1334 (20.3)	

ASD = absolute standardized mean difference.

Hospital treatment preference was calculated by dividing the total number of patients who started TXA within 2 days after burr hole surgery for CSDH by the total number of burr hole surgeries for CSDH performed at each hospital. To ensure stable estimates of the instrumental variable, we excluded patients who were admitted to hospitals with a hospital volume of fewer than 10 cases per year in the instrumental variable analysis. A two-stage least-squares estimation model, which was also adjusted for all covariates, was applied to the instrumental variable analysis. The correlation between continuous instrumental variables and TXA use after burr hole surgery was

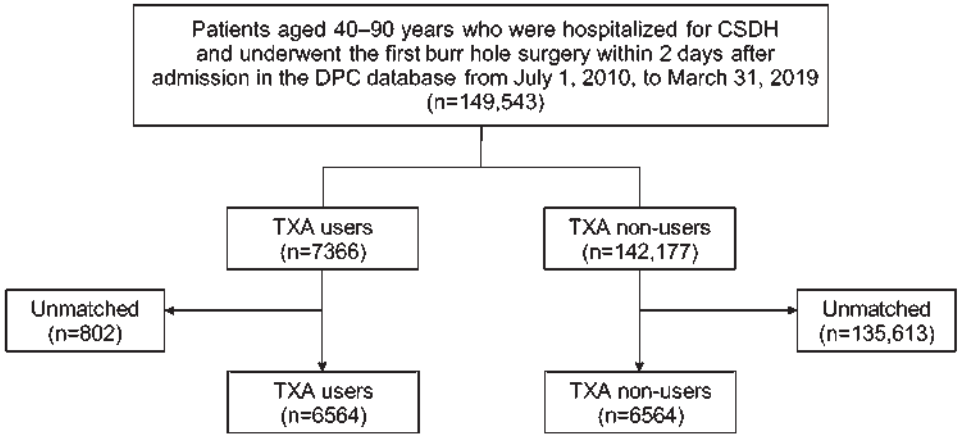

FIG. 1. Study flowchart.

tested using the F-statistic derived from the first stage of the model. An F-statistic of > 10 was considered a strong instrumental variable.

All statistical analyses were performed using R (version 3.6.3, The R Foundation for Statistical Computing). All statistical tests were two-sided. Statistical significance was defined as $p < 0.05$ or assessed with the 95% confidence interval.

Results

A total of 149,543 patients from 1100 hospitals were eligible for the analyses (Fig. 1). Of these, 7366 (4.9%) patients started oral TXA within 2 days after surgery; 8797 (5.9%) patients required reoperation within 1 year after surgery.

Table 1 presents the baseline characteristics of TXA users and nonusers before and after propensity score matching. Before matching, TXA was more likely to be used in patients who were treated at a later study period, those who were treated in higher-volume hospitals, and those who had lower JCS scores on admission. One-to-one propensity score matching created 6564 matched pairs. After propensity score matching, the baseline characteristics were finely balanced between the two groups, with an absolute standardized mean difference of < 0.1. In the TXA users of the matched population, the median TXA dose was 750 mg/day. The C-statistic was 0.92 (95% CI 0.92–0.92).

Table 2 presents the study outcomes in the matched population. The reoperation rate was significantly lower in TXA users than in nonusers (1.9% vs 6.1%, $p < 0.001$). There was no significant difference in the incidence rates of deep venous thrombosis, pulmonary embolism, cerebral infarction, and composite adverse events. Occurrence of myocardial infarction was significantly less frequent in TXA users than in nonusers (0.0% vs 0.2%, $p = 0.026$). Total hospitalization costs were also significantly lower in TXA users than in nonusers ($5229 vs $5344, $p < 0.001$).

Table 3 presents the risk differences and 95% CIs for reoperation rates in TXA users compared with nonusers. In the propensity score–matched analysis, TXA use was associated with a significantly lower risk for reoperation, with a risk difference of –4.1% (95% CI –4.8% to –3.4%). Instrumental variable analysis was conducted on 141,083 patients from 778 hospitals with a hospital volume of at least 10 patients per year. The instrumental variable of hospital treatment preference was strongly associated with TXA use (F-statistic = 38,211). Two-stage least-squares analysis using the instrumental variable showed a significant association between TXA use and lower reoperation rate with a risk difference of –4.9% (95% CI –6.2% to –3.6%).

TABLE 2. Comparison of study outcomes between the matched patients

Outcome	TXA Users (n = 6564)	TXA Nonusers (n = 6564)	p Value
Reop, n (%)*	126 (1.9)	400 (6.1)	<0.001
Deep venous thrombosis, n (%)	7 (0.1)	6 (0.1)	0.999
Pulmonary embolism, n (%)	2 (0.0)	1 (0.0)	0.999
Cerebral infarction, n (%)	25 (0.4)	21 (0.3)	0.658
Myocardial infarction, n (%)	2 (0.0)	11 (0.2)	0.026
Composite adverse event, n (%)†	36 (0.5)	39 (0.6)	0.817
Hospitalization cost, median (IQR)‡	$5229 ($4158–6864)	$5344 ($4223–7423)	<0.001

* Reoperation within 1 year after the first burr hole surgery.
† Composite adverse events included deep venous thrombosis, pulmonary embolism, cerebral infarction, and myocardial infarction.
‡ Total hospitalization costs for both initial admission and readmission.

TABLE 3. Risk difference for reoperation rates in TXA users compared with nonusers

Outcome	Risk Difference, % (95% CI)
Propensity score–matched analysis	–4.1 (–4.8 to –3.4)
Instrumental variable analysis	–4.9 (–6.2 to –3.6)

Discussion

Our analyses revealed that oral TXA use after burr hole surgery for CSDH was associated with a significantly lower reoperation rate. Furthermore, total hospitalization costs were significantly lower among TXA users.

We found a substantial recurrence rate after burr hole surgery, with the need for reoperation in 5.9% of the patients, which was consistent with the results of previous studies.[1–5] As the number of older patients, who are at the highest risk of recurrence[23] and vulnerable to repetitive surgery,[24] is expected to increase in the future,[1] these results highlight the need for adjuvant treatment that reduces the reoperation rate after CSDH surgery.

Based on the understanding of the inflammatory response in the development of CSDH, medical treatments, including corticosteroids, atorvastatin, and angiotensin-converting enzyme inhibitors, have been explored; however, to date, no established adjuvant treatment has been established.[25,26] Evidence regarding TXA use in CSDH management is limited to only case series, except for a prospective study that compared 72 patients who received 750 mg of TXA per day after burr hole surgery with 82 controls.[13] The study found a substantially lower reoperation rate in the TXA group (1.4% vs 9.8%), but the difference was not statistically significant. This could be explained by the small sample size of the study, which resulted in insufficient statistical power. The use of a large nationwide database enabled us to show for the first time the significant benefit of TXA in CSDH treatment based on a comparative study. The results reflect real-world practice, suggesting that our findings are generalizable.

Compared with other potential medical treatments, TXA has several advantages. First, TXA has a favorable safety profile. The most common adverse effects are mild gastrointestinal disturbances and headache.[6,11] Theoretically, TXA use can promote thromboembolic events; however, previous large trials have shown that this adverse effect was not clinically significant at doses of 1–2 g.[27–29] Our results showed no significant increase in thromboembolic events in TXA users compared with nonusers, which were consistent with the results of previous studies. The median TXA dose of 750 mg/day used in this study was lower than the dose regimen used in previous trials. These results suggest that adjuvant TXA can reduce the reoperation rate after burr hole surgery in patients with CSDH without significant adverse effects. Second, there are only a few known interactions between TXA and other drugs.[11] Older individuals, who are at the highest risk of CSDH[1–5] and its recurrence,[23] commonly are on a regimen of multiple medications for two or more chronic health conditions. As the risk of polypharmacy-associated harm increases with the magnitude of drug-drug interactions,[30] a low drug interaction profile is favorable. Finally, TXA is inexpensive. In Japan, oral TXA (750 mg) is available for less than $1. The significantly lower total hospitalization cost in TXA users suggested that adjuvant oral TXA after burr hole surgery for CSDH is favorable from a cost-effectiveness perspective.

Given the advantages of TXA, our results highlight a promising opportunity for TXA as an adjuvant treatment after burr hole surgery for CSDH. To confirm our findings, further large-scale randomized controlled studies are warranted.

Limitations

This study had several limitations. First, it was a retrospective study. Although we adjusted for confounding factors using propensity score–matched analysis, unmeasured confounding factors may have biased our results. For example, radiological findings and the use of drainage systems might be associated with the recurrence rate, although the association between these factors and recurrence after burr hole surgery for CSDH remains controversial.[31,32] However, the results of the sensitivity analysis using instrumental variable analysis were consistent, suggesting that our results were robust. Second, surgical indications for recurrent CSDH were not standardized between hospitals, although surgery is generally considered for symptomatic patients with radiological evidence of cerebral compression.[33] Third, hospitalizations in one hospital cannot be linked with those in another hospital in the DPC database. Based on the clinical experience in Japan, we assumed that reoperations were conducted at the same hospital and the likelihood of undergoing reoperation in another hospital was not associated with TXA use; however, if both of these assumptions do not hold, our results could be biased. Fourth, the doses and duration of TXA use after discharge were not determined because related data were not included in the database. Finally, surgical outcomes may differ in other countries with diverse demographics and surgical procedures. Our results need to be validated externally.

Conclusions

Adjuvant therapy with TXA after burr hole surgery, administered orally and started within 2 days after surgery, was significantly associated with a reduced risk of reoperation in patients with CSDH. Further studies are required to validate these findings.

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Disclosures

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

Conception and design: Shibahashi. Acquisition of data: Ohbe, Yasunaga. Analysis and interpretation of data: Shibahashi, Ohbe. Drafting the article: Shibahashi. 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: Shibahashi. Statistical analysis: Shibahashi, Ohbe. Administrative/technical/material support: Ohbe, Yasunaga. Study supervision: Yasunaga.

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