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MISCELLANEOUS

Tranexamic acid and post-tonsillectomy hemorrhage: propensity score and instrumental variable analyses

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Abstract

Purpose Although post-tonsillectomy hemorrhage occurs rarely, it can be life-threatening. Previous studies showed that tranexamic acid (TXA) had insignificant association with the rate of post-tonsillectomy hemorrhage, but those findings were limited by small sample sizes. The purpose of this study was to examine the effectiveness of TXA in preventing post-tonsillectomy hemorrhage using nationwide database.

Methods Data of a retrospective cohort of 117,598 patients from 750 hospitals, who had undergone tonsillectomy between 2010 and 2016, were drawn from the Diagnosis Procedure Combination database in Japan and studied.

Results Propensity score-matched analysis showed no significant differences in proportions of reoperation or blood transfusion after tonsillectomy between the treatment (TXA from the day of tonsillectomy) and control groups (1.50% vs. 1.47%, $p=0.64$). Instrumental variable analysis also showed no significant differences (odds ratio, 0.98; 95% confidence interval, 0.86–1.13; $p=0.82$). Higher proportions of reoperation or blood transfusion were significantly associated with male sex, older age, emergency hospitalization, prolonged anesthesia, and medium hospital volume (annual number of tonsillectomies).

Conclusions Administration of TXA from the day of tonsillectomy is not associated with reduction in reoperation or blood transfusion rates.

Keywords Post-tonsillectomy hemorrhage · Tranexamic acid · Reoperation for hemostasis · Propensity score matching · Instrumental variable analysis

Introduction

Tonsillectomy is one of the most common surgery performed by otolaryngologists worldwide. Postoperative complications are rare; however, post-tonsillectomy hemorrhage is potentially life-threatening.

Post-tonsillectomy hemorrhage can be divided into two categories: primary hemorrhage (within 24 h of tonsillectomy) and secondary hemorrhage (more than 24 h after tonsillectomy) [1]. Primary hemorrhages reportedly occur in 0.2–2.2% of patients and secondary hemorrhages rates in 0.1–13.2% [1–4]. Hemostasis is usually achieved by direct pressure on the bleeding point, electrocautery under local or general anesthesia, or ligation of bleeding vessels under general anesthesia.

Tranexamic acid (TXA) is an antifibrinolytic agent that inhibits activation of plasminogen to plasmin [5]. Several studies have found that TXA is associated with reducing risk of bleeding in cardiothoracic and orthopedic surgery [6, 7]. In ENT surgery, TXA is sometimes used to prevent bleeding, including peri-tonsillectomy.

A systematic review and meta-analysis of seven studies with control groups ($n=2444$) found that TXA was associated with a significant reduction in tonsillectomy blood loss volume, but had no impact on the rate of post-tonsillectomy hemorrhage [5]. However, this systematic review was mostly composed of studies published in the 1970s and the sample was small.

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In the present retrospective observational study of data drawn from a national inpatient database in Japan, we investigated whether administration of TXA is associated with a reduced rate of post-tonsillectomy hemorrhage requiring reoperation for hemostasis.

Materials and methods

We used the Diagnosis Procedure Combination (DPC) database, which is a national inpatient database in Japan that contains the following administrative claims data and discharge abstract data: hospital identifier, date of hospital admission, patient age and sex, length of stay, discharge status, main diagnosis on admission, complications after admission, surgical procedures, blood transfusion, and drugs and devices used.

The University of Tokyo Institutional Review Board approved this study and, because only anonymous data were used, waived the requirement for informed consent.

Patient selection

Data were obtained for patients who had undergone tonsillectomy from July 2010 to March 2016. We excluded patients with benign pharyngeal tumors (ICD-10 codes D104, D105, D107, D109, and D370); malignant head and neck tumors, including carcinomas of unknown primary, (C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C30, C31, C32, C76, C77, C78, C79, and C80); receiving dialysis; with hereditary bleeding disorders such as factor VIII deficiency, factor IX deficiency, and von Willebrand disease; deficiency of other clotting factors (D66, D67, D680, D682); liver disease (K703, K717, K712, K729, K740, K741, K742, K753, K744, K745, K746, K761, and B18); and lymphoma (C81, C82, C83, C84, and C85). We also excluded those who were taking anticoagulants or antiplatelet drugs, had received heparin for more than 3 days preoperatively and aged more than 61 years.

We allocated the eligible patients into two groups, namely, who had and had not administration of TXA intravenously from the day of tonsillectomy.

Independent variables

The main exposure was administration of TXA intravenously from the day of tonsillectomy. We obtained the following from the data base: sex, age, height, weight, indication for surgery, comorbidities, perioperative medications, anesthesia time, academic hospital or not, smoking status, emergency hospitalization or not, and hospital volume (annual number of tonsillectomies).

Outcomes

The primary outcomes were (i) post-tonsillectomy hemorrhage requiring reoperation for hemostasis under general anesthesia or (ii) blood transfusion, during the same hospitalization or rehospitalization.

Statistical analysis

We used the χ^2 test to compare rates of reoperation and blood transfusion between the TXA and control groups.

In the propensity score (PS) matched groups, we used the χ^2 test to compare reoperation and transfusion between the two groups. Because administration of TXA was strongly associated with hospital characteristics, we performed further analysis using the instrumental variable (IV) method. The threshold for significance was $p < 0.05$. We used IBM SPSS Statistics version 25.0 (IBM, Armonk, NY, USA) and STATA version 15.0 (StataCorp, College Station, TX, USA) for all analyses.

Propensity score matching

We performed PS matching between TXA and control groups using estimated PS for each patient. To estimate PS, we fitted a logistic regression model for the control group as a function of patient characteristics, treatments, and hospital factors. Patient characteristics comprised sex, age (≤ 15, 16–40, and 41–60 years), body mass index (< 18.5, 18.5–22.9, 23–24.9, 25–29.9, and ≥ 30 kg/m^2), smoking status (nonsmoker, current/past smoker), Charlson comorbidity index (0 or ≥ 1), tonsillectomy for noninfectious diseases (IgA nephropathy and tonsillar hypertrophy) or not, and with or without peritonsillar abscess. We classified body mass index according to the definition of the World health Organization (WHO). Treatment factors included emergency admission or not, general anesthesia time (≥ 180, < 180 min), and with or without intravenous steroid administration. Hospital factors included the type of hospital and hospital volume, which we defined as the average number of tonsillectomies per year. We classified hospital volume into three categories, low (≤ 40 tonsillectomies/year), medium (41–66), and high (≥ 67). We categorized hospital volume into tertiles to ensure almost equal numbers of patients in the three categories.

We calculated c-statistics and performed a one-to-one matched analysis using nearest-neighbor matching with 0.2 standard deviations of the logit of the PS as the caliper value. To estimate the balance of covariates after PS matching, we calculated standardized differences to

compare the characteristics of patients between the treatment and control groups. We defined a standardized difference of > 10% as out of balance.

Instrumental variable analysis

Hidden biases caused by unmeasured confounders cannot be removed with multivariable logistic regression analyses or PS analyses. We, therefore, performed IV analysis to confirm our PS analysis. IV analyses require the following assumptions. First, IV should be highly correlated with the treatment assigned. Second, IV must not be correlated with patient characteristics. Third, IV must not directly affect patient outcomes except through treatment [8].

In the present study, we defined the IV as "use of TXA in the directly preceding patient". The ability of TXA to prevent post-tonsillectomy hemorrhage is controversial; thus, administration of TXA may depend on the attending physicians' preference and experience. In particular, the decisions about using tranexamic acid of a physician treating consecutive post-tonsillectomy patients may be affected by whether or not the directly preceding patient has received TXA. This variable meets the above-mentioned three assumptions and can, therefore, act as an IV, thereby allowing a "natural experiment" for an unbiased estimate of the outcome, even in the presence of unmeasured confounders.

We used a two-stage residual inclusion method for our IV analysis [9]. In the first-stage model, we analyzed the association between IV and treatment assignment with adjustment for covariates. We determined the raw residual for each patient by calculating the difference between the model-predicted probability of receiving TXA and the actual receipt of it. We included the residuals as an additional covariate in the second-stage model, in which we analyzed the association between treatment and outcome. The IV analysis was performed using robust standard errors.

Results

We started with a cohort of 117,598 patients who had undergone tonsillectomy from 1 July 2010 to 31 March 2016.

We then excluded 2,449 patients who had benign pharyngeal tumors, malignant head and neck tumors, liver disease, hereditary bleeding disorders, or lymphoma, 98 who were receiving dialysis; 1,705 who were taking anticoagulants or antiplatelet drugs before tonsillectomy; 355 who received heparin before tonsillectomy; and 2,063 aged more than 61 years. We then classified the remaining 110,928 eligible patients from 745 hospitals into those who received TXA from the day of tonsillectomy (TXA group, $n = 50{,}501$) and those who did not (control group, $n = 60{,}427$) (Fig. 1).

Table 1 shows the characteristics of patients in the two groups. Age, body mass index, smoking status, and indication for surgery are out of balance between the groups. After PS-matching analysis, distribution of the patient characteristics was well balanced. The c-statistic was 0.6.

Table 2 shows the proportions of outcomes (combined reoperation and blood transfusion). There was no significance difference in outcome rates between the control and TXA groups (1.33% vs. 1.45%, $p = 0.09$), including after PS-matching analysis (1.50% vs. 1.47%, $p = 0.64$).

The IV analysis confirmed that there was an insignificant difference in outcome rates between the groups (Table 3). The F statistic was 39,596 ($p < 0.001$). We consider that use of TXA for the directly preceding patient was a sufficiently strong instrumental variable for predicting TXA administration. In addition, male patients were more likely to require reoperation than female patients. Older age, emergency hospitalization, and prolonged anesthesia were also significant risks for reoperation or blood transfusion. In contrast, underweight, tonsillectomy for non-infectious disease, peritonsillar abscess, and academic hospital were associated with lower rates of these outcomes.

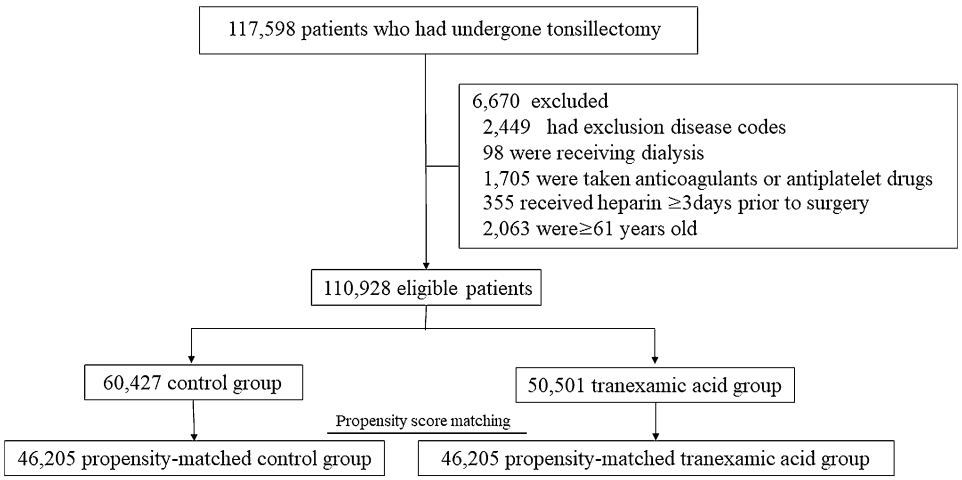

Fig. 1 Flow chart showing selection of patients

Table 1 Characteristics of patient in unmatched and propensity score-matched groups

	Unmatched groups					Matched groups				Standardized difference, %
	Tranexamic acid group		Control group		Standardized difference, %	Tranexamic acid group		Control group		
	(*n* = 50,501)		(*n* = 60,427)			(*n* = 46,205)		(*n* = 46,205)		
Sex										
Male	29,725	(58.9)	36,167	(59.9)	2.0	26,733	(57.9)	26,868	(58.1)	0.6
Female	20,776	(41.1)	24,260	(40.1)	2.0	19,472	(42.1)	19,337	(41.9)	0.6
Age (years)										
≤ 15	19,497	(38.6)	32,809	(54.3)	31.9	19,497	(42.2)	19,501	(42.2)	0.0
16–40	25,570	(50.6)	22,722	(37.6)	26.5	21,814	(47.2)	22,023	(47.7)	0.9
41–60	5,434	(10.8)	4,896	(8.1)	9.1	4,894	(10.6)	4,681	(10.1)	1.5
Body Mass Index (kg/m^2)										
< 18.5	8,767	(17.4)	12,938	(21.4)	10.3	8,763	(19.0)	8,344	(18.1)	2.3
18.5–22.9	16,292	(32.3)	16,166	(26.8)	12.1	14,838	(32.1)	14,377	(31.3)	1.7
23.0–24.9	5,617	(11.1)	5,120	(8.5)	8.9	4,392	(9.5)	4,831	(10.5)	3.2
25.0–29.9	6,727	(13.3)	6,121	(10.1)	9.9	5,467	(11.8)	5,832	(12.6)	2.4
≥ 30.0	2,764	(5.5)	2,488	(4.1)	6.3	2,411	(5.2)	2,400	(5.2)	0.1
Missing	10,334	(20.5)	17,594	(29.1)	20.1	10,334	(22.4)	10,321	(22.3)	0.1
Smoking										
Nonsmoker	36,446	(72.2)	46,636	(77.2)	11.5	32,587	(70.5)	34,082	(73.8)	7.2
Current/past smoker	10,736	(21.3)	9,741	(16.1)	13.2	10,306	(22.3)	9,414	(20.4)	4.7
Unspecified	3,319	(6.6)	4,050	(6.7)	0.5	3,312	(7.2)	2,709	(5.9)	5.3
Charlson comorbidity index on admission										
0	48,410	(95.9)	57,650	(95.4)	2.2	44,123	(95.5)	44,229	(95.7)	1.1
≥ 1	2,091	(4.1)	2,777	(4.6)	2.2	2,082	(4.5)	1,976	(4.3)	1.1
Tonsillectomy for non-infectious disease	15,234	(30.2)	23,430	(38.8)	18.2	14,653	(31.7)	14,967	(32.4)	1.5
Peritonsillar abscess	665	(1.3)	757	(1.3)	0.6	663	(1.4)	539	(1.2)	2.4
Emergency admission	447	(0.9)	641	(1.1)	1.8	447	(1.0)	349	(0.8)	2.3
Anesthesia time (minutes)										
≤ 180	47,974	(95.0)	57,442	(95.1)	0.3	43,712	(94.6)	43,959	(95.1)	2.4
> 180	2,472	(4.9)	2,912	(4.8)	0.4	2,438	(5.3)	2,199	(4.8)	2.4
Missing	55	(0.1)	73	(0.1)	0.4	55	(0.1)	47	(0.1)	0.5
Intravenous steroid administration	6,894	(13.7)	8,154	(13.5)	0.5	6,859	(14.8)	6,392	(13.8)	2.9
Hospital volume										
Low	16,765	(33.2)	19,083	(31.6)	3.4	15,795	(34.2)	15,105	(32.7)	3.2
Medium	17,710	(35.1)	19,845	(32.8)	4.7	14,404	(31.2)	15,833	(34.3)	6.6
High	16,026	(31.7)	21,499	(35.6)	8.1	16,006	(34.6)	15,267	(33.0)	3.4
Type of hospital										
Academic	12,729	(25.2)	14,743	(24.4)	1.9	10,748	(23.3)	10,912	(23.6)	0.8
Non-academic	37,772	(74.8)	45,684	(75.6)	1.9	35,457	(76.7)	35,293	(76.4)	0.8

Table 2 Reoperation or blood transfusion rates in tranexamic acid and control groups

Group	Unmatched group			Matched group		
	No	Outcome no. (%)	*p* value	No	Outcome no. (%)	*p* value
Control	60,427	803 (1.33)	0.09	46,205	695 (1.50)	0.64
Tranexamic acid	50,501	731 (1.45)		46,205	678 (1.47)	

Table 3 Odds ratios for reoperation or blood transfusion by instrumental variable analysis

Variables	Odds ratio	95% Confidence interval	*p* value
Tranexamic acid	0.98	0.86–1.13	0.82
Male	1.47	1.30–1.65	< 0.001
Age (years)			
≤ 15	1.00		
16–40	1.87	1.52–2.29	< 0.001
41–60	1.26	0.97–1.62	0.08
Body Mass Index (kg/m^2)			
< 18.5	0.80	0.65–0.98	0.03
18.5–22.9	1.00		
23–24.9	1.01	0.86–1.19	0.91
25–29.9	0.99	0.84–1.15	0.86
≥ 30	0.97	0.79–1.19	0.76
Missing	0.60	0.48–0.76	< 0.001
Smoking			
Nonsmoker	1.00		
Current/past	1.02	0.90–1.17	0.71
Unknown	0.95	0.77–1.16	0.60
Comorbidity	0.91	0.70–1.18	0.48
Tonsillectomy for non-infectious disease	0.78	0.67–0.92	0.002
Peritonsillar abscess	0.50	0.33–0.73	< 0.001
Emergency hospitalization	7.30	5.36–9.96	< 0.001
Anesthesia time (minutes)			
≤ 180	1.00		
> 180	13.7	12.2–15.4	< 0.001
Missing	1.95	0.61–6.25	0.26
Intravenous steroid administration	0.97	0.84–1.12	0.68
Hospital volume			
Low	1.00		
Medium	1.32	1.17–1.50	< 0.001
High	1.03	0.90–1.18	0.65
Academic hospital	0.59	0.52–0.67	< 0.001

Discussion

In this PS and IV analyses using data from a national inpatient database, TXA from the day that tonsillectomy was performed was not significantly associated with post-tonsillectomy hemorrhage. Previous studies have shown significant associations between male sex, older age, prolonged anesthesia, and non-academic hospitals and higher rate of postoperative bleeding, which is consistent with our results [1, 10, 11]. Another study showed that immediate tonsillectomy for abscess is not associated with postoperative bleeding [2], whereas in our study, we found a lower rate of postoperative bleeding patients who had undergone immediate tonsillectomy for abscess.

Several studies have investigated the relationship between obesity and post-tonsillectomy hemorrhage [12, 13]. One of these studies showed that overweight or obesity (BMI ≥ 25) was not associated with an increased rate of post-tonsillectomy hemorrhage, whereas underweight (BMI < 18.5) was associated with a lower rate of post-tonsillectomy hemorrhage [13]. Our study showed a similar trend.

One of the strengths of our study was the large number of patients drawn from a nationwide inpatient database in Japan. We performed several analyses to confirm the results. The PS-matching and IV analyses showed similar results, suggesting that our findings are robust.

TXA is a synthetic lysine analogue that facilitates antifibrinolysis via competitive reversible blockade of lysine-binding sites on plasminogen molecules and as a non-competitive inhibitor of plasmin. These actions inhibit conversion of plasminogen to plasmin on the surface of fibrin, thus stabilizing fibrin clots [14, 15].

In this study, we did not show that TXA is effective in preventing post-tonsillectomy hemorrhage. We consider

that this may be because our main outcome was reoperation for secondary post-tonsillectomy hemorrhage. Secondary bleeding usually occurs when the primary scab or necrotic tissue in the tonsillar bed sloughs off before the wound has completely healed [10]. Mechanical stimulation, for example by swallowing food, induces secondary post-tonsillectomy hemorrhage. Thus, stabilization of fibrin clots mediated by TXA cannot prevent secondary bleeding. We also consider that the short half-life of TXA [15] contributed to our findings. In this study, the period of administration of TXA was almost within 7 days, and TXA was most frequently used on the day 1. From a biological perspective, administration of TXA for only 1 day cannot prevent post-tonsillectomy bleeding.

Previous studies have investigated the adverse effects of TXA administration in several types of operative procedure. Seizures, thromboembolism, and renal dysfunction were reported in cardiothoracic surgery [6, 16]. However, in another study, these major events did not occur in patients undergoing tonsillectomy, whereas minor adverse effect such as nausea, headache, vomiting, and dizziness did [5, 13]. We consider the explanation for this discrepancy is that the dose of TXA is lower in the perioperative period of tonsillectomy than in that of cardiothoracic surgery.

We found that TXA is safe, but did not show that it prevents post-tonsillectomy hemorrhage. Thus, administration of TXA may not be justifiable.

This study had several limitations. First, it was difficult to distinguish administration of TXA after post-tonsillectomy hemorrhage from planned administration on the day of tonsillectomy. Second, we could not accurately ascertain the dose of TXA administered from the database. Third, we could not know the variability of skill and technique of tonsillectomy.

Conclusion

Our results show that administration of TXA from the day of tonsillectomy does not reduce rates of reoperation or blood transfusion.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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