Journal of Cardiothoracic and Vascular Anesthesia ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

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journal homepage: www.jcvaonline.com

Original Article

Evaluating the Effect on Mortality of a No-Tranexamic acid (TXA) Policy for Cardiovascular Surgery

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Objectives: The authors stopped using tranexamic acid (TXA) in April 2013. The present study aimed to examine the impact of a "no-TXA-use" policy by comparing the adverse effects of TXA and clinical outcomes before and after the policy change in patients undergoing cardiovascular surgery.
Design: A single center retrospective cohort study.
Setting: A single cardiovascular center.
Participants: Patients undergoing cardiovascular surgery between January 2008 and July 2015 (n = 3,535).
Interventions: Patients' outcomes before and after the policy change were compared to evaluate the effects of the change.
Measurements and Main Results: The seizure rate decreased significantly after the policy change (6.9% *v* 2.7%, p < 0.001). However, transfusion volumes and blood loss volumes increased significantly after the policy change (1,840 mL *v* 2,030 mL, p = 0.001; 1,250 mL *v* 1,372 mL, p < 0.001, respectively). Thirty-day mortality was not statistically different (1.6% *v* 1.4%, p = 0.82), nor were any of the other outcomes. Propensity-matched analysis and segmented regression analysis showed similar results.
Conclusions: The mortality rate remained the same even though the seizure rate decreased after the policy change. Blood loss volume and transfusion volume both increased after the policy change. TXA use provides an advantageous benefit by reducing the need for blood transfusion.

Key Words: blood transfusion; tranexamic acid; cardiovascular diseases

PATIENTS UNDERGOING cardiac surgery have increased risk of potentially life-threatening excessive bleeding,[1] and many observational studies have shown that both blood transfusion and bleeding are strongly associated with poor outcomes after cardiac surgery.[2–4] Also, global populations are aging, and this will continue in future decades, increasing the demand for blood products.[5] Therefore, reducing bleeding and blood transfusion rates are necessary to meet future supply and demand for blood products.

Source of Support: This research was supported in part by the Research Grant on Regulatory Science of Pharmaceuticals and Medical Devices from Japan Agency for Medical Research and development, AMED, and a grant-in-aid from the Takeda Science Foundation.

Conflict of Interest: Shigeki Miyata received research support from Daiichi Sankyo Co, Ltd, and Mitsubishi Tanabe Pharma Corp. He also received speaker honoraria from Daiichi Sankyo Co, Ltd. None of the other authors declare any conflict of interest.

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http://dx.doi.org/10.1053/j.jvca.2017.10.018
1053-0770/

Tranexamic acid (TXA) is a synthetic lysine-analogue antifibrinolytic that reduces the risk of bleeding during cardiac surgery. However, a risk of thromboembolic events[6] and seizures with TXA is a concern for potentially worsened patient outcomes. In fact, one study revealed that in-hospital mortality was approximately 5-fold higher in patients with TXA-associated seizures compared with those without seizures,[7] and that even moderate TXA doses are associated with doubled seizure and in-hospital mortality rates.[7] Although it is controversial whether TXA is associated with poor outcomes, some hospitals substituted epsilon-aminocaproic acid, which is no longer available in Japan, for TXA because of these concerns.[8] The authors also stopped using TXA in April 2013, which enabled them to conduct a before-and-after study to investigate the safety and efficacy of TXA in patients undergoing cardiovascular surgery.

The present study aimed to examine the impact of this "no-TXA-use" policy by comparing the adverse effects associated with TXA and clinical outcomes before and after the policy change in patients undergoing cardiovascular surgery.

Materials and Methods

Patients and Study Design

This study was a retrospective, single-center, cohort study, which was approved by the ethics committee of the National Cerebral and Cardiovascular Center, Osaka, Japan and met the guidelines of the Helsinki Declaration. Because of concern regarding TXA's safety, the authors implemented a "no-TXA-use" policy in April 2013; after April 2013, the authors withdrew all TXA from the operating room. The authors usually target a 10 g/dL hemoglobin level to administer red blood cells, and this policy did not change over the study period. The authors planned this trial with 80% power to detect a difference in mortality after propensity-score matching based on previous comparisons (4.1% *v* 1.5%)[7] between patients receiving TXA (TXA group) before the policy and patients not receiving TXA after the policy (non-TXA group). Using a chi-square test with a 2-sided type I error rate of 5%, the authors calculated a required sample size of 708 patients for each group. The authors estimated a 30% patient drop-off rate during the matching process; therefore, at least 1,012 patients were needed for each group. Based on this calculation, data before changing the policy were collected from April 2008 to March 2013 (60 months), and data after changing the policy were collected from April 2013 to July 2015 (28 months). During these periods, the authors enrolled consecutive patients undergoing cardiac surgery such as coronary artery bypass grafting (CABG), valve replacement or repair, and major aortic surgery (Table 1). Patients with missing characteristics data were excluded. Next, the authors compared the outcomes of study participants investigated before the policy change with those measured after the policy change to evaluate the effects of the policy change. However, they did not randomly-allocate patients to the groups (before and after the policy change), and patients may not have been comparable in their demographics and characteristics, as a result. Therefore, any outcome differences between the groups may not have resulted from the policy change, but rather, may have resulted from confounding. To adjust for confounding, the authors performed propensity-score matching to balance patients' backgrounds and to evaluate the effect of TXA administration. The TXA group and non-TXA group were matched using propensity-score matching. Because previous studies demonstrated that seizure and in-hospital mortality risk may be higher in patients undergoing open-heart surgery compared with CABG-only surgery,[7,9,10] the authors performed sensitivity analyses by excluding CABG-only patients. Finally, they used an interrupted time-series design, which is considered the strongest quasi-experimental design for estimating interventional effects in nonrandomized settings, to analyze the effect of the policy change.

Data Collection

The authors used data from the Japan Adult Cardiovascular Database, which captures clinical information from almost all Japanese hospital units performing cardiovascular surgery.[11] The data-collection form has variables that are nearly identical to those in the Society for Thoracic Surgeons National Database. However, these databases lack data on postoperative convulsive seizures and anesthetic management such as TXA dose and transfusion volume; therefore, the authors collected these data from electronic medical records and incorporated the data into the analyses.

Primary Outcome

The primary outcome was 30-day mortality measured from the Japan Adult Cardiovascular Database.

Secondary Outcomes

Secondary outcomes included adverse effects associated with TXA (seizures, thromboembolism, and renal dysfunction) and other clinical outcomes (reoperation for bleeding, transfusion volume, intraoperative blood loss, duration of mechanical ventilation, and length of intensive care unit [ICU] stay). The authors defined convulsive seizures as clinically apparent seizures during ICU stay, and all patients with seizures underwent routine cerebral computed tomographic scans to exclude ischemia or bleeding. The authors defined thromboembolism as pulmonary embolism, stroke, limb ischemia, and cardiac infarction, and renal dysfunction as renal failure requiring dialysis.

Anesthesia, Management of Anticoagulation, and TXA Administration

Patients received no premedication. After intravenously inducing anesthesia with fentanyl (1.5–2 μg/kg) and propofol (1 mg/kg), rocuronium (1 mg/kg) was given intravenously to facilitate orotracheal intubation with a cuffed tube. All patients

Please cite this article as: Maeda T, et al. (2017), http://dx.doi.org/10.1053/j.jvca.2017.10.018