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*Original Article*

# Randomized Controlled Trial of Oral Tranexamic Acid Intervention for the Prevention of Type II Endoleak after Endovascular Abdominal Aneurysm Repair

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**Purpose: The purpose of this study was to evaluate tranexamic acid (TA) for the prevention of type II endoleak (EL2) at a high level of evidence by a randomized controlled trial.**
**Methods: Patients who underwent endovascular aneurysm repair (EVAR) between May 2017 and January 2020 were included. Patients in the TA group were given 750 mg of TA daily for a month after EVAR. The incidence of EL2, blood coagulation/fibrinolytic ability, and changes in aneurysm diameter were compared between two groups.**
**Result: On the 7th day after EVAR, EL2 was found in 14 patients (34.1%) in the TA group and in 7 patients (15.9%) in the non-TA group. It was also found in 12 patients (29.3%) in the TA group and 6 patients (13.6%) in the non-TA group at 1 month after EVAR. There was no significant difference in the incidence of EL2 between the two groups (p = 0.051, 0.08). Blood tests revealed that fibrin degradation product and D-dimer were significantly suppressed in the TA group, there was no significant difference in the change of diameter regardless of the TA intake.**
**Conclusion: This study proved anti-fibrinolytic effect of the TA, but it alone had not enough power to decrease EL2 after EVAR.**

**Keywords:** type II endoleak, endovascular aneurysm repair, tranexamic acid, abdominal aortic aneurysm

## Introduction

Stent graft surgery for abdominal aortic aneurysms was developed in the 1990s. This surgery was initially performed on high-risk patients by using a hand-made device. Since then, commercially available devices have been developed, and the surgical procedure has been stabilized. As a result, the indications of this technique have been gradually extended to include lower-risk patients. In the early 2000s, the EUROSTAR registry and EVAR1 trial showed better short-term results with stent graft surgery than with open surgery.[1,2] However, the medium-to-long term results of stent graft surgery have been reported more recently, and according to these reports, stent graft surgery did not always yield better results than open surgery.[3] Endoleaks are one of the most important factors responsible for this finding. An endoleak is a complication peculiar to stent graft treatment for aortic aneurysm and is involved in postoperative aneurysm enlargement in some cases. Among the different types of endoleaks, type II endoleak (EL2) is particularly problematic because it occurs regardless of

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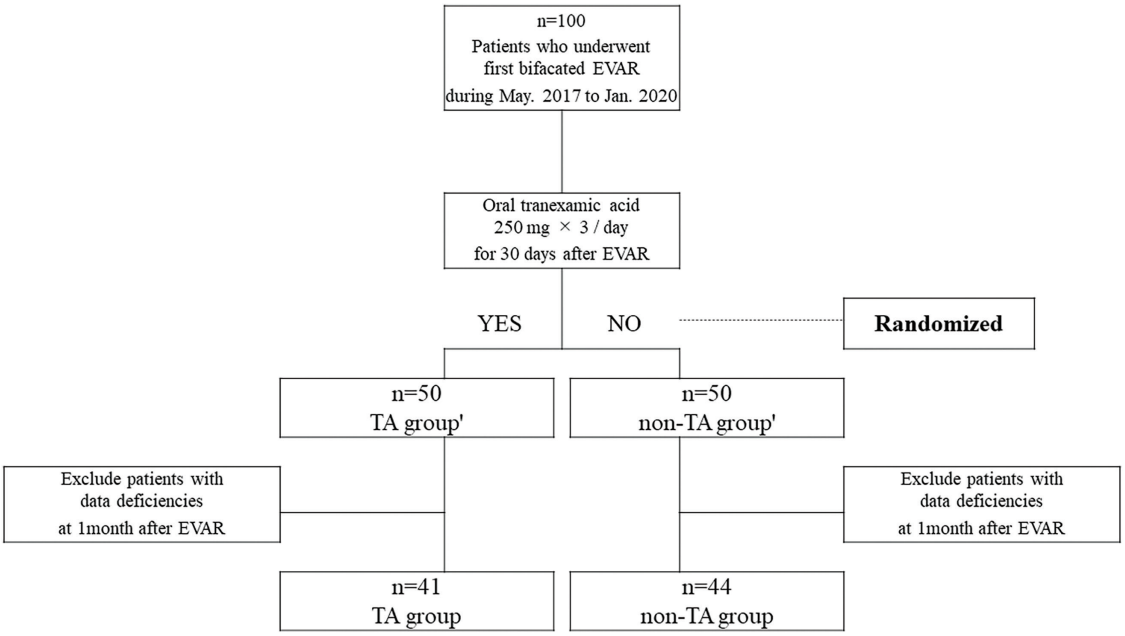



**Fig. 1** Flowchart of patient selection. EVAR: endovascular aneurysm repair; TA: tranexamic acid

the skill of the surgeon. If EL2 occurrence cannot be prevented and the aneurysm sac is enlarged, the patient will require additional treatment such as transcatheter embolization or hemostasis with laparotomy. In high-risk cases, these treatments are often difficult and can yield unfavorable outcomes such as a ruptured aneurysm.

In recent years, Shingaki et al. have reported that the antifibrinolytic effect of tranexamic acid (TA) is effective in suppressing EL2.[4] Conversely, Hiraoka et al. reported that postoperative oral TA was not effective in suppressing EL2.[5] Notably, both reports were retrospective studies. In fact, only a few reports have discussed the relationship between oral TA and EL2, and to the best of our knowledge, there are no reports that have analyzed this relationship prospectively. Therefore, based on the hypothesis that oral TA suppresses EL2, we conducted a prospective randomized controlled trial to obtain higher level evidence for the effectiveness of oral TA in suppressing EL2 after stent graft surgery.

## Materials and Methods

This clinical study was initiated after obtaining approval from the ethics committee of the authors' hospital (IRB No: 2018-CR014). All patients who participated in this study received appropriate information about the study from the authors and signed informed consent. Patients who underwent endovascular aneurysm repair (EVAR) at our hospital between May 2017 and January 2020 were included in this study. Patients who underwent re-do surgery or received treatment for iliac limbs alone were excluded. A total of 100 patients included in this study were randomly divided into two groups evenly: patients in one group received 750 mg of TA every day (250 mg after each meal) for 30 days after stent graft surgery, while those in the other group did not receive TA. The two groups thus obtained were defined as "TA group" and "non-TA group," respectively. No blinding strategy was adopted in this study (open-label trial). Randomization was performed with a random number table prepared using Excel 2016 (Microsoft, Redmond, WA, USA). Patients with insufficient data one month after stent graft surgery were excluded from this study in each group. The new groups thus obtained were defined as the TA and non-TA groups (**Fig. 1**). The following preoperative characteristics were investigated: aneurysm diameter, number of lumbar arteries, patency of the inferior mesenteric artery (IMA), and device selection. Patient characteristics such as hypertension, diabetes mellitus, smoking history, respiratory distress, renal failure (estimated glomerular filtration rate <45 mL/min/1.73 $m^2$), and the history of antiplatelet or anticoagulant therapy were also investigated. The diameter of the aneurysm was defined by measuring the short axis of the largest part of the aneurysm using an axial slice of CT angiography (CTA).

The primary endpoint was the incidence of EL2 at 1 week and 1 month after EVAR, which was evaluated using CTA. Changes in the aneurysm diameter at 1 week,

**Table 1 Participants' baseline characteristics**

| | TA group (n = 41) | non-TA group (n = 44) | p value |
|---|---|---|---|
| Age (y.o.) | 76.0 ± 8.3 | 75.6 ± 7.9 | 0.82 |
| Male | 32 (78.0%) | 39 (88.6%) | 0.19 |
| Hypertension | 28 (68.3%) | 38 (86.4%) | <0.05 |
| Diabetes mellitus | 12 (29.3%) | 7 (15.9%) | 0.14 |
| Smoking history | 31 (75.6%) | 35 (79.5%) | 0.66 |
| Renal failure(eGFR <45) | 10 (24.4%) | 14 (31.8%) | 0.45 |
| Respiratory distress | 16 (39.0%) | 24 (54.5%) | 0.15 |
| Antiplatelet/Anticoagulant therapy | 19 (46.3%) | 15 (34.1%) | 0.25 |
| Indication | | | |
| AAA | 31 (75.6%) | 40 (90.9%) | <0.01 |
| CIAA (concomitant AAA) | 10 (24.4%) | 4 (9.1%) | <0.01 |
| Maximum aneurysm diameter (mm) | 48.5 ± 8.8 | 52.2 ± 7.0 | <0.05 |
| Patent IMA | 35 (85.4%) | 32 (72.7%) | 0.15 |
| Number of patent LA | 5.4 ± 1.9 | 5.6 ± 1.6 | 0.69 |
| Device | | | |
| Gore C3 Excluder | 26 (63.4%) | 19 (43.2%) | 0.06 |
| Medtronic Endurant II | 14 (34.1%) | 23 (52.3%) | 0.09 |
| Endologix AFX2 | 1 (2.4%) | 2 (4.5%) | 0.59 |

TA: tranexamic acid, y.o.: years old; eGFR: estimated glomerular filtration rate, AAA: abdominal aortic aneurysm; CIAA: common iliac artery aneurysm, IMA: inferior mesenteric artery, LA: lumbar artery

1 month, 6 months, and 1 year after EVAR, and the results of the blood coagulation/fibrinolysis test at 3 days, 7 days, and 1 month after EVAR were investigated as secondary endpoints. The rate of change in aneurysm diameter from baseline to 6 months and 1 year was also evaluated.

Continuous data were reported as the mean ± standard deviation. Categorical data were presented as absolute numbers and proportions in the study cohort. Differences between the groups were evaluated by Student's *t*-test or Mann–Whitney *U*-test for continuous data, based on the normality of the data. Chi-squared test or Fisher's exact test was used to compare categorical variables.

## Results

Of the 100 patients enrolled in this study, 85 were included in the analyses (**Fig. 1**). Specifically, the TA group had 41 patients (32 male patients; 78%) and the non-TA group had 44 patients (39 male patients; 88.6%). The average age of the patients was 76.0 ± 8.3 years in the TA group, and 75.6 ± 7.9 years in the non-TA group, with no statistically significant difference between the two groups. The devices used were C3 Excluder (GORE, Newark, DE, USA) in 45 patients, Endurant (Medtronic, Dublin, Ireland) in 37 patients, and AFX2 (Endologix, Irvine, CA, USA) in 3 patients. As for the patient background, hypertension was present in 28 patients (68.3%) in the TA group and 38 patients (86.4%) in the non-TA group, showing a significant difference between the groups ($p < 0.045$). In contrast, the groups showed no significant differences in the incidence of diabetes mellitus, smoking history, respiratory distress, renal failure, and taking antiplatelet or anticoagulant therapy. In the TA group, EVAR was indicated for 31 (75.6%) aneurysms in the abdominal aorta and 10 (24.4%) in the common iliac artery with concomitant abdominal aortic aneurysms. On the other hand, the non-TA group included 40 (90.9%) abdominal aortic aneurysms and 4 (9.1%) common iliac artery aneurysms with concomitant abdominal aortic aneurysms. In addition, the maximum diameter of the aneurysm in the non-TA group was significantly larger than that in the TA group (52.2 ± 7.0 mm vs. 48.5 ± 8.8 mm, respectively; $p < 0.05$). The IMA was patent in 35 patients (85.4%) in the TA group and 32 patients (72.7%) in the non-TA group. The mean number of patent lumbar arteries was 5.4 ± 1.7 in the TA group and 5.6 ± 1.6 in the non-TA group (**Table 1**). No significant differences were observed in preoperative blood hemoglobin concentration, renal function, and blood coagulation ability between the two groups.

In the TA group, EL2 was observed in 14 patients (34.1%) at 7 days after surgery and in 12 patients (29.3%) at 1 month after surgery. On the other hand, in the non-TA group, EL2 was observed in seven patients (15.9%) at 7 days after surgery and in six patients (13.6%) at 1 month after surgery. Although the differences were not statistically

**Table 2 Incidence of type II endoleak and maximum aneurysm diameter at 7 days and 1 month after surgery in both groups**

| | TA group (n = 41) | Non-TA group (n = 44) | p value |
|---|---|---|---|
| POD 7 | | | |
| Maximum diameter of aneurysm (mm) | 48.9 ± 8.7 | 52.4 ± 7.0 | <0.05 |
| Type II endoleak | 14 (34.1%) | 7 (15.9%) | 0.051 |
| From IMA | 4 (28.6%) | 3 (42.9%) | |
| From LA | 9 (64.3%) | 4 (57.1%) | |
| From IMA + LA | 1 (7.1%) | 0 (0.0%) | |
| POM 1 | | | |
| Maximum diameter of aneurysm (mm) | 48.6 ± 8.9 | 52.3 ± 7.1 | <0.05 |
| Type II endoleak | 12 (29.3%) | 6 (13.6%) | 0.08 |

TA: tranexamic acid; POD: postoperative date; POM: postoperative month; IMA: inferior mesenteric artery; LA: lumbar artery

significant, EL2 tended to occur more frequently in the TA group than in the non-TA group (7 days after EVAR: p = 0.051, 1 month after EVAR: p = 0.08) (**Table 2**). No re-intervention was performed for EL2 within 1 year postoperatively. The maximum diameters of aortic aneurysms 7 days and 1 month after EVAR were 49.2 ± 8.4 mm and 48.9 ± 8.6 mm, respectively, in the TA group and 52.4 ± 7.0 mm and 52.3 ± 7.1 mm, respectively, in the non-TA group. There was no significant change in the diameter of the aneurysms between the preoperative and early postoperative phases (**Table 2**). There were no cases of type I and III endoleaks.

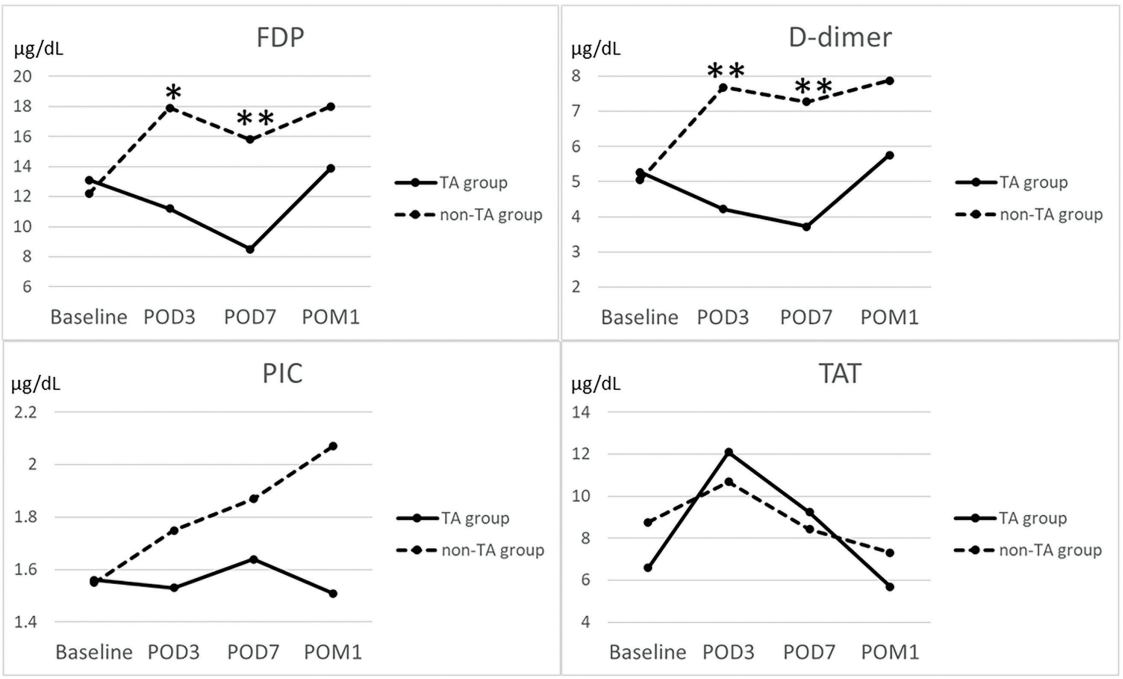
Blood tests showed that the fibrin degradation product (FDP) and the D-dimer levels at 3 days after EVAR were significantly different between the groups (FDP: 11.2 ± 9.7 vs. 17.9 ± 16.7 μg/mL in the TA group and in the non-TA group, respectively, p <0.05; D-dimer: 4.22 ± 3.77 vs. 7.68 ± 6.89 μg/mL in the TA group and in the non-TA group, respectively, p <0.01). The differences became more prominent 7 days after EVAR (FDP: 8.5 ± 5.1 vs. 15.8 ± 9.0 μg/mL in the TA group and in the non-TA group, respectively, p <0.01; D-dimer: 3.72 ± 2.50 vs. 7.27 ± 4.61 μg/mL in the TA group and in the non-TA group, respectively, p <0.01), but they became insignificant 1 month after surgery. The plasmin-α2 plasmin inhibitor complex (PIC) level was lower in the TA group than in the non-TA group up to 1 month after surgery, but the differences were not significant. The thrombin–antithrombin complex (TAT) levels did not differ significantly between the two groups until 1 month after EVAR (**Fig. 2**).

The maximum diameter of aneurysms at 6 months and 1 year after EVAR were investigated to evaluate the mid-term outcomes. We also investigated the rate of change from the preoperative aneurysm diameter. Six months after EVAR, the aneurysm diameter was 46.3 ± 9.7 mm in the TA group and 48.4 ± 8.4 mm in the non-TA group. One year after EVAR, it was 45.7 ± 11.1 mm and 46.7 ± 9.6 mm, respectively. The mean aneurysm diameter did not decrease postoperatively in both groups. Conversely, the rate of change in aneurysm diameter showed a 5.1% ± 8.8% reduction in the TA group and 6.2% ± 9.1% reduction in the non-TA group at 6 months after EVAR, and an 8.5% ± 13.6% reduction and 10.6% ± 12.6% reduction, respectively, at 1 year after EVAR (**Table 3**). The rate of change in the aneurysm diameter also did not differ significantly between the two groups.

No adverse events, such as thrombus formation due to oral TA, were observed during the study period.

## Discussion

The first stent graft surgery was reported by Parodi et al. in 1991.[6] Since then, minimally invasive surgery has gradually become predominant in the treatment of abdominal aortic aneurysms. According to some reports, EVAR has a lower early postoperative mortality rate than open surgery.[2,7] In addition, shorter hospital stays and lower complication rates have been cited as other advantages of EVAR in recent studies.[8–10] In 2007, the use of commercially available stent grafts was approved in Japan. Currently, more than 60% of patients with abdominal aortic aneurysms are treated by stent graft surgery. Although EVAR has become widespread and has shown its effectiveness, the high rate of reinterventions for graft-related complications has become concerning.[11,12] Among these complications, EL2 can occur in certain patients regardless of the skill of the surgeon. The frequency of EL2 has been reported to be 16%–50%, thus




＊: p<0.05, ＊＊: p<0.01

**Fig. 2** Postoperative transition of coagulation/fibrinolysis markers in blood tests. FDP: fibrin degradation product; PIC: plasmin-α2 plasmin inhibitor complex; TAT: thrombin–antithrombin complex; POD: postoperative day; POM: postoperative month; TA: tranexamic acid

**Table 3 Maximum aneurysm diameter and its rate of change at 6 months and 1 year after surgery in both groups**

| POM 6 | TA group (n = 35) | Non-TA group (n = 38) | p value |
|---|---|---|---|
| Maximum diameter of aneurysm (mm) | 46.3 ± 9.7 | 48.4 ± 8.4 | |
| Rate of change (ΔD, %) | –5.1 ± 8.8 | –6.2 ± 9.1 | 0.31 |
| **POY 1** | **TA group (n = 32)** | **Non-TA group (n = 37)** | **p value** |
| Maximum diameter of aneurysm (mm) | 45.7 ± 11.1 | 46.7 ± 9.6 | |
| Rate of change (ΔD, %) | –8.5 ± 13.6 | –10.6 ± 12.6 | 0.25 |

TA: tranexamic acid; POM: postoperative month; POY: postoperative year

accounting for up to half of all endoleaks.[13–15] In cases that do not show a change in the diameter of the aneurysm even with an EL2, additional treatment is not necessary. However, expansion of the aneurysm will necessitate additional laparotomy or catheterization. Oral TA is effective for EL2 prevention,[4] although other studies have reported otherwise.[5,16] Moreover, these studies were retrospective. Therefore, we decided to examine the effect of oral administration of TA on EL2 in a randomized controlled trial.

Our study demonstrated that oral TA did not significantly suppress EL2. The dose of TA was set at 250 mg × 3/day, which was the same as that in a previous study by Shingaki et al.[4] However, the duration of oral intake was 1 month in our study, whereas it was 6 months in the study by Shingaki et al. Thus, it is possible that the duration of oral TA administration was too short in our study. Many patients with abdominal aortic aneurysm have other arteriosclerotic diseases (e.g., coronary artery disease, cerebrovascular disease, and peripheral arterial disease) and often take antiplatelet drugs daily. We considered that long-term administration of TA to such patients after EVAR was problematic, and thus set the administration period to 1 month. Blood tests showed significant differences in FDP and D-dimer values at 3 and 7 days after EVAR. Shingaki et al. reported that the increase in the FDP level was significantly suppressed in the group receiving TA,[4] while Pong et al. reported a significant correlation between TA administration and suppression of D-dimer levels.[17] In addition,

no intergroup difference was observed in TAT, a coagulation activation marker. Conversely, PIC, a fibrinolytic activation marker, tended to be suppressed in the TA group. These findings prove that TA sufficiently suppressed the fibrinolytic system, even at the lower dose set in this study. However, it is undeniable that different results might have been obtained by extending the administration period of TA. Nevertheless, our results showed no significant intergroup differences in FDP and D-dimer values 1 month after surgery.

Our findings also showed no significant intergroup differences in aneurysm diameter and diameter changes, which were evaluated as secondary endpoints. When the average diameter change rate values were compared, the aneurysm diameter did not change in both groups; thus, oral administration of TA did not show a significant aneurysm-reducing effect. Another clinical study reported that oral TA is effective in reducing aneurysms after EVAR. However, to the authors' knowledge, the dose of TA was twice as much as the usual dosage in all other reports.[5,16] As mentioned above, our study showed a significant difference in FDP and D-dimer values on blood coagulation/fibrinolysis tests, indicating that TA did exert its desired effects. Nevertheless, it could be considered that the doses in our study were not sufficient to induce shrinkage of the aneurysm.

Despite the lack of significant results for the endpoints, our study was a prospective randomized controlled trial, and the results represented a high level of evidence. One limitation of this study was that the TA administration period and dose were moderated to avoid the possibility of adverse events. In recent years, embolization of the IMA during stent graft surgery has been reported to significantly suppress EL2.[18] Based on these findings, intraoperative IMA embolization is recommended in our country's guideline. Our study included no cases of intraoperative IMA embolization. Thus, IMA embolization can be assumed to suppress EL2 more than oral administration of TA. In the future, it will be useful to investigate whether the combination of IMA embolization and oral TA administration can effectively suppress EL2, or whether oral administration of TA is effective in EL2 cases after EVAR with IMA embolization.

## Conclusions

In this study, we demonstrate that oral TA suppressed the fibrinolytic system in patients who underwent EVAR. However, the EL2 suppressing effect of TA was not proved. Future research shall study EL2 inhibitory effect on patients who underwent EVAR in combination with other factors, such as IMA embolization.

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## Author Contributions

Conceived and designed the study: Yusuke Imaeda and Hiroyuki Ishibashi. Collected the data: All authors. Performed the analysis: Yusuke Imaeda. Wrote the paper: Yusuke Imaeda. Revised the paper: All authors.

## Disclosure Statement

Yusuke Imaeda and the co-authors of this study have no conflicts of interest.

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