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*Commentary*

# Commentary on Post, *et al*. Ultra-early tranexamic acid after subarachnoid hemorrhage: A randomized controlled trial. Lancet 2021

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## ABSTRACT

**Background:** Tranexamic acid (TA) administration in aneurysmal subarachnoid hemorrhage (SAH) within the first 24 hours may reduce the incidence of early aneurysmal rebleeding. However, this is also the potential for an increased risk of delayed cerebral ischemia if TA is administered for more than 72 hours following the initial aneurysmal rupture.

**Methods:** In the ultra-early tranexamic acid after subarachnoid hemorrhage randomized controlled trial by Post *et al*., patients were randomized to receive TA within the first 24 hours, or until start of aneurysm treatment. These results were compared to a matched control group.

**Results:** Ultra-early administration (≤24 h) of TA reduced the incidence of rebleeding, and did not alter the incidence of delayed cerebral ischemia and/or extracranial thrombosis. Further, no significant differences were noted between the TA group and control arm in the incidence of good (modified Rankin scores 0-3) clinical outcomes at 6 months.

**Conclusion:** Ultra-early administration of TA (≤24 h) resulted in a lower rate of recurrent hemorrhage, without increasing the incidence of delayed cerebral ischemia in SAH patients.

**Keywords:** Randomized controlled trial, Subarachnoid hemorrhage, Tranexamic acid,

## INTRODUCTION

Cerebral aneurysmal re-rupture in subarachnoid hemorrhage (SAH) most frequently occurs within the first 6 h and is most likely due to antithrombotic therapy, hypertension, coagulopathy, Valsalva maneuvers, multisystemic, and metabolic disturbances. Recently, we have focused on delineating the potential benefits of "early (i.e. </= 24 hours)" administration of the antifibrinolytic agent, tranexamic acid (TA).

## TA – PHYSIOLOGICAL ACTION

TA administration in SAH patients has multiple physiological benefits as well as risks. TA forms a reversible complex that displaces plasminogen from fibrin, resulting in inhibition of both fibrinolysis and proteolytic activity of plasmin; decreasing the potential for aneurysmal rebleeding. However, possible side effects of TA may include increasing the risk of delayed cerebral ischemia if administered beyond 72 hours following the initial aneurysmal rupture [Table 1].[1]

## ULTRA-EARLY TRANEXAMIC ACID AFTER SUBARACHNOID HEMORRHAGE (ULTRA) TRIAL

Post *et al*. performed an open-label randomized controlled trial (RCT) that involved eight treatment centers, and 16 referral hospitals in the Netherlands (2013–2019).[2] This RCT included 955 adults (median age 58.4 years) who had CT confirmation of spontaneous SAH; with CT angiogram negative patients being excluded. Patients were randomized into two groups; 480 in the TA treatment arm (i.e. 1 g given as a 10 min bolus followed by 1 g every 8 h typically for the first 24 h (≤ 24 h) versus 475 in the control arm (placebo) [Table 2].

**Table 1:** Possible side effects of tranexamic acid.

- Nausea, vomiting
- Diarrhea
- Hypotension
- Thrombosis (e.g., with prolonged usage)

**Table 2:** ULTRA randomized controlled trial.

| Tranexamic acid treatment arm | Control (Placebo) arm |
|---|---|
| *n*=480 | *n*=475 |
| Good 6-month outcome (mRS 0–3) – OR 0.87 (95% CI 0.67–1.13) | |
| *n*=287 (60%) | *n*=300 (64%) |
| Excellent 6-month outcome (mRS 0–2) – OR 0.74 (95% CI 0.57–0.96) | |
| *n*=229 (48%) | *n*=262 (56%) |

**Table 3:** ULTRA randomized controlled trial multivariable logistic regression analysis.

| Tranexamic acid treatment arm | Placebo (control) arm |
|---|---|
| Hydrocephalus – OR 1.26 (95% CI 0.98–1.63) | |
| *n*=292 (61%) | *n*=262 (56%) |
| Seizures – OR 1.52 (95% CI 1.00–2.33) | |
| *n*=59 (12%) | *n*=40 (8%) |
| CT-proven pre-aneurysmal treatment rebleeding – OR 0.70 (95% CI 0.46–1.07) | |
| *n*=42 (9%) | *n*=57 (12%) |
| Delayed cerebral ischemia – OR 1.01 (95% CI 0.74–1.37) | |
| *n*=108 (23%) | *n*=106 (22%) |
| Extracranial thrombosis – OR 1.13 (95% CI 0.41–3.15) | |
| *n*=8 (2%) | *n*=7 (2%) |
| Thromboembolic events during endovascular therapy – OR 0.81 (95% CI 0.48––1.38) | |
| *n*=29 (11%) | *n*=33 (13%) |

## TIMING OF ADMINISTRATION OF TA

Patients randomized to the TA treatment arm received therapy within an average of 3 hours following admission, after initial CT confirmation of their SAH diagnosis. The median time to aneurysm treatment after CT diagnosis was 14 hours (IQR 5–20 hours).

## OUTCOMES

Sixty-percent of TA patients versus 64% of control group patients had good 6-month clinical outcomes (modified Rankin scores 0–3). However, 48% of TA patients versus 56% of control group patients had excellent 6-month outcomes (modified Rankin scores 0–2) [Table 2]. Incidences of hydrocephalus and seizures were noted to be higher in the TA treatment arm [Table 3].

## IMPACT OF ULTRA-EARLY TA ADMINISTRATION

Ultra-early TA administration (≤24 h) resulted in a lower rate of aneurysmal rebleeding prior to definitive aneurysmal treatment. Notably, however, it did not predispose patients to more thrombotic complications during endovascular therapy, nor did it increase the incidence of delayed cerebral ischemia and/or extracranial thrombosis [Table 3]. Further studies should be conducted to investigate whether TA use is associated with increased incidences of hydrocephalus and seizures.

## CONCLUSION

This RCT, by Post *et al*. demonstrated that ultra-early administration of TA in aneurysmal SAH for maximum of 24 hours did not alter the incidence of delayed cerebral ischemia or extracranial thrombosis.

### Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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