

Does tranexamic acid prevent the expansion of hematoma in spontaneous intracerebral hemorrhage in a randomized controlled trial?

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Abstract

Background: Hypertensive spontaneous intracerebral hemorrhage (ICH) is common cause of death and disability in Thailand. Tranexamic acid (TXA) showed its efficacy in reduction of number of patients with ICH expansion but in hemorrhagic stroke the evidence is limited. This study aims to assess the effect of tranexamic acid (TXA) on hematoma growth of patients with spontaneous ICH compared to a placebo.

Methods: A triple-blinded randomized controlled trial was conducted to evaluate the efficacy of combining a rapid administration of TXA with combination with strict blood pressure control to prevent hematoma expansion on patients with acute hypertensive ICH (< 24 hours). A total of 40 participants were included. Twenty patients were assigned to receive tranexamic acid and 20 to placebo.

Results: For primary outcome, despite tranexamic acid group tended to have less expansion risk (15% for tranexamic acid group versus 25% for placebo group, RR 0.71) but had no statistically difference (p -value 0.695). None of patient had surgical treatment, death, or serious adverse event.

Conclusions: This study showed tranexamic acid did not affect stabilizing the hematoma over placebo in spontaneous intracerebral hemorrhage patients in small volume of hematoma (< 30 ml.)

Key words: Intracerebral hemorrhage, tranexamic acid, hematoma expansion

บทคัดย่อ

การศึกษาการให้ยา Tranexamic acid มีผลต่อการป้องกันภาวะเลือดขยายตัวของก้อนเลือดในสมองในผู้ป่วยหลอดเลือดในสมองแตกหรือไม่

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ภาวะหลอดเลือดในสมองแตกเป็นภาวะฉุกเฉินทางประสาทศัลยศาสตร์ที่พบได้บ่อยเป็นสาเหตุสำคัญของการเสียชีวิตและพิการในประเทศไทย ซึ่งพบว่า ยา tranexamic acid สามารถช่วยลดการขยายตัวของก้อนเลือดได้ แต่อย่างไรก็ตามการศึกษาผลของยา tranexamic acid ต่อภาวะเส้นเลือดในสมองแตกนั้นยังไม่ได้ข้อสรุปชัดเจนในปัจจุบัน

วิธีการศึกษา: เป็นการศึกษาแบบ randomized controlled trial เพื่อเปรียบเทียบประสิทธิผลของยา tranexamic acid (TXA) กับ ยาหลอก (placebo) ในการป้องกันการขยายตัวของก้อนเลือดในระยะเวลา 24 ชั่วโมง ซึ่งผลของศึกษาในผู้ป่วยทั้งสิ้น 40 รายแบ่งเป็นกลุ่มได้ TXA 20 รายและ placebo อีก 20 ราย

ผลการศึกษา: พบว่ายา tranexamic acid ลดการขยายตัวของเลือดที่ออกได้ 15% เทียบกับ placebo 25% (risk ratio 0.71, p -value 0.695) โดยในผู้ป่วยทั้งสองกลุ่ม ไม่พบการเสียชีวิต หรือต้องได้รับการผ่าตัดกายหลัง และไม่มีภาวะแทรกซ้อนจากยา

สรุป: จากการศึกษาี้ การให้ยา tranexamic acid ไม่มีความแตกต่างกับการให้ยาหลอกในผู้ป่วยภาวะเลือดออกในสมองที่มีขนาดน้อยกว่า 30 มิลลิลิตร

Introduction

Hypertensive intracerebral hemorrhage or spontaneous ICH (SICH) is a common cause of death and disability in Thailand. The incidence of SICH patients is 10–20 per 100,000 people and have the worst outcomes of all stroke subtypes with 30-day mortality ranging from 30–50%.^{1,2}

In Thailand, the cerebrovascular mortality rate increased every year.^{3,4} The poor prognostic factor of hemorrhagic stroke was size of hematoma, hematoma expansion and intraventricular hemorrhage.^{5,6} An increase in hematoma size during the first 24 hours was observed in 23–38% of patients. The growth of the hematoma volume is associated with a poor functional

outcome and an increased mortality rate. Prevention of hematoma expansion with medical treatment may therefore be beneficial to the patient's outcome.

Tranexamic acid (TXA) showed its efficacy in reduction of number of patients with ICH expansion in traumatic brain injury but in hemorrhagic stroke the evidence is limited.^{7–9} Some study showed that tranexamic acid prevent hematoma expansion significantly comparing to placebo but some studies show no efficacy in preventing ICH expansion as well as prognosis and mortality rate^{10,11}

Because there is uncertainty about the effectiveness in reducing ICH expansion, and the number of studies is small. This study aims to assess the effect of

TXA on hematoma growth of patients with spontaneous ICH compared to a placebo.

Methods

Research design

A triple-blinded randomized controlled trial was conducted to evaluate the efficacy of combining a rapid administration of TXA with a maintenance dose infusion in combination with strict blood pressure control for the prevention of hematoma expansion on patients with acute hypertensive ICH (< 24 hours) referring to the emergency department of Maharaj Nakorn Chiang Mai Hospital.

Study Subjects

Adult patients with acute (24 hours after ictus) spontaneous ICH were identified and enrolled from the stroke service at the emergency department of Maharaj Nakorn Chiang Mai Hospital. The vast majority of inclusion criteria is hypertensive ICH except brain stem and intraventricular hemorrhage. The principal exclusion criteria included brain stem hemorrhage, intraventricular hemorrhage, secondary ICH (vascular malformations, tumor), coagulopathy or platelet dysfunction, anti-coagulants or antiplatelet used, recent (12 months) ischemic events (ischemic stroke, myocardial infarction), liver and renal impairment and pregnancy or breastfeeding.

Randomization, allocation and masking

Block randomization was used on the participants, with block sizes of 4 chosen at random. <https://www.sealedenvelope.com/simple-randomiser/v1/lists> created the algorithm. They were randomly assigned to the two intervention arms. Patients, nurse who were in-

involved in patient management and radiological doctors were masked to treatment allocation. The intervention was distributed to sealed envelope containing number of intervention group. Following randomization, the sealed envelope was opened by an external unmasked person not involved in patient management or evaluation who inserted TXA or placebo (0.9% NaCl) into two bags of normal saline, and gave the appropriately labeled masked intervention to the study team for administration to the patient.

Intervention

Patients were randomized to receive either intravenous TXA or a placebo. The drugs were given intravenously as a 1 gram 100 ml. of 0.9% sodium chloride over 10 min, followed by another one gram in 250 ml. of 0.9% sodium chloride, which was infused over 8 hours. The comparator group was a matching placebo (normal saline 0.9%), administered with an identical regimen. Brain imaging by CT was done as part of routine care before enrolment. A second CT scan was done after 24 hours \pm 8 hours of treatment to assess hematoma expansion. All 40 patients were given a labetalol infusion intravenously and achieved the required blood pressure range of 140–160 mmHg within 1 hour, and it was maintained throughout their 24 hours in the ward.

Study outcomes

The primary outcome was expansion of the ICH, defined as expansion by 25% or more on any dimension (height, length, or width) on the second scan.

The Secondary outcomes were death, neurosurgical operation and any in-hospital thromboembolic events (myocardial infarction, pulmonary embolism,

deep vein thrombosis, and stroke)

Statistical methods

Hematoma expansion was expressed by number and percentage of patients with hematoma expansion > 25% in any dimension and risk ratio. P-value was calculated using Fisher exact test and significance was taken at a *p*-value less than 0.05.

Results

Recruitment started on, July 2019, and ended on September, 2020. A total of 40 participants were included. Twenty patients were assigned to receive TXA and 20 to placebo. The mean age was 58.2 years and 27 (67%) participants were male. Twenty-nine (72%) participants had a hematoma located at basal

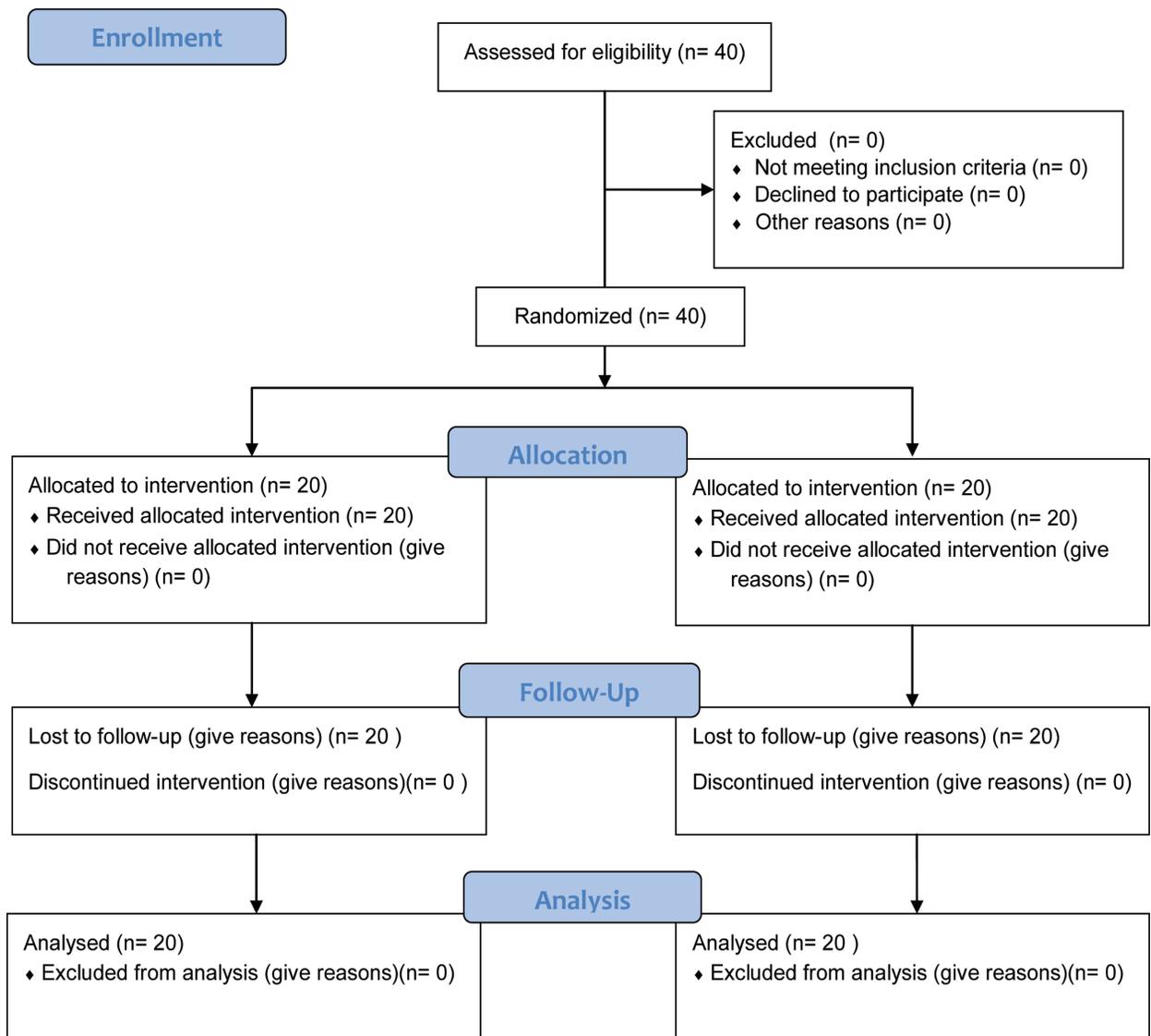


Diagram 1 Flow diagram

ganglion. The blood parameters, including hemoglobin, platelets, coagulation profile were within normal range. The most common underlying disease was hypertension. The demographic and characteristic data of both groups were not statistically different (Table 1). The

volume of hematoma of TXA group tended to be larger but not reach statistical difference.

For primary outcome, despite TXA group tended to have less expansion risk (15% for tranexamic acid group versus 25% for placebo group, RR 0.71) but

Table 1 Baseline characteristics

Parameters	Treatment		p-value
	Tranexamic acid (n=20)	Placebo (n=20)	
Age, Mean (SD)	58.50 (13.42)	57.80 (14.29)	0.874
Male gender, n (%)	14 (70.00)	13 (65.00)	1.000
Symptoms			1.000
Depressed consciousness, n (%)	14 (70.00)	15 (75.00)	
Speech problem, n (%)	13 (65.00)	13 (65.00)	
Headache, n (%)	1(5)	1(5)	
Underlying Disease), n (%)			1.000
Hypertension	15 (75.00)	14 (70.00)	
Dyslipidemia	3 (15.00)	4 (20.00)	
DM	2 (10.00)	2 (10.00)	
GCS 13-15 on admission, n (%)	13(65)	13(65)	1.000
GCS 13-15 at 24 hrs, n (%)	15(75)	18(90)	0.407
Location, n (%)			0.480
Basal ganglion	16 (80.00)	13 (65.00)	
Thalamus	4 (20.00)	6 (30.00)	
Other (Parietal lobe)	0 (0.00)	1 (5.00)	
Hematocrit, mean (SD)	40.68 (5.62)	40.22 (6.96)	0.819
PT, mean (SD)	11.23 (1.16)	11.00 (0.75)	0.461
PTT, mean (SD)	29.73 (4.12)	30.31 (3.08)	0.617
INR, mean (SD)	1.02 (0.11)	1.00 (0.07)	0.491
MAP at first appear in ER, mean (SD)	123 (16)	131 (20)	0.189
MAP at drug administration, mean (SD)	110 (8)	109 (13)	0.917
MAP at 24 hours after symptoms, mean (SD)	106 (10)	105 (10)	0.800
Hematoma volume at 1st CT scan			
mean (SD)	17.30 (13.91)	11.39 (9.12)	0.120
Volume, n (%)			0.097
≤ 10 ml	9 (45.00)	11(55.00)	
10.1 – 20 ml	3 (15.00)	6 (30.00)	
20.1 – 30 ml	1 (5.00)	2 (10.00)	
> 30.1 ml	7 (35.00)	1 (5.00)	

Table 2 Hematoma volume expansion

	Treatment			p-value
	Tranexamic acid (n=20)	Placebo (n=20)	RR (95%CI)	
Primary outcome				
Hematoma expansion > 25% in any dimension, n (%)	3 (15.00)	5 (25.00)	0.71 (0.27, 1.83)	0.695
Secondary outcome				
Death / neurosurgical operation / thromboembolic event	0	0	0	

had no statistical difference (p -value 0.695). None of patient had surgical treatment, death, or serious adverse event. (Table 2)

Discussion

This study is about the effect of TXA in spontaneous intracerebral hemorrhage in the tertiary care as university hospital. We found no significant hematoma volume expansion (> 25%) between groups although tranexamic acid group tended to have a lower risk of expansion (RR 0.71) even baseline hematoma volume tended to be larger (17.30 ml (13.91) vs. 11.39 ml (9.12)). This limitation may be small sample size.

TICH-2 study showed that tranexamic acid had benefits to reduce hematoma expansion, early death especially in moderate-sized baseline hematoma (30–60 ml) group¹². In our study, most of the patients had small hematoma volume (< 30 ml), TXA could not show any its benefit in moderated-size ICH (30–60ml).

Using criteria-based, such as > 25% is count as expansion, for detection of hematoma expansion may be more suitable than absolute volume comparison because it is more clinically significant. Such as Arumugam A, et al trial (2015), which showed statistical differences (14.3 vs. 17.9 ml, p -value 0.001).¹⁰

From meta-analysis and systematic review of

TXA and any cause of ICH that included 14 RCT, they found TXA group had a lower incidence of hematoma expansion.¹³ However, this study had significant heterogeneity and subgroup analysis did not show a difference in spontaneous intracerebral hemorrhage. Combined thrombotic events such as deep vein thrombosis (DVT), pulmonary embolism (PE), stroke or transient ischemic attack (TIA) had a significant difference in TXA group. Both groups had no mortality and poor functional outcome did not significantly differ between two groups.

These results of no complications such as ischemic stroke, DVT, PE and death confirms the same as previous studies that tranexamic acid in spontaneous ICH is safe and low complications if used in proper dosage and duration.^{11,12,14}

The strengths of this study include its triple blinding, allocation concealment, low risk of bias, high adherence to treatment, and very few missing data on primary outcomes. Despite we used triple blind randomization. However, the limitation of this study was some imbalance in volume in both groups, however it is no statistically significant. Another limitation is that our study size is small and may have no power to demonstrate difference between the groups. More sample size is suggested in next study. The future research in a more specific groups, such as in larger volume of

hematoma, patients who have a contraindication to surgery such as coagulopathy, multiple co-morbidity may be of interest.

Conclusions

This study showed that tranexamic acid did not affect stabilizing the hematoma over placebo in spontaneous intracerebral hemorrhage patients in small volume of hematoma (< 30 ml). Future research should investigate which subgroups of patients might benefit. Tranexamic acid may be safe and has low complications if using in proper dose. Tranexamic acid is inexpensive, easy to administer, seems to be safe, and is widely available.

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