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## Abstract

**Background:** Mortality and morbidity associated with intracerebral Hemorrhage ICH is still high. Up to now, there are no evidence-based effective treatments for acute ICH. This study is to assess the effect of tranexamic acid (TXA) on hematoma growth of patients with spontaneous ICH compared to a placebo.

**Methods:** We performed a single-blinded, randomised placebo-controlled trial of TXA (intravenous 1g bolus, followed by infusion TXA 1 g/hour for 8 hours) in acute (< 8 hours) primary ICH. Strict blood pressure control (target SBP 140-160 mmHg). A repeat Computed Tomography brain was done after 24 hours to reassess hematoma growth. The primary objective is to test the effect of TXA on hematoma growth. Other objective was to test the feasibility, tolerability, and adverse events of TXA in primary ICH.

**Results:** Statistical analysis showed significant hematoma growth in control group after 24 hours compared to baseline (14.3300 vs 17.9940,  $P = 0.001$ ) whereas the treatment group there is no significant hematoma size expansion between baseline and after 24 hours ( $P = 0.313$ ).

**Conclusions:** This study showed a significant hematoma volume expansion in the control group compared to the treatment group.

**Keywords:** high altitude, hypoxia, therapeutics

## Introduction

Spontaneous intracerebral haemorrhages (ICH) account for 10 – 15% of all strokes with an incidence of 10–30 cases per 100,000 people/year, and their incidence is expected to double in the next 30 years. Mortality and morbidity associated with ICHs is still high. Until recently, there were no effective evidence-based treatments for acute ICH. ICH growth remains an important predictor of patient outcomes. Tranexamic acid (TXA), an anti-fibrinolytic drug, is known to reduce haemorrhaging in other conditions. The purpose of this study was to assess the effect of TXA compared to a placebo on the growth of haematomas in patients with spontaneous ICH.

## Study aims

### General

- i. To determine the effect of TXA as an antifibrinolytic agent compared to a placebo.
- ii. To determine the adverse events of TXA compared to a placebo.

### Specific

- i. To evaluate the size and volume of haematomas using brain computed tomography (CT) scans and to compare the findings between the treatment and control groups.
- ii. To determine which group of patients underwent surgical intervention at the end of the study.
- iii. To determine the influence of blood pressure on haematoma expansion.

- iv. To determine the Glasgow Outcome Scale (GOS) between the treatment and control groups.

## Methods

### Research design

A single-blinded randomised 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 haematoma expansion.

### Study setting and period

The study was conducted in the Department of Neurosurgery at the Hospital Sultanah Aminah Johor (Jalan Abu Bakar, 80100 Johor Bharu Malaysia) from September 2012 to October 2013, and ethical approval was obtained for the study (approval no.: NMRR-12-285-11650).

### Patients

#### Selection criteria

The inclusion and exclusion criteria for this study are listed below.

#### Inclusion criteria

- i. Patients aged  $\geq 18$  years (either sex);
- ii. Non-surgically managed patients who were evaluated by the on-call neurosurgeon and were deemed inappropriate for surgical intervention;
- iii. Event within 8 hours of onset;
- iv. Hypertensive intracerebral bleed; and
- v. Supratentorial lesion.

#### Exclusion criteria

- i. Patients on anticoagulant therapy;
- ii. Brainstem bleed;
- iii. Intraventricular bleed on the 1st brain CT brain, including patients who developed an intraventricular bleed during the study;
- iv. Malignant hypertension;
- v. Subarachnoid haemorrhage suggestive of a ruptured aneurysm;
- vi. Trauma;
- vii. Blood Disorder (e.g., haemophilia and idiopathic thrombocytopenic purpura);
- viii. Infection (e.g., dengue haemorrhagic fever);
- ix. Hepatic or renal impairment;
- x. Previous venous thrombosis or embolic disease;
- xi. Recent ischaemic event (within 12

months), such as ischaemic stroke, myocardial infarction, or peripheral artery disease; and

- xii. Pregnant or breast-feeding women (pregnancy was excluded in women of child-bearing age using a urine pregnancy test).

### Sample size calculation

Based on the study objectives, the size and volume of the haematomas were evaluated in the treatment and control groups using brain CT scans.

The power and sample size software

- i.  $\alpha = 0.05$  (level of significance)
- ii. Power = 0.9
- iii. standard deviation or = 2.5
- iv.  $\delta$  or detectable difference = 3.5
- v.  $m = 1$  ratio between the two groups
- vi. Sample size = 15 per arm
- vii. Dropout rate: 20% (5 patients)
- viii. Total sample required: 30 patients

### Techniques for data collection

1. Patients with an ICH admitted to the Hospital Sultanah Aminah Johor were selected according to the inclusion and exclusion criteria.
2. Patients admitted to the emergency department with the clinical signs and symptoms of a stroke underwent urgent brain CT scans. Each patient's complete history was obtained from the patient or the patient's family members. Data were documented in the data collection form.
3. CT brain scans (section thickness, 5 mm) were performed by the on-call radiologist. The site, size, and volume of the haematoma were documented in a formal report.
4. Once the patient history, clinical assessment, and CT brain findings fulfilled the inclusion criteria, an information form was given to the patient or the patient's legal authorised representative, and consent was obtained.
5. Patients or their family members randomly chose one envelope from a box containing 30 closed envelopes. Each envelope represented either the drug or control group, which was assigned using a random sequence programmer.
6. Patients in the drug group were blinded and received a rapid administration of TXA (1 g diluted in 100 mL of 0.9% saline) over a period of 10 min. The initial

dose was followed by a maintenance dose of 1 g/h for 8 hours.

7. The patient's blood pressure was controlled using a 200 mg labetalol hydrochloride injection. The diluted solution was administered at a rate of 2 mL/min to deliver 2 mg/min. The infusion was adjusted accordingly to achieve a systolic pressure of 140–160 mmHg.
8. After 24 hours, another CT brain scan was performed, and a blinded radiologist evaluated the size and volume of the haematoma.
9. Adverse events due to TXA that occurred within 24 hours of the treatment were documented by the investigator or pharmacist.
10. All data were collected and analysed using SPSS Inc., version 12 (SPSS, Chicago, IL, USA) by a blinded statistician.

#### *Haematoma volume calculation technique*

##### *Planigraphic methods*

The planimetric measurements were performed by a blinded radiologist using the planning station of the BrainLab® neuronavigation equipment (BrainLab, Munich, Germany). The DICOM files of the CT images were transferred to the workstation using PatXFer® 2.0 and were exported to Iplan® 2.6 Cranial software (BrainLab), a component of the utilities package used for planning navigation. Using the axial cuts of the CT slices, the haematoma edges were individually determined for each slice using the available software tools (i.e., the brush and smart brush). This software calculates the total haematoma volume of each slice from the axial cut and is expressed in cm<sup>3</sup>. The total volume of the haematoma was obtained by multiplying the total volume of each section by the slice thickness.

## **Result**

### *Descriptive analysis*

From September 2012 to October 2013, this study screened 68 cases of spontaneous ICH. Among these 68 cases, 30 fulfilled the inclusion criteria and were enrolled in the study (Table 1). Fifteen cases were randomised into the treatment group, and the other 15 cases were randomised into the control group.

Patient number 6, 14, and 15 (highlighted in blue) had hematoma expansion (volume: range, 6.32–13.79 cm<sup>3</sup>) within 24 hours of observation

and strict blood pressure control (systole, 140–160 mmHg) (Table 2).

Patient number 3, 4, 5, and 11 (highlighted in red) had a reduction in hematoma size (range, -0.17 to -2.41 cm<sup>3</sup>). The other 11 patients had hematoma expansion (range, 0.02–2.07 cm<sup>3</sup>) (Table 3).

The treatment group shows smaller hematoma volume expansion (range, 0.02–2.07 cm<sup>3</sup>) than the control group (range, 0.77–13.79 cm<sup>3</sup>) (Table 4).

The control group had a significant hematoma expansion compared to the treatment group ( $P < 0.001$ ) (Table 5).

## **Discussion**

Spontaneous ICH accounts for 10–15% of all strokes worldwide ICH (50,51) patients have the worst outcomes of all stroke subtypes with a 30-day mortality ranging from 30–50% (51,52). The long-term outcome for ICH is also dismal, with as much as 75% of patients being either severely disabled or deceased after 1 year (51).

In Malaysia, ICH is the third most common cause of death and the number one killer in those aged  $\geq 65$ . Its burden is likely to increase in the coming years due to the growing elderly population [70]. The national incidence of stroke is estimated at 40 000 cases annually. It has been reported that race and ethnicity significantly influence the risk and associated outcomes. The prognosis of haemorrhagic stroke varies depending on the severity, location, and size of the haemorrhage. Lower GCS scores are associated with poorer prognoses and higher mortality rates (17).

A larger volume of blood at presentation is also associated with a poor prognosis. In addition, the growth of the haematoma volume is associated with a poor functional outcome and an increased mortality rate. There have been no comprehensive databases on the incidence of stroke in Malaysia (43)

This single-blinded randomised control trial, which was conducted from September 2012 to October 2013 in non-traumatic ICH patients, is the first TXA drug trial completed in Malaysia. In this small study population, the majority of patients (13) were 40–49 years old, and the mean age of the patients was 52.93 8.90 years. A large number of cases with ICH were reported within this age group.

The racial composition of the patients in this study were primarily Malaysian (54%) followed by Chinese (43%) and Indian (3%), which is

**Table 1:** The demographics of 30 patients with intracerebral hemorrhage admitted to the Hospital Sultanah Aminah Johor from September 2012 to October 2013

Variables	n (%)	Mean
Age		52.93
Sex		
Female	12 (40%)	
Male	18 (60%)	
Ethnicity		
Malays	16 (54%)	
Chinese	13 (43%)	
Indian	1 (3%)	
Co-morbidities		
Unknown	9 (30%)	
Hypertension	13 (43.3%)	
Hypertension/Diabetes mellitus	8 (26.6%)	
Defaulted treatment		
Yes	21	
No	–	
Time of onset to 1st CT brain scan (Mean value)		5.5 h (range, 4.2–6.0 h)
Time from 1st CT brain scan to study drug (TXA) administration (Mean value)		30 min (20–45 min)
GCS Score on admission (range, 13–15/15)		
15/15	11 (36.6%)	
14/15	17 (56.6%)	
13/15	2 (6.66%)	
Symptoms of presentation		
Headache/giddiness	10 (33.3%)	
Nausea/vomiting	6 (20%)	
Hemiparesis	23 (76.6%)	
Hemiparesis/slurred speech	7 (23.3%)	
Hematoma location		
Caudate	2 (6.6%)	
Thalamus	4 (13.3%)	
Internal capsule	24 (80%)	
Right hemisphere	23 (77%)	
Left hemisphere	7 (23%)	
Adverse events from TXA		
Nausea	None	
Vomiting	None	
Insomnia	None	

*Continued on next page*

Table 1 continued

Abdominal discomfort	None	
Diarrhea	None	
Skin rashes	None	
Vision disturbances (color vision)	None	
<b>Blood Parameters</b>	<b>Mean Value (n = 30)</b>	
Hemoglobin	12.6 g/dL (range, 11.8–15.3 g/dL)	
Platelets	284 ×10 <sup>9</sup> (range, 158–310 ×10 <sup>9</sup> )	
TWBC	8.2 (range, 7.5–13.0)	
<b>Coagulation Profile</b>	<b>Admission (Mean value)</b>	<b>After 24 h (Mean value)</b>
PT	10.6	9.8
APTT	30.6	32.5
INR	0.9	1.15
Fibrinogen Level	3.5 g/L	2.9 g/L
Normal range, 1.5–4.5		
<b>BP</b>	<b>Systole (Mean value)</b>	<b>Diastole (Mean value)</b>
BP on arrival to A&E	185 mmHg (range, 205–172 mmHg)	90 mmHg (range, 78–110 mmHg)
BP during the administration of TXA	145 mmHg (range, 135–160 mmHg)	85 mmHg (range, 78–90 mmHg)
BP from admission to the 2nd CT brain scan (24 h)	150 mmHg (range, 135–164 mmHg)	84 mmHg (range, 78–90 mmHg)

Abbreviations: CT = computed tomography; TXA = tranexamic acid; GCS = Glasgow Coma Scale; TWBC = total white blood cells; PT = prothrombin time; APTT = activated partial thromboplastin time; BP = blood pressure; A&E = accident and emergency.

representative of the ethnic distribution of the population in Johor Bharu. Male patients had a higher number of stroke occurrences (60%) than female patients (40%). Previous studies on ICH conducted in Malaysia and worldwide have indicated that the hormones of female patients protect them during their reproductive ages.

Hypertension has been reported as the most common significant and independent risk factor for ICH). In our study, we noted that patients with hypertension alone accounted for 43% of all patients. All of the known cases of hypertension and diabetes in this study defaulted treatment. Untreated hypertension is highly prevalent among ICH patients and is a significant risk factor for haemorrhagic stroke [18]. The incidence of ICH is substantially greater among those who have ceased their antihypertensive medication (34). A

high mean arterial blood pressure on admission was reported to be an independent predictor of early death in ICH patients.

The GCS of 30 patients were within the range of 13–15/15, and the majority of patients had a GCS score of 14/15 (56%). The GCS scores in our study population were good because of our inclusion criteria (e.g., the presenting haematomas were smaller (< 30 mL), without intraventricular extension, and were strictly supratentorial in origin without involving other vital brain structures). The common presenting symptoms were hemiparesis (50%), hemiparesis with slurred speech (23%), hemiparesis with giddiness (17%), and hemiparesis with nausea (10%).

The duration between symptom onset and the 1st CT scan was 5.5 h in the control group and

**Table 2:** The difference in hematoma volume (cm<sup>3</sup>) in the control group on admission and after 24 hours and between the 2nd brain computed tomography (CT) scan and the 2nd brain CT

Patient no.	GCS on admission	1 <sup>st</sup> brain CT (cm <sup>3</sup> )	GCS > 24 h	2 <sup>nd</sup> brain CT (cm <sup>3</sup> )	Differences in volume (cm <sup>3</sup> )
1	15/15	9.11	15/15	11.75	+ 2.64
2	14/15	20.68	14/15	21.45	+0.77
3	14/15	17.10	15/15	18.15	+1.05
4	15/15	6.58	15/15	8.11	+1.53
5	13/15	8.32	14/15	12.26	+3.94
6	14/15	19.35	10/15	25.70	+6.35
7	14/15	13.46	14/15	17.59	+4.13
8	15/15	6.29	15/15	7.03	+0.74
9	14/15	12.75	14/15	14.53	+1.78
10	14/15	15.08	14/15	18.72	+3.64
11	14/15	14.53	14/15	17.60	+3.07
12	14/15	13.12	14/15	16.49	+3.37
13	14/15	15.59	14/15	17.43	+1.84
14	14/15	19.32	10/15	25.64	+6.32
15	13/15	23.67	9/15	37.46	+13.79

Paired samples statistics: control group-Hematoma size in 1st CT scan, mean is 14.3300 with SD 5.21202 and 2nd CT scan mean is 17.9940 with SD 7.62482. Paired T-Test showed significant hematoma size expansion in control group after 24 hours compared to baseline (14.3300 vs 17.9940,  $P = 0.001$ ).

**Table 3:** The difference in hematoma volume (cm<sup>3</sup>) in the treatment group on admission and after 24 hours and between the 1st brain computed tomography (CT) scan and the 2nd brain CT

Patient no.	GCS on admission	1 <sup>st</sup> brain CT (cm <sup>3</sup> )	GCS > 24 h	2 <sup>nd</sup> brain CT (cm <sup>3</sup> )	Differences in volume (cm <sup>3</sup> )
1	14/15	20.05	14/15	22.12	+2.07
2	15/15	8.23	14/15	9.56	+1.33
3	14/15	4.83	14/15	4.66	- 0.17
4	15/15	7.09	15/15	4.68	-2.41
5	14/15	18.80	15/15	17.90	-0.90
6	15/15	6.001	15/15	6.213	+0.212
7	14/15	14.06	15/15	14.13	+0.07
8	15/15	0.96	15/15	1.12	+0.16
9	14/15	12.09	14/15	12.52	+0.43
10	15/15	10.06	15/15	10.08	+0.02
11	15/15	9.38	15/15	9.04	-0.34
12	14/15	15.74	15/15	16.48	+0.74
13	14/15	14.12	14/15	15.85	+1.73
14	15/15	12.55	15/15	13.10	+0.55
15	15/15	5.71	15/15	6.61	+ 0.90

Paired samples statistics: Treatment group-Hematoma size in 1st CT scan, mean is 10.6447 with SD 5.37401 and 2nd CT scan mean is 10.9375 with SD 5.78161. There is no significant hematoma size expansion between baseline and after 24 hours ( $P = 0.313$ ).



5.9 h in the treatment group. The present study aimed to enroll patients within 8 hours of onset because haematoma expansion peaks from 4.5–12 hours and is seldom > 24 hours.

The common location of cerebral haematoma secondary to hypertensive bleeding has been documented in many studies and case series. These locations included the basal ganglia/internal capsule (40–50%), lobar regions (20–50%), thalamus (10–15%), pons (5–12%), cerebellum (5–10%), and other brainstem sites

(1–5%) (Maria et al. 2014). In our study, we observed similar locations that included the internal capsule (24, 80%), thalamus (4, 13%), and caudate (2, 7%). The haematoma was in the right hemisphere in 77% of the patients and in the left hemisphere in 23% of the patients. The pathophysiology was due to chronic hypertension producing a small vessel vasculopathy, which was characterised by lipohyalinosis, fibrinoid necrosis, and development of Charcot-Bouchard aneurysms and endarteries throughout the brain, including the lenticulostrates, thalamoperforators, paramedian branches of the basilar artery, superior cerebellar arteries, and anterior inferior cerebellar arteries (40).

In this study, we noted that blood parameters such as haemoglobin platelets, coagulation profile, and fibrinogen levels were within normal ranges in the treatment and control groups. This was likely a result of the exclusion criteria, which excluded patients with abnormal blood parameters that might have hindered the effect of TXA. Interestingly, we observed that patient nos. 6, 14, and 15 in the control group had leukocytosis (TWBC ≥ 11,000 m/L3) upon admission. These patients had significant neurological deterioration (GCS, 9–10/15) after admission in the ward within 4–6 hours despite maintaining their blood pressure within the range of 140–160 mmHg. An urgent CT scan was performed and revealed haematoma expansion; however, the early sign of leukocytosis in these patients may have been an early predictor for neurological deterioration. In a previous study, a white blood count (WBC) >10,000/mL3 upon presentation or within the first 72 hours was highly associated with subacute deterioration, and there was no association with the febrile state and subacute deterioration. All 30 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

**Table 4:** Volume expansion differences after 24 hours between the treatment and control groups

Patient No.	Treatment group (cm <sup>3</sup> )	Control group (cm <sup>3</sup> )
1	+2.07	+2.64
2	+1.33	+0.77
3	- 0.17	+1.05
4	-2.41	+1.53
5	-0.90	+3.94
6	+0.212	+6.35
7	+0.07	+4.13
8	+0.16	+0.74
9	+0.43	+1.78
10	+0.02	+3.64
11	-0.34	+3.07
12	+0.74	+3.37
13	+1.73	+1.84
14	-0.55	+6.32
15	+ 0.90	+13.79

Control group hematoma expansion size, median is 0.85572 with SD 3.31420 and treatment group hematoma size, mean is 0.27983 with SD 1.08378.

**Table 5:** Statistical analysis using the Mann-Whitney U test

Intervention	1 <sup>st</sup> brain CT Median value (range)	2 <sup>nd</sup> brain CT Median value (range)	Differences Median value (range)	P-value
Treatment group	10.06 (0.96–20.05)	10.08 (1.12–22.12)	0.2120 (-2.41–2.07)	P = 0.313
Control group	14.53 (6.29–23.67)	17.59 (7.03–37.46)	3.07 (0.74–13.79)	P = 0.001

In control group hematoma size; median 3.0700, Interquartile range 2.60 with SD 3.31420. In treatment group hematoma size; median 0.2120, interquartile range 1.07 with SD 1.08378. Control group showed significant hematoma expansion compared to treatment group (14.3300 vs 17.9940, P = 0.001).

the ward. The 2010 AHA management guidelines consider the acute lowering of SBP to 140 mmHg as “probably safe”. This is a new recommendation since the 2007 guidelines.

Both groups were monitored under intensive blood pressure control—the SBP was strictly maintained between 140–160 mmHg using an infusion of labetalol. However, there was significant ongoing haematoma expansion due to the extravasations of blood despite strict blood pressure control. When comparing the haematoma volume from the 1st brain CT scan on admission with that from the 2nd brain CT after 24 h, the control group showed haematoma expansion ranging from 0.77–13.79 cm<sup>3</sup>. Patient nos. 6, 14, and 15 had haematoma expansion ranging from 6.32–13.79 cm<sup>3</sup> within 24 h during observation. The expansion observed in these patients might have resulted from their SBP, which was high on admission (systolic > 200 mmHg; diastolic > 100 mmHg). These patients underwent urgent craniotomy/craniectomy and evacuation of blood clots. The blood parameters, including the INR, were within normal range. This clearly shows that bleeding from the haematoma continued within the first 24 h of onset. This finding has been proven in earlier studies; in a non-coagulopathic state, haematoma expansion was 9–30% when SBP was controlled within the range of 150–160 mmHg. This suggests that treatment to prevent haematoma expansion should be initiated as soon as possible after the onset of ICH or its diagnosis.

The treatment group received a bolus administration of TXA (1 g over 10 min) followed by a maintenance dose (1 g infusion over 8 h) with strict blood pressure control (SBP, 140–160 mmHg), and the haematoma volume expansion range was 0.02 – 2.07 cm<sup>3</sup> in 11 patients. This finding indicates that TXA played an important role in stabilizing the haematoma by preventing breakdown of the fibrin network.

It is even more surprising that in patient nos. 3, 4, 5, and 11, a comparison between the 1st brain CT and 2nd brain CT revealed that the haematoma volume had reduced in size (range, -0.17 to -2.41 cm<sup>3</sup>). The finding of physiological blood clot retraction and haematoma reduction in these patients may be explained by the mechanisms of TXA, which prevent early degradation of the fibrin network and promotes fibrin adhesion to the haematoma. Larger haematomas in the treatment group expanded (2.07 cm<sup>3</sup>), whereas smaller haematoma expanded on a much smaller scale (0.16–1.33 cm<sup>3</sup>). This was probably due to the availability of free lysine in the blood; thus, the dose adequacy is questionable. However,

none of the patients in the treatment group showed adverse effects to TXA during the course of treatment.

In our study population of 30 patients, GCS scores were within the range of 13–15/15. These scores correlate well with the haematoma size (<0 ml) and location, which were mostly in the right hemisphere (77%), which is the non-dominant hemisphere.

The overall outcome in the treatment group after 30 days ranged from severe disability to good recovery, with a mean GOS score of 4.4. Control group outcomes ranged from the vegetative state to good recovery, with a mean GOS score 3.6. Three patients in the control group, patient nos. 6, 14 and 15, underwent urgent craniotomy for haematoma expansion but did not recover to their initial GCS scores. Patient nos. 14 and 15 were in the vegetative state due to multifocal infarctions, whereas patient number 6 recovered up to a GOS score of 3 (severe disability). However, no mortality was noted within 30 days.

## Conclusions

This study showed a significant haematoma volume expansion in the control group compared to the treatment group. TXA is very effective in stabilising the haematoma once the patient's blood pressure is controlled. Therefore, the present study has proven the benefits of TXA. It is important to acutely lower the systolic pressure (140 mmHg) upon admission (AHA 2010) prior to administering antifibrinolytic agents and to maintain strict blood pressure control over the following 24 hours. Therefore, every patient who presents with spontaneous ICH secondary to uncontrolled hypertension, which is non-surgically managed, should be treated with a combination of a bolus administration of TXA (1 g) and a maintenance dose via infusion (1 g over 8 hours) with strict blood pressure control rather than blood pressure control alone. However, a multicentre double-blinded randomised study is needed to further evaluate the dose adequacy and its significance.

## Study limitations

There are a few limitations to this study. The main limitation was that patients were enrolled within 8 h of symptom onset. Another limitation included the strict blood pressure control (systolic pressure, 140–160 mmHg). Two patients in the control group were withdrawn because of uncontrolled hypertension (systolic



pressure > 200 mmHg for > 8 hours), and 3 patients in the treatment group were withdrawn because of data loss.

## Recommendations and future research

This study has unveiled a potential antifibrinolytic agent, TXA, which has proven benefits in controlling haematoma expansion. This was the first study on TXA performed in Malaysia, and it is hoped that this study will pave the way for future research on primary ICH. The following studies are recommended for future research:

- a) A phase II trial investigating a larger population of ICH patients to further validate the efficacy of TXA;
- b) A study on the use of TXA that compares a strict blood pressure control of <140 mmHg with 140–160 mmHg; and
- c) A study to develop new TXA protocols for ICH.

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## Conflict of Interests

None.

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