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Original Research Article

Effect of Tranexamic Acid on Expansion of Haematoma and Functional Recovery in Acute Intracerebral Haemorrhage

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Conflict of interest: Nil

Abstract

Aim: This study evaluated the efficacy of tranexamic acid in reducing thrombus expansion while controlling prolonged bleeding. In addition, it was attempted to analyze whether the shortens hospital stay and/or overall disease outcome.

Materials and Methods: In a randomized, placebo-controlled, parallel-group study conducted for approximately 1 year, 60 adults with acute intracerebral hemorrhage who reached hospital within 8 hours of onset of strokesymptoms (or the last time they were well) were registered.

Results: The greater the hematoma burden, the higher the mRS value. In both scenarios, there is no significant difference between mRS values for cases and controls, with p-values for mRS at 1 and 3months of 0.82 and 0.839, respectively.

Conclusion: There was no significant difference in mRS after 1 month between the two groups. The difference in mRS after 3 months was also not significant. There was no significant difference in ICH volumechange between the two groups.

Keywords: Tranexamic acid, placebo-control, modified Rankin Scale (mRS), ICH

Introduction

CVA is one of the leading causes of mortality and morbidity in the world. Although, 20% of all strokes are attributed to spontaneous intracerebral hemorrhages, it accounts for nearly 50 % of all stroke deaths worldwide [1]. In CVA intensive blood pressure lowering is the most effective strategy to improve functional outcome, as no new effective interventions have yet been developed to prolong survival [2]. In the Eastern coastal belt of India, ICH accounts for 32% of all stroke cases reported, and42 % of case fatality rate. Novel effective interventions for prolonging survival have not yet been developed, making intensive blood pressure lowering, the most effective

strategy in improving functional outcome [2].

One of the most dreaded consequences is secondary to haematoma expansion which is found in about a quarter of intra cerebral hemorrhages detected by sequential CT scan, MRI imaging and CT Angiography, which is usually done within the first few hours of onset of symptoms up to 24 hours whichis the usual time for the haematoma expansion [3-6]. Haematoma expansion leads to worsening cerebral oedema and thus worsened functional neurological status. The degree of hematoma leads to worsening cerebral edema, which leads to worsening functional neurological status. In patients with traumatic bleeding, use of tranexamic acid has been shown to significantly reduce mortality without increasing Vaso occlusiveevents [7].

Significant reduction in mortality without increase in vaso occlusive events by the use of the antifibrinolytic agent Tranexamic acid has been found in patients with traumatic haemorrhage [7]. It has been observed through a meta-analysis, that an early use of tranexamic acid resulted in significant reduction of subsequent intracranial bleeding.[8] This positive outcome may be explained by corroborative evidence as shown in CRASH-2 trial, which suggested death due to early bleeding post trauma [9]. One drug therapy which has been tried with the aim to limit haematoma expansion is use of recombinantfactor VII [10]; however, a meta-analysis of such trials found no benefit on functional outcome. Due to the above stated beneficiary action and easy administration without significant vaso-occlusive events, Tranexamic acid has been studied in few randomized control trials [11].

Materials and Methods

In a randomized, placebo-controlled, parallel group study carried between August 2019 and August 2020, after having obtained ethical committee approval, 60 adults with acute non traumatic intracerebral haemorrhage were included in the study if they reached hospital within 8 h of stroke symptom onset (or time last seen well). Inclusion criteria were adults aged 16 – 60 yrs with Acute ICH reaching hospital within 8 hrs of symptom onset. Key exclusion criteria were intracerebral haemorrhage secondary to anticoagulation, thrombolysis, trauma, or a known underlying structural abnormality; patients for whom tranexamic acid was thought to be contraindicated and prestroke dependence (modified Rankin Scale [mRS] score >4).

CVA (ICH) was diagnosed according to clinical symptoms of the same along with radiological confirmation of intracerebral bleeding. Semiautomated segmentation of the ICH was done on digital imaging and communications in medicine–compliant images to give ICH volumes. We obtained written informed consent from each participant if they had the capacity to provide it. Study participants were randomized into two groups A and B. The intervention group received tranexamic acid intravenously asa 1 g loading dose in 100 mL normal saline {0·9%} infused over 10 mins, followed by another1 g in 500 mL normal saline {0·9%} infusion over 8 hrs. The control group received matching placebo (normal saline0·9%), administered by an identical regimen. At randomization, we recorded the participants' age, sex, and medical history, as well as an assessment of the intracerebral haemorrhage location. We assessed prestroke dependence and stroke severity with the mRS. Participants were assessed for the haematoma volume and expansion by CT scan brain imaging done at onset and after 24 hours. Haematoma expansionhas been defined as an absolute increase of more than 6 mL or a relative growth of greater than 33%. Functional and clinical recovery was assessed at 1st and 3rd month of ICH onset.

Measure of functional recovery i.e; mRS was done at 1 month and 3 months on OPD basis, and inpatientbasis if death occurred after proper history taking and examination. mRS scale is a functional status score of disability graded from 0 to 6. A shift in mRS score at 90 days was decided as the primary outcome. Intention-to-treat analysis was done to the patients receiving Tranexamic acid and compared with the placebo group. GCS was calculated at the time of presentation. An increase in haematoma size was defined as an increase in 6 ml or 33% increase of previous haematoma size Safety outcomes in terms of death and vaso occlusive symptoms like ischemic CVA, TIA, MI , DVT, pulmonary embolism were decided.

Statistical Methods

Unpaired t test was used to compare quantitative data between cases and control. Using proportion test, we compared qualitative data between cases and control. Pearson correlation was used to find the correlation between the variables.

Results

In both cases and control groups, we found higher number of patients in age group > 40 yrs. There were 23 male patients in case group and 22 males in control group. p = 0.5812 indicates that homogenous groups were taken, as depicted in Figure 1. There was a preponderance of male patients in both the groups.

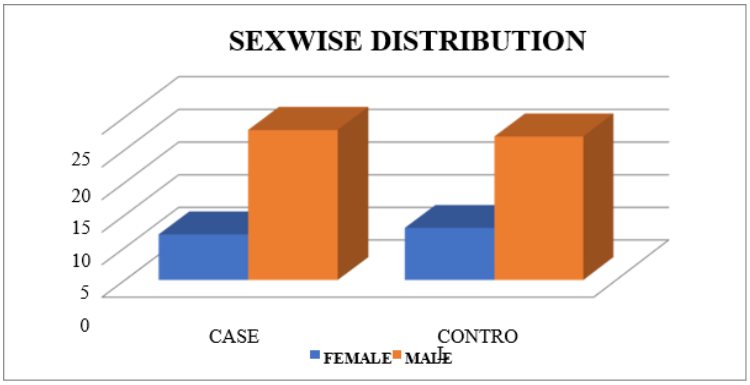

Figure 1: Comparison of sex distribution between case and control.

On observation, as depicted in Figure 2, 56.7 % of the patients in the case group were Hypertensive & 66.7 % in the control group were Hypertensive. There was no significant difference on comparison withp value = 0.144

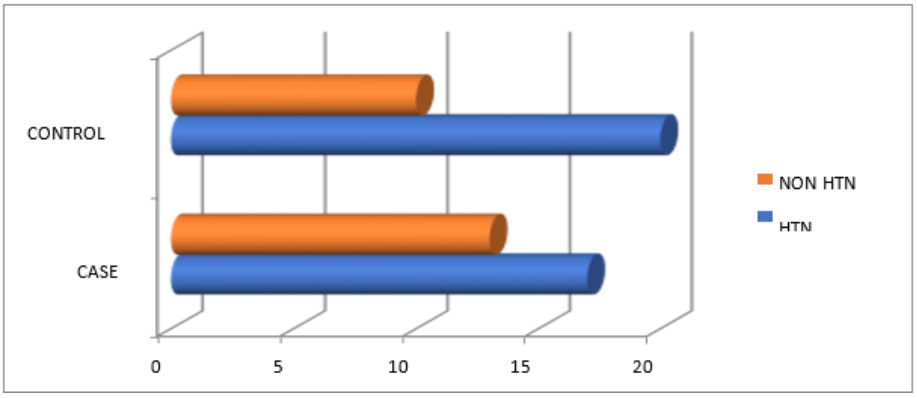

Figure 2: Comparison between Hypertensive and non-Hypertensive patients in both case and controlgroups.

Figure 3 shows that there is a positive correlation between systolic BP &Haematoma volume at onset witha relative risk of 0.078.

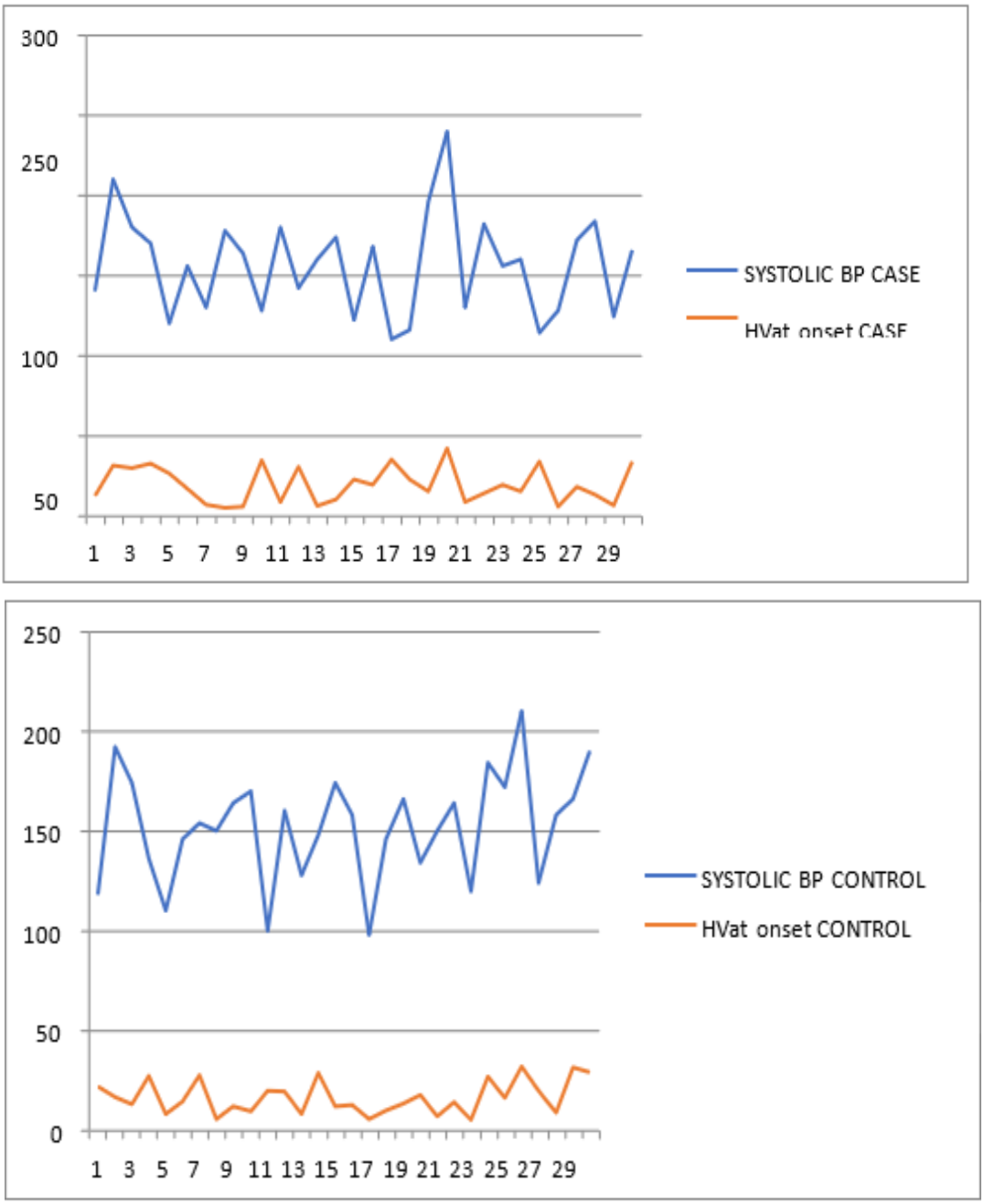

Figure 3: X axis represents haematoma volume in cm3 Y axis represents Systolic BP in mmHg.

Figure 4 depicts the relative proportion of patients in different mRS groups in both cases and control groupat 1 and 3 months.

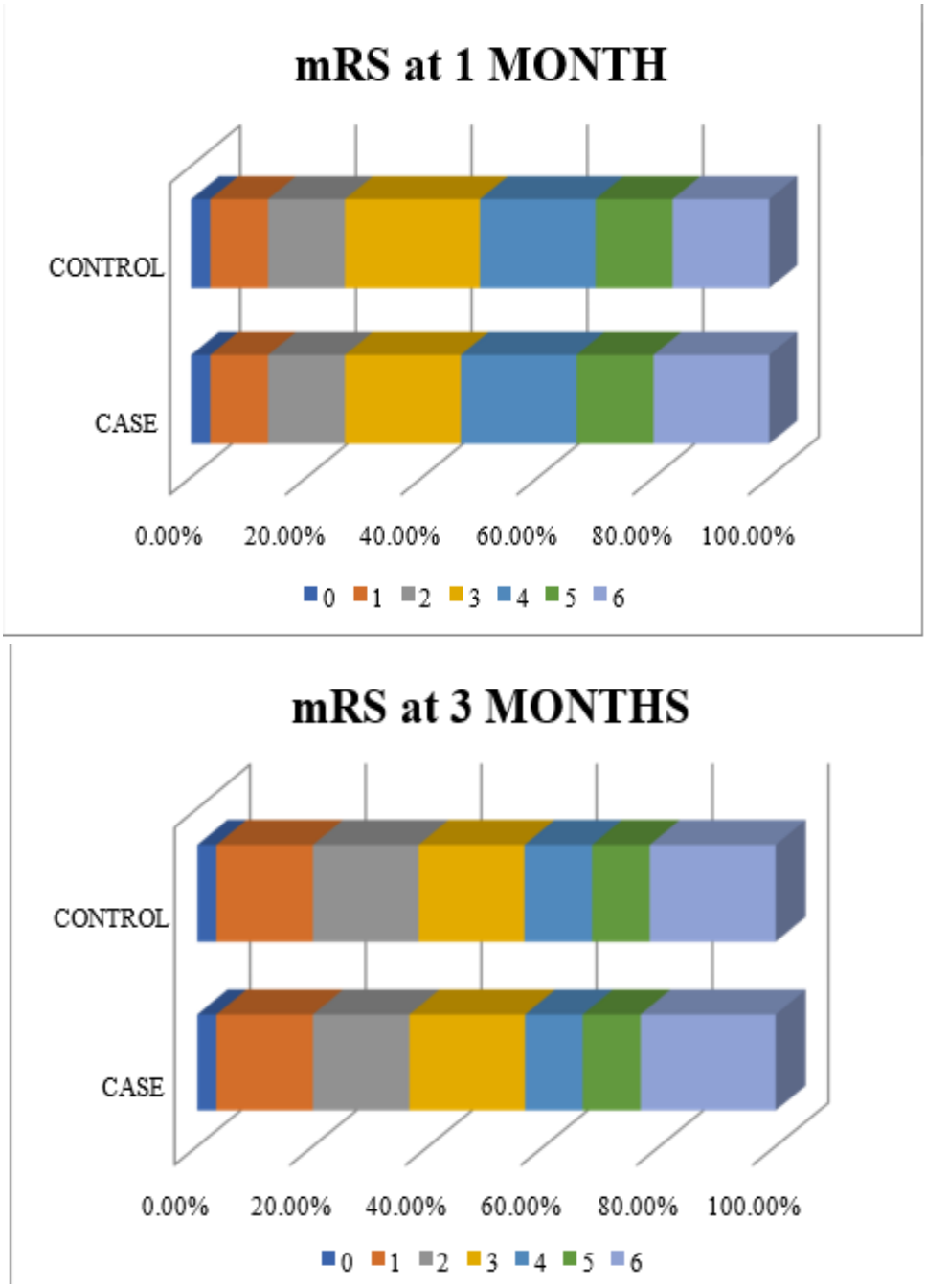

Figure 4: Comparison of mRS value at 1 month and 3 months between case and control.

Figure 5 depicts haematoma volume change in cases and control groups. By using unpaired t test, the difference was not found to be significant with p value of 0.4077.

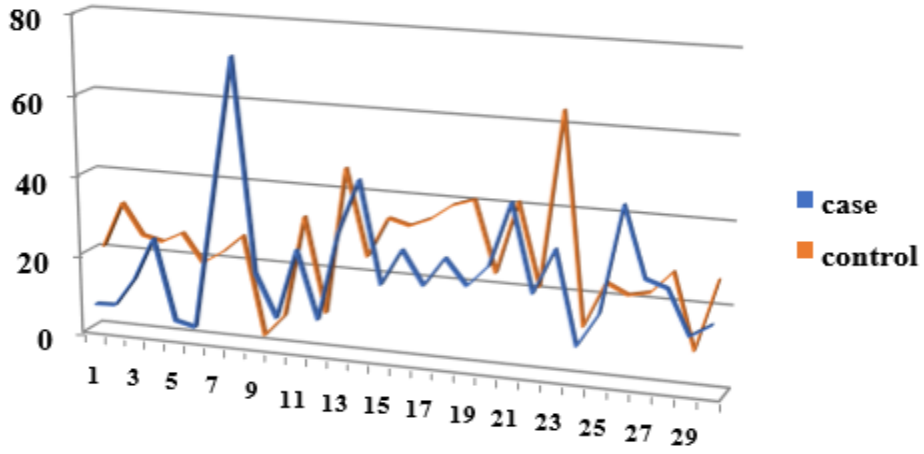

Figure 5: X axis represents percentage of haematoma volume change and Y axis represents number of patients/cases.

In both the scenarios, as shown in figure 6, the average haematoma volume in mRS value < 3 in both cases and control groups is about 9.14 and 10.5 respectively. Similarly, for mRS> 3 , the average haematoma volume in both cases and control groups is 27.9 and 23.3 respectively, which indicates that larger haematoma volumes were seen correlating with higher mRS values. We also found that the deviation is more in > 3 mRS patients than in patients with mRS< 3

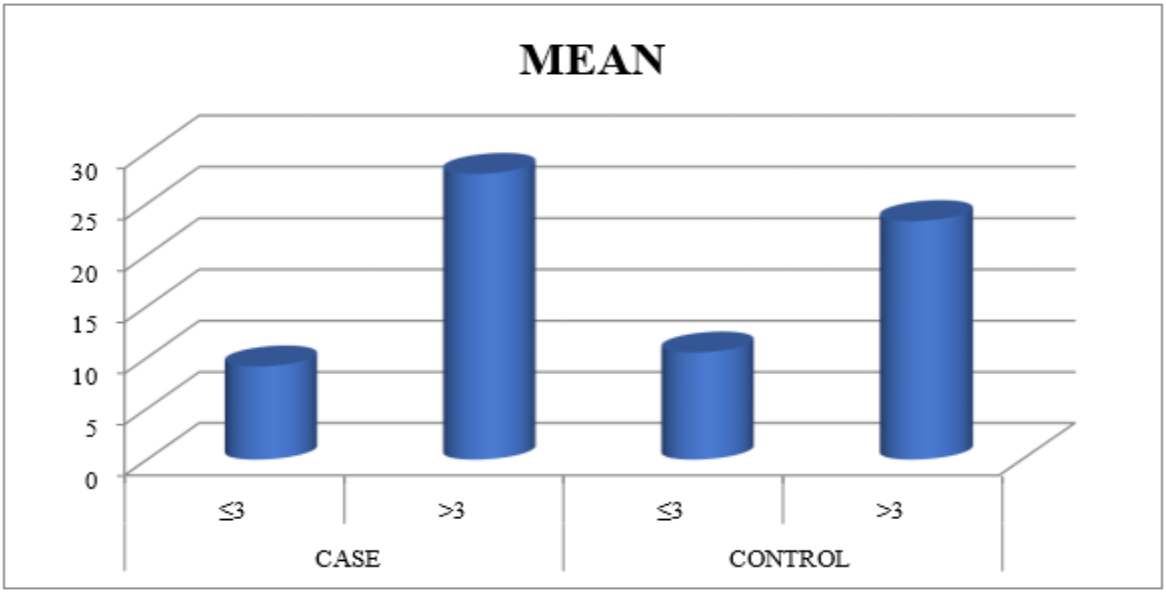

Figure 6: Comparison between mRS and haematoma volumes between cases and control.

By using unpaired t test, we didn't find any significant difference in mRS values in cases and control inboth the scenarios, with p value of 0.82 and 0.839 in mRS at 1 month and 3 months respectively.

Discussion

In this study, anthropometrical, biochemical parameters, ICH volume change and mRS at 90 days of 30 patients receiving Tranexamic acid were compared with 30 control patients receiving placebo. ICH volume calculation was done using Ellipsoid volume equation and disability was quantified using the modified Rankin scoring scale.Study population was divided into two groups. Group A consisted of cases comprising of patients with ICH presenting within 8 hours of onset of ICH and received Tranexamic acid. Group B comprised of patients presenting within 8 hours of onset of ICH receiving placebo. In our study mean age was 49.7±7 years 48.5≠7 years in the Group A and Group B respectively. Among all of our patients 75 % of the total population are males.

General distribution as shown as follows. Group A 23 Male 7 Female. Group B 22 Male 8 Females. Mean SBP in Group A and B were 156±31 mm Hg and 152≠27 mm Hg respectively as shown. The overall mean BP was 156 ± 31versus 152 ± 27which was higher than arterial BP found in Indian population with a mean value of SBP of 120+/- 90 as seen in ICMR INDIAB study phase 2. In this trial of tranexamic acid versus placebo after acute intracerebral haemorrhage, there was no significant difference between the groups in the primary outcome of functional status at day 90, with insignificant haematoma volume change (measured in percentage). However, in the tranexamic acid group, we detected significant reductions in the prespecified secondary outcomes of early death and serious adverse events, consistent with tranexamic acid having an antifibrinolytic effect after intracerebral haemorrhage.

Tranexamic acid was associated with insignificant reduction in haematoma expansion and smallerhaematoma volumes. We found no evidence of an increase in serious adverse effects with tranexamic acid; notably, there was no increase in venous thromboembolism in this significantly older population with more comorbidities than participants in previous studies of tranexamicacid.It is therefore unlikely that any potential benefit of tranexamic acid was offset by harm, as has been suggested with recombinantfactor VIIa.

In a phase 3 trial, there was no evidence of clinical benefit from recombinant factor VIIa, which was associated with a reduction in haematoma expansion but an increased risk of arterial occlusive events. Although tranexamic acid and recombinant factor VIIa are both haemostatic agents, tranexamic acid actsthrough antifibrinolytic mechanisms and recombinant factor VIIa is a procoagulant, so they have differentrisk-benefit profiles.

To date, the only intervention to improve functional outcome after intracerebral haemorrhage is early intensive blood pressure lowering. Although no significant effects on haematoma growth were detected in INTERACT-2, secondary analysis suggested that blood pressure lowering did attenuate bleeding in a dose-dependent manner. The interaction between baseline systolic blood pressure and treatment in our study suggests that participants with lower blood pressure were more likely to benefit from tranexamic acid. This finding could have been confounded by stroke severity, given that larger haematomas have increased blood pressure and worse outcomes.

The strengths of this study include its double-blinding, allocation concealment, low risk of bias, high adherence to treatment, and very few missing data on primary outcomes. Treatment groups were well balanced for baseline factors. The use of approved brief and proxy consent processes allowed the rapid enrolment of patients without the capacity to consent, which is important to

avoid bias in acute stroke studies. Our inclusion criteria were deliberately broad to reflect the clinical population. The study had several other limitations.

Wide inclusion criteria led to a heterogeneous population with more severe strokes, larger haematoma volumes, and a greater proportion of lobar haematoma and intraventricular hemorrhage than populations in other intracerebral haemorrhage trials, which could have diluted any potential treatment effect. Finally, despite efforts to ensure rapid treatment, most participants were enrolled more than 3 h after the onset of intracerebral haemorrhage.

Identification of patients most likely to benefit from hemostatic therapy on the basis of factors other thantime of onset has been suggested, but enrichment with the CTA spot sign has yet to be successful.

In summary, tranexamic acid did not affect functional status at day 90. No potential benefits were seen with reductions in haematoma expansion, early death, and serious adverse events. The observed effect size was smaller than anticipated and is compatible with a lack of efficacy or the presence of a smaller treatment effect than expected. Future research should investigate which subgroups of patients might benefit.

Tranexamic acid is inexpensive, easy to administer, seems to be safe, and is widely available, soeven a modest treatment effect could have an important impact on the global scale. The mean value of ICH volume in case and control groups were 23.172 and 26.08 respectively.

There was a non-significant difference of mRS at the end of 1 month in the two groups. Also, the difference of mRS at the end of 3 months was non-significant. There was nonsignificant difference in the ICH volume changes between the two groups. Larger randomized trials are warranted.

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