Incidence and predictors of early seizures in intracerebral haemorrhage and the effect of tranexamic acid

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Word count for text: 4071 (including references and tables)

Word count for abstract: 245

Number of tables: 5

Number of figures: 1

Abstract

Introduction

Seizures are common after intracerebral haemorrhage (ICH). Tranexamic acid increases the risk of seizures in non-ICH population but its effect on post-ICH seizures is unknown. We explored the risk factors and outcomes of seizures after ICH and if tranexamic acid increased the risk of seizures in the Tranexamic acid for IntraCerebral Haemorrhage-2 (TICH-2) trial.

Patients and methods

Seizures were reported prospectively up to day 90. Cox regression analyses were used to determine predictors of seizures within 90 days and early seizures (ES, ≤7 days). We explored the effect of early seizures on day 90 outcomes.

Results

Of 2325 patients recruited, 193 (8.3%) had seizures including 163 (84.5%) early seizures and 30 (15.5%) late seizures (> 7 days). Younger age (adjusted hazard ratio [aHR] 0.98 per year increase, 95% confidence interval [CI] 0.97-0.99; p=0.008), lobar haematoma (aHR 5.84, 95%CI 3.58-9.52; p<0.001), higher National Institute of Health Stroke Scale (aHR 1.03, 95%CI 1.01-1.06; p=0.014) and previous stroke (aHR 1.66, 95%CI 1.11-2.47; p=0.013) were associated with early seizures. Tranexamic acid did not increase the risk of seizure within 90 days. Early seizures were associated with worse mRS (aOR 1.79, 95%CI 1.12-2.86, p=0.015) and increased risk of death (aOR 3.26, 95%CI 1.98-5.39; p<0.001) at day 90.

Discussion and conclusion

Lobar haematoma was the strongest independent predictor of early seizures after ICH. Tranexamic acid did not increase the risk of post-ICH seizures in the first 90 days. Early seizures resulted in worse functional outcome and increased risk of death.

Clinical Trial registration-URL: https://www.isrctn.com Unique identifier: ISRCTN93732214

Keywords: seizures, intracerebral haemorrhage, tranexamic acid, randomised controlled trial, incidence

Introduction

Seizures occur in approximately 4 to 14% of patients with acute intracerebral haemorrhage (ICH).[1-7] The incidence of seizure is approximately 30% when subclinical or non-convulsive seizures are diagnosed by continuous electroencephalogram (EEG).[8, 9] Younger age, lobar haematoma, stroke severity and haematoma expansion have been identified as risk factors for early seizures after ICH.[1, 5, 9] In patients with early seizures, larger haematoma and intraventricular haemorrhage volume, lobar location and lower Glasgow Coma Scale increase the risk of recurrent seizures beyond 7 days.[10] Similarly, cortical involvement, younger age and larger haematoma volume increase the risk of late-onset seizures.[10, 11] In addition, previous lobar ICH, pre-ICH dementia, presence of white matter disease on neuroimaging and APOE ε4, which suggest underlying cerebral amyloid angiopathy are known risk factors for late seizures.[10, 11]

In non-ICH patients, seizure is a known complication of tranexamic acid with an estimated incidence of 2.7%.[12] It increased the risk of seizure by approximately five times according to one meta-analysis (pooled OR 5.39, 95% CI 3.29-8.85; $I^2 = 0\%$; $p < 0.001$).[12] Tranexamic acid acts directly to increase the excitability of the neural network by inhibiting gamma-aminobutyric acid type A ($GABA_A$) and glycine receptors, both major mediators of inhibition in the central nervous system (CNS).[13, 14] However, as most studies reporting seizures in people treated with tranexamic acid involved patients who underwent cardiac surgery, it is unclear whether tranexamic acid increases the risk of seizures in patients with ICH.

The impact of seizures on outcomes in ICH is debatable. Several studies reported an increased in-patient and 30-day mortality rate, two to three fold higher in patients with seizures compared to those with no seizures.[8, 15, 16] Others found no differences in mortality amongst patients with and without seizures.[5] Paradoxically, several studies found that seizures independently decreased morbidity and mortality in patients with ICH.[17, 18] Bruning *et al* and Mehta *et al* both found patients with early seizures tended to have less severe neurological deterioration and less altered consciousness level at presentation, hence the lower mortality rates.[17, 18] EEG was not routinely performed in both studies and it is possible that patients who had severe ICH had subclinical or non-motor seizures but were not diagnosed to have seizures.[17, 18]

Given the uncertainties with regards to post-ICH seizures highlighted above, we aimed to explore the risk factors for early seizures after ICH and whether administration of tranexamic acid increased the risk of seizure. Secondly, we aimed to examine the effect of post-ICH seizure on clinical outcomes.

Methods

Study design and population

We analysed data from the Tranexamic acid for IntraCerebral Haemorrhage-2 (TICH-2), a prospective phase 3 double-blind placebo-controlled randomised controlled trial that explored the efficacy and safety of tranexamic acid for treatment of acute spontaneous ICH involving 124 centres from 12 countries. Patients aged > 18 years with acute spontaneous ICH within 8 hours of symptoms onset were eligible while secondary ICHs were excluded. Participants received 2g of intravenous

tranexamic acid or a matching placebo. Details of the trial have been previously described.[19, 20] Seizure was a pre-specified safety outcome up to 90 days from onset. Site investigators were prompted to file a serious adverse event (SAE) report when seizures occurred. The SAE reports were adjudicated by independent assessors blinded to treatment allocation, based on clinical and diagnostic information provided by site investigators.

Definitions

Early seizure (ES) was defined as the occurrence of seizure(s) within 7 days from the onset of ICH.[21] Late seizure was defined as an occurrence of seizure(s) after 7 days from the onset of ICH.[21] Any seizure refers to occurrence of seizure within the first 90 days and is the summation of early and late seizures.

Statistical analysis

Descriptive analysis was performed to describe the baseline characteristics of patients who had and did not have seizures using Mann-Whitney U, Chi-square and Student t-test where appropriate. Due to the small number and relatively short follow-up duration for late seizures, we limited the analyses on predictors and effects of seizures to early seizures. Multivariable Cox proportional hazards regression was performed to identify predictors of any seizure and early seizures in our cohort, including age, sex and treatment allocation a priori and variables that were significant on univariate analyses. Multiple linear regression and multivariable logistic regression analyses were used to explore the effect of early seizures on outcomes, including death, dependency, quality of life, disability, cognition and depression. 95% confidence intervals (CI) are given and P values of <0.05 were

considered statistically significant. All analyses were performed using SPSS version 24 (IBM, Armonk, NY).

Results

Of 2325 patients recruited, 193 (8.3%) had seizures. Early seizures comprised 84.5% (n=163) of seizures, including 79 (41.1%) within 24 hours and 31 (16.1%) within 6 hours of onset. Late seizures comprised 15.5% (n=30) of all seizures. Median onset-to-seizure time was 31.5 hours [IQR 9.25, 91.75]. 85 (44.0%) had a single episode of seizure, 79 (40.9%) had multiple episodes of seizures and for 29 (15%) patients' data on the number of seizure episodes was not available. In the first seven days, 136 (83.4%) patients received antiepileptic therapy, 16 (9.8%) did not and information was missing for 11 (6.7%). Long term antiepileptic treatment was not routinely recorded.

Patients with seizures within 90 days and early seizures were more likely to have worse premorbid modified Rankin Scale, previous ischaemic stroke and ICH as well as more severe impairment (higher NIHSS and lower GCS). (Table 1).

Patients with any seizure and early seizures were more likely to have larger, lobar haematoma and midline shift (Table 2). Periventricular leukoaraiosis was more common in patients with any seizures compared to those with no seizures. On 24-hour CT scans, patients with any seizures and early seizures had more haematoma expansion, intraventricular extension and oedema growth (Table 2).

From the Cox regression analysis, which was adjusted for a priori variables of age, sex and treatment allocation and variables that were significant on univariate analyses, the strongest predictor of any seizure was lobar location with an adjusted hazard ratio [aHR] of 4.83 (95% CI [confidence interval] 3.07-7.60; p<0.001). Similarly, lobar location was the strongest predictor of early seizure with aHR 5.84 (95%CI 3.58-9.52; p<0.001). Other significant predictors of any seizure and early seizures include younger age, higher NIHSS and previous ischaemic stroke (Table 3). Larger haematoma volume was not a significant predictor.

Tranexamic acid did not increase the risk of any seizures (aHR 0.89, 95%CI 0.66-1.19; p=0.42) or early seizures (aHR 0.86, 95%CI 0.62-1.18; p=0.34; Table 3). Kaplan-Meier curves showed no significant difference in seizure-free survival between tranexamic acid and placebo (Figure 1). Exploratory analysis showed that the incidence of seizures did not differ between the treatment groups whether a full dose (2g) or less than full dose was given, or by the degree of renal impairment (examined since TXA is renally excreted), although only 38 participants had an eGFR < 30mls/min (Table 4).

Within the first seven days, early seizures were associated with increased neurological deterioration (n=102, 63% vs 618, 29.1% in those with no early seizure; p<0.001), neurosurgery (22, 13.5% vs 95, 4.5%; p=0.001), invasive ventilation (28, 17.2% vs 133, 6.2%; p<0.001) and intensive care unit admission (37, 22.7% vs 190, 8.9%; p<0.001). Amongst patients who survived beyond seven days, day 90 death, dependency, disability, mood, cognition and quality of life were all significantly worse in patients with early seizure (Table 5). Sensitivity analyses showed that

patients with seizure <6 hours, <24 hours and with single or multiple seizures similarly had worse day 90 outcomes (Supplemental Table 1 & 2). The hazard ratio of death within 90 days was increased in patients with early seizures (aHR 2.40, 95%CI 1.67-3.46; p<0.001; Supplemental Table 3 with Supplemental Figure 1 showing a Kaplan-Meier curve of time to death in patients with early seizures and no early seizures).

Discussion

Lobar location of haematoma was the strongest independent predictor of seizure within 90 days and early seizures after ICH. This is in agreement with previous studies, which had reported lobar location as a risk factor for early seizure with an odds ratio of 2 to 16.[1, 5, 7, 22] In addition, ICH severity as indicated by worse NIHSS and previous stroke/TIA were independent predictors of early seizure. The pathophysiology of early seizures after ICH is unclear but was hypothesised to be related to physical disruption of cortical networks by haematoma or irritation by blood products.[5, 10] Our findings do not support haematoma or oedema size or mass effect as an independent risk factor for early post-ICH seizures. Previous studies found haematoma size as a risk factor for seizures[23] while others did not.[1, 5, 7, 22] Indeed, one study found the risk of early seizures to be lower with larger haematoma.[4] Haematoma expansion was reported as a risk factor in one study.[9] Younger age was a predictor for early seizure in our study in agreement with de Herdt *et al*[7] and Woo *et al*[1], though other studies found no significant association between age and occurrence of early seizures.[4, 5]

Tranexamic acid did not increase the risk of seizures in the current large study and this should allay concerns about using tranexamic acid in ICH. The risk of seizures with tranexamic acid was highlighted in a systematic review by Zhang *et al* which reported a pooled odds ratio of 5.4.[12] However, the population studied were largely patients who underwent cardiac surgery and mostly used higher doses of tranexamic acid (>50 mg/kg). In the same study, higher doses of tranexamic acid were associated with a higher incidence of seizures.[12] Comparatively, the dose used in the TICH-2 trial was relatively low (2 g or approximately 28mg/kg for an average adult weight of 70kg).

There were also concerns that adverse events may be increased in patients with renal impairment as tranexamic acid is mainly excreted through the kidneys. A pharmacokinetic study of tranexamic acid in patients who underwent cardiac surgery reported elevated plasma levels of tranexamic acid and high incidence of seizures (8%) in patients with advanced kidney disease.[24] The authors proposed that a safe dose of tranexamic acid in patients with eGFR of <60 mL/min/1.73m^2 to be a loading dose of <30 mg/kg and maintenance of < 10m/kg.[24] In our cohort, 318 (13.7%) patients had an eGFR of < 60 mL/min/1.73m^2 but the risk of seizures was not increased in these patients. This may be because the dose used in TICH-2 was lower than the threshold dose that may increase the risk of seizures in patients with renal impairment.

Early seizures were associated with neurological deterioration in the first week and led to worse day 90 outcomes in terms of higher death, dependency, disability, cognition, depression and quality of life. This is despite accounting for other known

prognostic factors such as age, baseline haematoma volume, IVH and lobar location. This is perhaps indicative that early excitotoxicity after ICH is detrimental and supports the need for preventive or treatment strategies. Current guidelines found little evidence in recommending primary seizure prophylaxis for ICH.[25] One small randomised controlled trial found that valproic acid did not reduce the risk of seizures at one year post-ICH although the incidence of early seizures was reduced.[26]

The strength of the current analysis is that it was a prospective multicentre trial with a large sample size, involving patients from 12 countries. Seizure was a pre-specified safety outcome and mandated reporting, which may have increased the capture rate. All serious adverse event (SAE) reports were adjudicated blinded to treatment allocation by independent expert assessors, further improve the validity of the data. This study was also the first randomised controlled trial to prospectively study the risk of seizures with the use of tranexamic acid in intracerebral haemorrhage. One limitation of the study is a relatively small number of patients with late seizures. In addition, as the latency of post-ICH epilepsy is much longer than 90 days[27, 28] we could not reliably determine the predictors or the effect of late seizures. This is perhaps best studied by longer-term registry-based research. Some data were not available, namely seizure semiology in a large proportion of patients, seizure classification, previous history of epilepsy and prior anti-epileptic use. The diagnoses of seizure were mainly made by clinical observation. As EEG was not routinely performed, some subclinical or non-convulsive seizures might have been missed, especially in people with depressed conscious level.[8, 9] These limitations occurred, as the primary research design was not to study post-ICH seizures but rather to ensure the safety of tranexamic acid with regards to seizures. Nevertheless, this represents a

pragmatic real-world scenario where neurology review and EEG is not always available to patients with seizure.

In conclusion, tranexamic acid did not increase the risk of seizures in spontaneous ICH within the first 90 days. Lobar haematoma was the strongest risk factor for seizures after ICH. Early seizure was associated with a worse clinical outcome. Future research on prevention and treatment of early seizure after ICH should consider focus on patients with lobar ICH.

Conflicting interests:

PB is Stroke Association Professor of Stroke Medicine. He has received consulting fees from Athersys, Nestle, Phagenesis and ReNeuron; he is an unpaid advisor to Platelet Solutions.

Funding: NIHR HTA grant (project code 11_129_109) and Swiss Heart Foundation

Informed consent: Written informed consent was obtained from the patient(s) or their representatives for their anonymized information to be published in this article.

Ethical approval: This study was approved by the national and institutional ethics review committee of participating countries/centres.

Guarantor: NS

Contributorship: NS and PMB designed the study. TJE and AKM adjudicated SAE

reports on seizures. RD and LAC are neuroradiologists who performed adjudications. ZKL measured haematoma and oedema volumes. ZKL wrote the first draft of the manuscript and performed statistical analysis. All authors revised and approved the final draft.

Acknowledgements: We would like to acknowledge Alessandro Adami (Al A) and Ana Casado (AC) for assistance in adjudicating neuroimaging data; and Azlina Ali and Kailash Krishnan in measurement of haematoma and oedema volumes.

Data sharing: After publication of the planned primary and secondary analyses, the trial data can be shared, upon reasonable request to the corresponding author and trial steering committee.

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Table 1 Clinical characteristics of patients with and without seizures

Characteristics	Any seizure			Early seizure		
	Yes (n=193, 8.3%)	No (n=2132, 91.7%)	P	Yes (n=163, 7.0%)	No (n=2162, 93%)	P
Age, years, mean (SD)	69.3 (13.3)	68.9 (13.9)	0.68	69.0 (13.3)	68.9 (13.9)	0.92
Male sex, n (%)	96 (49.7)	1205 (56.5)	0.069	85 (52.1)	1216 (56.2)	0.31
Premorbid mRS, median [IQR]	0 [0, 1]	0 [0, 1]	0.001	0 [0, 1]	0 [0, 1]	0.015
Systolic blood pressure, mmHg, mean (SD)	172.8 (30.8)	175.0 (29.7)	0.34	173.7 (31.0)	174.9 (29.7)	0.63
Glasgow Coma Scale, median [IQR]	14 [11, 15]	15 [12, 15]	0.001	14 [11, 15]	15 [12, 15]	0.004
NIHSS, median [IQR]	15 [8.5, 20]	12 [6, 18]	0.001	16 [8, 20]	12 [6, 18]	0.002

Prior antiplatelet, n (%)	58 (30.1)	553 (26.0)	0.22	51 (31.3)	560 (25.9)	0.13
Previous stroke/TIA, n (%)	42 (22.0)	288 (13.6)	0.002	35 (21.6)	295(13.8)	0.006
Previous ICH, n (%)	19 (9.9)	107 (5.0)	0.005	15 (9.3)	111 (5.2)	0.027
Ischaemic heart disease, n (%)	22 (10.8)	181 (8.6)	0.17	18 (11.1)	185 (8.7)	0.29
Hypertension, n (%)	111 (58.1)	1310 (61.8)	0.31	97 (59.9)	1324 (61.6)	0.66
Diabetes mellitus, n (%)	26 (13.5)	286 (13.4)	0.97	20 (12.3)	292 (13.5)	0.67
Atrial fibrillation, n (%)	6 (3.1)	65 (3.1)	0.95	6 (3.7)	65 (3.0)	0.62
Onset-CT time, hours, mean (SD)	2.4 (1.3)	2.3 (1.3)	0.15	2.4 (1.3)	2.3 (1.3)	0.40
Tranexamic acid, n (%)	91 (47.2)	1070 (50.2)	0.42	76 (46.6)	1085 (50.2)	0.38

Chi-squared, t-Student and Mann-Whitney U tests are used for comparisons of categorical variables (n, %), mean (SD) and median [IQR] respectively. ICH=intracerebral haemorrhage; IQR=interquartile range, mRS= modified Rankin Scale; NIHSS=National Institute of Health Stroke Scale; SD=standard deviation; TIA=transient ischaemic attack

Table 2 Baseline and 24-hour CT findings in patients with and without seizures

Characteristics	Any seizure			Early seizure		
	Yes (n=193, 8.3%)	No (n=2132, 91.7%)	P	Yes (n=163, 7.0%)	No (n=2162, 93%)	P
Baseline CT						
Haematoma location						
Lobar, n (%)	106 (55.8)	582 (27.8)	<0.001	90 (55.6)	598 (28.2)	<0.001
Deep, n (%)	78 (41.1)	1373 (65.6)	<0.001	68 (42.0)	1383 (65.2)	<0.001
Infratentorial, n (%)	6 (3.2)	139 (6.6)	0.060	4 (2.5)	141 (6.6)	0.036
Intraventricular haemorrhage, n (%)	66 (34.7)	641 (30.5)	0.22	55 (34.0)	652 (30.6)	0.37
Haematoma volume, mL, mean (SD)	33.2 (31.4)	23.1 (26.6)	<0.001	32.5 (31.7)	23.4 (26.7)	<0.001
Perihaematomal oedema volume, mL, mean (SD)	15.8 (15.3)	12.7 (15.5)	0.011	15.3 (14.5)	12.8 (15.5)	0.057

Midline shift, mm, mean (SD)	5.9 (2.5)	5.9 (2.8)	0.78	5.8 (2.4)	5.9 (2.8)	0.84
Midline shift ≥5 mm, n (%)	44 (23.5)	327 (15.7)	0.005	35 (21.9)	336 (15.9)	0.049
Old infarct(s), n (%)	114 (60.0)	1279 (60.7)	0.85	93 (57.4)	1300 (60.9)	0.38
Cerebral atrophy, n (%)	178 (93.7)	1921 (91.2)	0.24	151 (93.2)	1948 (91.2)	0.39
Periventricular leukoaraiosis, n (%)	101 (52.3)	957 (44.9)	0.040	84 (51.9)	974 (45.6)	0.13
24- hour CT						
Haematoma expansion, n (%)	55 (34.8)	513 (26.4)	0.031	47 (35.1)	523 (26.9)	0.040
Absolute haematoma growth, mL, mean (SD)	7.6 (18.2)	4.7 (14.7)	0.052	8.4 (19.2)	4.7 (14.6)	0.035
Absolute oedema growth, mL, mean (SD)	9.7 (16.6)	6.4 (11.8)	0.014	10.6 (16.9)	6.4 (11.8)	0.005
Intraventricular haemorrhage extension[a], n (%)	26 (15.1)	154 (7.8)	0.003	21 (14.5)	158 (7.9)	0.005

Change in midline shift, mm, mean (SD)	0.8 (4.2)	1.2 (3.7)	0.48	1.0 (4.3)	1.2 (3.7)	0.83

Chi-squared and t-Student tests are used for comparisons of categorical variables (n, %) and mean (standard deviation) respectively.

[a]Intraventricular haemorrhage extension was present if intraventricular haemorrhage was present on 24-hour CT but not on baseline CT.

Table 3 Multivariable Cox regression analyses of predictors of seizures within 7 and 90 days

Variables	**Any seizure ≤90 d [a]Adjusted HR (95%CI)**	**P**	**Early seizure ≤7 d [a]Adjusted HR (95%CI)**	**P**
Age (years)	0.98 (0.97-0.99)	0.004	0.98 (0.97-0.99)	0.008
Sex (male)	0.96 (0.70-1.30)	0.77	1.01 (0.72-1.40)	0.98
Premorbid mRS	1.15 (1.00-1.32)	0.051	1.07 (0.91-1.25)	0.41
NIHSS	1.03 (1.01-1.05)	0.019	1.03 (1.01-1.06)	0.014
Prior stroke/TIA	1.69 (1.17-2.43)	0.005	1.66 (1.11-2.47)	0.013
Prior intracerebral haemorrhage	1.11 (0.65-1.89)	0.71	1.20 (0.68-2.14)	0.53
Lobar location	4.83 (3.07-7.60)	<0.001	5.84 (3.58-9.52)	<0.001
Baseline haematoma volume (per 10 mL)	1.07 (0.98-1.17)	0.13	1.07 (0.97-1.17)	0.16
PHO volume (per 10 mL)	1.08 (0.87-1.33)	0.49	1.12 (0.90-1.40)	0.31
Midline shift ≥5mm	1.30 (0.85-1.99)	0.23	1.11 (0.69-1.78)	0.67
Periventricular leukoaraiosis	1.41 (1.00-1.99)	0.049	1.31 (0.91-1.90)	0.15
Tranexamic acid	0.89 (0.66-1.19)	0.42	0.86 (0.62-1.18)	0.34

CI=confidence interval; HR=hazard ratio; mRS=modified Rankin Scale; NIHSS=National Institute of Health Stroke Scale; PHO=perihaematomal oedema; TIA=transient ischaemic attack. [a]Adjusted for a priori variables of age, sex and treatment allocation and variables that were significant on univariate analyses

Table 4 Incidence of seizures by treatment groups according to subgroups of treatment completion and estimated glomerular filtration rate

Subgroups	N	Any seizures ≤90 days		
		Tranexamic acid	Placebo	P
Treatment completion[a]				
Full dose	2207	80 (7.3)	89 (8.0)	0.49
Less than full dose	100	8 (16.7)	13 (24.5)	0.33
eGFR (mL/min/1.73m2)[b]				
≥60	1857	73 (7.8)	83 (9.0)	0.34
30-59	280	10 (7.5)	13 (8.8)	0.69
<30	38	3 (13.6)	1 (6.3)	0.46

Data are number (%) and statistics are Chi-Squared test. [a]Treatment not given at all in 15 patient; completion status was uncertain in 3 patients. [b]Estimated glomerular filtration rate (eGFR) not available in 150 patients.

Table 5 Effects of early seizures on day 90 outcomes

Outcomes	Early seizure (n=139, 85.3%)	No early seizure (n=1962, 90.7%)	OR/MD (95% Confidence interval)	P
Death[a]	38 (27.9)	237 (12.2)	3.26 (1.98, 5.39)	<0.001
mRS>3[a]	88 (64.7)	947 (48.6)	1.79 (1.12, 2.86)	0.015
Barthel Index[b]	42.6 (43.9)	60.7 (41.1)	-11.8 (-17.1, -6.6)	<0.001
EQ-5D HUS[b]	0.26 (0.40)	0.39 (0.40)	-0.08 (-0.14, -0.03)	0.005
TICS-m[b]	10.6 (12.7)	17.4 (11.5)	-3.0 (-4.9, -1.1)	0.002
ZDS[b]	73.1 (31.4)	59.1 (26.9)	6.6 (1.7, 11.4)	0.008

[a]Binary logistic regression (OR, odds ratio) and [b]multiple linear regression (MD, mean difference) adjusted for age, sex, premorbid modified Rankin Scale, prior antiplatelet therapy, National Institute of Health Stroke Scale, systolic blood pressure, onset to CT <3 hours, baseline haematoma volume, intraventricular haemorrhage and lobar location. Analysis limited to 2101 participants who survived beyond 7 days.
EQ-5D HUS=EuroQoL-5 Dimensions Health Utility Status; ICU=intensive care unit; mRS= modified Rankin Scale; TICS-m=modified Telephone Interview Cognitive Status; ZDS=Zung Depression Scale

Figure 1 Kaplan-Meier curves show seizure-free survival after intracerebral haemorrhage according to treatment group. There was no significant difference in the seizure event curves between treatment group (log-rank test p=0.41).