Predictors of symptomatic intracranial haemorrhage after thrombolysis in basilar artery occlusion

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Background and purpose: To find out factors associated with development of symptomatic intracranial haemorrhage (sICH) in patients with basilar artery occlusion. Patients were treated with intravenous alteplase and full-dose anticoagulation with heparin.

Methods: The data is from a consecutive cohort of 176 BAO patients treated at Helsinki University Central Hospital during the period between 1995-2013. sICH was judged according to European Cooperative Acute Stroke Study II. The extent of baseline ischemia was evaluated with posterior circulation Acute Stroke Prognosis Early CT score (pc-ASPECTS). Modified Rankin Scale (mRS) at three months was used to rate the outcome. Favourable outcome was rated as 0 to 2 and unfavourable as 3 to 6.

Results: 13.6% of patients developed sICH. Pc-ASPECTS under 8 independently increased the risk of sICH ($p = 0.031$). 70.3% of patients had 3-month mRS 3 to 6, among whom were all sICH cases. High mean systolic blood pressure two hours after thrombolysis was independently associated with development of sICH ($p = 0.034$). Platelet count at baseline and 24 hours after tPA and heparin administration was lower in patients with sICH than without sICH. Activated partial thromboplastin time (APTT) values didn’t associate with developing sICH.

Interpretation: Low to normal platelet count, extensive baseline ischemic changes and high systolic blood pressure at 2 hours after treatment increased the risk of developing sICH.
Contents
1 Introduction ......................................................................................................................... 1
2 Material ............................................................................................................................... 4
3 Methods ............................................................................................................................... 5
4 Results .................................................................................................................................. 7
5 Discussion ............................................................................................................................ 17
6 Conclusions .......................................................................................................................... 19
7 References ........................................................................................................................... 20
8 Original article ..................................................................................................................... 22
1 Introduction

Basilar artery occlusion (BAO) is a rare but severe form of brain infarction. About one per cent of all strokes is caused by BAO. Patients often have preceding non-specific symptoms such as vertigo or headaches, which are followed by decreased consciousness, quadripareisis, pupillary and oculomotor abnormalities, dysarthria and dysphagia. (1) The onset of symptoms is slow in more than 60% of cases and instantaneous in 20% of cases. Most patients, more than 99%, have two or more symptoms. (2) Differential diagnostic alternatives are intracranial bleeding including subarachnoid haemorrhage (SAH), non-convulsive epileptic seizures, hypoxic-ischemic encephalopathy and hypoglycaemia (3). The most frequent causes of BAO are atherosclerotic occlusions resulting from local thrombosis at the site of severe BA stenosis and embolic occlusions from cardiac and large artery sources (1). Diagnosis can be made on the basis of a cranial computed tomography (CT) with CT-angiography, magnetic resonance angiography (MRA) or digital subtraction angiography (DSA) (3).

Treatment aims to recanalization of occluded basilar artery. If recanalization does not occur, 85-95% of patients will die. (3) Treatment alternatives are antithrombotic agents, intravenous thrombolysis (IVT), intra-arterial thrombolysis (IAT), and mechanical endovascular treatment performed in an angio suite (1). Systematic analysis has shown that there is “no significant difference in functional independence with endovascular therapy after intravenous tissue plasminogen activator (tPA), as compared with intravenous tPA alone” in BAO (4). With mechanical endovascular treatment there can even be a 90% recanalization rate but there is no evidence of superiority of endovascular treatment over IVT concerning clinical outcomes (1).

Since no controlled randomized trials have compared these acute treatment options with each other, the choice of treatment is based on the local guidelines and accessibility. Further research is needed to secure improvements in the treatment of BAO (1). A third of BAO patients will become independent after thrombolysis. About half of patients with recanalization will become independent. (3) The long-term quality of life of the survived BAO patients have rarely been systemically analysed (5).
In Finland, primary treatment for BAO is IVT with alteplase and concomitant intravenous heparin infusion. A requirement for IVT is that extensive ischemic changes in the brainstem or other vertebro-basilar (VB) regions have not developed (6). Contraindications for thrombolytic therapy are a duration of BAO exceeding 12 hours in the instantaneous onset phenotype or 48 hours in the progressive (slow-onset) phenotype, absent brain stem reflexes and/or a lack of spontaneous respiration, haemorrhage in brain imaging, detective haemostasis and multiple comorbidities with a limited life expectancy (3).

Alteplase is a tissue plasminogen activator that converts plasminogen to plasmin, which degrades fibrin clots (7). Alteplase is given 0.9 mg/kg, a maximum of 90 mg, first 10% by bolus and the rest by intravenous infusion during an hour (6). Heparin inactivates clotting factors such as thrombin, factor Xa and other proteases (7). Heparin-infusion is used to prevent rethrombosis. Heparin is monitored using the activated partial thromboplastin time (APTT). In the last years, patients with BAO have been treated with low-molecular-weight heparin (LMWH) by bolus and subsequent subcutaneous enoxaparin 0.75 - 1 mg/kg twice daily. (6)

Some of the recognized outcome predictors include age, severity of stroke symptoms evaluated by National Institutes of Health Stroke Scale (NIHSS), time to treatment, occlusion length, thrombus volume, clot location, and possible collaterals (1). The absence of hyperlipidaemia and presence of prodromal minor stroke were associated with a poor outcome in a previous study (8).

If a patient develops symptomatic intracranial haemorrhage (sICH), mortality increases and survivors have a worse prognosis (1). The known predictors of sICH after thrombolysis in BAO are age, baseline NIHSS, and admission blood glucose. In ischemic anterior circulation stroke patients, age > 75 years, NIHSS ≥ 10 on admission and glucose > 8 mmol/l on admission predict the development of sICH. Also, early infarct signs and a dense cerebral artery sign in a CT head scan do increase the risk. (9)
Here, we tested whether routine heparin infusion with IVT is associated with intracranial haemorrhage. The intention was to test demographic-, physiological- and treatment-related factors affecting the development of symptomatic intracranial haemorrhage. The results have also been published as an original article, which is in the end of this thesis. (10).
2 Material

The data were from a consecutive cohort of BAO patients treated at Helsinki University Central Hospital during the period between 1995-2013. The number of patients was 176. Patients were treated with IV 0.9 mg/kg alteplase and immediately after or before thrombolysis with full-dose anticoagulation with either intravenous unfractionated heparin (UFH) or LMWH. Heparin was continued until the patient was mobilized. The APTT target was between 75 and 100 seconds and it was monitored every 4 to 6 hours. If APTT values exceeded 180 seconds they were recoded to 181 seconds.

We gathered the data from the electronic and paper patient charts manually and double-checked a random sample. The data we gathered consisted of the age of patients; NIHSS on admission, right after the treatment and 24 hours after the treatment; whether the patients developed a symptomatic intracranial haemorrhage (sICH) or not and if they did, the delay between the treatment and sICH; haemoglobin on admission; the leukocyte count on admission; the thrombocyte count on admission and 24 hours after the treatment; proteinuria on admission; the creatinine level on admission; the APTT level on admission and the first ten APTT values registered; delays from heparin administration to each APTT value; maximal APTT values after heparin administration in every 12 hours up to 120 hours; systolic and diastolic blood pressure levels on admission and at 2/4/8/12/24/48 hours; blood glucose on admission and the highest blood glucose levels at days one to seven after intervention. Comparisons were made between the patients who developed sICH as a complication of intervention and those who did not.
3 Methods

Statistical analysis was carried out using SPSS statistical software 21.0. Distributions of the continuous variables were tested for normality. Univariate analyses were performed with the $t$-test or Mann–Whitney $U$ test, as appropriate. We conducted a $t$-test for blood pressure differences between sICH and non-sICH groups. Non-normal data were tested by non-parametric tests between sICH and non-sICH groups. P-values lower than 0.05 were considered significant.

The extent of baseline ischemia was evaluated with the posterior circulation Acute Stroke Prognosis Early CT score (pc-ASPECTS) for CT (69% of patients) and magnetic resonance imaging (MRI) (31% of patients). Post-treatment CT or MRI was obtained about 24 hours after thrombolysis and additional CT if needed. sICH was judged according to European Cooperative Acute Stroke Study II (ECASS-II) (11). Recanalization was rated as partial to complete and nil to minimal in post-treatment angiography. We used the modified Rankin Scale (mRS) at three months to rate the outcome. A favourable outcome was rated as 0 to 2 and unfavourable as 3 to 6. MRS is explained in more detail in Table 1.
## MODIFIED RANKING SCORE

<table>
<thead>
<tr>
<th>SCORE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Table 1. Modified ranking score from (12).
4 Results

Out of 176 BAO patients who were treated with alteplase and full-dose heparin, 24 (13.6%) developed sICH. One patient died before CT scan control. 90% of sICHs occurred within 48 hours from the treatment. Blood pressures at bleeding are estimates of the real pressures since the values taken were the closest ones to the detection of sICH on head scan. Blood pressure values were normally distributed.

In Table 2 we present baseline characters of sICH and non-sICH patients. Out of sICH-patients there were 8 (33.3%) females and 16 (66.7%) males. The proportions didn’t differ compared to non-SICH patients. Among the whole cohort, patients’ mean age was 65 years and standard deviation 14 years. Diabetes mellitus type II was present in 13.1%, hypertension in 50.9%, previous stroke in 23.4%, dyslipidaemia in 37.1% and congestive heart failure in 5.7% of cases. These demographics did not differ between sICH and non-sICH patients. Medication including statins, antihypertensives, antiplatelets, insulin, oral diabetes medication and anticoagulation prophylaxis medication didn't differ between sICH and non-sICH patients.
Table 2. Baseline characters for patients with and without sICH.

<table>
<thead>
<tr>
<th>Parameter, median (IQR, range)</th>
<th>sICH -(n=151)</th>
<th>sICH +(n=24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>64 (18, 27-92)</td>
<td>69 (18, 28-94)</td>
<td>0.354</td>
</tr>
<tr>
<td>Male</td>
<td>101 (66.9)</td>
<td>16 (66.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>20 (19, 1-42)</td>
<td>25 (20, 3-39)</td>
<td>0.138</td>
</tr>
<tr>
<td>pc-ASPECTS&lt;8</td>
<td>41 (27.2)</td>
<td>12 (50)</td>
<td><strong>0.031</strong></td>
</tr>
<tr>
<td>VB-leucoaraiosis</td>
<td>18 (15.9)</td>
<td>2 (10.5)</td>
<td>0.774</td>
</tr>
<tr>
<td>Baseline glucose, mmol/l</td>
<td>7.1 (3, 4.2-17.7)</td>
<td>7.8 (4.4, 5.2-18.5)‡</td>
<td>0.324</td>
</tr>
<tr>
<td>Peak glucose&lt;48 h</td>
<td>6.7 (2.3, 4.1-16.7)‡</td>
<td>7.7 (2.7, 5.2-15)§</td>
<td>0.062</td>
</tr>
<tr>
<td>Baseline systolic BP, mmHg</td>
<td>152 (23)</td>
<td>145 (22)</td>
<td>0.203</td>
</tr>
<tr>
<td>Baseline diastolic BP</td>
<td>83 (17)</td>
<td>76 (18)</td>
<td>0.070</td>
</tr>
<tr>
<td>Systolic BP (2 h)</td>
<td>147 (26)</td>
<td>160 (22)</td>
<td><strong>0.034‡</strong></td>
</tr>
<tr>
<td>Diastolic BP (2 h)</td>
<td>76 (17)</td>
<td>83 (24)</td>
<td>0.093‡</td>
</tr>
<tr>
<td>Baseline platelet count, E9/l</td>
<td>218 (81, 82-387)</td>
<td>183 (63, 107-312)</td>
<td><strong>0.011‡</strong></td>
</tr>
<tr>
<td>Baseline haemoglobin, g/l</td>
<td>142 (21, 89-186)</td>
<td>138 (28, 96-167)</td>
<td>0.474#</td>
</tr>
<tr>
<td>Baseline leucocytes, E9/l</td>
<td>9.1 (3.7, 2.7-22.8)</td>
<td>8.2 (3.7, 5.7-17.3)</td>
<td>0.404#</td>
</tr>
<tr>
<td>Baseline creatinine, µmol/l</td>
<td>78 (25, 38-272)**</td>
<td>80 (40, 50-180)</td>
<td>0.159</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18 (11.9)</td>
<td>5 (20.8)</td>
<td>0.324</td>
</tr>
<tr>
<td>Condition</td>
<td>Count (%)</td>
<td>Count (%)</td>
<td>p-value</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>---------</td>
</tr>
<tr>
<td>Hypertension</td>
<td>76 (50.3)</td>
<td>13 (54.2)</td>
<td>0.827</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>56 (37.1)</td>
<td>9 (37.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>33 (21.9)</td>
<td>6 (25)</td>
<td>0.792</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>10 (6.6)</td>
<td>0</td>
<td>0.361</td>
</tr>
<tr>
<td>Prior antiplatelet</td>
<td>40 (26.5)</td>
<td>9 (37.5)</td>
<td>0.327</td>
</tr>
<tr>
<td>Prior warfarin</td>
<td>13 (10.1)</td>
<td>1 (4.8)</td>
<td>0.693*</td>
</tr>
<tr>
<td>OTT, min</td>
<td>447 (747, 48-10910)</td>
<td>604 (1151, 85-3015)</td>
<td>0.256</td>
</tr>
<tr>
<td>Recanalization</td>
<td>80 (66.7)</td>
<td>5 (38.5)</td>
<td>0.066*</td>
</tr>
</tbody>
</table>

* >85% data available; †76% availability; ‡>91% availability; §>66% availability; ||>98% availability; #94% availability; **96% availability. Mean (SD) for BP values. NIHSS= National institutes of health stroke scale; OTT=Onset to treatment time; VB=vertebro-basilar.
Pc-ASPECTS less than 8 points was considered as extensive ischemic changes on the basis of the original report (13). Patients with sICH more commonly had pc-ASPECTS <8 compared to non-sICH patients (50% vs. 27%, \( p = 0.031 \)). 123 (70.3%) patients had mRS 3 to 6 outcome three months after thrombolysis and these included all sICH cases. The mean delay from the treatment to sICH was 21 hours (SD 18 h, 2.3-73 h). Three months after thrombolysis 69 (39.4%) patients had died and out of them 22 were sICH patients. Only two sICH patients survived (8.3%).

Mean systolic blood pressure two hours after thrombolysis associated with development of sICH. The higher the pressure the greater the risk of sICH, mean 160 mmHg vs. non-sICH 147 mmHg (\( p = 0.034 \)). Systolic blood pressure two hours after tPA administration was higher in patients with sICH than without sICH. This is shown in Figure 1. The blue line represents patients without sICH and the red line patients with sICH. Diastolic blood pressure values didn't differ.
Figure 1. Median systolic blood pressures within the two groups.

Blood glucose right after tPA administration and maximal values on the days 1 to 7 were equal between the groups. Median blood glucose is shown in Figure 2.
Figure 2. Median blood glucose between the two groups.

Platelet count at baseline and 24 hours after tPA and heparin administration was lower in patients with sICH than with non-sICH; 183 vs. 218 E9/l at baseline ($p = 0.011$) and 169 vs. 204 E9/l at 24 h ($p = 0.035$). Mean platelet count at baseline and at 24 hours is shown in Figure 3. The blue lines represent patients without sICH and the red lines patients with sICH.
Figure 3. Platelet count between the two groups.

Figure 4 shows median APTT values measured before heparin infusion and after that in twelve-hour periods up to 120 hours.
Figure 4. Median APTT values at different times between the two groups.

In Figure 5 there are median APTT values before heparin infusion and after that the first to tenth measured APTT values. It is seen that APTT values didn’t differ with sICH and non-sICH patients so they didn’t correlate with developing sICH.
Figure 5. Median APTT values in administration and the first to tenth measured APTT after the treatment.

In Figure 6 there are the APTT values obtained closest to sICH detection. Red dots represent those five patients in whom the delay from APTT measurement to sICH detection was more than three hours. The black dots represent patients in whom the delay was ≤ 2 hours. The blue x-axis represents the peak and the range of APTT values per 12-hour intervals.
Figure 6. The APTT values of sICH patients.
5 Discussion

The main intention of this research was to determine whether the heparin treatment associates with the development of sICH. Heparin effect is measured by APTT values. We found only three factors that differed between patients with sICH and without sICH, and these were pc-ASPECTS <8 prior to treatment, the platelet count at baseline and 24 hours after treatment and systolic blood pressure two hours after treatment. A low to normal perithrombolytic platelet count was associated with sICH. The higher the systolic blood pressure at two hours, the higher the risk of sICH development. The mean blood pressure of sICH patients was 160 mmHg and that of non-sICH patients 147 mmHg at 2 h. Both these were still below the acceptable 185 mmHg. Why is the two-hour point significant while the other times are not? The blood content of actilyse (recombinant tissue plasminogen activator) is highest close to the infusion and 2 h was the first registered time of blood pressure measurements.

Earlier studies have shown association of blood pressure with sICH after IVT in BAO. In a large study with 11 080 patients high systolic blood pressure 2 to 24 hours after thrombolysis was associated with poor outcome and sICH. The optimal systolic blood pressure values were 141 to 150 mmHg and predicted the best outcome. If antihypertensives were given to the newly recognized moderate hypertensive patients that predicted favourable outcome. (14) In another smaller study there wasn't association with high blood pressure and sICH but there was poorer outcome with higher blood pressures (15).

Platelet count in association to sICH has not been studied extensively before in our best knowledge. Nevertheless there have been studies that show that antiplatelet agents associate with developing ICH after recombinant tPA. Also an association between sICH and atrial fibrillation, leucoaraiosis, congestive heart failure, higher age and higher glucose has been shown in a large meta-analysis with 65 264 acute ischemic stroke patients. (16) In our study there wasn’t any association between congestive heart failure and sICH but there were very few patients with this condition. We didn’t find any correlation with age and developing sICH in accordance with a prior study (17), but there is also previous study with larger sample showing age as a predictor of sICH (9).
In the present study half of the patients with sICH had pc-ASPECTS <8 and all sICH patients had unfavourable outcome (mRS 3-6). In a larger study with 619 BAO-patients extensive ischemic changes on baseline were a predictor for poor outcome and in a meta-analysis of acute ischemic stroke patients treated with recombinant tPA they were a predictor for IVT-associated sICH(8,16). The APTT values didn’t differ in patients with or without sICH and, indeed, over 50% of sICH patients had targeted APTT values (75-100).

Early hyperglycaemia can increase the risk of early-term death of spontaneous intracranial haemorrhage patients when hyperglycaemia is defined to be more than 7.5 mmol/l (18). The admission blood glucose over 8 mmol/l was a predictor for sICH in a larger patient cohort (9) but in our study there wasn’t correlation between sICH and high admission blood sugar. Most of our patients had their blood glucose under 10 mmol/l and that could partly explain our results. The gender didn’t have association with developing sICH in our study and this is similar to another study (19).

Our study may be biased by some factors. The cohort is from a single centre and the sample size is quite small, yet BAO is a rare form of ischemic stroke and sICH is more rare a condition. IVT treatment is the routine BAO treatment used in Helsinki, Finland. Missing data was highest for blood glucose after the hyperacute period and proportion of missing data was higher for patients with sICH than without sICH at later time points (34% vs. 24% < 48 h; Table 2). This most probably correlates with the severe condition of the patients leading to omitting the glucose measurements.

In further studies it would be interesting to analyse more intensively the long-term quality of the lives of BAO patients. Another very important improvement would be to compare IVT and IAT treatments in randomized controlled trial, but that is not likely to happen. Present research should be continued with bigger sample size so the results would be more reliable and there could be strategies to minimize the risk of sICH. Our patient’s APTT values didn’t affect developing sICH but if they targeted lower would the results be different or would the use of LMWH give more even anticoagulation?
6 Conclusions

We found three factors that associated with the development of sICH. Extensive baseline ischemic changes, i.e. pc-ASPECTS under 8, was the most significant factor which made sICH more likely. Clinically significant factors also included a low to normal platelet count and high systolic blood pressure at 2 hours after treatment. However, more studies are needed to confirm these findings. APTT values didn’t have association with sICH. The results are in line with previous studies showing association of blood pressure with sICH and maybe in the future, we should more actively treat the blood pressure of BAO patients, even below the present guidelines, to prevent symptomatic intracranial haemorrhage.
7 References


(12) Available at: http://www.neuroems.com/2014/06/17/stroke-the-survivor/.


Symptomatic intracranial haemorrhage after thrombolysis with adjuvant anticoagulation in basilar artery occlusion

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Keywords: cerebral hemorrhage, cerebrovascular disease, cohort study, computerized tomography, stroke

Background and purpose: Our aim was to determine factors associated with symptomatic intracranial haemorrhage (sICH) in basilar artery occlusion patients treated with intravenous thrombolysis (IVT) and adjuvant anticoagulant therapy.

Methods: A registry of 176 consecutive patients with angiography-proven basilar artery occlusion who received IVT with alteplase and heparin between 1995 to 2013 was assessed. Post-treatment sICH was evaluated with the European Cooperative Acute Stroke Study II criteria. Unfavourable outcome was defined as a modified Rankin Scale score of 3–6 at 3 months.

Results: Twenty-four patients developed sICH (13.6%, sICH\textsuperscript{+}), all of whom had unfavourable outcome and only two (8.3%) sICH\textsuperscript{+} patients survived. On admission, sICH\textsuperscript{+} patients more frequently had extensive ischaemic changes defined as posterior circulation Acute Stroke Prognosis Early CT Score (PC-ASPECTS) < 8 (50% vs. 27% in sICH\textsuperscript{−}, \textit{P} = 0.031) and lower platelet counts (183 vs. 218 E\textsuperscript{9}/l; \textit{P} = 0.011). They also had higher systolic blood pressure (SBP) (median 160 vs. 147 mmHg, \textit{P} = 0.034) immediately after IVT. In multivariable regression analysis, lower platelet values [odds ratio (OR) 0.99, 95% confidence interval (CI) 0.97–0.996; \textit{P} = 0.006], PC-ASPECTS < 8 on admission (OR 3.6, 95% CI 1.3–10.3; \textit{P} = 0.017) and higher SBP after treatment (OR 1.03, 95% CI 1.01–1.05; \textit{P} = 0.017) were independently associated with sICH. Ninety per cent of the sICHS occurred within 48 h from IVT/anticoagulation treatment. No differences in activated partial thromboplastin times prior to or after the treatment were observed between sICH\textsuperscript{+} and sICH\textsuperscript{−} patients.

Conclusions: The risk of sICH was largely determined by extension of ischaemic changes on admission computed tomography. Clinically relevantly, also higher post-thrombolytic SBP as described earlier and lower perithrombolytic platelet counts do increase the risk, a finding requiring confirmation in other patient series.

Introduction

In posterior circulation strokes and basilar artery occlusion (BAO), the occurrence of post-thrombolytic intracranial haemorrhage (ICH) has occasionally been reported to be lower than in anterior circulation strokes [1,2], although another registry reported a rate reasonably in line with anterior circulation strokes [3]. The rates of symptomatic intracranial haemorrhage (sICH) in BAO have varied from 6% [3] even up to 30% with an endovascular multimodal approach [4], but the definitions of (s)ICH were not uniform. The issue of sICH, however, is crucial in BAO since in addition to variable recanalization therapies many centres apply anticoagulation [5] despite lack of formal guidelines (Table 1). Our long-standing in-house protocol also recommends
starting full anticoagulation at the time of thrombolysis whenever a BAO diagnosis has been established and intracranial haemorrhage ruled out on admission head scan [6–8]. Incentives to this empirically evolved approach have been recurrent posterior circulation strokes and re-occlusions, reported to occur at rates from 10% up to 30% [9,10].

A recent meta-analysis on post-thrombolytic sICH concluded that similar factors predict both ICH and poor outcome [11]. In hemispheric stroke thrombolysis, the SEDAN score including admission blood sugar >8 mmol/l, early infarct and dense artery signs on computed tomography (CT), age >75 years and National Institutes of Health Stroke Scale (NIHSS) ≥10 predicts development of sICH [12]. Age and stroke severity are strong predictors across all sICH risk scores [13,14]. A reliable way is still being sought to predict sICH after BAO recanalization therapies.

Since the development of sICH showed a strong correlation with poor outcome and death after BAO intravenous thrombolysis (IVT) in our previous analysis [7], this led us to analyse factors associated with post-thrombolytic sICH in BAO thrombolysis with adjuvant anticoagulation.

Methods

Patients

The cohort consisted of 176 consecutive BAO patients treated with intravenous 0.9 mg/kg recombinant tissue plasminogen activator (rtPA) and concomitant unfractionated heparin (UFH) in Helsinki University Central Hospital from 1995 to April 2013. All patients were registered prospectively and additional data were retrieved from patient charts. All cardiovascular conditions refer to a diagnosis prior to BAO [6–8]. No approval by the ethical committee was required as data were collected as part of routine care.

Physiological and laboratory variables

Systolic and diastolic blood pressures (BPs) were measured prior to, during (between 15 min intervals up to 2 h) and after (30 min intervals up to 8 h and 60 min up to 24 h). BP values on admission and at 2, 4, 8, 12, 24 and 48 h after tPA administration were registered. Blood glucose on admission and maximal levels on days 1–7 were registered. Laboratory data included admission whole blood and platelet counts and creatinine concentration. During anticoagulation with UFH, a target activated partial thromboplastin time (APTT) was set between 75 and 100 s. The dynamics of APTT values from admission to the tenth consecutive value or until discontinuation of heparin treatment or until suspicion/detection of sICH (when heparin was stopped) were analysed. All APTT values exceeding 180 s were recoded to 181 s. Delays between heparin administration and each consecutive APTT value were also registered along with maximal APTT values for each 12 h interval up to 120 h.

Imaging

The extent of baseline ischaemia was evaluated with the posterior circulation Acute Stroke Prognosis Early
CT Score (PC-ASPECTS) for either CT ($n = 121/176$, 69%) or magnetic resonance imaging (MRI) (31% of patients). PC-ASPECTS <8 represented extensive ischaemic changes [15]. Post-treatment CT or MRI was obtained in all patients approximately 24 h after thrombolysis and additional CT was obtained whenever clinical deterioration occurred or ICH was suspected. sICH was judged according to European Cooperative Acute Stroke Study II (ECASS II) criteria [16]. Thrombolysis in myocardial infarction (TIMI) was scored from post-treatment CT angiography ($n = 53$; 41%) and time-of-flight MR angiography ($n = 78$). Recanalization was dichotomized as partial to complete (TIMI 2–3) and nil to minimal (TIMI 0–1) in post-treatment angiography [17] available for 131 of 176 patients (74%) with the preference of using the same modality as for pre-treatment angiogram. All radiological data were evaluated in a blinded fashion.

Clinical outcome

Unfavourable outcome was rated as modified Rankin Scale (mRS) 3–6, favourable outcome as mRS 0–2. mRS was assessed by video-trained, certified stroke neurologists either by appointment or by telephone interview of patients or caregivers.

<table>
<thead>
<tr>
<th>Parameter, median (IQR) or n (%)</th>
<th>sICH– ($n = 151$)</th>
<th>sICH+ ($n = 24$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years ($n = 121/176$)</td>
<td>64 (18, 27–92)</td>
<td>69 (18, 28–94)</td>
<td>0.354</td>
</tr>
<tr>
<td>Male</td>
<td>101 (66.9)</td>
<td>16 (66.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18 (11.9)</td>
<td>5 (20.8)</td>
<td>0.324</td>
</tr>
<tr>
<td>Hypertension</td>
<td>76 (50.3)</td>
<td>13 (54.2)</td>
<td>0.827</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>56 (37.1)</td>
<td>9 (37.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>10 (6.6)</td>
<td>0</td>
<td>0.361</td>
</tr>
<tr>
<td>Prior antiplatelet</td>
<td>40 (26.5)</td>
<td>9 (37.5)</td>
<td>0.327</td>
</tr>
<tr>
<td>Prior warfarin</td>
<td>13 (10.1)</td>
<td>1 (4.8)</td>
<td>0.693</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>20 (19, 1–42)</td>
<td>25 (20, 3–39)</td>
<td>0.138</td>
</tr>
<tr>
<td>OTT, min</td>
<td>447 (747, 48–10 910)</td>
<td>604 (1151, 85–3015)</td>
<td>0.256</td>
</tr>
<tr>
<td>PC-ASPECTS $&lt; 8$</td>
<td>41 (27.2)</td>
<td>12 (50)</td>
<td>0.011</td>
</tr>
<tr>
<td>VB-leucoaraiosis</td>
<td>18 (15.9)</td>
<td>2 (10.5)</td>
<td>0.774</td>
</tr>
<tr>
<td>Recanalization</td>
<td>80 (66.7)</td>
<td>5 (38.5)</td>
<td>0.066</td>
</tr>
<tr>
<td>Baseline glucose, mmol/l</td>
<td>7.1 (3, 4.2–17.7)</td>
<td>7.8 (4.4, 5.2–18.5)</td>
<td>0.324</td>
</tr>
<tr>
<td>Peak glucose $&lt; 48$ h</td>
<td>6.7 (2.3, 4.1–16.7)</td>
<td>7.7 (2.7, 5.2–15.4)</td>
<td>0.062</td>
</tr>
<tr>
<td>Baseline systolic BP, mmHg</td>
<td>152 (23)</td>
<td>145 (22)</td>
<td>0.203</td>
</tr>
<tr>
<td>Baseline diastolic BP</td>
<td>83 (17)</td>
<td>76 (18)</td>
<td>0.070</td>
</tr>
<tr>
<td>Systolic BP (2 h)</td>
<td>147 (26)</td>
<td>160 (22)</td>
<td>0.034</td>
</tr>
<tr>
<td>Diastolic BP (2 h)</td>
<td>76 (17)</td>
<td>83 (24)</td>
<td>0.093</td>
</tr>
<tr>
<td>Baseline platelet count, E9/l</td>
<td>218 (81, 82–387)</td>
<td>183 (63, 107–312)</td>
<td>0.011</td>
</tr>
<tr>
<td>Baseline haemoglobin, g/l</td>
<td>142 (21, 89–186)</td>
<td>138 (28, 96–167)</td>
<td>0.474</td>
</tr>
<tr>
<td>Baseline leucocytes, E9/l</td>
<td>9.1 (3.7, 2.7–22.8)</td>
<td>8.2 (3.7, 5.7–17.3)</td>
<td>0.404</td>
</tr>
<tr>
<td>Baseline creatinine, mmol/l</td>
<td>78 (25, 38–272)</td>
<td>80 (40, 50–180)</td>
<td>0.159</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter, median (IQR) or n (%)</th>
<th>sICH– ($n = 151$)</th>
<th>sICH+ ($n = 24$)</th>
<th>$P$</th>
</tr>
</thead>
</table>
| Mean (SD) for BP values. OTT, onset to treatment time; VB, vertebro-basilar.
| a>85% data available; b76% availability; c>91% availability; d>66% availability; e>98% availability; f94% availability; g96% availability. Bold indicates significant value ($P < 0.05$).
Systolic BP was higher in patients with than without sICH 2 h after rtPA infusion, without significant changes thereafter (Fig. 1a). Blood glucose levels did not differ between patients with and without sICH (Fig. 1b).

The time until first follow-up APTT measurement was similar for patients with and without sICH with a median of 4 h (IQR 2.5; range 0.5–21.5) and 4.5 h (2.5; 2–16.5), respectively. Thereafter, the intervals were 4–6 h in both groups and followed the institutional guideline. There were no differences in the maximum or consequent APTT values on repeated measurements between patients with and without sICH (Fig. 2a). Figure 2b shows the most relevant APTT values, i.e. those that were obtained very close to the detection of sICH. The admission platelet count was significantly lower in patients with sICH and remained lower at 24 h after IVT (Fig. 3).

In multivariable regression analysis extensive baseline ischaemic changes, lower platelet count on admission and higher systolic BP at 2 h were associated with sICH (Table 3).

Discussion

The detailed data from the present cohort allow us to estimate what affects the occurrence of sICH after IVT with adjuvant anticoagulation in BAO patients. Half of the patients with PC-ASPECTS score <8 corresponding to extensive ischaemic changes experienced sICH. Randomized clinical trials have studied mostly anterior circulation strokes, and early infarct signs exceeding one-third of the middle cerebral artery supply area are considered a contraindication for IVT [18]. In BAO no such cut-off exists, naturally also due to the lethal course of the disease if left untreated. Besides extensive baseline ischaemia, increased BP immediately after IVT and low-normal perithrombolysis platelet count are associated with sICH risk as well. The latter modifiable factors could be amenable to future therapeutic strategies that aim at minimizing the sICH risk besides the evident need for recanalization therapies.

The frequency of sICH per the ECASS II criteria in our protocol with full-dose heparin was 14% which is comparable to or smaller than reported for intra-arterial thrombolysis, mechanical devices and the bridging approach (Table 1) but higher than the 6% reported from the BASICS registry [19].

Systolic BP was higher in patients with sICH (160 mmHg) than without sICH (147 mmHg) 2 h after starting rtPA (Fig. 1a), yet it was far below the 185 mmHg considered acceptable after IVT [18]. The inherent effect of high BP variability on sICH cannot be captured by multivariate analysis due to the small number of sICHs in our patient cohort, similar to a German IVT-treated cohort [20], but the effect is evident in larger cohorts [21].

Extensive ischaemic changes on baseline scan have been found by us [7] and others [22] to predispose to sICH after BAO treatment and were also a strong predictor for IVT-associated sICH in a meta-analysis.
on ischaemic stroke [11]. The predictive value of the NIHSS score for the presence of artery occlusion was suggested to be poorer in the posterior circulation than in the anterior circulation [23], and the cut-off value for baseline NIHSS for favourable outcome was found to be lower in posterior circulation than in anterior circulation strokes [24]. Last but not least, in line with the BASICS registry showing no effect of age >75 years on the incidence of sICH age was not found to be an independent risk factor either [25].

The possible effect of lower thrombocyte count on post-thrombolytic sICH has been investigated in only a few studies [11]. Prior observation of an association between low platelet count and any post-thrombolytic ICH [26] agrees with our finding that it predisposes also to a sICH. However, our data do not show any antiplatelet or warfarin use to be associated with sICH as suggested in a meta-analysis on stroke IVT [11], although such medications could intuitively potentiate the effect of lower platelet count to promote sICH formation. Perhaps something could be learned from the prior stroke literature on platelets and spontaneous ICH expansion, yet results are conflicting [27]. Anyhow, a randomized study on platelet transfusion is under way in ICH patients [28]. Wisdom should be adopted across stroke subtypes, since in traumatic ICH the need for platelet transfusion is suggested to be guided by antiplatelet assay results [29].

Animal experiments have suggested that heparin enhances the thrombolytic effect of rtPA [30,31]. Heparin induced thrombocytopenia is an adverse event in patients receiving UFH and usually occurs after a week [32]. In none of our patients was the perihemorrhagic platelet count reduced by 50%, and in no

<table>
<thead>
<tr>
<th>Platelet count at baseline</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC-ASPECTS &lt;8 at baseline</td>
<td>3.6</td>
<td>1.26–10.27</td>
<td>0.017</td>
</tr>
<tr>
<td>Post-thrombolytic systolic BP (2 h)</td>
<td>1.03</td>
<td>1.01–1.05</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Figure 2 Activated partial thrombin time (APTT) values and sICH. (a) There were no differences in peak APTT values between patients with (red) and without (blue) sICH. The two drops in the peak APTT values are explained by the detection of almost 70% of sICHs by 24 h and all sICHs by 73 h after tPA injection. (b) The most relevant APTT values obtained time-wise closest to sICH detection. The red dots represent five patients in whom the delay between APTT measurement and sICH detection was >3 h; in all other patients it was ≤2 h. For comparison, the peak (median, IQR) APTT values per 12-h intervals in patients without sICH are outlined in blue on the x axis.

Figure 3 Perithrombolytic platelet counts and sICH. The platelet counts were lower in patients with sICH (red) than without sICH (blue) at baseline and 24 h after IVT and full-dose heparin treatment. *P = 0.011 at baseline; *P = 0.035 at 24 h.
case was heparin induced thrombocytopenia clinically confirmed. Since no correlation was found between APTT and sICH, a full-dose anticoagulant regimen was continued in BAO thrombolysis. However, our current protocol advises a target of 2.0–2.5-fold the baseline APTT levels and heparin dosing is adjusted by weight [33]. At present, UFH has been replaced by low-molecular-weight heparin in most acute cardiac indications including ST-elevation myocardial infarction [34].

The shortcomings of our study are that the cohort is derived from a single centre and the partly retrospective nature of the data collection. Yet the treatment protocol has remained stable for a long time and access to original patient data was available. The relatively low number of sICHs underpowers statistical analysis. Our data on IVT and anticoagulation may naturally not be transferable to centres where BAO patients receive only IVT. In the absence of a non-anticoagulated reference group firm conclusions on the role of anticoagulation in development of sICH cannot be drawn.

In conclusion, these data encourage vigilance for a burden of multiple, concomitant sICH risk factors in BAO thrombolysis, especially in severely ill patients with extensive baseline ischaemic changes in the vertebro-basilar area. Intensive follow-up and treatment of BP even below guidelines may be warranted if the risk of sICH is estimated as high due to multiple coexisting factors, possibly including also a low platelet count.

Acknowledgements
TS and DS had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis. The authors thank Dr Olli S. Mattila for reviewing the literature on experimental anticoagulation data. Funds were received from Maire Taponen Foundation (TS), Finnish Academy (PJJ), Sigrid Jusélius Foundation (PJJ), Paavo Nurmi Foundation (PJJ) and Helsinki University Hospital District Government Subsidiary Research Funds (PJJ).

Disclosure of conflicts of interest
DS, OS, HS, PJL: none. TS received a consultancy fee from Boehringer Ingelheim.

References
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SYMPTOMATIC ICH IN BAO THROMBOLYSIS 499