**APPENDIX**

**I. APPENDIX I**

Patient assessment

1. Inclusion and exclusion criteria

2. Consent

3. CT imaging

Did not meet inclusion/ exclusion or CT imaging criteria or consent not obtained

All IVH patients

with third and/or fourth ventricle obstruction

requiring EVD placement

ICH unstable or > 30 ml

Ineligible

ICH/IVH stable, ICH ≤ 30 ml (n = 80)

Eligible

EVD alone (n = 45)

EVD + rtPA (n = 35)

Days 1 – 7

CT scans documentation of procedures

Follow-up

(Days: 30, 90)

Documentation of complications

Functional: mRS, GOS

CT/MRI scans

**Figure A1.** Flow-chart of the study design and assessment occasions. *CT, computed tomography;* *MRI, magnetic resonance imaging; EVD, external ventricular drain; GOS, Glasgow outcome scale; ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; mRS, modified Rankin Scale; rt-PA, recombinant tissue plasminogen activator.*

**II. APPENDIX II: STUDY RESULTS**

**Table A1.** Baseline characteristics of patients treated with EVD+IVF or EVD alone.

|  |  |  |  |
| --- | --- | --- | --- |
| Baseline variables | EVD (n=45) | EVD+IVF (n=35) | p value |
| Age (years),  *± SD* | 57.1±11.3 | 57.1±14.3 | 0.997 |
| Sex (male), *n (%)* | 30 (66.7%) | 26 (74.3%) | 0.623 |
| *Health insurance status, n (%)* |
| Yes | 25 (55.6) | 23 (65.7) | 0.358 |
| No | 20 (44.4) | 12 (34.3) | - |
| *Resident regions, n (%)* |
| Urban | 29 (64.4) | 22 (62.9) | 0.884 |
| Rural | 16 (35.6) | 13 (37.1) | - |
| *Employment, n (%)* |  |  |  |
| Currently employed | 19 (42.2) | 15 (42.9) | 0.968 |
| Unemployed - Retired | 20 (44.4) | 12 (34.3) | 0.579 |
| Unemployed - volunteer, student, unemployed | 4 (8.9) | 6 (17.1) | 0.502\* |
| *Risks of intracranial hemorrhage* |
| Stroke, *n (%)* | 2 (4.4%) | 3 (8.6%) | 0.649\* |
| Hypertension, *n (%)* | 25 (55.6%) | 26 (74.3%) | 0.104 |
| Diabetes, *n (%)* | 7 (15.6%) | 2 (5.7%) | 0.286\* |
| Smoking, *n (%)* | 4 (8.9%) | 3 (8.6%) | 1.000\* |
| Antiplatelet use, *n (%)* | 1 (2.2%) | 0 | - |
| Alcohol abuse, *n (%)* | 3 (6.7%) | 2 (5.7%) | - |
| Seizures, *n (%)* | 1 (2.2%) | 0 | - |
| Liver disease, *n (%)* | 1 (2.2%) | 0 | - |
| Renal disease, *n (%)* | 1 (2.2%) | 0 | - |
| *Clinical and laboratory characteristics* |
| GCS, *median (IQR)* | 7 (4-13) | 8 (5-14) | 0.062 |
| HR (bpm), *median (IQR)* | 95 (68-137) | 95 (63-140) | 0.923 |
| Systolic BP (mmHg),  *± SD* | 170.7±31.1 | 167.7±29.3 | 0.667 |
| Diastolic BP (mmHg),  *± SD* | 97.6±20.9 | 97.4±15.8 | 0.976 |
| Temp. (oC),  *± SD* | 36.8±1.0 | 36.7±0.5 | 0.714 |
| Hemiplegia, *n (%)* | 34 (75.6) | 28 (80.0) | 0.637 |
| Pre-admission mRS = 1, *n (%)* | 2 (4.4) | 3 (8.6) | 0.649 |
| Pre-admission mRS = 0, *n (%)* | 43 (95.6) | 32 (91.4) |  |
| On admission mRS, *median (IQR)* | 5 (5-5) | 5 (4-5) | 0.257 |
| On admission GOS, *median (IQR)* | 2 (2-2) | 2 (2-3) | 0.234 |
| Serum urea (mmol/L),  *± SD* | 5.9±3.4 | 5.5±2.0 | 0.504 |
| Serum creatinine (µmol/L),  *± SD* | 82.2±31.7 | 84.6±33.7 | 0.724 |
| SGOT (UI/L),  *± SD* | 43.2±33.4 | 31.5±24.3 | 0.087 |
| SGPT (UI/L),  *± SD* | 22.6±17.2 | 19.2±23.5 | 0.462 |
| WBC (G/L),  *± SD* | 15.7±5.9 | 14.9±5.4 | 0.521 |
| RBC (T/L),  *± SD* | 4.81±0.6 | 4.83±0.5 | 0.886 |
| Platelet count (G/L),  *± SD* | 247.9±86.2 | 248.1±59.9 | 0.992 |
| INR,  *± SD* | 1.05±0.13 | 1.01±0.1 | 0.151 |
| *Imaging characteristics* |
| Graeb score, *median (IQR)* | 9 (6-12) | 8 (6-12) | 0.863 |
| Supratentorial ICH, *n (%)* | 37 (82.2%) | 26 (74.3%) | 0.389 |
| ICH volume (mL)\*\*,  *± SD* | 13.9±7.2 | 14.4±7.4 | 0.799 |
| Evans ratio\*\*\*,  *± SD* | 0.42±0.06 | 0.41±0.07 | 0.649 |
| Index clot location, *n (%)* |  |  |  |
| *Central grey nuclei* | 36 (80%) | 26 (74.3%) | 0.470 |
| *Internal capsular* | 1 (2.2%) | 1 (2.9%) | 0.687\* |
| *Others* |
| Ictus to hospital arrival (hours), *median (IQR)* | 4 (1-20) | 6 (1-20) | 0.188 |
| Ictus to EVD (hours), *median (IQR)* | 10 (2-23) | 10 (2-22) | 0.68 |
| Ictus to IVF (hours), *median (IQR)* | - | 23 (18-40) | - |

*\* Fisher’s exact test (1-sided); \*\* calculated by the ABC/2 method; \*\*\* measured by dividing the maximal width of the frontal horns by the maximal width of the inner table of the cranium at the level of the frontal horns; GCS, Glasgow Coma Scale; HR, heart rate; BP, blood pressure; Temp., temperature; mRS, modified Rankin Scale, GOS, Glasgow Outcome Scale; INR, international normalized ratio; CT, computed tomography; EVD, external ventricular drainage; ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; IVF, intraventricular fibrinolysis; IQR, interquartile range; Urban was defined as a city, suburb, outskirts, or town.*

**Table A2.** Time from symptom onset to hospital arrival, EVD placement and assignment

|  |  |  |  |
| --- | --- | --- | --- |
| Time periods | EVD (n=45) | EVD+IVF (n=35) | p value |
| *Ictus to hospital arrival (hours), n (%)* |
| < 6 | 30 (66.7) | 17 (48.6) | 0.100 |
| 6 to < 12 | 5 (11.1) | 9 (25.7) | 0.090 |
| 12 to 24 | 10 (22.2) | 9 (25.7) | 0.700 |
| *Ictus to EVD (hours), n (%)* |
| < 12 | 26 (57.8) | 20 (57.1) | 0.950 |
| 12 to < 24 | 19 (42.2) | 15 (42.9) | 0.950 |
| 24 to 72 | 0 (0) | 0 (0) | - |
| *Ictus to assignment (hours), n (%)* |
| 12 to < 24 | 29 (64.4) | 21 (60.0) | 0.680 |
| 24 to < 36 | 15 (33.3) | 12 (34.3) | 0.900 |
| 36 to 72 | 1 (2.3) | 2 (5.7) | - |

*EVD, external ventricular drainage*

**Table A3.** Treatment variables by group

|  |  |  |  |
| --- | --- | --- | --- |
|  | EVD (n=45) | EVD+IVF (n=35) | p value |
| Total number of alteplase doses, *median (IQR)* | N/A | 3 (1-8) | - |
| Length of ventilator support (days), *median (IQR)* | 3 (2-20) | 3 (2-14) | 0.570 |
| Length of ventilator support (days)↋, *median (IQR)* | 5 (2-20) | 4 (2-14) | 0.413 |
| Length of EVD placement (days), *median (IQR)* | 5 (2-15) | 7 (2-14) | 0.018 |
| Length of EVD placement (days)↋, *median (IQR)* | 7 (2-15) | 7 (3-14) | 0.956 |
| Tracheostomy, *n (%)* | 14 (31.1%) | 11 (31.4%) | 0.976 |
| *CT/MRI scans, n (%)* |  |  |  |
| 30-day (n = 80) | 4 (8.9) | 20 (57.1) | <0.001\* |
| 90-day (n = 57) | 6 (23.1) | 13 (41.9) | 0.422\* |
| Ventriculoperitoneal shunt, *n (%)* | 0 | 2 (5.7%) | 0.188\* |
| Length of stay in emergency ICU (days), *median (IQR)* | 8 (2-54) | 14 (2-53) | 0.002 |
| Length of stay in emergency ICU (days)↋, *median (IQR)* | 14 (6-54) | 17 (9-53) | 0.058 |
| Discharged to die, *n (%)* | 21 (46.7%) | 5 (14.3%) | 0.002 |
| ≤ first 3 days of care | 14 (31.1%) | 0 | - |
| > first 3 days of care | 7 (15.6%) | 5 (14.3%) | 0.241 |

*\* Fisher’s exact test (1-sided); IQR, interquartile range; "Discharged to die" defined as patients were in grave condition or dying and were released to die at home, as requested by the patients themselves or by their family members.*

**Table A4.** The changes of Glasgow Coma Scale (GCS) by treatment groups

|  |  |  |  |
| --- | --- | --- | --- |
| GCS | EVD | EVD+IVF | p value |
| *n* | *median (IQR)* | *n* | *median (IQR)* |
| On admission | 45 | 7 (4-13) | 35 | 8 (5-14) | 0.062\*\* |
| Day 1\* | 45 | 7 (3-15) | 35 | 10 (3-15) | < 0.001\*\* |
| Day 2 | 33 | 8 (3-15) | 34 | 11 (3-15) | < 0.001\*\* |
| Day 3 | 29 | 9 (3-15) | 33 | 11 (5-15) | 0.001\*\* |
| Day 4 | 27 | 10 (3-15) | 33 | 11 (5-15) | 0.004\*\* |
| Day 5 | 25 | 10 (3-15) | 33 | 11 (7-15) | 0.010\*\* |
| Day 6 | 23 | 10 (4-15) | 33 | 12 (8-15) | 0.012\*\* |
| Day 7 | 22 | 10 (4-15) | 33 | 13 (8-15) | 0.009\*\* |

*GCS, Glasgow Coma Scale; \* the first day after assignments to each group; \*\* Mann-Whitney U test*

**Table A5.** The changes of Graeb score by treatment groups

|  |  |  |  |
| --- | --- | --- | --- |
| Graeb score | EVD | EVD+IVF | p value |
| *n* | *median (IQR)* | *n* | *median (IQR)* |
| On admission | 45 | 9 (6-12) | 35 | 8 (6-12) | 0.863\*\* |
| Day 1\* | 45 | 8 (4-11) | 35 | 7 (4-10) | 0.001\*\* |
| Day 2 | 34 | 8 (4-10) | 34 | 5 (2-8) | < 0.001\*\* |
| Day 3 | 31 | 7 (2-8) | 33 | 4 (1-6) | < 0.001\*\* |
| Day 7 | 25 | 6 (1-8) | 33 | 2 (1-5) | < 0.001\*\* |

*\* The first day after assignments to each group; \*\* Mann-Whitney U test*

**Table A6.** The changes of closed ICP by treatment groups

|  |  |  |  |
| --- | --- | --- | --- |
| Closed ICP (mmHg)\* | EVD | EVD+IVF | p value |
| *n* |  *± SD* | *n* |  *± SD* |
| Day 1\*\* | 45 | 20.8±18.0 | 35 | 13.3±3.4 | 0.009\*\*\* |
| Day 2 | 31 | 16.4±10.6 | 34 | 13.6±7.5 | 0.217\*\*\* |
| Day 3 | 27 | 14.9±8.4 | 32 | 13.5±6.2 | 0.466\*\*\* |
| Day 4 | 24 | 13.2±5.1 | 29 | 13.5±4.5 | 0.793\*\*\* |
| Day 5 | 20 | 13.6±5.6 | 24 | 12.5±3.2 | 0.436\*\*\* |
| Day 6 | 14 | 12.6±2.4 | 23 | 12.3±3.3 | 0.760\*\*\* |
| Day 7 | 12 | 13.9±3.3 | 16 | 12.4±2.7 | 0.183\*\*\* |

*ICP, intracranial pressure; \* Closed ICP was defined as the ICP measured while the CSF drainage system was closed for 15 minutes or more (A patient could have up to 8 closed ICPs measured a day. However, in this study we randomly selected only one from all closed ICPs that a patient had).; \*\* the first day after assignments to each group; \*\*\* Mann-Whitney U test*

**Table A7.** The changes of daily cerebrospinal fluid (CSF) volume by treatment groups

|  |  |  |  |
| --- | --- | --- | --- |
| CSF (mL/24h) | EVD | EVD+IVF | p value |
| *n* |  *± SD* | *n* |  *± SD* |
| Day 1\* | 43 | 167.4±56.2 | 35 | 248.1±100.5 | < 0.001 |
| Day 2 | 29 | 185.1±61.9 | 32 | 232.7±75.2 | 0.010 |
| Day 3 | 25 | 182.9±60.0 | 28 | 225.6±74.8 | 0.027 |
| Day 4 | 21 | 176.3±64.5 | 24 | 195.6±68.3 | 0.338 |
| Day 5 | 17 | 173.8±91.7 | 22 | 188.2±89.5 | 0.626 |
| Day 6 | 13 | 187.8±99.5 | 19 | 204.7±48.6 | 0.578 |
| Day 7 | 9 | 185.6±92.8 | 11 | 175.5±72.6 | 0.788 |

*CSF, cerebrospinal fluid; \* the first day after assignments to each group*

**Table A8.** The changes of heart rate (HR) by treatment groups

|  |  |  |  |
| --- | --- | --- | --- |
| HR (bpm) | EVD | EVD+IVF | p value |
| *n* | *median (IQR)* | *n* | *median (IQR)* |
| On admission | 45 | 97 (68-137) | 35 | 96 (63-140) | 0.923 |
| Day 1\* | 45 | 102 (60-150) | 35 | 100 (70-150) | 0.193 |
| Day 2 | 34 | 110 (70-150) | 34 | 100 (80-125) | 0.222 |
| Day 3 | 29 | 100 (70-144) | 33 | 100 (70-130) | 0.415 |
| Day 4 | 27 | 100 (70-150) | 33 | 100 (70-124) | 0.834 |
| Day 5 | 25 | 100 (70-147) | 33 | 100 (72-124) | 0.975 |
| Day 6 | 23 | 101 (75-136) | 33 | 100 (76-130) | 0.375 |
| Day 7 | 22 | 101 (80-122) | 33 | 100 (70-126) | 0.190 |

*HR, heart rate; \* the first day after assignments to each group*

**Table A9.** The changes of systolic blood pressure (SBP) by treatment groups

|  |  |  |  |
| --- | --- | --- | --- |
| SBP (mmHg) | EVD | EVD+IVF | p value |
| *n* |  *± SD* | *n* |  *± SD* |
| On admission | 45 | 170.7±31.1 | 35 | 167.7±29.3 | 0.667 |
| Day 1\* | 45 | 163.1±26.9 | 35 | 166.5±21.1 | 0.533 |
| Day 2 | 34 | 165.0±24.5 | 34 | 164.7±27.9 | 0.963 |
| Day 3 | 29 | 161.4±26.4 | 33 | 163.0±20.3 | 0.782 |
| Day 4 | 27 | 156.3±29.6 | 33 | 159.1±21.9 | 0.677 |
| Day 5 | 25 | 158.4±18.4 | 33 | 160.6±19.5 | 0.661 |
| Day 6 | 23 | 159.1±15.9 | 33 | 161.2±19.9 | 0.679 |
| Day 7 | 22 | 150.0±14.1 | 33 | 155.8±17.3 | 0.201 |

*SBP, systolic blood pressure; \* the first day after assignments to each group*

**Table A10.** The changes of diastolic blood pressure (DBP) by treatment groups

|  |  |  |  |
| --- | --- | --- | --- |
| DBP (mmHg) | EVD | EVD+IVF | p value |
| *n* |  *± SD* | *n* |  *± SD* |
| On admission | 45 | 97.6±20.9 | 35 | 97.4±15.8 | 0.976 |
| Day 1\* | 45 | 90.5±16.4 | 35 | 94.0±13.1 | 0.301 |
| Day 2 | 34 | 88.8±18.1 | 34 | 94.7±17.9 | 0.183 |
| Day 3 | 29 | 87.2±20.5 | 33 | 92.7±11.5 | 0.209 |
| Day 4 | 27 | 91.8±24.0 | 33 | 89.1±12.3 | 0.591 |
| Day 5 | 25 | 88.0±15.5 | 33 | 89.4±11.4 | 0.695 |
| Day 6 | 23 | 88.7±10.6 | 33 | 88.5±10.9 | 0.943 |
| Day 7 | 22 | 85.9±10.9 | 33 | 90.9±10.7 | 0.099 |

*DBP, diastolic blood pressure; \* the first day after assignments to each group*

**Table A11.** The changes of body temperature by treatment groups

|  |  |  |  |
| --- | --- | --- | --- |
| Temp. (oC) | EVD | EVD+IVF | p value |
| *n* |  *± SD* | *n* |  *± SD* |
| On admission | 45 | 36.8±1.0 | 35 | 36.8±0.5 | 0.714 |
| Day 1\* | 45 | 38.4±1.2 | 35 | 38.0±0.8 | 0.099 |
| Day 2 | 34 | 38.5±0.9 | 34 | 38.5±0.6 | 0.867 |
| Day 3 | 29 | 38.7±0.9 | 33 | 38.7±0.8 | 0.791 |
| Day 4 | 27 | 38.8±0.9 | 33 | 38.7±0.9 | 0.945 |
| Day 5 | 25 | 38.9±0.9 | 33 | 38.8±0.8 | 0.572 |
| Day 6 | 23 | 38.9±0.8 | 33 | 38.5±0.8 | 0.047 |
| Day 7 | 22 | 38.6±0.6 | 33 | 38.4±0.9 | 0.276 |

*Temp., body temperature; \* the first day after assignments to each group*

**Table A12.** Mortality rates for the 30-day and 90-day timepoints

|  |  |  |
| --- | --- | --- |
|  | 30 days | 90 days |
| EVD (n=45) | EVD+IVF (n=35) | p value | EVD (n=45) | EVD+IVF (n=35) | p value |
| Mortality | 19 (42.2%) | 4 (11.4%) | 0.003 | 28 (62.2%) | 7 (20%) | < 0.001 |
| Survival | 26 (57.8%) | 31 (88.6%) | 0.003 | 17 (37.8%) | 28 (80%) | < 0.001 |



**Figure 2A.** Kaplan-Meier curve demonstrating survival in the treatment group of intraventricular haemorrhage (IVH) patients with acute obstructive hydrocephalus (AOH). The treatment groups were categorized as external ventricular drainage (EVD) alone (EVD group) or combined EVD with intraventricular fibrinolysis (IVF) by low-dose rt-PA (EVD+IVF group). A significant difference in survival exists between the curves (p < 0.001 with the log-rank test). The dashed line represents the EVD+IVF group, and the straight line represents the EVD group.

**Table A13.** Association between mortality and potential determinants: Cox's regression analysis (backward elimination) (56 men and 24 women)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Steps | Potential determinants | Unit | Hazard Ratio (HR) | 95% CI for HR | p-value |
| Lower | Upper |
| 1 | Baseline GCS | 1 (point) | 0.856 | 0.712 | 1.029 | 0.098 |
| Baseline Graeb score | 1 (point) | 1.163 | 0.890 | 1.518 | 0.269 |
| Alteplase | 1 (mg) | 0.697 | 0.528 | 0.921 | 0.011 |
| First-day closed ICP | 1 (mmHg) | 1.038 | 1.018 | 1.058 | <0.001 |
| Initial ICH volume | 1 (mL) | 1.024 | 0.975 | 1.074 | 0.346 |
| 2 | Baseline GCS | 1 (point) | 0.860 | 0.717 | 1.030 | 0.102 |
| Baseline Graeb score | 1 (point) | 1.147 | 0.878 | 1.499 | 0.316 |
| Alteplase | 1 (mg) | 0.696 | 0.526 | 0.920 | 0.011 |
| First-day closed ICP | 1 (mmHg) | 1.037 | 1.018 | 1.057 | <0.001 |
| 3 | Baseline GCS | 1 (point) | 0.855 | 0.710 | 1.030 | 0.100 |
| Alteplase | 1 (mg) | 0.709 | 0.536 | 0.938 | 0.016 |
| First-day closed ICP | 1 (mmHg) | 1.034 | 1.016 | 1.053 | <0.001 |

*Baseline GCS, Glasgow Coma Scale obtained on admission; Baseline Graeb score, Graeb score obtained on admission; Alteplase, number of 1mg/1mL-alteplase doses; First-day closed ICP, ICP measured while the CSF drainage system was closed for 15 minutes or more on first day after assignment; Initial ICH volume, ICH volume obtained on admission; HR, Hazard Ratio; CI, Confidence Interval.*

Among five potential determinants of mortality (i.e., baseline GCS, baseline Graeb score, alteplase, first-day closed ICP and initial ICH volume) revealed that only alteplase (defined as the number of 1 mg/1 mL alteplase doses) and first-day closed ICP (defined as ICP measured while the CSF drainage system was closed for 15 minutes or more on first day after assignment) were significantly associated with mortality. While each additional dose of 1 mg alteplase was associated with a 29.1% decrease in mortality risk (hazard ratio = 0.709 [95%CI 0.536 - 0.938], p = 0.016), each 1-mmHg increase in first-day closed ICP was associated with a 1.034-fold increase in mortality risk (hazard ratio = 1.034 [95%CI 1.016 - 1.053], p < 0.001). Though the effect size for first-day closed ICP was modest (Hazard Ratio = 1.034), its association with mortality risk was highly significant (p < 0.001).

**Table A14.** mRS score frequencies for the 30-day and 90-day timepoints

|  |  |  |
| --- | --- | --- |
| mRS | 30 days | 90 days |
| EVD (n=45) | EVD+IVF (n=35) | p value | EVD (n=26) | EVD+IVF (n=31) | p value |
| 0 | 0 | 0 | - | 0 | 3 (9.7%) | 0.103\* |
| 1 | 0 | 1 (2.9%) | 0.437\* | 1 (3.8%) | 2 (6.5%) | 0.567\* |
| 2 | 0 | 0 | - | 4 (15.4%) | 5 (16.1%) | 0.615\* |
| 3 | 3 (6.7%) | 9 (25.7%) | 0.018 | 3 (11.5%) | 6 (19.4%) | 0.333\* |
| 4 | 6 (13.3%) | 14 (40.0%) | 0.006 | 3 (11.5%) | 11 (35.5%) | 0.036 |
| 5 | 17 (37.8%) | 7 (20.0%) | 0.085 | 6 (23.1%) | 1 (3.2%) | 0.029\* |
| 6 | 19 (42.2%) | 4 (11.4%) | 0.003 | 9 (34.6%) | 3 (9.7%) | 0.021 |

*\* Fisher’s exact test (1-sided); mRS, modified Rankin Scale*

**Table A15.** mRS score frequencies for the 30-day and 90-day timepoints

|  |  |  |
| --- | --- | --- |
| mRS | 30 days | 90 days |
| EVD (n=45) | EVD+IVF (n=35) | p value | EVD (n=26) | EVD+IVF (n=31) | p value |
| 0 - 3 | 3 (6.7%) | 10 (28.6%) | 0.008 | 8 (30.8%) | 16 (51.6%) | 0.112 |
| 4 - 6 | 42 (93.3%) | 25 (71.4%) | 0.008 | 18 (69.2%) | 15 (48.4%) | 0.112 |

*mRS, modified Rankin Scale; Good outcome was defined as mRS, 0 to 3*

**Table A16.** GOS score frequencies for the 30-day and 90-day timepoints

|  |  |  |
| --- | --- | --- |
| GOS | 30 days | 90 days |
| EVD (n=45) | EVD+IVF (n=35) | p value | EVD (n=26) | EVD+IVF (n=31) | p value |
| 1 | 19 (42.2%) | 4 (11.4%) | 0.003 | 9 (34.6%) | 3 (9.7%) | 0.021 |
| 2 | 15 (33.3%) | 5 (14.3%) | 0.051 | 6 (23.1%) | 0 | 0.006\* |
| 3 | 8 (17.8%) | 18 (51.4%) | 0.001 | 3 (11.5%) | 10 (32.3%) | 0.063 |
| 4 | 3 (6.7%) | 6 (17.1%) | 0.133\* | 6 (23.1%) | 11 (35.5%) | 0.308 |
| 5 | 0 | 2 (5.7%) | 0.188\* | 2 (7.7%) | 7 (22.6%) | 0.125 |

*\* Fisher’s exact test (1-sided); GOS, Glasgow Outcome Scale*

**Table A17.** GOS score frequencies for the 30-day and 90-day timepoints

|  |  |  |
| --- | --- | --- |
| GOS | 30 days | 90 days |
| EVD (n=45) | EVD+IVF (n=35) | p value | EVD (n=26) | EVD+IVF (n=31) | p value |
| 1 - 2 | 34 (75.6%) | 9 (25.7%) | < 0.001 | 15 (57.7%) | 3 (9.7%) | < 0.001 |
| 3 - 5 | 11 (24.4%) | 26 (74.3%) | < 0.001 | 11 (42.3%) | 28 (90.3%) | < 0.001 |

*GOS, Glasgow Outcome Scale; Good outcome was defined as GOS, 3 to 5*

**Table A18.** GOS score frequencies for the 30-day and 90-day timepoints

|  |  |  |
| --- | --- | --- |
| GOS | 30 days | 90 days |
| EVD (n=45) | EVD+IVF (n=35) | p value | EVD (n=26) | EVD+IVF (n=31) | p value |
| 1 - 3 | 42 (93.3%) | 27 (77.1%) | 0.04\* | 18 (69.2%) | 13 (41.9%) | 0.04\* |
| 4 - 5 | 3 (6.7%) | 8 (22.9%) | 0.04\* | 8 (30.8%) | 18 (58.1%) | 0.04\* |

*\* Fisher’s exact test (1-sided); GOS, Glasgow Outcome Scale; Good outcome was defined as GOS, 4 to 5*

**Table A19.** Complications in the treatment groups

|  |  |  |  |
| --- | --- | --- | --- |
|  | EVD (n=45) | EVD+IVF (n=35) | p value |
| Intracranial re-bleeding, *n (%)* | 5 (11.1%) | 2 (5.7%) | 0.328\* |
| Catheter tract bleeding, *n (%)* | 1 (2.2%) | 2 (5.7%) | 0.406\* |
| Catheter occlusion, *n (%)* | 8 (17.8%) | 2 (5.7%) | 0.099\* |
| Ventriculitis, *n (%)* | 4 (8.9%) | 3 (8.6%) | 0.640\* |
| Chronic hydrocephalus, *n (%)* | 3 (6.7%) | 10 (28.6%) | 0.036\* |
| Untreated chronic hydrocephalus, *n (%)* | 3 (6.7%) | 8 (22.9%) | 0.107\* |
| Pneumonia, *n (%)* | 9 (20%) | 12 (34.3%) | 0.150\* |
| Urinary tract infection, *n (%)* | 3 (6.7%) | 4 (11.4%) | 0.360\* |
| Gastrointestinal bleeding, *n (%)* | 0 | 1 (2.9%) | 0.440\* |

*\* Fisher’s exact test (1-sided); intracranial re-bleeding was defined as combined ICH and IVH re-bleeding.*

**Table A20.** Relationship between the functional outcome (30-day mRS) and the change in Graeb score: linear regression analysis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Potential determinant | Unit | Coefficients | 95% CI for coefficients | p-value |
| Lower | Upper |
| (Constant) | 1 (point) | 4.903 | 4.401 | 5.405 | < 0.001 |
| Change in Graeb score | 1 (point) | 0.142 | 0.027 | 0.257 | 0.016 |
| Change in Graeb score | 5 (point) | 0.710 | 0.137 | 1.283 | 0.016 |

*Change in Graeb score defined as the difference between two Graeb scores obtained on admission and at day 3; CI, confidence interval.*

**Table A21.** Comparison of poor functional outcomes among patients in the EVD+IVF group, according to "discharged to die" status

|  |  |  |  |
| --- | --- | --- | --- |
| 30-day poor functional outcomes | Not discharged to die(n = 30) | Discharged to die(n = 5) | p value |
| mRS=4-6, *n (%)* | 20 (66.7) | 5 (100.0) | 0.292\* |
| mRS=5, *n (%)* | 5 (16.7) | 2 (40.0) | 0.256\* |
| GOS=1-2, *n (%)* | 4 (13.3) | 5 (100.0) | <0.001\* |
| GOS=2, *n (%)* | 3 (10.0) | 2 (40.0) | 0.139\* |
| 90-day poor functional outcomes | Not discharged to die(n = 29) | Discharged to die(n = 2) |  |
| mRS=4-6, *n (%)* | 13 (44.8) | 2 (100.0) | 0.226\* |
| mRS=5, *n (%)* | 1 (3.4) | 0 (0.0) | 1.000\* |
| GOS=1-2, *n (%)* | 1 (3.4) | 2 (100.0) | 0.006\* |
| GOS=2, *n (%)* | 0 | 0 | - |

*\* Fisher’s exact test; mRS, Modified Rankin Scale; GOS, Glasgow Outcome Scale; "Discharged to die" defined as patients were in grave condition or dying and were released to die at home, as requested by the patients themselves or by their family members.*

**III. APPENDIX III**

**Actilyse®**

In Vietnam, Actilyse® was supplied by Boehringer Ingelheim (Germany) and was only available in the following pack size: one vial of powder with 50 mg alteplase and one vial with 50 mL of sterilised Water for Injections. Actilyse® was stored in the Pharmacology Department or the Emergency Department below 30°C and protected from light. After mixing with sterilised water for injections, Actilyse® was used immediately. If not used immediately or divided into multiple doses for each vial, Actilyse® was stored in a refrigerator (2 - 8°C) and used within 24 hours.