Cerebrolysin for the Treatment of Aneurysmal Subarachnoid Hemorrhage in Adults: A Retrospective Chart Review

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ABSTRACT

Introduction: Cerebrolysin is a neuroprotective drug used in the treatment of acute ischemic stroke. To our knowledge, this drug has never been evaluated in patients with aneurysmal subarachnoid hemorrhage (SAH). The aim of this study was to evaluate the effect of Cerebrolysin in patients with aneurysmal SAH.

Methods: Aneurysmal SAH patients who had their aneurysm obliterated at our institution from 2007 to 2016 were retrospectively studied. Patients received Cerebrolysin treatment or standard care only (control group). Subgroup analyses were performed according to Hunt and Hess grade (good grade B, N = 216; poor grade C, N = 246) and treatment procedure (clip or coil).

Results: In good-grade patients (N = 216), clinical outcomes and mortality did not differ significantly between the control and Cerebrolysin groups. In poor-grade patients (N = 246), the mortality rate was significantly lower in the Cerebrolysin group (8.7%) than in the control group (25.4%, p = 0.006). In patients who received microsurgical clipping (N = 328), the mortality rate was significantly lower in the Cerebrolysin group (7.3%) than in the control group (18.5%, p = 0.016).

Conclusion: Cerebrolysin injection during the acute period of SAH appeared to reduce the mortality rate, especially in poor-grade patients. This study suggests the potential of Cerebrolysin for treating aneurysmal SAH. Further studies are needed to confirm our results.

Keywords: Aneurysmal subarachnoid hemorrhage; Brain hemorrhage; Cerebrolysin; Cerebrovascular disorders; Neuroprotective agents; Mortality
INTRODUCTION

Aneurysmal subarachnoid hemorrhage (SAH) is a devastating disease with high morbidity and mortality. However, treatment remains insufficient, and drugs to improve patient outcomes are not well established. SAH is a complex pathology and involves vasospasm, acute or chronic hydrocephalus, systemic inflammation, and stressful treatments including surgical procedures. Many agents such as clazosentan, simvastatin, and magnesium sulfate have been assessed in large clinical studies; however, in clinical practice the effects have been disappointing [1–3].

Cerebrolysin (EVER Neuro Pharma™) is a neuropeptide preparation that mimics the action of endogenous neurotrophic factors in brain protection and recovery. It has been shown to be effective against excitotoxicity, inhibits free radical formation, has neurotrophic activity, improves cellular survival, and stimulates sprouting, synaptogenesis, and neurogenesis [4–9]. Several clinical studies have shown beneficial effects of Cerebrolysin in stroke, dementia, and traumatic brain injury [10–13]. A recent meta-analysis of nine randomized, double-blind, placebo-controlled stroke studies with 1879 patients confirmed the early beneficial effect of Cerebrolysin on global neurologic deficits [14]. Recently, Cerebrolysin has been successfully tested for its neurorecovery potential in patients with moderate-to-severe strokes with treatment initiation in the acute and subacute phase [11, 15, 16].

This study investigated potential benefits of Cerebrolysin in patients with aneurysmal SAH. To our knowledge, no such studies have been performed with Cerebrolysin before.

METHODS

Study Design

We retrospectively reviewed medical charts from patients with SAH who underwent aneurysmal occlusion at our institution between January 2007 and December 2016. There was no significant change in surgical or endovascular instruments or treatment protocols during this period. The inclusion criteria were: (1) both sexes 18–85 years old, (2) having SAH within 48 h before admission, and (3) aneurysm obliterated with either clip or coil within 72 h after SAH. Exclusion criteria were early death within 72 h of admission, procedural complication, patients who discontinued Cerebrolysin treatment within 3 days, previous stroke or neurologic deficits, mental disability, psychologic disorders, or lost to follow-up within 3 months. All procedures performed in this study were in accordance with the ethical standards of the institution and with the 1964 Helsinki Declaration and its later amendments. For this type of study, formal consent is not required. This study is not registered as a clinical trial because of its retrospective design. This study was approved by the institutional review board at the author’s institute (HYUH IRB 2017-10-007-001).

Treatment Groups

Patients received Cerebrolysin treatment or standard care only (control group). Cerebrolysin was administered at daily doses of 30 ml for at least 3 days. Cerebrolysin was diluted in 1000 ml normal saline and was administered as a slow intravenous infusion over 24 h. Treatment was initiated within 48 h after SAH.

Data Collection

Demographic information, radiologic findings, treatment, and clinical parameters were reviewed. These data included sex, age, hypertension, diabetes mellitus, treatment (clip or coil), and circulation (anterior or posterior). The Glasgow Coma Scale (GCS) and Hunt and Hess grade [17] were used to record each patient’s initial condition. The modified Fisher Scale, concomitant intracerebral hemorrhage (ICH), SAH sum score [18], and intraventricular hemorrhage (IVH) sum score [19] were recorded to evaluate initial radiologic findings. SAH sum score (0–30) was calculated as the mean of the Hijdra score, which is the sum of the amount of blood in ten cistern or fissure points (0–3 each).
|                          | Control (N = 328) | Cerebrolysin (N = 134) | p value |
|--------------------------|------------------|------------------------|---------|
| Female                   | 221 (67.4%)      | 84 (62.7%)             | 0.391   |
| Age (years)              | 55.0 [47.0; 66.0] | 56.0 [48.0; 62.0]      | 0.876   |
| Operation type           |                  |                        |         |
| Clip                     | 232 (70.7%)      | 96 (71.6%)             | 0.934   |
| Coil                     | 96 (29.3%)       | 38 (28.4%)             |         |
| Circulation              |                  |                        |         |
| Anterior                 | 294 (89.6%)      | 124 (92.5%)            | 0.430   |
| Posterior                | 34 (10.4%)       | 10 (7.5%)              |         |
| Hunt and Hess grade      |                  |                        |         |
| Grade 1                  | 25 (7.6%)        | 9 (6.7%)               | 0.567   |
| Grade 2                  | 126 (38.4%)      | 56 (41.8%)             |         |
| Grade 3                  | 93 (28.4%)       | 34 (25.4%)             |         |
| Grade 4                  | 79 (24.1%)       | 30 (22.4%)             |         |
| Grade 5                  | 5 (1.5%)         | 5 (3.7%)               |         |
| Modified Fisher scale    |                  |                        |         |
| 1                        | 31 (9.5%)        | 12 (9.0%)              | 0.096   |
| 2                        | 5 (1.5%)         | 5 (3.7%)               |         |
| 3                        | 119 (36.3%)      | 35 (26.1%)             |         |
| 4                        | 173 (52.7%)      | 82 (61.2%)             |         |
| GCS score                | 13.0 [9.5; 15.0] | 14.0 [8.0; 15.0]       | 0.964   |
| Concomitant ICH          | 94 (28.7%)       | 47 (35.1%)             | 0.212   |
| Bicaudate index          | 17.6 [14.9; 20.2]| 15.7 [13.9; 18.3]      | < 0.001*|
| SAH sum score            | 19.0 [11.0; 26.0]| 25.0 [14.0; 28.0]      | 0.002*  |
| IVH sum score            | 1.0 [0.0; 4.0]   | 1.0 [0.0; 3.0]         | 0.375   |
| Smoking                  | 86 (26.2%)       | 39 (29.1%)             | 0.604   |
| Hypertension             | 126 (38.4%)      | 49 (36.6%)             | 0.790   |
| Diabetes mellitus        | 19 (5.8%)        | 14 (10.4%)             | 0.118   |
| Permanent shunt operation| 47 (14.3%)       | 21 (15.7%)             | 0.822   |
| Angiographic vasospasm   | 100 (30.5%)      | 55 (41.0%)             | 0.038*  |
| Delayed cerebral ischemia| 43 (13.1%)       | 23 (17.2%)             | 0.325   |
| Days of Cerebrolysin     | 0.0 [0.0; 0.0]   | 13.0 [10.0; 20.0]      |         |
| Length of stay (days)    | 24.0 [16.0; 47.0] | 22.0 [15.0; 46.0]      | 0.289   |
| mRS                      | 2.0 [1.0; 5.0]   | 2.0 [1.0; 5.0]         | 0.398   |

*Adis
IVH sum score (0–12) was calculated as the mean Graeb score, which is the sum of the score for each ventricle (lateral ventricles, 0–4; third ventricle, 0–2; fourth ventricle, 0–2). Chronic hydrocephalus leading to permanent shunt operation was reviewed. Angiographic vasospasm was defined as a 50% decrease of the intracranial artery diameter by imaging or diagnostic angiography. Delayed cerebral ischemia was defined as the occurrence of focal neurologic impairment or a decrease of at least two points on the GCS score or one of its individual components lasting at least 1 h that could not be attributed to other causes [20]. A blinded neuroradiologist at our institution recorded radiologic findings. The modified Rankin Scale (mRS) was used to evaluate clinical outcome 3 months after SAH [21]. Mortality was defined as in-hospital death later than 72 h after SAH ictus.

### Treatment of SAH Patients

All patients had their aneurysm obliterated by either microscopic aneurysm neck clipping or endovascular coil embolization with or without stent assist. The therapy was chosen by the neurovascular team based on age, mental status, aneurysm location, size, and neck/dome presentation. All patients with posterior circulation including the vertebral and basilar arteries were treated with endovascular coil embolization. Blood pressure and glucose were managed strictly with close observation according to our institution’s protocol. Patients in the Cerebrolysin group were not treated any differently from the control group except for Cerebrolysin.

### Patient Group Classification

Subgroup analyses were performed according to the severity of subarachnoid hemorrhage classified by the Hunt and Hess grade (good grade ≤ 2, N = 216; poor grade ≥ 3, N = 246) and treatment procedure (clipping, coiling).

### Statistical Analysis

Non-parametric data were compared with chi-square and Fisher’s exact tests. Parametric variables with a normal distribution were compared by independent t test and those without a normal distribution by Mann-Whitney U test. Descriptive summaries were reported as mean (± standard deviation) for continuous variables with normal distribution, median [interquartile range (IQR)] for continuous variables without normal distribution, and frequency (percentage) for categorical variables. All data were analyzed with R version 3.3.2 (https://www.r-project.org/; R Foundation for Statistical Computing, Vienna, Austria).

### RESULTS

#### Total Aneurysmal SAH Patients

Overall, 548 aneurysmal SAH patients were treated at our institution from 2007 to 2016; of these, 462 patients were included in this study. Patients were excluded because of early death within 72 h (N = 15), procedural complication (N = 8), previous neurologic deficits (N = 9), etc.
Table 2  Demographic features, radiologic findings, and clinical outcomes in good-grade SAH patients

|                       | Control (N = 151) | Cerebrolysin (N = 65) | \( p \) value |
|-----------------------|-------------------|-----------------------|---------------|
| Female                | 104 (68.9%)       | 39 (60.0%)            | 0.268         |
| Age                   | 53.0 [44.0; 64.0] | 55.0 [47.0; 59.0]     | 0.581         |
| Operation type        |                   |                       |               |
| Clip                  | 103 (68.2%)       | 45 (69.2%)            | 1.000         |
| Coil                  | 48 (31.8%)        | 20 (30.8%)            |               |
| Circulation           |                   |                       |               |
| Anterior              | 141 (93.4%)       | 61 (93.8%)            | 1.000         |
| Posterior             | 10 (6.6%)         | 4 (6.2%)              |               |
| Hunt and Hess grade   |                   |                       |               |
| Grade 1               | 25 (16.6%)        | 9 (13.8%)             | 0.766         |
| Grade 2               | 126 (83.4%)       | 56 (86.2%)            |               |
| Modified Fisher scale |                   |                       |               |
| 1                     | 27 (17.9%)        | 9 (13.8%)             | 0.357         |
| 2                     | 2 (1.3%)          | 2 (3.1%)              |               |
| 3                     | 66 (43.7%)        | 23 (35.4%)            |               |
| 4                     | 56 (37.1%)        | 31 (47.7%)            |               |
| GCS score             | 15.0 [15.0; 15.0] | 15.0 [15.0; 15.0]     | 0.761         |
| Concomitant ICH       | 23 (15.2%)        | 14 (21.5%)            | 0.352         |
| Bicaudate index       | 16.7 [14.5; 19.4] | 15.8 [14.1; 17.7]     | 0.043*        |
| SAH sum score         | 14.0 [8.0; 22.0]  | 17.0 [10.0; 27.0]     | 0.051         |
| IVH sum score         | 0.0 [0.0; 1.0]    | 1.0 [0.0; 2.0]        | 0.106         |
| Smoking               | 40 (26.5%)        | 21 (32.3%)            | 0.480         |
| Hypertension          | 46 (30.5%)        | 24 (36.9%)            | 0.440         |
| Diabetes mellitus     | 5 (3.3%)          | 7 (10.8%)             | 0.061         |
| Permanent shunt       | 15 (9.9%)         | 5 (7.7%)              | 0.791         |
| Angiographic vasospasm| 49 (32.5%)        | 19 (29.2%)            | 0.758         |
| Delayed cerebral ischemia| 18 (11.9%)| 7 (10.8%)             | 0.991         |
| Days of Cerebrolysin  | 0.0 [0.0; 0.0]    | 12.0 [9.0; 17.0]      |               |
| Length of stay (days) | 22.0 [17.0; 34.0] | 18.0 [15.0; 26.0]     | 0.015*        |
| mRS                   | 1.0 [1.0; 2.0]    | 1.0 [0.0; 2.0]        | 0.145         |
| Clinical outcome      |                   |                       |               |
| Favorable (mRS 0–2)   | 119 (78.8%)       | 50 (76.9%)            | 0.898         |
| Unfavorable (mRS 3–6) | 32 (21.2%)        | 15 (23.1%)            |               |
discontinuation of Cerebrolysin within 3 days ($N = 19$), and follow-up loss within 3 months ($N = 35$). Of 462 patients with SAH, 134 were included in the Cerebrolysin group and 328 in the control group. Demographic features, radiologic findings, and clinical outcomes are presented in Table 1. Median treatment duration with Cerebrolysin was $13 \ [10.0; 20.0]$ days. Baseline parameters did not differ between groups except for the initial bicaudate index, which was higher in the control group (median; 17.6 vs. 15.7, $p < 0.001$) and for the SAH sum score, which was higher in the Cerebrolysin group (median; 25.0 vs. 19.0, $p = 0.002$). Angiographic vasospasm occurred more often in the Cerebrolysin group than in the control group (41.0 vs. 30.5, $p = 0.038$). Three months after SAH, patients of both groups had a median mRS score of 2; the mortality rate was significantly higher in the control group (17.4%) than in the Cerebrolysin group (9.0%, $p = 0.031$).

### Good-Grade SAH Patients (Hunt and Hess Grade ≤ 2)

Of 216 patients with Hunt and Hess grade ≤ 2, 65 were included in the Cerebrolysin group and 151 in the control group. Demographic features, radiologic findings, and clinical outcomes are shown in Table 2. Median treatment duration with Cerebrolysin was $12 \ [9.0; 17.0]$ days. Baseline parameters did not differ between groups except for the initial bicaudate index, which was significantly higher in the control group (median; 17.5 vs. 15.5, $p < 0.001$) and for the SAH sum score, which was significantly higher in the Cerebrolysin group (median; 25.0 vs. 19.0, $p = 0.007$). Angiographic vasospasm occurred more often in the Cerebrolysin group compared with the control group (52.2% vs. 28.8%, $p = 0.001$). Three months after SAH, patients of both groups had a median mRS score of 4; the mortality rate was significantly higher in the control group (25.4%) than in the Cerebrolysin group (8.7%, $p = 0.006$).

### Poor-Grade SAH Patients (Hunt and Hess Grade ≥ 3)

Of 246 patients with Hunt and Hess grade ≥ 3, 69 were included in the Cerebrolysin group and 177 in the control group. Demographic features, radiologic findings, and clinical outcomes are shown in Table 3. Median treatment duration with Cerebrolysin was $14 \ [12.0; 21.0]$ days. Baseline parameters did not differ between groups except for the initial bicaudate index, which was significantly higher in the control group (median; 18.1 vs. 15.7, $p = 0.001$) and for the SAH sum score, which was significantly higher in the Cerebrolysin group (median; 27.0 vs. 25.0, $p = 0.001$). Angiographic vasospasm occurred more often in the Cerebrolysin group compared with the control group (52.2% vs. 28.8%, $p = 0.001$). Three months after SAH, patients of both groups had a median mRS score of 4; the mortality rate was significantly higher in the control group (25.4%) than in the Cerebrolysin group (8.7%, $p = 0.006$).

### Clip and Coil Patients

Of 462 patients, 328 (71.0%) had microsurgical aneurysm neck clipping and 134 (29.0%) had endovascular coil embolization. Demographic features, radiologic findings, and clinical outcomes are shown in Table 4. In clip patients, the initial bicaudate index was significantly higher in the control group (median; 17.5 vs. 15.5, $p < 0.001$) and the SAH sum score was significantly higher in the Cerebrolysin group (median; 25.0 vs. 19.0, $p = 0.007$). Angiographic

| Table 2 continued | Control ($N = 151$) | Cerebrolysin ($N = 65$) | $p$ value |
|-------------------|---------------------|------------------------|-----------|
| Mortality         | 12 (7.9%)           | 6 (9.2%)               | 0.964     |

SAH subarachnoid hemorrhage, GCS Glasgow Coma Scale, ICH intracerebral hemorrhage, IVH intraventricular hemorrhage, mRS modified Rankin Scale
*Indicates statistical significance ($p < 0.05$)
|                          | Control ($N = 177$) | Cerebrolysin ($N = 69$) | $p$ value |
|--------------------------|---------------------|-------------------------|-----------|
| Female sex               | 117 (66.1%)         | 45 (65.2%)              | 1.000     |
| Age                      | 56.0 [49.0; 68.0]    | 56.0 [50.0; 65.0]       | 0.599     |
| Operation type           |                     |                         |           |
| Clip                     | 129 (72.9%)         | 51 (73.9%)              | 0.997     |
| Coil                     | 48 (27.1%)          | 18 (26.1%)              |           |
| Circulation              |                     |                         |           |
| Anterior                 | 153 (86.4%)         | 63 (91.3%)              | 0.406     |
| Posterior                | 24 (13.6%)          | 6 (8.7%)                |           |
| Hunt and Hess grade      |                     |                         |           |
| Grade 3                  | 93 (52.5%)          | 34 (49.3%)              | 0.286     |
| Grade 4                  | 79 (44.6%)          | 30 (43.5%)              |           |
| Grade 5                  | 5 (2.8%)            | 5 (7.2%)                |           |
| Modified Fisher scale    |                     |                         |           |
| 1                        | 4 (2.3%)            | 3 (4.3%)                | 0.133     |
| 2                        | 3 (1.7%)            | 3 (4.3%)                |           |
| 3                        | 53 (29.9%)          | 12 (17.4%)              |           |
| 4                        | 117 (66.1%)         | 51 (73.9%)              |           |
| GCS score                | 11.0 [6.0; 13.0]    | 8.0 [6.0; 13.0]         | 0.447     |
| Concomitant ICH          | 71 (40.1%)          | 33 (47.8%)              | 0.339     |
| Bicaudate index          | 18.1 [15.3; 21.3]   | 15.7 [13.7; 18.8]       | 0.001*    |
| SAH sum score            | 25.0 [14.0; 27.0]   | 27.0 [23.0; 29.0]       | 0.001*    |
| IVH sum score            | 2.0 [0.0; 5.0]      | 2.0 [1.0; 4.0]          | 0.994     |
| Smoking                  | 46 (26.0%)          | 18 (26.1%)              | 1.000     |
| Hypertension             | 80 (45.2%)          | 25 (36.2%)              | 0.257     |
| Diabetes mellitus        | 14 (7.9%)           | 7 (10.1%)               | 0.757     |
| Permanent shunt          | 32 (18.1%)          | 16 (23.2%)              | 0.466     |
| Angiographic vasospasm   | 51 (28.8%)          | 36 (52.2%)              | 0.001     |
| Delayed cerebral ischemia| 25 (14.1%)          | 16 (23.2%)              | 0.128     |
| Days of Cerebrolysin     | 0.0 [0.0; 0.0]      | 14.0 [12.0; 21.0]       |           |
| Length of stay (days)    | 30.0 [15.0; 67.0]   | 33.0 [16.0; 70.0]       | 0.547     |
| mRS                      | 4.0 [2.0; 6.0]      | 4.0 [2.0; 5.0]          | 0.525     |

Clinical outcome
vasospasm developed more often in the Cerebrolysin group (33.6% vs. 47.9%, \( p = 0.021 \)), and delayed cerebral ischemia was not statistically different between groups (12.5% vs. 20.8%, \( p = 0.079 \)). Three months after SAH, the mortality rate was significantly lower in the Cerebrolysin group (median; 7.3% vs. 18.5%, \( p = 0.016 \)). No significant group differences were observed in the mRS. Coil patients did not differ in baseline characteristics or outcome parameters.

**Safety**

The median treatment duration with Cerebrolysin was 13.0 days. Table 5 shows the rate of adverse events with severe intensity for both groups. The most common adverse event was pneumonia followed by urinary tract infection, acute renal failure, and myocardial infarction. There was no significant difference between the two groups.

**DISCUSSION**

The current study showed excellent outcomes in both study groups and a similar low mortality rate in SAH patients with good grade according to Hunt and Hess. In contrast, in patients with poor grade, the mortality rate was significantly higher in the control group (25.4% versus 8.7%) than in Cerebrolysin-treated patients. These findings are reminiscent of previous studies showing beneficial effects of Cerebrolysin especially in more severely affected patients of different brain pathologies. The results of the CASTA trial reported a reduced mortality rate in more severely affected ischemic stroke patients treated with Cerebrolysin [22]. Similarly, Khalili et al. showed that Cerebrolysin is associated with improved functional recovery, decreased mortality rate, and better outcome in patients with severe disability after traumatic brain injury [23].

Of note, our study showed a lower mortality rate in the Cerebrolysin group in patients with microsurgical clipping but not in patients with endovascular coiling. This might be because surgical clipping was more frequently performed in patients with higher Hunt and Hess grades and in patients with concomitant ICH because of the advantage of evacuating the hematoma simultaneously. Although angiographic vasospasm and delayed cerebral ischemia occurred more often in poor-grade SAH patients treated with Cerebrolysin, the mortality rate was higher in the control group.

Inhibition of brain edema seems to be a key mechanism for lowering the mortality rate in the acute phase after SAH. Maintaining the blood-brain barrier integrity can reduce vasogenic edema, and anti-inflammatory effects contribute to decreased cytotoxic edema [24]. An intracranial hemorrhage rat model showed that Cerebrolysin inhibited brain edema and the inflammatory response and protected the integrity of the blood-brain barrier [10]. In a mouse stroke model study, Cerebrolysin inhibited the effect of proinflammatory mediators such as TNF-\( \alpha \), IL-1\( \beta \), IL-6, and NF-\( \kappa \)B [21, 22]. Unfortunately, we could not assess the effect of Cerebrolysin on brain edema formation in the

**Table 3 continued**

|                       | Control (\( N = 177 \)) | Cerebrolysin (\( N = 69 \)) | \( p \) value |
|-----------------------|--------------------------|-----------------------------|--------------|
| Favorable (mRS 0–2)   | 62 (35.0%)               | 20 (29.0%)                  | 0.452        |
| Unfavorable (mRS 3–6) | 115 (65.0%)              | 49 (71.0%)                  |              |
| Mortality             | 45 (25.4%)               | 6 (8.7%)                    | 0.006*       |

*SAH* subarachnoid hemorrhage, *GCS* Glasgow Coma Scale, *ICH* intracerebral hemorrhage, *IVH* intraventricular hemorrhage, *mRS* modified Rankin Scale

*Indicates statistical significance (\( p < 0.05 \))
| Table 4 Demographic features, radiologic findings, and clinical outcomes by operation type (clip versus coil) |
|---------------------------------------------------------------|
| **Clip (N = 328)**                                        | **Coil (N = 134)**                                |
| **Control (N = 232)**                                      | **Cerebrolysin (N = 96)**                       | **Control (N = 96)**                           | **Cerebrolysin (N = 38)** |
| Female                                                     | 155 (66.8%)                                      | 59 (61.5%)                                      | 66 (68.8%)                                      | 25 (65.8%)                                      | 0.424                      | 0.601                      | 0.900                      | 0.639                      |
| Age                                                        | 55.0 [48.0; 66.0]                                 | 55.0 [49.0; 61.5]                               | 55.1 ± 13.3                                     | 56.4 ± 14.4                                     | 0.601                      | 0.639                      | 0.900                      | 0.639                      |
| Circulation                                               |                                                 |                                                 |                                                 |                                                 |                                  |                                  |                                  |                                  |
| Anterior                                                  | 232 (100.0%)                                     | 96 (100.0%)                                     | 62 (64.6%)                                      | 28 (73.7%)                                      | 0.420                      | 0.420                      | 0.900                      | 0.900                      |
| Posterior                                                 | 0 (0.0%)                                         | 0 (0.0%)                                        | 34 (35.4%)                                      | 10 (26.3%)                                      | 0.778                      | 0.778                      | 1.000                      | 1.000                      |
| Hunt and Hess grade                                       | 3.0 [2.0; 4.0]                                   | 3.0 [2.0; 4.0]                                  | 2.5 [2.0; 3.0]                                  | 2.0 [2.0; 3.0]                                  | 0.778                      | 0.778                      | 1.000                      | 1.000                      |
| Modified Fisher scale                                      |                                                 |                                                 |                                                 |                                                 |                                  |                                  |                                  |                                  |
| 1 and 2                                                   | 22 (9.5%)                                        | 11 (11.5%)                                      | 14 (14.6%)                                      | 6 (15.8%)                                       | 0.734                      | 0.734                      | 1.000                      | 1.000                      |
| 3 and 4                                                   | 210 (90.5%)                                      | 85 (88.5%)                                      | 82 (85.4%)                                      | 32 (84.2%)                                      | 0.843                      | 0.843                      | 0.951                      | 0.951                      |
| GCS score                                                 | 13.0 [8.0; 15.0]                                 | 13.0 [7.0; 15.0]                               | 14.0 [12.0; 15.0]                               | 14.0 [9.0; 15.0]                                | 0.843                      | 0.843                      | 0.872                      | 0.872                      |
| Bicaudate index                                           | 17.5 ± 3.9                                      | 15.5 ± 3.2                                      | < 0.001*                                        | 17.8 [15.1; 20.8]                               | 0.778                      | 0.778                      | 1.000                      | 1.000                      |
| SAH sum score                                             | 19.0 [12.0; 26.0]                                | 25.0 [14.0; 28.0]                               | 0.007*                                          | 17.5 [8.5; 26.0]                                | 0.843                      | 0.843                      | 0.951                      | 0.951                      |
| IVH sum score                                             | 1.0 [0.0; 4.0]                                   | 1.0 [0.0; 4.0]                                  | 0.989                                           | 1.0 [0.0; 4.0]                                  | 0.197                      | 0.197                      | 0.813                      | 0.813                      |
| Concomitant ICH                                           | 81 (34.9%)                                       | 41 (42.7%)                                      | 0.229                                           | 13 (13.5%)                                      | 0.673                      | 0.673                      | 0.951                      | 0.951                      |
| Smoking                                                   | 66 (28.4%)                                       | 20 (20.8%)                                      | 0.197                                           | 29 (30.2%)                                      | 0.673                      | 0.673                      | 0.813                      | 0.813                      |
| Hypertension                                              | 82 (35.3%)                                       | 37 (38.5%)                                      | 0.673                                           | 44 (45.8%)                                      | 0.251                      | 0.251                      | 0.459                      | 0.459                      |
| Diabetes mellitus                                         | 16 (6.9%)                                        | 11 (11.5%)                                      | 0.251                                           | 3 (3.1%)                                        | 0.673                      | 0.673                      | 0.459                      | 0.459                      |
| Permanent shunt                                           | 38 (16.4%)                                       | 17 (17.7%)                                      | 0.896                                           | 9 (9.4%)                                        | 0.251                      | 0.251                      | 1.000                      | 1.000                      |
| Angiographic vasoispasm                                   | 78 (33.6%)                                       | 46 (47.9%)                                      | 0.021*                                          | 22 (22.9%)                                      | 0.896                      | 0.896                      | 1.000                      | 1.000                      |
| Delayed cerebral ischemia                                 | 29 (12.5%)                                       | 20 (20.8%)                                      | 0.079                                           | 14 (14.6%)                                      | 0.896                      | 0.896                      | 0.447                      | 0.447                      |
| Days of Cerebrolysin                                      | 14.0 [11.0; 20.5]                                | 23.0 [11.0; 28.0]                               | 0.007*                                          | 23.0 [11.0; 28.0]                                | 0.843                      | 0.843                      | 1.000                      | 1.000                      |
| Length of stay (days)                                     | 27.0 [17.0; 60.0]                                | 23.0 [16.0; 50.5]                               | 0.372                                           | 18.0 [14.0; 32.0]                                | 0.843                      | 0.843                      | 1.000                      | 1.000                      |
| mRS score                                                 | 2.0 [1.0; 5.0]                                   | 3.0 [1.0; 5.0]                                  | 0.239                                           | 1.0 [1.0; 4.0]                                  | 0.572                      | 0.572                      | 0.743                      | 0.743                      |
| Clinical outcome                                          |                                                 |                                                 |                                                 |                                                 |                                  |                                  |                                  |                                  |
| Favorable (mRS 0–2)                                       | 119 (51.3%)                                      | 46 (47.9%)                                      | 0.663                                           | 62 (64.6%)                                      | 0.239                      | 0.239                      | 1.000                      | 1.000                      |
| Unfavorable (mRS 3–6)                                     | 113 (48.7%)                                      | 50 (52.1%)                                      | 0.342                                           | 34 (35.4%)                                      | 0.663                      | 0.663                      | 1.000                      | 1.000                      |
current study, but it would be interesting to address this in future studies.

One of the limitations of this study was the retrospective design. Accordingly, data from medical records were limited and did not allow precise matching of patients in terms of baseline characteristics. Furthermore, treatment with Cerebrolysin was limited to the acute phase of SAH, and treatment duration varied between 8 and 21 days. For efficacy assessment, no data were available regarding functional disability or cognitive or neuropsychologic outcome. Due to the exclusion of patients who died within 72 h (N = 15), the mortality rate might have been slightly underestimated. However, to our knowledge, this is the largest study that evaluated the effects of Cerebrolysin in aneurysmal SAH patients. Despite the limited level of evidence of this retrospective study, we think that these results are promising and could provide guidance for future randomized studies evaluating the effect of Cerebrolysin on SAH patients.

**CONCLUSIONS**

Hemorrhagic stroke including aneurysmal SAH is a devastating disease causing severe brain damage. This study suggests a potential benefit of Cerebrolysin to reduce the mortality rate in patients with aneurysmal SAH, which should be further evaluated in clinical studies.

**ACKNOWLEDGEMENTS**

We thank the participants of this study.

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**Table 4 continued**

|                  | Clip (N = 328) | Cerebolysin (N = 96) | p    | Coil (N = 134) | Cerebolysin (N = 38) | p    |
|------------------|----------------|----------------------|------|----------------|----------------------|------|
|                  | Control (N = 232) | Cerebolysin (N = 96) |      | Control (N = 96) | Cerebolysin (N = 38) |      |
| Mortality        | 43 (18.5%)       | 7 (7.3%)             | 0.016* | 14 (14.6%)     | 5 (13.2%)            | 1.000 |

*SAH subarachnoid hemorrhage, GCS Glasgow Coma Scale, ICH intracerebral hemorrhage, IVH intraventricular hemorrhage, mRS modified Rankin Scale
*Indicates statistical significance (p < 0.05)

**Table 5** Comparison of adverse events of severe intensity between control and Cerebolysin groups

|                  | Control (N = 328) | Cerebolysin (N = 134) | p value |
|------------------|-------------------|-----------------------|---------|
| Pneumonia        | 29 (8.84%)        | 12 (8.96%)            | 1.000   |
| Urinary tract infection | 18 (5.49%)     | 8 (5.97%)              | 0.986   |
| CSF infection    | 3 (0.91%)         | 2 (1.49%)             | 0.630   |
| Acute renal failure | 17 (5.18%)    | 4 (2.99%)             | 0.434   |
| Pulmonary embolism | 5 (1.52%)       | 1 (0.75%)             | 0.678   |
| Acute cholecystitis | 0 (0.00%)      | 1 (0.75%)             |         |
| Myocardial infarction | 14 (4.29%)  | 5 (3.73%)             | 1.000   |
| Severe adverse event | 82 (25.0%)   | 31 (23.1%)            | 0.761   |

CSF cerebrospinal fluid
**Funding.** No funding or sponsorship was received for this study. EVER Pharmaceuticals funded the article processing charges and open access fee.

**Authorship.** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

**Disclosure.** Yung Ki Park, Hyeong-Joong Yi, Kyu-Sun Choi, Young-Jun Lee, Dong-Won Kim, and Sae Min Kwon have nothing to disclose.

**Compliance with Ethics Guidelines.** All procedures performed in this study were in accordance with the ethical standards of the institution and with the 1964 Helsinki Declaration and its later amendments. For this type of study, formal consent is not required. This study was approved by the institutional review board at the author’s institute (HYUH IRB 2017-10-007-001).

**Data Availability.** The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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