Adv Ther
https://doi.org/10.1007/s12325-018-0832-8

BRIEF REPORT

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

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Received: July 10, 2018/Published online: November 9 2018

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 ≤ 2, $N = 216$; poor grade ≥ 3, $N = 246$) 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.

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

Published online: 09 November 2018

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^{TM}) 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).

Table 1 Demographic features, radiologic findings, and clinical outcomes in total SAH patients

	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

Table 1 continued

	Control (N = 328)	Cerebrolysin (N = 134)	p value
Clinical outcome			
Favorable (mRS 0–2)	181 (55.2%)	70 (52.2%)	0.636
Unfavorable (mRS 3–6)	147 (44.8%)	64 (47.8%)	
Mortality	57 (17.4%)	12 (9.0%)	0.031*

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

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 permanent shunt operation was reviewed. Angiographic vasospasm was defined as > 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 ($N = 9$),

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%)	

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 ($p < 0.05$)

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; 16.7 vs. 15.8, $p = 0.043$). Length of stay was significantly reduced by 4 days in the Cerebrolysin group, with statistical significance (22 vs. 18 median days, $p = 0.015$). Three months after SAH, patients of both groups had a median mRS score of 1; no significant group differences were reported for mortality.

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 3 Demographic features, radiologic findings, and clinical outcomes in poor-grade SAH patients

	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			

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 ($p < 0.05$)

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-α, IL-1β, IL-6, and NF-κB [21, 22]. Unfortunately, we could not assess the effect of Cerebrolysin on brain edema formation in the

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)**	***p***	**Control (*N* = 96)**	**Cerebrolysin (*N* = 38)**	***p***
Female	155 (66.8%)	59 (61.5%)	0.424	66 (68.8%)	25 (65.8%)	0.900
Age	55.0 [48.0; 66.0]	55.0 [49.0; 61.5]	0.601	55.1 ± 13.3	56.4 ± 14.4	0.639
Circulation						
Anterior	232 (100.0%)	96 (100.0%)		62 (64.6%)	28 (73.7%)	0.420
Posterior	0 (0.0%)	0 (0.0%)		34 (35.4%)	10 (26.3%)	
Hunt and Hess grade	3.0 [2.0; 4.0]	3.0 [2.0; 4.0]	0.778	2.5 [2.0; 3.0]	2.0 [2.0; 3.0]	0.832
Modified Fisher scale						
1 and 2	22 (9.5%)	11 (11.5%)	0.734	14 (14.6%)	6 (15.8%)	1.000
3 and 4	210 (90.5%)	85 (88.5%)		82 (85.4%)	32 (84.2%)	
GCS score	13.0 [8.0; 15.0]	13.0 [7.0; 15.0]	0.843	14.0 [12.0; 15.0]	14.0 [9.0; 15.0]	0.872
Bicaudate index	17.5 ± 3.9	15.5 ± 3.2	< 0.001*	17.8 [15.1; 20.8]	16.9 [14.8; 21.8]	0.706
SAH sum score	19.0 [12.0; 26.0]	25.0 [14.0; 28.0]	0.007*	17.5 [8.5; 26.0]	23.0 [11.0; 28.0]	0.102
IVH sum score	1.0 [0.0; 4.0]	1.0 [0.0; 2.0]	0.989	1.0 [0.0; 4.0]	2.0 [0.0; 6.0]	0.099
Concomitant ICH	81 (34.9%)	41 (42.7%)	0.229	13 (13.5%)	6 (15.8%)	0.951
Smoking	66 (28.4%)	20 (20.8%)	0.197	29 (30.2%)	10 (26.3%)	0.813
Hypertension	82 (35.3%)	37 (38.5%)	0.673	44 (45.8%)	12 (31.6%)	0.189
Diabetes mellitus	16 (6.9%)	11 (11.5%)	0.251	3 (3.1%)	3 (7.9%)	0.459
Permanent shunt	38 (16.4%)	17 (17.7%)	0.896	9 (9.4%)	4 (10.5%)	1.000
Angiographic vasospasm	78 (33.6%)	46 (47.9%)	0.021*	22 (22.9%)	9 (23.7%)	1.000
Delayed cerebral ischemia	29 (12.5%)	20 (20.8%)	0.079	14 (14.6%)	3 (7.9%)	0.447
Days of Cerebrolysin		14.0 [11.0; 20.5]			12.0 [8.0; 16.0]	
Length of stay (days)	27.0 [17.0; 60.0]	23.0 [16.0; 50.5]	0.372	20.0 [15.0; 33.5]	18.0 [14.0; 32.0]	0.407
mRS score	2.0 [1.0; 5.0]	3.0 [1.0; 5.0]	0.239	1.0 [1.0; 4.0]	2.0 [1.0; 4.0]	0.743
Clinical outcome						
Favorable (mRS 0–2)	119 (51.3%)	46 (47.9%)	0.663	62 (64.6%)	24 (63.2%)	1.000
Unfavorable (mRS 3–6)	113 (48.7%)	50 (52.1%)		34 (35.4%)	14 (36.8%)	

Table 4 continued

	Clip (N = 328)			Coil (N = 134)		
	Control (N = 232)	Cerebrolysin (N = 96)	p	Control (N = 96)	Cerebrolysin (N = 38)	p
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 Cerebrolysin groups

	Control (N = 328)	Cerebrolysin (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

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 bain 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.

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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