CEREBROLYSIN IN NEUROLOGY AND INTENSIVE CARE: NEW CLINICAL TRIALS AND THEIR IMPLICATIONS FOR ROUTINE CARE

Cerebrolizyna w neurologii i intensywnej terapii: nowe badania kliniczne oraz ich implikacje praktyczne

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Abstract

Introduction and objective: Cerebrolysin is a multimodal cerebroprotective agent that may improve the function of the blood–brain barrier, the neurovascular unit, and plasticity-related processes following central nervous system injury. This study aims to provide a comprehensive overview and critical evaluation of new clinical data (published after 2020) on the use of cerebrolysin in the acute phase of ischaemic stroke, including combination therapy with reperfusion strategies, and in neurointensive care for patients with traumatic brain injury (TBI). **Materials and methods:** A narrative review of randomised clinical trials (RCTs) involving cerebrolysin, meta-analyses, and prospective/observational studies was conducted, including analysis of the primary endpoints: National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), haemorrhagic transformation (HT/sHT), safety, and treatment feasibility. **Results:** In the acute phase of ischaemic stroke, a meta-analysis of 14 RCTs showed a modest benefit in NIHSS scores without a consistent effect on 90-day mRS outcomes; CEREHETIS reported lower sHT when cerebrolysin was added early to thrombolysis, while the multinational C-REGS2 registry demonstrated a favourable ordinal shift in 90-day mRS and improved cognition without additional safety concerns. Observational post-thrombectomy studies, including cyclic regimens with 12-month follow-up, suggested higher odds of functional independence and reduced HT, although causal inference remains limited. In TBI, the CAPTAIN trial (185 moderate-to-severe cases) demonstrated a benefit on a multidomain global outcome at 90 days with comparable safety. Broader meta-analyses suggested improvement in Glasgow Outcome Scale scores, without a clear effect on mortality and with substantial heterogeneity across studies. **Conclusions:** Cerebrolysin appears most promising as an adjunct to reperfusion and rehabilitation in the acute phase of ischaemic stroke and as supportive therapy in TBI. Definitive multicentre RCTs are needed to refine patient selection, timing, and dosing.

Streszczenie

Wprowadzenie i cel: Cerebrolizyna jest preparatem o wielomodalnym działaniu cerebroprotekcyjnym, mogącym wpływać na działanie bariery krew–mózg, jednostki nerwowo-naczyniowej, oraz procesy plastyczności po uszkodzeniu ośrodkowego układu nerwowego. Celem pracy jest syntetyczna prezentacja i krytyczna ocena nowych danych klinicznych (opublikowanych po 2020 roku) dotyczących zastosowania cerebrolizyny w ostrej fazie udaru niedokrwiennego, w tym jako terapii skojarzonej z reperfuzją, oraz w neurointensywnej opiece u pacjentów z pourazowym uszkodzeniem mózgu. **Materiał i metody:** Przeprowadzono przegląd narracyjny randomizowanych badań klinicznych, metaanaliz oraz badań prospektywnych i obserwacyjnych, uwzględniając analizę NIHSS (National Institutes of Health Stroke Scale), zmodyfikowaną skalę Rankina (mRS), transformację krwotoczną (HT), w tym objawową (sHT), a także bezpieczeństwo i wykonalność leczenia. **Wyniki:** Badania nad terapią łączoną cerebrolizyną z dożylną trombolizą z użyciem tkankowego aktywatora plazminogenu (CEREHETIS, CERE-LYSE) wykazały redukcję sHT po trombolizie i szybszą poprawę ocenianą w skali NIHSS, przy braku różnic w 90-dniowym mRS. W rejestrze C-REGS2 u chorych z umiarkowaną ostrą fazą udaru niedokrwiennego cerebrolizyna wiązała się z korzystnym przesunięciem rozkładu mRS i lepszymi wynikami funkcji poznawczych. Trzy badania obserwacyjne po trombektomii, w tym jedno z 12-miesięczną obserwacją (CEREBROLYSIN-WIM Study) sugerują większą szansę uzyskania niezależności funkcjonalnej i redukcję HT/sHT, jednak brak randomizacji ogranicza możliwość wyciągania wniosków przyczynowych.

W pourazowym uszkodzeniu mózgu projekt CAPTAIN (185 chorych) wykazał korzystny wpływ na globalny wielowymiarowy punkt końcowy oceniany w 90. dobie, przy porównywalnym bezpieczeństwie. Metaanalizy wskazują na poprawę wyników w skali Glasgow, bez redukcji śmiertelności, przy istotnej heterogenności danych. **Wnioski:** Istnieją obiecujące przesłanki dotyczące roli cerebrolizyny jako terapii wspomagającej reperfuzję/rehabilitację w ostrej fazie udaru niedokrwiennego oraz jako interwencji wspomagającej w pourazowym uszkodzeniu mózgu. Potrzebne są jednak wieloośrodkowe randomizowane badania kliniczne z precyzyjną selekcją pacjentów oraz optymalizacją czasu, dawki i długości leczenia.

Keywords: cerebrolysin; reperfusion; acute ischaemic stroke; spinal stroke; traumatic brain injury

Słowa kluczowe: cerebrolizyna; reperfuzja; udar niedokrwienny; udar rdzenia; pourazowe uszkodzenie mózgu

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Introduction

The treatment of acute ischaemic stroke (AIS) has undergone a fundamental transformation with the widespread adoption of reperfusion therapies – intravenous thrombolysis using tissue plasminogen activator (tPA) and mechanical thrombectomy (MT). The primary therapeutic goal remains the rapid restoration of blood flow in the occluded vessel responsible for the ischaemia. However, growing clinical experience indicates that the technical success of recanalisation does not always translate into full functional recovery. This issue is particularly relevant in strokes caused by large vessel occlusion (LVO), where, despite successful recanalisation, secondary injury mechanisms may predominate, including neurovascular unit dysfunction, cytotoxic and vasculogenic oedema, microthrombi, microcirculatory disturbances, and blood–brain barrier (BBB) disruption leading to haemorrhagic transformation (HT). In clinical practice, this results in a discrepancy between the technical success of the procedure (usually >90%) and functional outcomes, as 30–50% of patients remain dependent in the long term (the so-called phenomenon of futile recanalisation).

Consequently, there has been a resurgence of interest in cytoprotective and neuroregenerative strategies, both as adjuncts to reperfusion therapy and as components supporting rehabilitation aimed at inducing brain plasticity [1]. In parallel, other adjuvant approaches are being explored (including therapeutic hypothermia, hyperbaric oxygen therapy, and ischaemic preconditioning). However, their implementation in routine clinical practice remains challenging because of both technical limitations and variability in individual treatment responses. These responses may depend on stroke location (subcortical, cortical, posterior fossa), aetiology (microangiopathy, macroangiopathy), treatment timing, collateral circulation, and other patient-specific factors [2].

Cerebrolysin is one of the most extensively studied neuroprotective agents for disorders of the central nervous system (CNS), in both preclinical and clinical settings [3]. It is a parenterally administered peptide-amino acid preparation whose composition and multimodal mechanism of action mimic those of endogenous neurotrophic factors, which translates into beneficial cytoprotective and neuromodulatory effects observed in ischaemic stroke, traumatic brain injury (TBI), mild cognitive impairment, Alzheimer's disease, vascular dementia, cerebral amyloid angiopathy, monogenic dementias (e.g. cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL), and other neurological disorders [4, 5]. The action of cerebrolysin involves diverse mechanisms of neuroprotection, neuroregeneration, and neuronal and synaptic plasticity. The neurotrophic components of cerebrolysin (including brain-derived neurotrophic factor and ciliary neurotrophic factor, nerve growth factor, orexins, and enkephalins) cross the BBB, initiate the intracellular Shh (sonic hedgehog) signalling pathway, lead to the activation of transcription factors, increased expression of endogenous neurotrophins, and inhibition of excitotoxic processes and oxidative stress, and also have a beneficial effect on microglial function. Preclinical and clinical studies have demonstrated a significant effect of cerebrolysin on endothelial and BBB function, including a reduced risk of haemorrhage following tPA administration through restoration of endothelial cell integrity and improvement of BBB function [6]. Encouraging results have also been reported in the subacute and chronic phases of stroke. In patients receiving cerebrolysin as an adjunct to early and intensive post-stroke rehabilitation, improvements in neurological status and the recovery of motor function and speech ability were observed, together with good tolerability and safety profiles [7]. Based on these data, cerebrolysin has received recommendations from numerous scientific societies (including the Vascular Diseases Section of the Polish Neurological Society (2019), the European Academy of Neurology together with the European Federation of Neurorehabilitation (2021), and the German Society for Neurorehabilitation (2020) for adjunctive use in early post-stroke rehabilitation, particularly in patients with moderate-to-severe stroke [8].

Similarly to the ischaemic cascade observed after stroke, TBI triggers complex processes of secondary injury involving glutamate-induced excitotoxicity, Ca^{2+} influx, mitochondrial dysfunction, oxidative stress, neuroinflammation, and damage to the BBB accompanied by oedema and microcirculatory disturbances. These mechanisms lead to progressive apoptosis, neurodegeneration, and deterioration of neurological function (Fig. 1) [9]. Preclinical models have demonstrated that cerebrolysin may also exert beneficial pharmacological effects in TBI by enhancing the brain's endogenous neuroprotective mechanisms through the maintenance of cellular neurotrophism, neuroprotection, and neuroplasticity [10]. In accordance with the recommendations of the STAIR XI scientific committee, cerebroprotective interventions targeting various stages of the ischaemic or post-traumatic cascade, when administered within an appropriate therapeutic window, are considered essential for improving treatment efficacy [11].

To date, evidence from randomised controlled trials (RCTs) and meta-analyses regarding the efficacy of cerebrolysin in combination with reperfusion therapies in AIS, or as part of intensive management in patients with moderate-to-severe TBI remains scarce and somewhat inconsistent. This is partly due to the inclusion of heterogeneous patient populations, including those with AIS not treated with reperfusion therapy or those with mild TBI. In recent years, however, results from new studies on cerebrolysin in neurological intensive care settings have emerged. These findings justify the need for a broader evaluation of the role of cerebrolysin as an adjunct to tPA or mechanical thrombectomy in ischaemic stroke, and as a supportive therapy alongside standard intensive care after TBI, where it is crucial to translate early radiological success following thrombectomy or stabilisation of vital functions after trauma into meaningful long-term functional recovery.

Objective

The aim of this study is to provide a comprehensive overview and critical evaluation of current data from clinical trials (with particular emphasis on studies published between 2020 and 2025) regarding the use of cerebrolysin in (1) the treatment of AIS, including in combination with reperfusion therapies, (2) intensive neurological care, particularly in TBI and subarachnoid haemorrhage (SAH).

Materials and methods

This paper is a narrative review based on key RCTs, meta-analyses, and more recent prospective and observational studies (including matched-cohort analyses) evaluating the efficacy of cerebrolysin in patients with AIS treated with reperfusion therapy (mechanical thrombectomy or thrombolysis), as well as in patients with TBI or SAH. The analysis focused on endpoints of practical and clinical significance, including neurological deficit severity assessed using the NIHSS (National Institutes of Health Stroke Scale), functional outcome measured with the modified Rankin Scale (mRS), independence evaluated by the Barthel Index (BI), the incidence of HT, including symptomatic haemorrhagic transformation (sHT), safety outcomes (adverse events), and the feasibility of and adherence to treatment protocols.

Results

Acute ischaemic stroke – new data in the era of reperfusion

Previous studies and meta-analyses involving patients with AIS who received non-interventional treatment and started cerebrolysin therapy within 48 hours of stroke onset have demonstrated an overall favourable safety

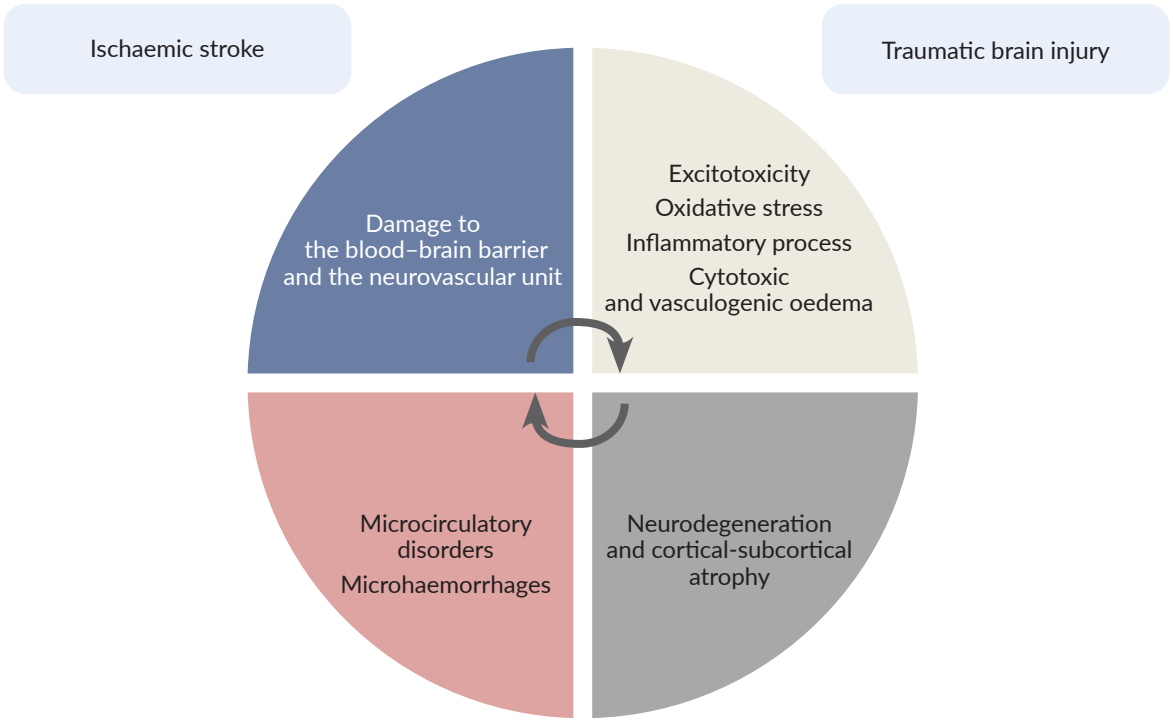


Figure 1. Common pathomechanisms of acute ischaemic stroke and traumatic brain injury

profile and suggested a possible trend towards accelerated neurological recovery, particularly in patients with moderate-to-severe stroke [12]. However, the populations analysed and the cerebrolysin treatment protocols used were highly heterogeneous, which adversely affected the quality of the analysed data [13]. In the recently published largest meta-analysis comprising 14 RCTs conducted between 2004 and 2025 (n = 2,884), which included two studies involving patients treated with thrombolysis, a significant improvement in neurological deficit was demonstrated in patients treated with cerebrolysin (mean difference in NIHSS reduction during hospitalisation vs the control group: 1.39 points; 95% CI: 0.53–2.25; p = 0.02), with no significant differences in functional independence, although this outcome was assessed over a broad time window (days 21–90) [14]. The authors of the meta-analysis emphasised the need for further high-quality studies to confirm the impact on long-term (90-day) functional outcomes.

In the era of reperfusion therapy, more recent studies have focused on two main objectives:

- increasing the proportion of patients achieving functional independence at 90 days;
- reducing HT/sHT and other reperfusion complications.

CEREHETIS – adjunctive thrombolytic therapy and the risk of HT

The prospective, randomised, open-label, multicentre CEREHETIS trial (2024) evaluated the early addition of cerebrolysin as an adjunctive therapy to tPA in patients with AIS involving the middle cerebral artery [15]. In the analysed cohort, patients in the intervention group (IG, n = 126) received 30 ml of cerebrolysin intravenously for 14 days in combination with tPA and standard care, while the control group (CG, n = 215) received tPA and standard care. The endpoints were haemorrhagic complications, including sHT and any HT, as well as functional outcome measured on the mRS at 90 days after onset. In the intention-to-treat (ITT) analysis, a significant reduction in sHT was observed in the cerebrolysin group (3.2% vs 9.3%; OR 0.248; 95% CI: 0.072–0.851; p = 0.019) with a trend towards a lower incidence of HT (15.9% vs 23.3%; p = 0.078). In the PP (per-protocol) analysis, the reduction was significant for both HT (13.7% vs 22.9%; OR 0.417; p = 0.032) and sHT (2.6% vs 9.0%; OR 0.171; p = 0.022). A post hoc analysis found that the reduction in HT risk was greatest in patients with a high predicted risk of haemorrhage according to the HTI scale (including low ASPECTS, signs of a hyperdense middle cerebral artery, atrial fibrillation) [16]. Additionally, a significant early improvement in neurological status was noted in the IG group (median NIHSS score on day 14: 2 vs 3 points; p <0.05), with no significant differences in functional status on the mRS at 90 days. The treatment was well tolerated. In the subgroup of patients undergoing advanced imaging (n = 33), a significant improvement in BBB permeability parameters on perfusion CT (product of permeability and surface area) and a smaller infarct volume at 14 days were observed in the cerebrolysin group. These findings support the hypothesis that stabilising the BBB through cerebroprotective treatment may contribute to reducing the incidence of haemorrhagic complications following reperfusion. The authors noted that the reduction in haemorrhagic risk achieved with cerebrolysin may allow anticoagulant therapy to be resumed 1–2 days earlier in patients at high risk of HT.

The results of the CEREHETIS trial were consistent with those of another prospective, randomised, double-blind, placebo-controlled trial (CERE-LYSE, 2013), which evaluated the safety and efficacy of combining alteplase with cerebrolysin in 119 patients with acute ischaemic stroke [17]. Treatment was initiated within 3 hours of symptom onset; 1 hour after thrombolysis, 30 ml of cerebrolysin or placebo was administered intravenously for 10 consecutive days. The trial was discontinued after the third interim analysis because no improvement in mRS at day 90 (primary endpoint) was demonstrated compared with placebo; however, in the secondary analysis, significantly more (p <0.01) patients in the cerebrolysin group achieved neurological improvement on the NIHSS score, including at 2 (45.8% vs 25.3%), 5 (66.1% vs 37.3%), 10 (72.1% vs 50.8%), and 30 (75.8% vs 57.6%) days.

Therapy added to mechanical thrombectomy

Several observational studies and pragmatic clinical trials have been published to date in populations treated with mechanical thrombectomy (MT), suggesting potential improvement in functional outcomes at 3 months and a significant reduction in haemorrhagic complications with the use of cerebrolysin.

In a pilot observational study, Poljakovic et al. (2021) evaluated patients with moderate or severe AIS (NIHSS >8) following unsuccessful recanalisation following treatment with MT (TICI (Thrombolysis in Cerebral Infarction) score <2b) and/or tPA [18]. The study included 44 patients, allocated to treatment with cerebrolysin (30 ml/day for 14–21 days, treatment initiation ≤24 hours from symptom onset; n = 23) or standard therapy (n = 21). At day 90, no significant differences were observed in the distribution of clinical outcomes (mRS); however, at 12 months, a trend towards a higher proportion of patients with mRS 0–3 was noted (70% vs 48%; p = 0.1), along with a significantly lower incidence of HT (13% vs 38%; p <0.05) and a favourable safety profile for cerebrolysin. The findings of this pilot study were important for the design of subsequent trials, as they indicated a potential therapeutic role for neuroprotective treatment for patients in whom standard reperfusion therapy had not yielded the expected results.

The study by ElBassiouny et al. (2025) involved a prospective assessment of the clinical course of AIS in patients receiving cerebrolysin as adjunctive therapy following successful MT (NIHSS ≥10, age 18–80 years; mTICI 2b/3, cardiogenic stroke) [19]. The analysis included 150 patients: 75 received 30 ml of cerebrolysin intravenously once daily for 14 days, initiated ≤8 hours after MT, while 75 formed the historical control group (MT ± IV rt-PA without cerebrolysin). The primary endpoint was the proportion of patients with mRS 0–2 at day 90, and secondary endpoints included NIHSS and mRS scores at days 14, 30 and 90, cognitive impairment assessed on the MoCA scale at day 90, symptomatic and asymptomatic HT, as well as mortality and adverse

events. The authors demonstrated a significantly higher proportion of patients achieving mRS 0–2 at 90 days in the cerebrolysin group compared with the control group (64% vs 34.7%, respectively; p <0.001) and statistically significantly (p <0.05) lower NIHSS and mRS scores at subsequent time points (14–90 days), alongside a significant (p <0.01) reduction in the incidence of any HT (20% vs 57.3%) and sHT (2.7% vs 41.3%), and lower three-month overall mortality (5.3% vs 32%). In the subgroup analysis of patients with ASPECTS ≤10, better functional outcomes (mRS 0–2 at 3 months) were observed with cerebrolysin compared with controls (ASPECTS 8–10: 50.7% vs 32%; ASPECTS 6–7: 13.3% vs 2.7%). All results were consistent both in the primary analysis cohort and in groups matched for stroke characteristics in the PSM analysis (n = 51 pairs).

The Cerebrolysin-WIM Study, conducted by Polish researchers (2025), assessed the efficacy of treatment in patients selected on the basis of a small infarct core, adequate collateral circulation (CTA-CS 2–3) and successful recanalisation (mTICI 2b–3) [20]. This was a single-centre, prospective, open-label study with blinded outcome assessment, compared with a historical control group matched using the PSM method (50 patients treated with cerebrolysin vs 50 controls). Cerebrolysin was administered in two cycles: 30 ml IV within 8 hours of symptom onset up to day 21 (cycle I) and again during the rehabilitation phase between days 69 and 90 (cycle II). The primary endpoint was the achievement of functional independence (mRS 0–2) by day 90, which occurred more frequently in the cerebrolysin group (68% vs 44%; p = 0.016; OR 2.7; 95% CI: 1.2–6.1; NNT 4.2) (Fig. 2). Treatment was also associated with a lower risk of secondary HT (14% vs 40%; p = 0.02; RR 0.37), faster neurological recovery (NIHSS on day 7: median 3 vs 6; p = 0.01), and better outcomes on functional scales (Barthel Index on day 30 and at 3 months). No differences in mortality at 30 and 90 days were observed between groups. The proportion of patients with mRS 0–2 at 90 days was higher among those who received tPA bridging therapy (80% vs 47.6%; p = 0.03; OR 4.4; 1.1–17.7), with ASPECTS <10 (61.3% vs 26.3%; p = 0.02; OR 4.4; 1.3–15.5), with a trend towards functional independence in patients without sHT (65.3% vs 34.7%; p = 0.07; OR 2.39; 0.9–6.4).

The Cerebrolysin-WIM trial is, to date, the only published study with a 12-month follow-up demonstrating that cerebrolysin use was associated with a higher likelihood of functional independence at 12 months after adjustment for potential confounding factors (aOR 6.10; 95% CI: 1.64–22.66; p <0.01) and a favourable shift towards lower disability across the entire 12-month mRS distribution (pooled OR for favourable shift 3.57; 95% CI: 1.42–8.93; p <0.01) [21]. Cumulative mortality at 12 months was similar in both groups (18% each). Among survivors, 6% of patients in the cerebrolysin group compared with 19% in the control group required institutional care (unadjusted OR 0.26; 95% CI: 0.07–0.99; NNT 8). In multivariate analysis, treatment with cerebrolysin (alongside mTICI 3 and CTA-CS 3) was a significant predictor of functional independence at 12 months (OR 3.5, 95% CI: 1.4–8.6, p <0.05).

A comparison of the four studies discussed suggests a significant beneficial effect of cerebrolysin on prognosis and functional independence by day 90, as well as on reducing the risk of secondary haemorrhage (Fig. 3). The clinical significance of these findings is potentially high (improved

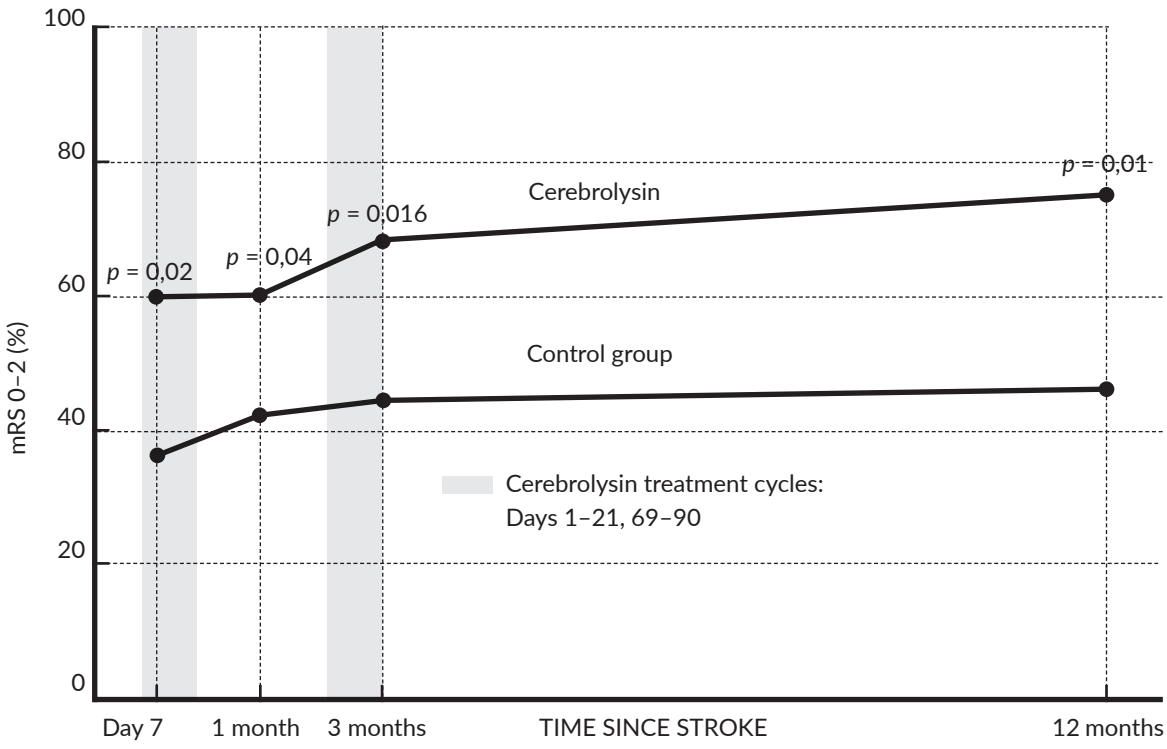
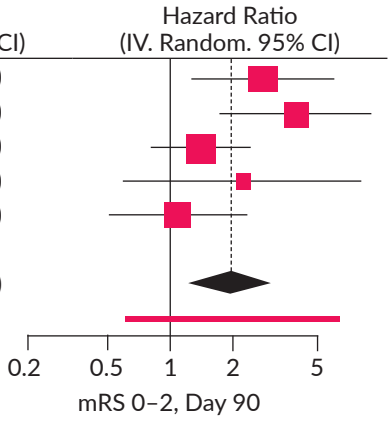


Figure 2. Comparison of the 12-month course of stroke in the cerebrolysin-treated group and the control group. mRS – modified Rankin Scale

A.

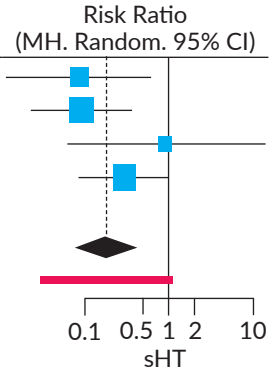
Study	logHR	SE	Weight	Hazard Ratio (IV. Random. 95% CI)
Staszewski et al. 2025	0.9953	0.4148	20.1%	2.71 (1.20; 6.10)
ElBassiouny et al. 2025	1.3695	0.4280	19.3%	3.93 (1.70; 9.10)
Khasanova et al. 2023	0.3240	0.2856	28.9%	1.38 (0.79; 2.42)
Poljakovic et al. 2021	0.7882	0.6801	10.1%	2.20 (0.58; 8.34)
Lang et al. 2013	0.0699	0.3893	21.6%	1.07 (0.50; 2.30)
Total (95% CI):			**100%**	**1.92 (1.19; 3.10)**
Prediction interval				**(0.58; 6.32)**



Heterogeneity: $Tau^2 \approx 0.1234$; $Chi^2 = 7.01$. df = 4 (P = 0.1356); $I^2 = 42.9\%$
Test for overall effect: Z = 2.68 (P ≈ 0.0074)

B.

Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio (MH. Random. 95% CI)
Staszewski et al. 2025	1	50	12	50	17.4%	0.08 (0.01; 0.62)
ElBassiouny et al. 2025	2	51	22	51	32.1%	0.09 (0.02; 0.37)
Poljakovic et al. 2021	1	23	1	21	10.0%	0.91 (0.06; 13.69)
Khasanova et al. 2023	3	117	18	201	40.5%	0.29 (0.09; 0.95)
Total (95% CI):		**241**		**323**	**100%**	**0.18 (0.07; 0.43)**
Prediction interval						**(0.03; 1.12)**



Heterogeneity: $Tau^2 \approx 0.1275$; $Chi^2 = 3.53$. df = 3 (P = 0.3173); $I^2 = 14.9\%$
Test for overall effect: Z ≈ −3.81 (P ≈ 0.0001)

Figure 3. Summary of studies evaluating cerebrolysin as an adjunct to reperfusion therapy in acute ischaemic stroke. **A.** Effect on functional outcome (mRS 0–2) at 90 days. **B.** Effect on symptomatic secondary transformation (sHT) at 24 hours. mRS – modified Rankin Scale, sHT – symptomatic secondary transformation

functional outcomes and safety of reperfusion following MT); however, interpretation is limited by the single-centre, non-randomised study design, and the results should therefore be regarded as preliminary and requiring confirmation in multicentre randomised trials.

Therapy complementing routine care in AIS

C-REGS2 (Cerebrolysin REGistry Study in Stroke 2) was a prospective, open-label, controlled trial evaluating the efficacy of cerebrolysin treatment in routine clinical practice compared with standard therapy; it was conducted in 16 countries between 2018 and 2024 in accordance with the GRACE guidelines [22]. Patients with AIS and moderate neurological deficit (NIHSS 8–15) were included in the study. A total of 1,769 patients were analysed (1,021 in the treatment group vs 748 in the control group). The median NIHSS score was 10; the cerebrolysin treatment regimen was individualised and most commonly involved a dose of 30 ml administered over 10 days. The effect size was reported as the generalised Mann–Whitney measure (MW), interpreted probabilistically as the likelihood of a better outcome in the active treatment group compared with the control group, where MW >0.50 indicates a treatment advantage. In the assessment of the primary endpoint (ordinal mRS analysis at 90 days), cerebrolysin proved significantly more effective than standard therapy (MW 0.6157; 95% CI: 0.59–0.64; p <0.0001; OR 2.03, NNT 8.6). The beneficial effect was also maintained in subgroup analyses (e.g. regardless of prior thrombolysis, which was received by only a small proportion of patients, approximately 20%). The superiority of cerebrolysin was also evident in secondary endpoints (mRS at day 21, NIHSS at days 21 and 90), with a moderate increase in the proportion of very good functional outcomes (mRS 0–1, OR 2.74; 95% CI: 2.12–3.60; p <0.0001) and functional independence (mRS 0–2; OR 2.88; 95% CI: 2.28–3.68; p <0.0001). Better results were also observed on the MoCA scale (MW 0.55; 95% CI: 0.53–0.58; p <0.0001), especially in patients with baseline cognitive deficits. No differences in safety were observed between the groups.

Acute spinal ischaemia and retinal ischaemia

Acute spinal cord ischaemia (Beck's syndrome) and retinal embolism, caused by occlusion of the anterior spinal artery and the central retinal artery respectively, are classified within the spectrum of ischaemic stroke of the CNS. They usually have a poor long-term prognosis, with persistent, significant long-term disability (including bilateral paresis or paralysis of the limbs below the level

of injury, loss of pain and temperature sensation, and autonomic dysfunction affecting the bladder or bowels) or monocular blindness. This report describes the case of a 78-year-old patient treated conservatively (anticoagulants, steroid therapy, intensive neurological rehabilitation) for spinal cord ischaemia, in whom clinical and radiological improvement was observed following administration of cerebrolysin (in two 10-day cycles). In this case, the favourable outcome following the use of cerebrolysin may have resulted primarily from stabilisation of the blood–spinal cord barrier, as well as potential neuroprotective and anti-oedema effects, which may have limited secondary spinal cord damage and promoted clinical improvement [23]. A similar beneficial effect has also been described in patients with retinal stroke, likely related to its effect on the blood–retinal barrier [24]. These findings require confirmation in further studies.

Intensive care and neurological care

Traumatic brain injury

In the field of intensive neurological care, the available evidence regarding cerebrolysin is also encouraging. The most frequently analysed aspect has been the effect of cerebrolysin on the course of TBI. Studies have included patients in varying neurological conditions and at different time points following TBI. Various doses of the drug (10–50 ml/day) and durations of therapy (5–30 days) have also been used. Most studies reported a favourable safety profile and a moderate, population-dependent trend toward potential benefits of cerebrolysin treatment in improving cognitive function and independence.

The CAPTAIN project comprised a prospective analysis of two randomised, double-blind, placebo-controlled phase IIIb/IV trials, which enrolled 185 patients with moderate or severe TBI (Glasgow Coma Scale, GCS 6–12) who received cerebrolysin in three cycles (50 ml/day for 10 days, followed by two cycles of 10 ml/day for 10 days) as an adjunct to standard care. Given the clinical complexity of TBI sequelae, including motor and cognitive deterioration (impairments in communication, processing speed, working memory, and mood), the primary multidimensional endpoint comprising 13 functional and neuropsychological measures was analysed using the Wei–Lachin method (a test for the global comparison of multiple correlated variables), with effect size expressed as a generalised MW measure for the composite outcome (MWcombined).

CAPTAIN I enrolled 46 patients (including 22 in the cerebrolysin group). In the analysis of individual scales, advantages were observed, among others, in the Stroop test and the Colour Connect the Dots Test Part 1/2 (Table 1) [25]. In the analysis of the primary endpoint in the ITT population, the result was borderline (p <0.1; MW = 0.63; 95% CI: 0.48–0.77; OR = 2.1), whereas in the PP analysis, patients treated with cerebrolysin showed significant improvement (p = 0.02; MW = 0.69; 95% CI: 0.53–0.85; OR = 3.2), with a safety profile comparable to that of placebo.

The CAPTAIN II trial enrolled 142 patients (mean age 47.4 years; mean GCS on admission 10.4) [26]. In the analysis of the primary endpoint in both the ITT and PP populations, a significant effect in favour of cerebrolysin was demonstrated at day 90 (MW = 0.59; 95% CI: 0.52–0.66; p = 0.01; MW = 0.602; 95% CI: 0.53–0.68; p <0.01; n = 74/55), with an advantage in favour of cerebrolysin on all 13 individual scales. Survival in patients treated with cerebrolysin did not differ from that in the control group. Subgroup analyses revealed a statistically significant reduction in anxiety levels in patients with moderate or severe post-traumatic disability, with a large effect size (standardised *mean difference*, SMD = 0.73) in the cerebrolysin-treated group [27].

A prospective meta-analysis of the CAPTAIN series (total of 185 patients; mean GCS 10.3; age 45.3 years) confirmed the beneficial effect of cerebrolysin on the global endpoint, which was significant at day 30 (MWcombined = 0.60; 95% CI: 0.52–0.66; p = 0.02; SMD = 0.31; OR = 1.69) and at day 90 (MWcombined = 0.60; 95% CI: 0.52–0.68; p = 0.015; SMD = 0.34; OR = 1.77), with good consistency between studies (I^2 = 0 in pooled analyses) and comparable safety [28].

A broader perspective is provided by a meta-analysis recently published by Polish authors, comprising 10 studies (n = 8,749) with varying treatment regimens (10–50 ml/day IV), treatment durations of 5–30 days, and treatment initiation ranging from 24 hours to over 20 months after injury; three of the studies were blinded [29]. The endpoints were the GCS, GOS (Glasgow Outcome Scale), mortality, and length of hospital stay. The results showed a significant improvement in GOS in favour of cerebrolysin (mean difference, MD: 0.42; 95% CI: 0.262–0.581; p <0.001, with significant heterogeneity between groups (I^2 = 70.55). A less consistent signal for improvement was observed on the GCS (MD 1.34; 95% CI: −0.258 to 2.945, with very high heterogeneity (I^2 = 94.20). No effect was found on length of hospital stay (MD −1.255 days; 95% CI: −6.422 to 3.913; p = 0.634; I^2 = 85.14) or on mortality. The meta-analysis suggested a potentially beneficial effect of treatment on clinical or functional outcomes as measured by the GOS (and probably also the GCS), but also highlighted limitations arising from heterogeneity, varying dosing regimens, and the lack of large RCTs, underscoring the need for further research to determine the optimal treatment protocol.

The largest retrospective cohort study to date (2015), involving 6,151 patients, demonstrated an improvement in the level of consciousness and functional status in the cerebrolysin group (as assessed by the GOS and mRS cores, respectively) compared with the control group [30]. In another retrospective study (2017), involving 129 patients with severe TBI, a beneficial effect of treatment with 10 ml/day for 30 days on functional status improvement at 3 and 6 months was observed [31]. Similarly, a meta-analysis of 8 studies conducted prior to 2018, with varying methodological quality, demonstrated that patients treated with cerebrolysin (n = 112) achieved a favourable outcome on the GOS more frequently than controls (OR 3.01; 95% CI: 1.7–5.1; p = 0.003) and that the likelihood of improved cognitive function was significantly higher in this group (OR 3.4; 95% CI: 1.8–5.2; p <0.001) [32].

Table 1. Summary of the results of the CAPTAIN I and II trials in traumatic brain injury (TBI) [25–28]

Study/ population	Intervention	Primary endpoint	Primary outcomes	Selected secondary outcomes	Safety analysis
CAPTAIN I RCT, DB, placebo; moderate/ severe TBI; GCS 6–12; *N* = 46 (active/ control group: 22/24)	Cerebrolysin 50 ml/day (10 days), then 10 ml/day (days 31–40 and 61–70) vs placebo; and standard medical care	Multidimensional composite endpoint of functional and neuropsychological scales (Wei–Lachin test; MWcombined) at days 10, 30 and 90	**IITT:** *p* <0.1; MW = 0.63 (95% CI: 0.48–0.77); SMD = 0.45; OR = 2.1 **PP:** *p* = 0.0240; MW = 0.69 (0.53–0.85); SMD = 0.69; OR = 3.2	Stroop Word/Dots *p* = 0.0415; MW = 0.6816; Colour Trails 1 *p* = 0.0223; MW = 0.72; Colour Trails 2 p = 0.0170; MW = 0.73	Comparable to placebo
CAPTAIN II RCT, DB, placebo; moderate/ severe TBI; *N* = 139 in analysis (80/59); age 47.4; GCS 10.4; BPRS 2.6	As above	As above	Day 90: MW = 0.59 (95% CI: 0.52–0.66); *p* = 0.0119	PP: Day 90: MW = 0.6026; p = 0.0058. Digit Symbol *p* = 0.0068; Stroop Word/Dots *p* = 0.0009; Digit Span Fwd *p* = 0.0164; Bwd *p* = 0.0014; Colour Trails 1 *p* = 0.008; HADS-D *p* = 0.004	Comparable to placebo
Pooled analysis *N* = 185; age 45.3; GCS 10.3; BPRS 2.8	As above	As above	Day 30: MW = 0.60; *p* = 0.0156; SMD = 0.31; OR = 1.69; Day 90: MW = 0.60; *p* = 0.0146; SMD = 0.34; OR = 1.77	PP: Day 90 (summary report) Wei–Lachin: MW = 0.6272; p = 0.0039; I^2 = 0	Cerebrolysin vs placebo: deaths 3.9% vs 8.4% SAEs 7.8% vs 18.1%

RCT – a randomised clinical trial; DB – double-blind; TBI – traumatic brain injury; GCS – the Glasgow Coma Scale; BPRS – Brief Psychiatric Rating Scale; ITT– intention-to-treat analysis; PP – per-protocol analysis; Wei–Lachin test – global test for multiple correlated endpoints; MW – Mann–Whitney effect; MWcombined – generalisation for a composite endpoint (Wei–Lachin); CI – confidence interval; SMD – standardised mean difference; OR – odds ratio; Digit Symbol – Digit Symbol Coding – symbol/ digit coding test; measure of processing speed; Digit Span Fwd/Bwd – forward/backward digit repetition (attention and working memory); HADS-D – Hospital Anxiety and Depression Scale; SAE – serious adverse events; I^2 – heterogeneity statistic in meta-analysis

Subarachnoid haemorrhage

In the only pilot randomised, double-blind, placebo-controlled trial published to date (2020) in patients with SAH from an aneurysm, the safety and feasibility of administering 30 ml/day of cerebrolysin intravenously for 14 days (initiated within ≤96 hours of onset) were assessed in comparison with placebo; 50 patients were enrolled in the study (25 vs 25) [33]. The treatment was logistically feasible (high completeness of dosing and follow-up) and was associated with a safety profile similar to that of placebo. However, no advantage was demonstrated in the primary functional endpoint at 6 months: the proportion of good functional outcomes (defined as GOSE 5–8) was 76% in the cerebrolysin group versus 68% in the placebo group (OR 1.49; 95% CI: 0.43–5.17). In secondary analyses (e.g. mRS), no significant differences were found between the groups. Given the high incidence of secondary ischaemia following SAH and the limited options for preventing vasospasm, further studies are warranted to determine the efficacy of cerebroprotective therapies in this high-risk population.

Discussion

The widespread adoption of intravenous thrombolysis and MT has substantially improved the prognosis in AIS, but has also highlighted the limitations of an approach focused solely on achieving recanalisation. Even with a high proportion of technically successful procedures, some patients remain dependent, suggesting that outcomes are also determined by processes occurring in the microcirculation and at the interface between the neurovascular unit and the blood–brain barrier. Persistent endothelial dysfunction, perfusion disturbances, vascular oedema and activation of the inflammatory response may sustain oxidative stress, adversely affect the metabolic penumbra and exacerbate secondary damage to peri-infarct tissue [34].

Cerebrolysin exerts neuroprotective and neurorestorative effects in ischaemic stroke and following TBI by inhibiting key components of the ischaemic and pro-inflammatory cascade, including glutamate-induced excitotoxicity and oxidative stress. As a result, it reduces DNA and protein damage, as well as cell necrosis and apoptosis. At the same time, it can support various brain

Table 2. Taxonomy of drugs with potential neuroprotective effects and their mechanisms of action in ischaemic stroke

Physiological targets	Mechanism	Examples from studies on cerebrolysin
"*Bridging*" neuroprotection with reperfusion therapy	Slowing the progression of the infarct in the pre- and early post-reperfusion phases. Maintenance of neuronal metabolism by increasing resistance to hypoxia.	1) CEREHETIS study: concurrent administration with an r-tPA infusion prior to reperfusion improved early neurological status [15]. 2) Rat model of transient middle cerebral artery occlusion: administration of cerebrolysin 3 hours after ischaemia reduced infarct volume by limiting the metabolic penumbra (activation of the CREB/PGC-1α pathway and inhibition of free-radical formation prevented lactate accumulation and lactic acidosis) [2].
BBB stabilisers	Improvement in BBB integrity before and after reperfusion.	1) CEREHETIS study: improvement in BBB function demonstrated on neuroimaging [15]. 2) Reduction in the risk of secondary haemorrhage with cerebrolysin demonstrated in various phase studies [15, 18]. 3) Preclinical study: improvement in BBB function following thrombolytic treatment with cerebrolysin via improved function of endothelial tight junctions and reduced pro-inflammatory and pro-coagulant activity [18].
Stabilisation of microcirculation	Protection of the integrity of arteriolar and capillary endothelium, prevention of the no-reflow phenomenon following reperfusion.	A randomised, double-blind, placebo-controlled trial in 46 patients with acute ischaemic stroke demonstrated a significant reduction in the pulsatility index post-stroke, suggesting an improvement in cerebral blood flow dynamics within the microcirculatory bed following cerebrolysin treatment [34]
Early neuroprotection and prevention of reperfusion injury	Slowing of pathological inflammatory and oxidative processes occurring immediately after reperfusion.	Preclinical (*in vitro*) study: cerebrolysin reduced neuronal death in models mimicking ischaemia, including glutamate toxicity, iodoacetate-induced metabolic inhibition, and ionomycin-induced calcium homeostasis deregulation [31]
Anti-oedema effect	Reduction in the risk of cerebral oedema and secondary herniation.	Studies by Woo et al. and Zhang et al. in patients with subarachnoid haemorrhage due to aneurysm or traumatic brain injury demonstrated a significant reduction in pro-inflammatory markers (IL-1β, IL-6, TNF-α and aquaporin-4) associated with vasculogenic oedema, suggesting that cerebrolysin may mitigate the harmful effects of cerebral oedema and thereby reduce secondary damage associated with increased intracranial pressure and herniation [32].
Delayed neuroprotection, induction of neuroplasticity	Reduction of the consequences of reperfusion injury, apoptosis and mitochondrial dysfunction. Promotion of synaptogenesis and neuroplasticity, improved neurovascular unit function.	1) Multiple preclinical studies have shown that cerebrolysin exerts neurotrophic and neuroprotective effects (by protecting against glutamate-induced excitotoxicity, promoting the proliferation of neuronal progenitor cells, which enhances the differentiation of neurons and oligodendrocytes through the upregulation of Shh signalling and its receptors, modulation of endogenous neurotrophin levels), which promotes improved recovery after stroke when administered within <48 hours in middle cerebral artery ischaemia models [31,33]. 2) The CARS study and meta-analyses have shown that cerebrolysin administered once daily for 21 days, starting 24–72 hours after stroke onset, has a beneficial effect on functional ability and overall fitness in patients in the early phase of post-stroke rehabilitation [26, 28].
BBB – blood–brain barrier; r-tPA – recombinant tissue plasminogen activator		

repair processes by promoting neuro-, synapto- and axonogenesis, aiding the restoration of neuronal function. These properties of cerebrolysin – primarily described in preclinical models – align well with the newly proposed taxonomy for neuroprotective drugs (Tab. 2).

Clinical studies have also demonstrated that cerebrolysin exhibits multimodal effects, influencing several elements of the ischaemia-reperfusion injury cascade and supporting neuronal plasticity processes in the subacute phase. The data from reperfusion studies presented in this paper suggest, above all, the potential to reduce haemorrhagic complications while maintaining a good safety profile. In CEREHETIS, early administration of cerebrolysin following tPA was associated with a significant reduction in sHT and a trend toward reduced HT, and in the subgroup with imaging assessment, improvements in BBB permeability parameters and smaller infarct volumes were noted [15]. In CERE-LYSE, despite no improvement in mRS at 90 days (primary endpoint), faster neurological improvement on the NIHSS at subsequent time points was observed, which may support the hypothesis of an early biological effect of the drug [17].

Although the evidence for the efficacy of cerebrolysin following stroke is derived predominantly from observational studies, several independent cohorts have demonstrated a significant reduction in haemorrhagic compli-

cations and a beneficial effect on functional outcomes. A pilot study by Poljakovic et al. suggested a lower risk of HT and a favourable trend at 12 months, although the sample size was small and included patients with suboptimal recanalisation outcomes [18]. The study by ElBassiouny et al. demonstrated a higher proportion of functionally independent patients (mRS 0–2) at 90 days and a significant reduction in HT/sHT compared with the historical control. These findings should be interpreted with caution given potential bias related to differences in care and patient selection [14].

Of particular interest are the results of the CEREBROLYSIN-WIM study, which selected patients with a small infarct core, adequate collateral circulation, and successful recanalisation. Treatment in two cycles was associated with a higher proportion of functional independence (mRS 0–2) at 90 days and a favourable shift in the mRS distribution, persisting up to 12 months after adjustment for key predictors of outcome following EVT [20, 21].

Registers based on real-world evidence provide an important complement to these studies. In the C-REGS2 registry, cerebrolysin used alongside standard therapy in moderate AIS was associated with a favourable shift in the mRS distribution at 90 days toward functional improvement and better cognitive outcomes, with no differences in safety compared with standard care [22].

A common theme across these studies is a reduced risk of haemorrhagic complications and improved functional outcomes, particularly in patients with extensive stroke at baseline. This is likely related to improved BBB function, which regulates many processes crucial for brain homeostasis, including microcirculation and the complex functions of the neurovascular unit. This may explain the beneficial effects of cerebrolysin in other CNS disorders involving primary (TBI, SAH) or secondary BBB damage (neurodegenerative diseases), and may also indicate efficacy in blood–spinal cord and blood–retinal barrier injury. However, the action of cerebrolysin in AIS and TBI extends beyond its beneficial effect on the BBB, as clinical improvement has also been observed in patients without hypertension and during long-term clinical follow-up (e.g. 12 months), where the impact of acute BBB damage is already minimal [21].

Furthermore, the neurotrophic effects of cerebrolysin and its role in improving brain plasticity have been well documented, including in post-stroke aphasia rehabilitation, as demonstrated in the recently published ESCAS study [7]. However, the effect of cerebrolysin on the course of the acute phase of haemorrhagic stroke and SAH remains insufficiently understood, although studies are already underway in these indications (e.g. the Polish CLINCH study) [35].

In TBI, the pathomechanisms of secondary damage (excitotoxicity, Ca^{2+}influx, mitochondrial dysfunction, oxidative stress, neuroinflammation, and BBB damage with microcirculatory disturbances) partially overlap with those observed in AIS, providing a biological rationale for cerebroprotective strategies. The CAPTAIN programme and several meta-analyses have demonstrated a significant effect in favour of cerebrolysin on functional outcomes at day 90, with a safety profile comparable to that of placebo, although these findings are limited by considerable heterogeneity in populations and dosing regimens [25–28]. From the perspective of ICU practice, it is particularly important that studies with higher methodological rigour did not show any signal of impaired safety, which is a prerequisite for conducting further pragmatic trials in patients with severe TBI, who are often burdened by systemic complications.

The most significant limitation of the current evidence remains the predominance of open-label and observational studies in the context of MT, as well as the frequent use of historical controls, which increases the risk of residual confounding (including differences in eligibility for EVT, time to reperfusion, post-reperfusion care standards, complication prevention, and the intensity and quality of rehabilitation). Similarly, in thrombolytic trials, the lack of a consistent effect on the mRS at 90 days may reflect insufficient power, differences in time windows and endpoint selection, and population heterogeneity. Consequently, current data on AIS should be regarded as promising yet still insufficient to draw definitive conclusions regarding efficacy.

From a practical standpoint, it seems most reasonable to focus future multicentre RCTs on patients before or shortly after reperfusion, in whom the risk of vascular complications and reperfusion injury is highest (e.g. low ASPECTS, increased risk of HT, significant neurological deficit, absence of collateral circulation). Research designs should include standardised high-quality rehabilitation, multidimensional endpoints (cognitive function, mood, quality of life, and imaging markers, e.g. BBB permeability) and longer follow-up (≥12 months). Only such an approach will allow a reliable determination of whether combining reperfusion with cerebroprotection translates into sustained improvements in prognosis and reductions in disability.

However, from a clinical perspective, while exercising caution in interpretation, data from recent years support considering cerebrolysin as a personalised adjunctive therapy in patients with moderate or severe stroke, particularly in early post-stroke rehabilitation and in scenarios with an increased risk of reperfusion injury, as well as in patients with moderate or severe TBI. The consistency of results across several cohorts, the favourable safety profile, and emerging recommendations from neurorehabilitation scientific societies suggest that further research is warranted, with key challenges including the identification of the population most likely to benefit, and the optimisation of the timing of initiation, dose, and duration of therapy.

Conclusions

- Cerebrolysin appears to be a promising adjunct to reperfusion therapy in ischaemic stroke, with the potential to mitigate reperfusion injury and improve both early neurological recovery and long-term functional outcomes. Further studies are needed to fully determine the role of cerebrolysin in the standard treatment protocol for acute ischaemic stroke, with particular emphasis on optimal dosing, timing of treatment initiation, and identification of patient subgroups most likely to benefit from this treatment.

- In neurointensive care for patients following TBI, the feasibility and safety of cerebrolysin have been demonstrated, whereas evidence regarding efficacy with regard to hard endpoints remains limited. Additional multicentre RCTs designed to reflect real-world ICU settings are needed.

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