Review Article

The possible role of Cerebrolysin in prevention of hemorrhagic transformation after acute ischemic stroke

Abstract

Hemorrhagic transformation (HT) is one of the most feared challenges in management of acute ischemic stroke (AIS) that affects both the treatment plan and the clinical prognosis. the risk for HT is not monocausal and it is almost impossible to define a single target for prevention of HT. Thus, we consider that it is worthwhile to investigate and review the possible role of Cerebrolysin as a multimodal, pleiotropic neuroprotective and neurotrophic agent in the prevention of HT. Cerebrolysin has been the subject of multiple animal and in vitro studies, the majority of which have yielded encouraging results in terms of pleiotropic and multimodal neuroprotective and neurorestorative activity.

Cerebrolysin has been investigated in multiple clinical trials. Over the past 10 years, among the studies investigating the effect of Cerebrolysin in acute ischemic stroke, 5 studies have reported the extent of hemorrhagic transformation as a part of the outcome. Lower HT rates were reported for Cerebrolysin treated patients versus controls across all studies. Thus, the reported results are consitent across all studies, however, the differences did not reach the level of statistical significance except for one study.

The interpretation of these results is limited by are several considerations. Despite these limitations, in the light of the clearly positive clinical results of Cerebrolysin on functional recovery and its favorable safety profile, a dose of 30 ml/day for 10-21 days may be given to reduce the risk of HT. This observation should be confirmed by further large randomized controlled clinical trials with standardization of the HT definition.

Key words: Neuroprotection, Cerebrolysin, Hemorrhagic transformation, Acute ischemic stroke.

Introduction

Hemorrhagic transformation (HT) is one of the most feared challenges in management of acute ischemic stroke (AIS) that affects both the treatment plan and the clinical prognosis. HT pathophysiology is still not fully understood. Cerebral ischemia initiates a cascade of cellular, metabolic, and inflammatory events that result in disruption of the blood-brain barrier (BBB) and the impairment of the autoregulatory capacity of the cerebral blood vessels, predisposing them to blood extravasation on reperfusion of the ischemic tissue. [1]

Various clinical, laboratory and radiological factors and scores have been proposed to be associated with increased risk of HT, such as old age, hypertension, atrial fibrillation, cardioembolic stroke, high NIHSS, hyperglycemia, low lipid profile, elevated globulin level, albuminuria, lower platelet count, delayed reperfusion, intravenous tissue plasminogen activator recombinant (IV rt-PA), concurrent use of antithrombotic agents or anticoagulants, fibrinolytic agents, and endovascular treatment. [2-4] Different radiological indices of early ischemic changes, large ischemic lesion volume, severe blood flow restriction, blood-brain barrier disruption, poor collaterals and high blood flow velocities have been reported to be associated with higher risk of HT. [2,5]

Consequently, the risk for HT is not monocausal and it is almost impossible to define a single target for prevention of HT. Thus, we consider that it is worthwhile to investigate and review the possible role of Cerebrolysin as a multimodal, pleiotropic neuroprotective and neurotrophic agent in the prevention of HT.

The concepts of cytoprotection and neurorecovery have been investigated in multiple preclinical and clinical studies in acute or chronic stroke in the past decades. Despite promising results with different agents, suggesting that they can ameliorate the evolution of the penumbra to core infarction, reduce reperfusion injury, improve tissue reperfusion, brain plasticity, or neurogenesis, none of these strategies have been recommended in humans so far. [6,7] A number of reasons could explain this outcome e.g., lack of persistent recanalization or reperfusion, too late intervention, suboptimal dosage, single mechanism of action targeting only one pathophysiological aspect of the ischemic cascade, or one type of cells in neurovascular unit

(NVU), mismatch between animals and humans, and/or unrobust methodological approaches that resulted in inconsistent evidence. [6,8,9] Therefore, the focus of modern stroke treatment should be shifted from neuroprotection to a neurovascular protection approach because elements of NVU show differential vulnerability evolving over differing time scales and their roles are crucial in blood-brain-barrier (BBB) regulation, cell preservation, inflammatory immune response during or after AIS. [6,10,11]

Cerebrolysin is a biotechnological product which consists of low molecular-weight neuropeptides and free amino acids with pharmacodynamic properties similar to those of naturally occurring neurotrophic factors. [12] It displays multifactorial cytoprotective properties, improves cellular survival, inhibits glutamate excitotoxicity, free radical formation, and proinflammatory mediators (e.g., TNF-a, IL-1b, IL-6, and NF-kB). Furthermore, it mimics the action of endogenous neurotrophic factors in brain protection and recovery. [6, 13-15]

Aim of the work

We aimed to investigate and review the possible role of Cerebrolysin as a neuroprotective agent in the prevention of HT.

Methodology and search strategy

We conducted a systematic review of the literature using a database search of MEDLINE (Bethesda, MD), PubMed, Scopus, and Web of Science (Clarivate Analytics, PA) to identify studies addressing 1) AIS, 2) HT and 3) Cerebrolysin. The search covered the past 10 years from January 2012 to October 2022 using the following key terms: 1) ‘‘Cerebrolysin’’ AND one of the following: 2) ‘‘Hemorrhagic transformation’’or 3): ‘‘Acute ischemic stroke’’.

We expanded our retrieval to also include clinical trials, cohort studies, multicenter studies, comparative studies, and case-control studies.

Results

Animal & In-Vitro Evidence

Cerebrolysin has been the subject of multiple animal and in vitro studies, the majority of which have yielded encouraging results in terms of pleiotropic and multimodal neuroprotective and neurorestorative activity.

A recent in vitro study demonstrated that Cerebrolysin protects the BBB and has a therapeutic effect on r-tPA and fibrin-impaired cerebral endothelial cell permeability by reducing proinflammatory and procoagulation proteins and by elevating tight junction proteins, therefore reducing hemorrhagic transformation, a major safety concern especially for patients at the end of the r-tPA time-window. [16]

Human Studies

Cerebrolysin has been the subject of multiple clinical trials. Various studies have shown that the intravenous administration of Cerebrolysin can improve the neurological outcomes of patients who have had an acute ischemic stroke, as well as its beneficial effects in combination with other pharmaceuticals as well as with physical, occupational or speech therapy. [10]

Over the past 10 years, among the studies investigating the effect of Cerebrolysin in acute ischemic stroke, 5 studies have reported the extent of hemorrhagic transformation as a part of the outcome (table 1). [1,17-20]

In the most recent published pilot trial, 44 severe stroke patients (NIHSS>8) were randomized to receive Cerebrolysin (30 ml/day for 14–21 days, n = 23) or standard therapy (n=21) following futile reperfusion therapy (rtPA and/or MT). There was no statistically significant difference in the distribution of clinical outcomes between groups at 90 days, most probably due to the relatively low number of patients. There was, however, a clear trend for a more favorable outcome (mRS 0-3) at month 12 in the Cerebrolysin group compared with controls (70% vs. 48% of the subjects; $p = 0.1$) and a statistically significant reduction of hemorrhagic transformation rates in patients receiving Cerebrolysin (13% vs. 38%, $p < 0.05$). [1]

Chang et al. (2021) focused on the combination of Cerebrolysin (30 ml/day for 21 days) with standardized rehabilitation therapy. The results showed that in individuals with severe motor impairment caused by acute ischemic stroke, conventional rehabilitation therapy combined with

Cerebrolysin results in better motor recovery compared to conventional rehabilitation therapy alone. HT was reported in 2 % of the placebo group with no reported HT in the Cerebrolysin group. [17]

An earlier study by Chang et al. (2016), which for the first-time evaluated neuroimaging of motor network plasticity when administering Cerebrolysin (30 ml/day for 21 days), revealed a positive influence of Cerebrolysin on cerebral tissue related to motor function. However, again due to the low number of patietns in this study, no significant difference was found between the two groups. HT was reported in 2.8 % of the placebo group with no reported HT in the Cerebrolysin group. [18]

Xue et al. (2016) conducted a clinical trial to test and assess the efficacy and safety of DL-3-n-butylphthalide (NBP) and Cerebrolysin (30 ml/day, for 10 days), in minimizing neurological and behavioral impairment after acute ischemic stroke. The findings of this study suggested that a 10-day treatment with NBP or Cerebrolysin could be used safely and may have favorable benefits in patients with AIS, especially in mild cases. HT was equally reported in 5 % of the Cerebrolysin and the placebo groups. [19]

Lang et al. conducted another trial to see if combining alteplase (rt-PA) with Cerebrolysin (30 ml/day, for 10 days), was safe and effective in reducing impairment following an acute ischemic stroke. They concluded that the neurotrophic agent combined with rt-PA was safe for the treatment of AIS, although it did not improve outcome at 90 days. Despite being not accompanied with rehabilitation, compared to the placebo group, considerably more patients had a favorable response in neurological outcome measures during the 10-day therapy period with Cerebrolysin, indicating a significantly faster recovery for patients who received the Cerebrolysin in combination with r-TPA. HT was reported in 3.4 % of the placebo group and 1.6 % of the Cerebrolysin group. [20]

Discussion and Limitations

Lower HT rates were reported for Cerebrolysin treated patients versus controls across all studies. Thus, the reported results are consitent across all studies, however, the differences did not reach the level of statistical significance except for one study by Poljakovics (2021).

The interpretation of these results is limited by are several considerations. Firstly, the study design and the inclusion criteria varied considerably across these studies and some studies were clearly underpowered, thus limiting the chances to detect statistically significant differneces despite the observed descriptive superiority of Cerebrolysin in reducing HT. Moreover, most of the studies investigated the efficacy of Cerebrolysin on the basis of functional outcomes assessed by Modified Rankin Scale (mRS), National Institutes of Health Stroke Scale (NIHSS), Barthel Index (BI), Fugl–Meyer Assessment and Action Research Arm Test while HT was only reported as a safety parameter. Only Poljakovic et al (2021) used HT as a part of the secondary efficacy outcome measures. [1, 17-20]

Furthermore, the definition of HT among the 5 studies was not standardized. Poljakovic et al (2021), defined HT as either symptomatic intracerebral hematoma (sICH), or asymptomatic intracerebral hematoma (aICH) demonstrated by neuroimaging (native computed tomography of the brain) performed after 24 h and at 7th day after symptoms onset [1], while Lang et al (2013) defined it as an incidence of treatment-related, secondary intracerebral (parenchymal) bleedings. [20] The other three studies did not provide a definition of HT. [17-19]

Despite these limitations, in the light of the clearly positive clinical results of Cerebrolysin on functional recovery and its favorable safety profile, a dose of 30 ml/day for 10-21 days may be given to reduce the risk of HT. [1,12,15,17-25]

Recommendations

Our observations should be confirmed by a further larger randomized controlled clinical trial with standardization of the HT definition. The upcoming results of the recently published clinical trial protocol by Staszewski et al. (2022) which will investigate if a combination of cytoprotection with Cerebrolysin with reperfusion therapy may modulate stroke recovery with a view to describing the optimal treatment window (acute and post-acute phase of stroke) will certainly shed more light on the effectiveness of Cerebrolysin to reduce HT after reperfusion

therapy. Furthermore, the results of this pilot study will not only shed light on the potential efficacy of Cerebrolysin as an adjunct treatment for AIS but will be essential in designing further double-blind RCTs on Cerebrolysin and will provide supplemental evidence for ongoing larger-scale projects with other neuroprotection agents in both acute and post-acute stroke patients.

Declarations

The manuscript has not been previously published in whole or in part or submitted elsewhere for review.

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Table 1. Trials involving the effect of Cerebrolysin on acute ischemic stroke in the past 10 years (adopted and modified from Muresanu et al., 2022 [15]								
Article	Intervention	Case Numbers	Type	Methods	Primary Endpoint	Secondary Endpoint	Results	HT
Poljakovic et al. 2021	Group 1 was treated with intravenous Cerebrolysin in addition to standard care after recanalisation therapy, and control group received standard care after recanalisation therapy alone.	23 Cerebrolysin 21 control	prospective, open-label, controlled study	Cerebrolysin (30 ml i.v. during 60 min/day) for a minimum of 14 and maximum of 21 days, starting no later than 24 h after symptoms onset.	NIHSS baseline, 24 h, 7 d, mRS discharge, 3m, 12 m	rate of haemorrhagic transformation after recanalisation therapy	No difference could be detected between the two groups in the mRS scale though the Cerebrolysin group showed descriptive superiority over the control group.	Two (8.7%) patients in the Cerebrolysin groupand 7 (33%) patients in the control group had an asymptomatic intracerebral haemorrhage (aICH) This difference reached borderline statistical significance (p = 0.055).
Chang et al., 2021	Cerebrolysin + Standardized rehabilitation therapy	59-Cerebrolysin 51-Placebo	Combined data from the both phase IV prospective, multicenter, randomized, double-blind, placebo-controlled trials	Cerebrolysin (30 ml/day) or placebo with standardized rehabilitation therapy for 21-day treatment course	Fugl–Meyer Assessment	Motor Evoked Potential (MEP)	FMA-upper limb: T1–T2 significant improvement in Cerebrolysin group MEP T1: positive response Cerebrolysin 33.9%/placebo 27.5% MEP T2: increased both groups, Cerebrolysin 42.4%/placebo 35.3%	Cerebrolysin = 0 PLACEBO = 1 (2%)
Chang et al., 2016	Cerebrolysin	35-Cerebrolysin 35-Placebo	Prospective, multicenter, randomized, double-blind, placebo-controlled,	Cerebrolysin (30 mL/day)or placebo for 21 days	Fugl–Meyer Assessment	National Institutes of Health Stroke Scale (NIHSS)	no significant difference was found between the two groupsTotal FMA: 42 Cerebrolysin,	Cerebrolysin = 0 PLACEBO = 1 (2.8%)

			parallel-group study				42.2 placebo NIHSS: 8.4 Cerebrolysin, 7 placebos	
Xue et al., 2016	Cerebrolysin vs. DL-3-n-butylphthalide (NBP)	20-Cerebrolysin 20-Placebo 20-NBP	Randomized, double-blind trial	10-day intravenous administration of NBPm Cerebrolysin (30 mL/day) or placebo)	National Institutes of Health Stroke Scale (NIHSS) and Barthel Index (BI)		NIHSS day 21: lower scores for Cerebrolysin and NBP group BI day 21: higher scores for Cerebrolysin and NBP group	Cerebrolysin = 1 (5%) PLACEBO 1 (5%) NBP 0
Lang et al. 2013	Cerebrolysin + Alteplase	60-Cerebrolysin 59-Placebo	Placebo-controlled, double-blind trial	Cerebrolysin (30 mL/day) or placebo (1 h after thrombolytic treatment) starting within three-hours after onset of symptoms, given for 10 days	Modified Rankin Scale (mRS)	National Institutes of Health Stroke Scale (NIHSS), Glasgow Outcome Scale (GOS), Barthel Index (BI)	mRS day 90: no significant improvement in Cerebrolysin group vs. placebo NIHSS, GOS, BI: no significant improvement in Cerebrolysin group vs. placebo	Cerebrolysin = 1 (1.6%) PLACEBO 1 (3.4 %)