A novel pharmacological treatment concept for neuroprotection in severe traumatic brain injury – two case reports

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Abstract

Severe traumatic brain injury is a leading cause of death and disability worldwide, resulting in a significant individual and socioeconomic burden. We present two cases of severe traumatic brain injury with surprisingly encouraging outcomes. We attribute this to the additional combined administration of citicoline and cerebrolysin.

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Running head : A multimodal concept for neuroprotection in sTBI

Abstract

Background

Severe traumatic brain injury (sTBI) is a leading cause of death and disability worldwide, resulting in a significant individual and socioeconomic burden. In current guidelines recommendations for neuroprotective or neuoregenerative drugs are missing. On the basis of two cases, we present a combined treatment with Cerebrolysin and Citicoline. Both drugs are well proven experimentally and clinically in their own effectiveness, but clinical data of the combination has hardly been reported. Our experience sheds light on a promising approach that may improve neurological outcome after sTBI.

Case presentation

A 29y male motorcyclist suffers polytrauma in the context of a high-speed accident. In addition to severe bilateral chest trauma, he sustained fractures in both thighs and an sTBI. In addition to surgical and standard neurocritical care according to the evidence-based guidelines, he receives neuroprotective therapy with Cerebrolysin (50ml/d) and Citicoline (3g/d), continuously administered intravenously (IV) for 21 days. The second patient of this case report, a 30y male ski tourer is admitted also by HEMS, after a after a fall over 300 m in open terrain. In addition to the sTBI, he suffers fractures in the cervical spine, ribs, pelvis and lower extremities, as well as lung contusions and massive soft tissue trauma. After first aid in a peripheral hospital, he is also treated in our department and receives the same neuroprotective drugs, like all of our patients with sTBI. With regard to the severity of the injuries (Injury Severity Score [ISS]: 43/50, Revised Trauma Score [RTS: 5.0304, 2.7794]) and an unfavourable outcome probability (Hukkelhoven Score) of 93.1% and 82.6%, the outcome of both patients is surprisingly encouraging one year after the accident. They achieved a Glasgow Outcome Score of 6 and 5 and graded 2 and 4 on the modified Rankin Scale, respectively. Currently, both are able to take care of themselves in matters of daily life to a large extent.

Conclusions:

The administration of neuroprotective drugs may improve the regeneration of cell membranes, improve blood brain barrier integrity and reduce neuroinflammation leading to secondary damage to the injured brain. Our clinical experience and data suggest that the combined administration of Citicoline and Cerebrolysin may contribute to better recovery, without relevant side effects. However, validating these results by means of a controlled, prospective study is required.

Keywords

case series, severe TBI, multi-modal therapy, neuroprotection, Citicoline, Cerebrolysin, secondary brain damage

Background

Severe traumatic brain injury (sTBI) is a leading cause of death and disability, especially among young male adults in low- and middle-income countries, shifting to elderly patients in developed countries. This so called "hidden pandemic" affects more than 13 million patients annually in Europe and the US alone. sTBI causes the death of about $11.8/10^5$ people in Austria, which is comparable to data from other European countries. In survivors, sequelae of sTBI often bring life-changing consequences such as motor- and cognitive deficits, which lead to a life of dependency. Thus, sTBI represents not only a significant individual but also a socioeconomic burden worldwide. The mechanisms of injury and underlying physiological and cellular processes accompanying the primary and secondary brain injuries are complex and require multimodal treatment. Nevertheless, current guidelines, e.g. from the Brain Trauma Foundation (BTF), aim to provide evidence-based recommendations for the various manifestations of sTBI. Outcomes may be improved by adequate early

care on scene, in the emergency department (ED), and in the intensive care unit (ICU). In addition, sTBI should not be understood as purely acute or static, but as a complex, acute to chronic neurodegenerative disease. This suggests the existence of a longer therapeutic window of time for pharmacological intervention and questions whether sTBI-induced damage can only be treated within a few hours after the trauma. In reducing secondary damage, anti-oxidants, branched-chain amino acids, and ω-3 polyunsaturated fatty acids have shown promising pre-clinical results for altering TBI outcome. However, up to now pharmacological research has not yet identified a "gold standard" to prevent secondary brain damage. Although there are promising data from animal studies, only Citicoline or Cerebrolysin have led to some positive findings in retrospective and prospective "real life" clinical trials. There were hints for reduced mortality and better functional outcome, measured by enhanced Glasgow Outcome Score (GOSE) and modified Rankin Scale (mRS). However, these agents – whether administered orally or intravenously - have fallen short to produce significant improvements when administered as single drugs and are critically discussed in large, randomized prospective trials.

Case 1

A 29-year-old caucasian male collides as motorcyclist head-on with a car at about 65 mph. Helmet is busted when colliding with the frame of the car's windscreen. Status on arrival of emergency medical service (EMS) on scene, pattern of injuries as well as measures of emergency care are displayed in Table 1. Whole-body CT scan in the ED reveals punctiform cerebral haemorrhages (especially in the left temporal lobe), bilateral serial rib fractures, a left scapular fracture, prehospitally drained pneumothorax on the left, laceration and atelectasis of the left lower lobe, ventrocranial edge detachment on the11th and 12th thoracic vertebrae, wedge shaped compression fractures of the 1st and 4th lumbar vertebrae, and multiple fractures in both hip joints. After placement of a probe to measure the intracranial pressure (ICP) in the ED, patient is admitted to ICU with stable ventilation and haemodynamic parameters (norepinephrine 0.2 µg/kg/min). Citicoline (3g/day) is added to usual standard care. ICP increases repeatedly up to 19 mmHg during the first days, responding to deepening of analgosedation and osmotherapy. Laboratory findings and haemodynamic support in the first 24 hours are displayed in Table 3.

The further course is relatively stable with regard to the ICP and receding brain oedema; weaning from ventilation is initiated from day 10. Subsequently, the patient shows extreme vegetative imbalance, so that in addition to the established antisympathetic (carvedilol) and antipsychotic medication (quetiapine, tiapride, oxazepam), continuous administration of propofol has to be re-established repeatedly. Three weeks after the accident, magnetic resonance tomography (MRT) reveals signs of intracranial axonal injuries and microbleeds (Figure 1) seen as spotted susceptibility artifacts on the anterior temporal lobe and in the frontobasal region (left > right), in the basal ganglia on both sides, as well as in the left posterior border zone and in the white matter on both sides too, high frontal to occipital. In summary, this matches with multilocular small shear haemorrhages, left frontobasal and temporal contusion zones, compatible with a diffuse axonal trauma stage 1. On day 21, patient finally undergoes stabilization of both femoral necks with interlocking nails. A dilatative tracheostomy is performed, too. Somatosensory evoked potentials (SSEPs) on day 23 show missing central answer on the right-brain side, on the left a central answer can be derived with limited accessibility. During the following days, the patient appears stressed, shows repeated periods of restlessness with sweating and tremors and moves the extremities in completely uncontrolled, stretching manner. Electroencephalogram (EEG) on day 28 shows signs of general diffuse brain dysfunction (moderate to severe) and reduced reactivity to photogenic stimuli, but no typical epileptic potentials.

On day 31, more or less with very limited hope for recovery, a supportive therapy with Cerebrolysin is initiated – a novel therapeutic approach for us at that time. 10 days later, the patient starts to react targeted to verbal stimulation for the first time. Improvement is growing rapidly, and neurological examination before transfer to open ward on day 45 states: the patient is now awake and keeps eye contact, gaze tracking is easier to the right than to the left, the muscular tone is generally increased. No cooperation can be achieved while examining facial muscles, but he shows indicated movement when prompted with fingers and forearm. There is a tendency for stretching spasm of the left leg spontaneously but uncontrolled, but no active movement

of the lower extremities when requested.

One month later, at the time of discharge from hospital (day 73) the patient presents himself awake and mobile in the armchair. He clearly follows now simple prompts; questions can be adequately answered with a nod of the head. He shows signs of a tetraparesis, pronounced on the left and a grasping reflex on the right.

One year after the accident, and after a series of botulinum toxin treatments in the rehabilitation centre, the disabling spastic increase in muscular tone of the right leg has significantly regressed. The patient is safely mobile, using a three-wheeled bicycle. Further six months later, patient is mobile on his own by public transportation and regular bicycle, visiting friends and cafes.

GOSE/mRS at discharge: 4/4, one year after the accident: 5/3, and after 18 months: 6/2

Findings of the final MRT examination 18 months after the accident (Figure 2) shows gliotic cicatricial high parietal left as sequelae of the axonal trauma, and a small defect on the left temporal lobe in the area of the previously recognizable contusion. In total – a clear improvement, especially the frontal contusion zone on the left has receded.

Case 2

A 30-year-old sportsman falls from a great height (approx. 300 m, Figure 2) during a ski tour. Rescue is delayed due to missing cell-phone connection in this remote area, as well as to weather conditions. Helicopter emergency service (HEMS) arrives approximately two hours after the accident. Status on arrival of HEMS, pattern of injuries as well as emergency measures are displayed in Table 1. The patient is admitted at the nearest trauma centre (level II) four hours after the accident. CT scan reveals cerebral contusions, traumatic subarachnoid (SAH) and subdural haemorrhage (SDH), an unstable fracture of the 4th cervical vertebra with spinal cord injury, a pneumothorax with rib fractures and multiple fractures of the upper and lower extremities. An external fixator is placed on both lower extremities, followed by plating and screwing of the cervical spine and the left hip on the next day. In a postoperative CT scan, extensive brain oedema and a new ischemic zone in the area of the posterior circulation compressing of the 4th ventricle.

After being rejected by the nearest neurosurgical university hospital because of the obviously hopeless situation, the patient was transferred to our institution (for lab findings and hemodynamic support on admission see Table 3). A CT scan (Figure 2) on arrival shows oedematous swelling of both cerebellar hemispheres and the right occipital lobe with space-occupying effect in the posterior cranial fossa, and a persistent dislocation fracture of the 4^{th} cervical vertebra. An external ventricular drainage (EVD) was placed, followed by suboccipital decompressive craniotomy with dural expansion surgery on the next day, after interdisciplinary discussion of prognosis, supported by deducible SSEPs over both hemispheres. In addition to standard medical care (comprising "optimal handling", deep analgosedation, haemodynamic and respiratory optimization) the patient received Cerebrolysin and Citicoline. After prolonged weaning, characterized by vegetative disbalances and delayed recovery from analgosedation, EEG findings stated severe abnormal EEG curves with general slowing, no distinct focus, nor typical epileptic potentials. On day 33 after the trauma, the consulting neurologist states: Contact via blink of an eye possible, pat. can follow this request. During the examination evaluation of pain is possible. Pat. can keep eye contact only for a short time. The right corner of the mouth can be raised a little if requested. Tongue cannot be stuck out. Upper extremities (UE): left distal increased tone in the sense of spasticity, right rather flaccid. Lower extremities (LE): both legs immobilized, no examination possible.

After 50 more days in acute rehabilitation process in ICU including changing the EVD to a ventriculoperitoneal shunt, the patient was transferred to a specialized clinic for neurorehabilitation. At that time, the report of the neurologist reads as follows: Patient is awake, follows simple prompts, speech comprehension appears to be well preserved, simple linguistic utterances are possible. Mimic muscles appear bilaterally symmetrical. UE can be lifted and held on the same side against gravity on request, degree of strength 3-4, increase in tone right > left. LE: Tone spastically increased on both sides, right > left. Left leg painful when

moving the hip, right leg can be lifted on request.

One year after the accident, the patient is finally discharged from the rehabilitation centre, able to move by himself with a rollator, and can independently manage the transfer from bed to wheelchair and vice versa. He shows pronounced deficits in short-term memory, long-term memory is well preserved. He is usually in a euthymic mood and looks forward to further development steps.

GOSE/mRS at discharge from hospital: 3/4, one year after the accident: 5/4, and after 18 months: 6/4

Treatment

Immediately after admission to the ICU of our level 1 trauma centre (General Hospital of Wiener Neustadt, Austria), all patients with sTBI (Glasgow Coma Score [GCS] 3-8, intubated on scene), who are not deemed hopeless in terms of survival, receive Cerebrolysin (50 ml/day) and Citicoline (3g/day), both given intravenously for 21 days, continuous via motor syringe, in addition to all standard measures according to BTF guidelines. We hypothesize that the combined effects of these two pleiotropic agents due to their anti-inflammatory properties, reconstitution of blood-brain-barrier, stimulation of membrane and axonal regeneration can optimize the neurocognitive outcome. Cerebrolysin is a standardized, lipid-free, low-molecular weight neuropeptide preparation, which passes the blood-brain-barrier and mimics the actions of endogenous neurotrophic factors. Proteins present in soluble tissue extracts and in the extracellular matrix have been shown to influence the survival and development of cultured neurons. The tissue extracts derived neuropeptides contained in Cerebrolysin promote neurotrophic stimulation (survival and maintaining the phenotype of highly differentiated neuronal cells), neuromodulation (changes in neuronal and synaptic plasticity synapses) , and metabolic regulation such as prevention of lactic acidosis as well as increasing the resilience against hypoxic conditions{Muresanu:2020dm}. In addition, Cerebrolysin significantly reduces tissue Plasminogen Activator (tPA)- and fibrin-damaged endothelial cell permeability, which is associated with a significant reduction in proinflammatory and procoagulatory activity. Citicoline (Cytidine 5´-diphosphocholine) is chemically identical to the essential endogenous intermediate in the biosynthetic pathway of phosphatidylcholine. It is hydrolysed to choline and cytidine triphosphate and crosses the blood-brain barrier to be reassembled to Citicoline inside the brain. It mediates neuronal membrane integrity and repair, accelerates the reabsorption of cerebral oedema and the restoration of the blood-brain barrier integrity after TBI. Furthermore, Citicoline increases cerebral dopamine and norepinephrine levels, which causes improved hypoxia tolerance.

Discussion

In these case reports, we describe the clinical development of two patients with sTBI, presenting with GCS 3-4 on site. After surgical intervention both required long-term care at the ICU, followed by intense rehabilitation measures. Motor vehicle accidents and falls from heights resulting from sports activities are typical causes in this age group and of high individual and socio-economic impact. It is of enormous importance to give especially young patients every chance for a life that is as free of disabilities as possible and to reintegrate them into their social environment and working process. Recovery of motor functions and cognitive abilities leads to a significant improvement of activities of daily living. The optimal care for sTBI patients must be started at the emergency site, must be continued through the emergency department- (ED) and the early surgical phase, with consequent ICU treatment as recommended by the BTF guidelines.(4,5) Starting at the earliest possible time, at the latest when the patient is admitted to the ICU, the described supplementary therapeutic concept should complement the standard treatment of sTBI patients. As to our knowledge, these are the first cases reporting this specific pharmacological combination in sTBI, resulting in unexpected favourable outcome (Table 2). In the recent literature, we found only one paper reporting a combined administration of Citicoline and Cerebrolysin in moderate TBI, a RCT with remarkable positive results.

There are two aspects, that we attribute to the continuous and high-dose administration of neuroregenerative drugs, among all other attempts to optimize the individual recovery of our patients: first, we did not observe the development of critical brain oedema in these patients - despite the extremely massive trauma in both cases - neither in the early nor in the later stages. Stabilisation of damaged cell membranes, reduction and/or acceleration of the absorption of brain oedema are well described effects of Citicoline. The need

for analgosedation and vasopressors was consecutively moderate. This naturally has a positive effect on gastrointestinal motility, which reduces the risk of translocation and bacteraemia. Overall, this results in better stability during the most critical phase of the first 10 days after the trauma.

Second, we observed a relatively good neurocognitive long-term outcome in these patients with regard to GOSE and mRS, despite the diffuse axonal trauma, typical for massive acceleration respectively deceleration trauma in all two cases. After a phase of "vegetative storm", typically a sign of diffuse axonal trauma, the patients developed positive cognitive abilities over the next few weeks. Despite the prolonged rehabilitation (especially in case 2), the patients recovered much better than expected in terms of cognitive competence and mood stability. The latter may be due in particular to the positive effects of Cerebrolysin, as was shown in the meta-analysis by Ghaffarpasand et al. and the recently published "CAPTAIN" trial. Cerebrolysin may stimulate neurotrophic activity and improve neuromodulation and metabolic regulation. Cerebrolysin as well as Citicoline were safe in toxicological tests, showing no significant systemic side effects. In rare cases ($< 1/1000$) agitation, loss of appetite, dizziness or pruritus was observed in awake (stroke) patients receiving Cerebrolysin. In a retrospective cohort study among 7,769 adult patients, Muresanu et al. did not find any difference in adverse effects between Cerebrolysin and placebo controls. Side effects of Citicoline are also very rare and of mild intensity; single cases suffering from headache, diarrhoea, elevated liver enzymes and weight loss were reported.

Limitations

Despite our experience with Citicoline for more than a decade, and about 4 years with Cerebrolysin, we are well aware of the limitations of these exemplary observations and the ongoing discussion about the effectivity of both drugs. Nevertheless, our data may be understood as a hint that neuroprotective and neuoregenerative mechanisms may be supported by these two externally supplied pharmacologic substances. The effects of our multimodal treatment concept have yet to be demonstrated in a large, prospective and randomized clinical trial.

Conclusions

Treatment of sTBI has to follow standardized protocols, essentially based on the Brain Trauma Foundation guidelines. The complementary medication with Citicoline and Cerebrolysin shall improve regeneration of cell membranes, reduce cerebro-endothelial cell permeability, neuroinflammation, neuronal degeneration and apoptosis. Additionally, neurotrophic stimulation can increase survival of highly differentiated neuronal cells; neuromodulation will amplify changes in neuronal and synaptic plasticity. Both drugs should be administered as soon as possible, intravenously and continuously for at least 21 days to cover the acute phase as well as the early rehabilitation period. The efficacy of this multimodal approach has to be proven in a multicentre, prospective and randomized trial.

References

Tables

Table 1 – Status and measures on scene

Table 2 – Injury severity and prognosis scores

Table 3 – Laboratory findings at 24 hours after admission in ICU

Figures

Figure 1a,b,c: MRT, Case 1

Legend:

(left) MRT of the 29-year-old male, 3 weeks after the accident. Diffusion-weighted (DWI) sequences (b=1000) demonstrated multifocal areas of abnormal bright signal along the corpus callosum and within the left corona

radiate and body of caudate nucleus corresponding to axonal injuries after the trauma. (Middle) On T2*-sequences multifocal areas of punctiform susceptibility artefacts (white arrow) at the grey-white matter junction, more pronounced at the left parietal region, in the corpus callosum and the temporal lobe (not shown) were visible, indicating small foci of posttraumatic bleeding. (Right) Follow-up MR 18 months later showed that the oedematous areas on DWI-sequences and the microbleeds had been resolved. The size of the ventricles and the sulci seem to be a bit wider than right after the accident.

Figure 2a,b: CCT scan, Case 2

Legend:

Cranial CT of a 30-year-old male, 1 day after the accident (left image) demonstrates extensive oedematous swelling within the anterior cerebellar lobes as well as in both posterior temporal and occipital lobes due to extensive hypoperfusion of the posterior circulation. The cerebellar tentorium (right image) is slightly bowed upwards and a slight compression of the basal cistern and the IV.ventricle is shown, however liquor flow was patent.

Abbreviations

BTF – Brain Trauma Foundation

CT – Computer Tomography

CCT – Cranial Computer Tomography

ED – Emergency Department

EEG – Electroencephalogram

EVD – External Ventricular Drainage

GCS – Glasgow Coma Score

GOSE – Glasgow Outcome Score

HEMS – Helicopter Emergency Service

ICP – Intracranial Pressure

ICU – Intensive Care Unit

L – lumbar

LE – Lower Extremities

mRS – modified Rankin Scale

MRT – Magnetic Resonance Tomography

RCT – Randomized Control Trial

SSEPs – Somatosensory Evoked Potentials

sTBI – severe Traumatic Brain Injury

TH – thoracic

UE - Upper Extremities

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HT and GH concepted and designed this paper; CD and IG contributed in acquisition and analysis of data; JK is responsible for radiologic examination and reporting. HT drafted the article; all authors revised it critically for important intellectual content and approved this version to be published.

I, Helmut TRIMMEL, as the corresponding author have the right to grant on behalf of all authors, an exclusive licence for contributions from all authors to permit this work if accepted, to be published.

Consent for publication

Written informed consent was obtained from the patients for publication of these case reports and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Ethics approval

Since both patients gave their written consent, the institutional board had no objection to the publication of the cases.

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Availability of data and material

All data is available from the authors.

Competing interests

All authors confirm that they have no competing interests.