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## Cognitive Impairment After Critical Illness: Prevention and Treatment

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**Why did you decide to investigate NTF-prep?**

Long-term cognitive impairment after critical illness (CIACI) was first described in 1999 (Hopkins 1999). In 1992 we noticed that in cardiac surgery with extracorporeal circulation patients there was a correlation between jugular bulb lactic acid and cognitive decline. We concluded that CIACI was a real dementia, not a post-traumatic stress disorder (Previgliano 2015). Pandharipande et al. revealed that impairment was independently associated with duration of delirium (Pandharipande et al. 2013). Analysing delirium pathophysiology under the physiologic mechanisms of brain cell death and survival, including the neurovascular unit (NVU) concept, led us to conclude that vascular ischaemia, necrosis and apoptotic mechanisms were involved or triggered in CIACI. Endogenous neurotrophic factors (ENTF), as brain-derived neurotrophic factor (BDNF), were found to be involved in almost all stages of development of neural circuits, with a key role in synaptic N-methyl-Daspartate transmission activity, inflammation and apoptosis regulation. Natural neurotrophic factor preparation (NTF-prep; commercially available as Cerebrolysin ®) acts like endogenous neurotrophic factors and showed clinical efficacy in Alzheimer's disease (AD), vascular dementia, ischaemic stroke and traumatic brain injury (TBI). We hypothesised that NTF-prep could play a neuroprotective role at delirium onset, or a neurotrophic or neurogenic one when CIACI was present.

**How might NTF-prep be useful for prevention and treatment of CIACI?**

NTF-prep was shown to stimulate angiogenesis, neurogenesis, remyelination, cell migration, suppression of apoptotic-like processes and recovery of functional NVU. These findings were translated into improved functional outcomes in various animal models. They were shown to act through sonic hedgehog and neurotrophic signal transduction pathways, which are part of the endogenous mechanisms of neuroprotection and neurorestoration. Our hypothesis is that due to this neuroprotective action NTF-prep could be effective in CIACI prevention. For this setting a 30 ml/day infusion for 10 days, as used for stroke, might prevent CIACI development. Once CIACI is present the clinical picture resembles mild cognitive impairment or mild dementia. In dementia, NTF-prep has showed improvement over placebo in 12 randomised controlled studies. In a trial in Argentina on NTF-prep in 202 AD and mixed dementia patients, we found a 70% improvement. For CIACI treatment we think the regimen of 10 ml/day for 20 days repeated each three months, as used in dementia, could be suitable.

**What might be the advantages of NTF-prep compared to the delirium care bundle?**

The delirium care bundle includes sedation suspension, spontaneous ventilation assays, early mobility and sleep hygiene programmes (Barr et al. 2013). While it is associated with significant improvements, it is an example of how endogenous defence mechanisms can be triggered. Awakening patients augments cerebral blood flow and generates local NTF release, as does physical activity. The muscle must be seen as an endocrine system with endocrine, autocrine or paracrine effects. There is a clear relationship between levels of IL6 and BDNF, exercise and improved cognitive function. As BDNF is a large molecule it cannot pass through the NVU and blood brain barrier (BBB), so an endocrine and paracrine activation gear promotes BDNF release within the brain. NTF-prep is produced by an enzymatic breakdown of purified porcine brain proteins, and contains a complex mixture of <10 kDa peptides that was shown to stimulate neurotrophic signalling pathway as well as endogenous production of NTFs. Therefore, NTF-prep acts in a similar way to ENTF, but is able to cross the BBB. In this way it could be used in conjunction with the delirium care bundle to protect the brain.

**What might be the potential risks of NTF-prep?**

A review of NTF-prep safety in randomised clinical trials of dementia and stroke found no differences with the placebo (Thome and Doppler 2012). Adverse effects were generally mild and transient. Prescribing information warns about anaphylactic reactions in less than 10-100 of patients. NTF-prep appears to be safe when used in combination with recombinant tissue plasminogen activator or cholinesterase inhibitors such as donepezil or rivastigmine.

**NTF-prep is already in use for TBI and stroke patients. What are the results? What is your own experience?**

A randomised clinical trial in 1,070 patients with acute ischaemic stroke found no significant difference 90 days after stroke onset between patients receiving the NTF-prep or placebo (Heiss et al. 2012). A post-hoc analysis, however, showed a trend in favour of the NTF-prep in patients with a National Institutes of Health Stroke Score >12. The cumulative mortality at day 90 was significantly lower; 20.2% in the placebo group and 10.5% in the treatment group. The morbidity was lower in the treatment group with an improvement of 4.8 points versus 1.8 points for placebo. A consistent, across all clinical studies in acute brain injuries, is accelerated recovery pattern reflecting activation of consciousness,

motor and cognitive functions. These clinical effects might be of relevance for supporting of the NTF-prep resulted in the recovery of cognitive deterioration as assessed at 1 and 3 months post-injury (Chen et al. 2013). Our experience, in 18 patients surviving severe TBI that developed posttraumatic dementia, treated with NTF-prep at the dementia dosage and quarterly cycles, showed significant improvement in memory, executive and motor function. Transcranial Doppler studies revealed significant improvements in cerebral blood flow velocities in both middle cerebral and basilar arteries, and in estimated cerebral perfusion pressure, with a decrease in pulsatility index reflecting a drop in cerebrovascular resistance.

**What further research is needed?**

Although NTF-prep is approved in many countries to treat dementia, stroke and TBI, and all these diseases have common pathways with CIACI, we still need to prove that our hypothesis on prevention is correct. A dedicated clinical development programme could provide the answer.

**DISCLOSURE:**
“Point-of-View” articles are part of the ICU Management Corporate Engagement Programme.

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