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Improving treatments and outcomes: an emerging role for zinc in traumatic brain injury

Elise C Cope[*], **Deborah R Morris**[*], and **Cathy W Levenson**
EC Cope and *DR Morris* are with the Department of Biomedical Sciences, Florida State University College of Medicine, Tallahassee, Florida, USA. *CW Levenson* is with the Department of Biomedical Sciences and Program in Neuroscience, Florida State University College of Medicine, Tallahassee, Florida, USA

Abstract

Traumatic brain injury is associated with a wide variety of behavioral deficits, including memory loss, depression, and anxiety. While treatments for these outcomes are currently limited, human clinical data suggest that supplemental zinc can be used during recovery to improve cognitive and behavioral deficits associated with brain injury. Additionally, pre-clinical models suggest that zinc may increase resilience to traumatic brain injury, making it potentially useful in populations at risk for injury.

Keywords

anxiety; depression; neuroprotection; traumatic brain injury; zinc

INTRODUCTION

Traumatic brain injury (TBI) constitutes a major worldwide health and socioeconomic problem. In fact, it affects more than 1.5 million Americans each year and is the leading cause of death in individuals under 25 years of age.[1] In addition to high rates of TBI in young drivers and athletes, approximately 20% of all soldiers on duty in Iraq and Afghanistan have suffered some type of TBI, making this one of the most common injuries of these wars.[2]

These data are disturbing given that these injuries can lead to a number of cognitive, social, and psychiatric complications that are often chronic and disabling. A wide variety of behavioral deficits including impairments in memory, attention, planning and executive function, depression, anxiety, aggressive outbursts, post-traumatic stress disorder, and poor social functioning have all been reported in TBI patients.[3] Major depression is the most common consequence of TBI, affecting as many as 40% of TBI patients.[4] Even persons with mild cases of TBI are not immune from the development of depression.[5]

Treatment options for TBI patients are currently very limited. While common antidepressant drugs such as selective serotonin reuptake inhibitors are often prescribed to treat TBI-associated depression, it appears that this treatment has limited effectiveness. While there

Correspondence: *CW Levenson*, Department of Biomedical Sciences, Florida State University College of Medicine, 1115 W. Call Street, Tallahassee, FL 32306-4300, USA. cathy.levenson@med.fsu.edu.
[*]These authors contributed equally to this review.

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have been some attempts to study the effectiveness of antidepressant drug therapies in populations with TBI, a recent review of the literature revealed that small sample sizes and variations in study designs limit the ability to establish evidence-based treatments for patients with TBI-related depression.[6] What is clear is that there is a significant need for the development of effective therapies for TBI patients to not only reduce the mortality rate, but also to improve the quality of life of TBI survivors. Furthermore, prophylactic treatments that reduce the severity of poor outcomes in the event of a TBI are needed for populations at risk for brain injury.

ZINC DEFICIENCY AND TRAUMATIC BRAIN INJURY

As shown in a clinical study, after head injury patients are at risk for the development of zinc deficiency. TBI patients have elevated urinary zinc losses that persist for weeks following injury and result in reduced serum zinc levels. It also appears that urinary zinc losses are proportional to TBI severity. In fact, the study found that the most severely injured patients had mean urinary zinc levels that were 14 times higher than normal values.[7]

Given that TBI patients are at risk for the development of zinc deficiency, a rat model of combined moderate zinc deficiency and brain injury was used to examine the outcomes of zinc deficiency after TBI. Zinc deficiency increased cell death at the site of cortical injury, as measured by TUNEL labeling, compared to zinc-adequate controls. Along with the development of zinc deficiency, there was evidence of both apoptotic and necrotic cell death for 4 weeks following the injury.[8] Increased cell death has also been reported with severe zinc deficiency in an animal model of TBI.[9]

These data led to the hypothesis that the development of zinc deficiency and the subsequent increase in cell death results in behavioral deficits after TBI. To test this hypothesis, rats were fed a diet with marginal levels of zinc for 4 weeks and then received a moderately severe bilateral TBI induced by controlled cortical impact to the frontal cortex. This model of injury induces edema that is evident in the first hours after injury using magnetic resonance imaging (Figure 1). By hour 48 post injury, the edema begins to dissipate and continued secondary cell death leads to the development of a necrotic core (Figure 1) that persists throughout the life of the animal. The resulting neuronal damage in this pre-clinical model of TBI results in behaviors consistent with depression, anxiety, and impaired spatial learning and memory. Furthermore, consistent with injury-induced stress, this model of TBI also resulted in significantly increased adrenal weights. Interestingly, use of a moderate model of zinc deficiency did not worsen these outcomes.[10] However, it is not known if a more severe model of zinc deficiency or injury would impair behavioral outcomes. This is a clinically relevant question given the reports that urinary excretion can be very high in severe TBI.

ZINC SUPPLEMENTATION AND TRAUMATIC BRAIN INJURY

Use of zinc as a treatment for traumatic brain injury

Young et al.[11] designed a clinical trial to test the hypothesis that zinc supplementation would not only maintain zinc balance in patients with moderate to severe brain injuries, but that improving zinc status in this population would help maintain visceral protein balance and inhibit muscle wasting. To test this hypothesis, 68 patients were randomly assigned to either a zinc adequate group (2.5 mg/day) or a zinc supplemented (12 mg/day) group. Within 72 h of injury, zinc was administered intravenously as zinc sulfate for a period of 15 days in conjunction with total parenteral nutrition. After this initial period of total parenteral nutrition, patients were given enteral zinc (22 mg/day, zinc gluconate) or placebo treatment for 3 months. After approximately 3 weeks, visceral proteins such as prealbumin and retinal-

binding protein were significantly increased in patients supplemented with zinc. One month after TBI, mortality in the zinc adequate control group was 26%, while the supplemental zinc group had a 12% mortality rate at the same time point. While caution should be exercised when interpreting the mortality data, because a larger number of patients in the adequate zinc group required craniotomies for hematoma evacuation, these data do suggest that zinc supplementation may improve survival.

More significantly, Glasgow Coma Scale scores were significantly improved in patients given the zinc supplementation compared to patients given adequate zinc. These improvements were seen as early as 2 weeks after the initiation of treatment and persisted throughout the course of the study. These data suggest that zinc supplementation may be a viable adjunct to treatment for TBI resulting in an improvement in outcomes associated with brain injury.

Use of zinc to improve resilience after traumatic brain injury

While the clinical study discussed above showed that zinc can be successfully used to treat TBI and improve outcomes, until recently it was not known whether zinc supplementation prior to injury could reduce the risk of poor outcomes in the event of a TBI. It was thus hypothesized that chronic zinc supplementation would result in improved behavioral resilience to TBI. The rationale for this hypothesis stems from a number of published reports showing that zinc supplementation can improve the efficacy of antidepressant drug therapy in patients with unipolar depression.[12] A 12-week clinical trial showed that patients previously refractory to antidepressant drugs showed improvements in depression scores when medication was supplemented with 25 mg zinc/day,[13] an amount of zinc that is not likely to produce any adverse effects. This work has been confirmed in animal models of depression. For example, in the rodent depression models of bulbectomy and chronic stress, a single injection of zinc at 30 mg/kg resulted in decreased immobility time in the forced swim test, which is correlated with an increase in antidepressant drug action.[14,15]

To test the hypothesis that zinc supplementation could result in improved resiliency to TBI, adult male rats were given 4 weeks of either a zinc supplemented (180 ppm) or zinc adequate (30 ppm) diet followed by a moderately severe TBI induced by controlled cortical impact. Rats supplemented with zinc showed significant reductions in depression-like behavior as measured by the 2-bottle saccharin preference test for anhedonia as well as trends towards reduced stress and anxiety. Zinc supplementation also significantly reduced adrenal weights of injured animals, suggesting that chronic zinc supplementation may reduce the physiological responses to stress correlated to anxiety.

In addition to its possible effects on TBI-induced depression and anxiety, zinc supplementation significantly improved cognitive behavior. While injury significantly impaired spatial learning and memory, zinc supplementation was very effective at preventing these deficits. In fact, at no point during the 10-day Morris water maze testing period for learning and memory was there any significant difference between zinc-supplemented injured animals and uninjured controls.[10]

Possible neurotoxic effects of supplemental zinc

While both human and animal data suggest that zinc supplementation can be used to improve outcomes after TBI, concerns about the possible neurotoxic effects of high levels of zinc in the central nervous system should be addressed. Specifically, it has been suggested that the accumulation of free zinc is neurotoxic after brain insults such as ischemia, seizures, and TBI.[16]

While most of the zinc in the central nervous system is tightly bound to proteins such as zinc finger proteins and other metalloproteins, about 10–20% is chelatable or "free zinc."[17] The hippocampus, where as much as 30% of the zinc is vesicular, appears to have the highest concentrations of free zinc. Other regions rich in free zinc include the olfactory bulb, cerebral cortex, amygdala, and cingulate cortex. Free zinc is coreleased with glutamate from synaptic vesicles, where it can modulate a variety of post-synaptic receptors and channels.[18]

The concern about the role of free zinc arises from data suggesting that mechanical cortical trauma or fluid percussion injury results in the rapid release of free zinc from pre-synaptic vesicles.[19] Zinc modulates the activity of post-synaptic glutamate receptors, including α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) receptors, n-methyl-d-aspartate (NMDA) receptors, as well as voltage-gated calcium channels. When activated, each of these receptors leads to influx of intracellular calcium, which, in excess, can then trigger post-synaptic cell death.[20] It has been hypothesized that this sequence of events leading to excitotoxic neuronal damage may occur in traumatic brain injury because high concentrations of zinc accumulate in degenerating hippocampal neurons following fluid percussion injury.[21] Furthermore in vivo and in vitro chelation of free zinc with calcium ethylenediaminetetraacetic acid (Ca-EDTA) reduced cell death by 50–85% in the dentate gyrus, cornus ammonis (CA1), and hilus of the hippocampus after injury.[19,22]

While these reports clearly indicate a protective effect of zinc chelation on neurons, other data have contradicted these findings. First, cell culture models of stretch injury have revealed that chelation treatment by N,N,N',N'-tetrakis (2 pyridylmethyl) ethylenediamine (TPEN) increases cellular reactive oxygen species.[23] Furthermore, using genetically modified mice (ZnT3 null mice) that did not have free vesicular zinc, Doering et al.[24] found that 24 h after TBI there was an increase in cell death when no free zinc was present. These data suggesting that free zinc may actually play a protective role were confirmed by chemical blocking of vesicular zinc by diethyldithiocarbamate or sodium selenite 1 h prior to TBI. This study showed that blocking free zinc increased cell death in wild-type mice, but had no effect in ZnT3 null mice.

Recent data have suggested that chelation of free zinc does not lead to improved outcomes after TBI. For example, rats treated with calcium ethylenediaminetetraacetic acid (Ca-EDTA) either prior to or following injury did not show improvements in spatial memory 2 weeks post-TBI.[25] Together, these data suggest that while free zinc may well be released from synaptic terminals after injury, prevention of this release may increase cell death. Furthermore, high concentrations of free zinc are not likely to be a significant factor in poor outcomes associated with TBI. Additional work is needed to determine the effect of zinc supplementation on free zinc distribution and accumulation in vulnerable regions of the brain such as the hippocampus after TBI.

CONCLUSION

The work reported in this review suggests a link exists between zinc supplementation and improvement in outcomes following TBI. Because TBI patients have increased urinary zinc losses and acutely reduced serum zinc levels, the available data show the importance of preventing zinc deficiency in this patient population. TBI patients should be monitored for zinc losses following injury and supplemented when needed, keeping in mind that the recommended upper limit of dietary zinc is 40 mg/day.

Although the data reported here show the potential usefulness of zinc for the prevention and treatment of poor outcomes associated with TBI, both the animal and human work have studied moderate and severe brain injury. No work has explored the use of zinc in milder

forms of TBI, such as concussion. Given the apparent frequency of concussions in athletic competitions at all levels (from elementary school through the professional ranks), and the recently expressed concerns about the long-term effects of concussion, future work should examine a possible role for zinc in the prevention of post-concussion syndrome. Furthermore, future preclinical and animal research should assess the optimal response by determining the effective dosage, timing, and therapeutic window for zinc treatment. Given the robust animal data on the use of zinc supplementation in providing behavioral resiliency to TBI, a clinical trial on resilience would also be beneficial, especially for populations that are susceptible to brain injuries, such as military personnel and certain athletes.

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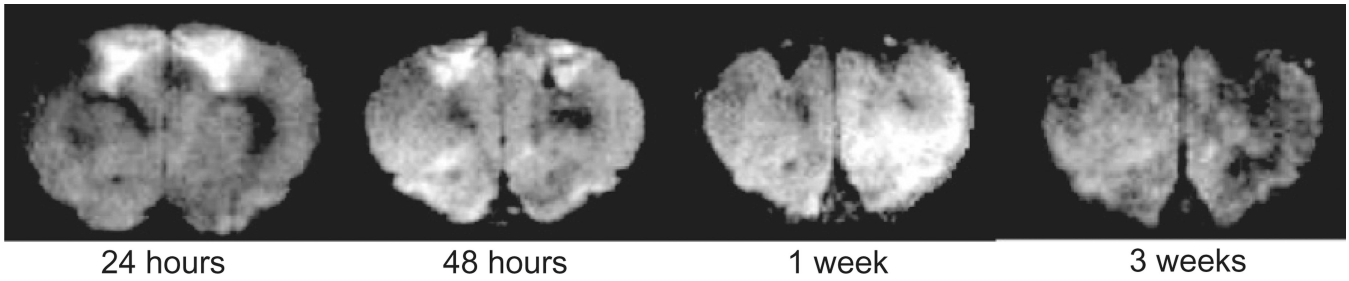

Figure 1. Magnetic resonance imaging of traumatic brain injury in a rat model

Injury to the frontal cortex was induced bilaterally, under anesthesia, by controlled cortical impact. Images were collected in vivo at the National High Magnetic Field Laboratory, Florida State University, using the 900 MHz Magnet with a field strength of 21.1 Tesla between 24 h and 3 weeks post-injury.