

# Combination therapy with vitamin D<sub>3</sub>, progesterone, omega-3 fatty acids and glutamine reverses coma and improves clinical outcomes in patients with severe traumatic brain injuries: A case series

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## ABSTRACT

**Introduction:** Traumatic brain injury (TBI) is a major public health problem and a leading cause of death and disability in the United States. Management of patients with TBI has changed very little over the last 20 years. **Case Series:** A case series of three patients with severe TBIs who were aggressively treated with vitamin D<sub>3</sub>, progesterone, omega 3-fatty acids, and enteral glutamine for six weeks, termed neuroceutical augmentation for traumatic brain injury (NATBI), with very favorable outcomes. **Conclusion:** A large clinical study trial using these four supplements (NATBI) together is warranted.

**Keywords:** Traumatic brain injury, Vitamin D<sub>3</sub>, Omega-3 fatty acids, Loveza, Progesterone, Cerebral edema, Glutamine

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## INTRODUCTION

Traumatic brain injury (TBI) is a major public health problem. According to CDC it affects over 1.7 million people annually in U.S. with 275,000 hospitalizations and 52,000 deaths [1]. The medical cost for treating TBI patients in the United States in 2010 was \$76.5 billion and rising annually [1]. Primary causes for TBI include the following: motor vehicle crashes, falls, assaults and sports or recreation-related injuries (concussions). Finding the right treatment to reduce mortality rates and improve the clinical outcomes in TBI patients has been elusive.

Management of patients with TBI has changed very little over the last 20 years. Advancements in the treatment of TBI requires great understanding of the biochemical mechanisms of the brain during a normal resting state as well as the metabolism after a severe traumatic event. Brain metabolism is markedly altered during TBI. After the initial insult to the brain, the brain's metabolism is altered and can increase up to 140% of its normal metabolism.

Vitamin D (a steroid hormone) and omega-3 fatty acids (an essential fatty acid) are both very powerful anti-inflammatory agents that reduce cerebral edema

and swelling. Glutamine becomes an essential amino acid during stress and produces the extra glucose (via the Cori cycle) that is used by the injured brain and the extra glucose used by the immune response system to fight off infection during stress. Progesterone (also a steroid hormone) is a neuroprotector of injured brain cells and potentiates the effect of vitamin D.

These agents are all immune modulators which work synergistically to prevent secondary brain injury by limiting or decreasing inflammation; an increasing well-recognized cause of ongoing brain swelling after a primary injury. They are also neuroprotectors that makes the neurons more resistant to stress, ischemia, hypothermia, hyperthermia, hypoglycemia, hyperglycemia, hypotension, and hypertension. Immune modulation with nutritional supplements is a rapidly advancing field with a very promising future in treating TBI as well as other critically injured/ill patients.

We present a case series of three patients with severe TBIs who were aggressively treated with vitamin D<sub>3</sub>, progesterone, omega-3 fatty acids and enteral glutamine for up to six weeks, termed neuroceutical augmentation for traumatic brain injury (NATBI), with very favorable outcomes [2–5]. Patients in a coma with severe TBI (Glasgow Coma Score <8) who were admitted to a Level I trauma center were evaluated in a prospective observational study. Patients were treated with a neuroceutical combination of vitamin D<sub>3</sub>, omega-3 fatty acids, progesterone, and glutamine initially via a nasogastric tube and later orally for six weeks. Primary outcomes were mortality rate and return to recovery which was defined as a Glasgow Coma Score (GCS) of 10 or greater. NATBI protocol works on multiple levels and neuroprotective pathways in TBI patients by down regulating cytokine production, preventing oxidative stress (free radical oxygen formation), decreasing cerebral edema, and inflammation, thus limiting secondary brain injury in contradistinction to progesterone therapy alone (Protect III study) [3–5]. In addition, our NATBI regimen is relatively inexpensive, safe, and very effective at reducing brain and systemic inflammation post-injury.

## CASE REPORT

**Case 1:** Patient 1 was a 17-year-old female restrained driver, who was involved in a single car, multiple rollover motor vehicle crash with a 10 foot ejection. She presented to the Emergency Department intubated and unresponsive with a GCS of five out of fifteen. Her physical exam was notable for a blood pressure of 105/56 mmHg, pulse of 87 beats/min, temperature of 37.7 C, respiratory rate of 20/min, and oxygen saturation of 100% on the ventilator. Her secondary survey revealed unequal pupils with discordant reactivity. Her right pupil was 8 mm and

non-reactive to light and her left pupil was 3 mm and reactive to light. Ominously, she was noted to have decerebrate posturing of both the upper and lower extremities bilaterally. On further examination, a five cm laceration to the right lower anterior thigh was identified and repaired. Her Focused Assessment Sonogram for Trauma (FAST) exam was negative.

The initial computed tomography (CT) scan of her head revealed multifocal, punctuate brain hemorrhages, consistent with a diffuse axonal injury (DAI) (Figure 1). CT scans of the cervical spine, chest, abdomen, and pelvis revealed bilateral spinous process fractures of C7, T1, and T2, a mid sternal body fracture, bilateral pulmonary contusions, and a distal right clavicle fracture. She also sustained a cardiac contusion associated post-injury arrhythmias, which were treated conservatively. An external ventricular drainage device was placed by neurosurgery to help monitor and manage her intracranial pressure and maintain her cerebral perfusion pressure within acceptable limits.

Upon her admission to the surgical intensive care unit (SICU), she was started on a regimen of vitamin D<sub>3</sub> 50,000 IU, progesterone 20 mg, omega-3 fatty acids 2 grams (Loveza), and enteral glutamine 20 grams via her nasogastric tube (NGT). Her decerebrate posturing resolved in less than 24 hours. By hospital day-3, she was able to follow simple commands while off sedation.

Her GCS and clinical status continued to improve and she was able to be extubated on hospital day-9. She was discharged to inpatient rehabilitation on hospital



Figure 1: A CT scan of the head with multiple punctuate hemorrhage and DAI (Case 1).

day-18. Although her GCS improved to 12 prior to rehab transfer, some residual right sided weakness remained. She rapidly progressed to a GCS of 15 during her recovery and was discharged home from inpatient rehab doing well after one month. In less than three months after her initial insult, she has returned to school full time and is completing her senior year of high school with her right sided weakness essentially resolved.

**Case 2:** Patient 2 was a 31-year-old male who was brought to the Emergency Room by ambulance due to altered mental status (AMS) and a witnessed seizure following an assault with suspected head trauma. He suffered blunt force trauma to his head secondary to being struck with a brick. His primary and secondary examinations were unremarkable with the exception of a GCS of 9. His vital signs were within normal limits and his hemodynamics were stable.

His initial CT scan of the head revealed a bilateral frontal intraparenchymal hemorrhage, with left frontal, parietal, temporal subdural hematomas (SDH), a left frontal subarachnoid hemorrhage (SAH) with a 7 mm right to left midline shift, cerebral edema and effacement of left frontal horn and right temporal hematoma (Figure 2), computed tomography scan of the cervical spine, chest, abdomen and pelvis were unremarkable.

On tertiary survey, his past medical history was noted to be significant for human immunodeficiency virus (HIV positive) infection, hepatitis A, syphilis, shingles, and alcohol abuse. His CD4 T-cell count on admissions was 46 mm<sup>3</sup> (normal mm<sup>3</sup>>500), consistent with a diagnosis of acquired immunodeficiency syndrome.

His mental status declined rapidly during his initial evaluation and management period in the ED, and he was taken to the operating room by neurosurgery for an emergent depressive hemicraniectomy. Due to the severity of his head injury and his multiple comorbidities, the patient's prognosis was deemed to be very poor by the neurosurgery service. Upon admission to the SICU, his GCS was 3T out of 15. He was immediately started on our NATBI protocol, with a regimen of vitamin D3, progesterone, loveza, and glutamine via orogastric tube.

His postoperative course was complicated by acute respiratory distress syndrome (ARDS), ventilator associated pneumonia (VAP) and acute sepsis. However, his condition improved with intravenous antibiotics, ventilatory management, and nutritional support. His GCS continually improved over the course of his ICU stay and he was able to be discharged to a long-term rehabilitation facility on hospital day-18 with a GCS score of 11T breathing spontaneously via his tracheostomy. One month after discharge, he was evaluated in the trauma clinic and was noted to have a GCS of 15. He was tolerating a regular diet, ambulating without assistance, and adjusting very well to home life. The only deficits reported were some memory loss, which he noted was improving on a daily basis.

**Case 3:** Patient 3 was a 23-year-old female who was an unrestrained passenger involved in a single car motor



Figure 2: A computed tomography scan of the head revealed a bilateral frontal intraparenchymal hemorrhage, left frontal, parietal, temporal subdural hematomas (SDH), a left frontal subarachnoid hemorrhage (SAH) with a 7 mm right to left midline shift, cerebral edema and effacement of left frontal horn and right temporal hematoma (case 2).

vehicle collision (hit a tree) with a fatality at the scene. Patient had a GCS of 3 out of 15 in the field with decerebrate posturing, according to emergency medical personnel. She was immediately intubated by paramedics at the scene.

Physical examination in the emergency department showed that the patient was hemodynamically unstable with a blood pressure of 90/60 mmHg, pulse of 128 min, respiratory rate of 18 min, and oxygen saturation of 100%. She required four units of packed red blood cells plus three liters of isotonic crystalloid to become hemodynamically stable.

Her pupils were 5 mm and sluggishly reactive to light bilaterally. She had massive facial edema and swelling. Her endotracheal tube was intact and in good position and confirmed with positive end-tidal CO<sub>2</sub>.

Computed tomography scans of the head, face and cervical spine revealed the following: diffuse SAH over the left frontoparietal lobes, cerebral edema, SDH, DAI, transtentorial herniation, tonsillar herniation (Figure 3); fracture of the right mandibular angle, body, and parasymphysis; but there was no cervical spine fracture or dislocation.

Computed tomography scans of the chest, abdomen, and pelvis showed the following: a mid sternal fracture,





Figure 3: Computed tomography scan of the head revealed a diffuse SAH over the left frontoparietal lobes, cerebral edema, SDH, DAI, transtentorial herniation and tonsillar herniation (case 3).

bilateral, multiple rib fractures, left pulmonary contusion, Grade 1 splenic laceration and a left acetabular fracture. X-rays of the lower extremities revealed a right, distal tibia/fibula fracture, which was stabilized by orthopedic surgery.

An external ventricular drainage (EVD) monitor was placed and revealed that the patient had an opening cerebral perfusion pressure of 27 cm H<sub>2</sub>O. Standard protocol for patients with elevated intracranial pressure (ICP) was initiated. Patient was admitted to the SICU and started on our NATBI protocol consisting of vitamin D<sub>3</sub>, progesterone, omega-3 fatty acid, and glutamine.

She had a prolonged hospital course which was complicated by refractory elevation of her ICP, prolonged coma with a depressed GCS of 4T to 8T, VAP, urinary tract infection (UTI) with urosepsis, candidemia with fungal sepsis and acute renal insufficiency.

Patient was transferred on hospital day –109 with a GCS of 8T and breathing spontaneously on tracheostomy collar to a long-term rehab facility. She continued to make satisfactory improvement during rehab, and was discharged from the long-term

rehabilitation facility to home six weeks later with a GCS of 12 to 13, talking, following commands, and eating with assistance. Patient was not ambulating when discharged and will require extensive ongoing physical therapy. She was lost to follow after discharge from the rehabilitation center.

All three patients, who had a very poor prognosis, survived their severe TBI and had a return of recovery to a GCS of 15 out of 15. Six months follow up revealed that all three patients, short-term memory lost had resolved.

## DISCUSSION

Emerging understanding of NATBI has a very promising future in the treatment of TBI. Vitamin D (classified as a vitamin) is actually a steroid hormone with pleiotrophic effects, which includes its action as immune modulator [6]. Of note, receptors for vitamin D are located on every cell and tissue of the human body including brain tissue. Vitamin D has been discovered to be very important in immunomodulation, regulation of inflammation and cytokines, such as IL-1 beta and tumor necrosis factor-alpha (which increases brain cell edema), cell proliferation, cell differentiation, apoptosis, and angiogenesis, in addition to the traditional calcium, magnesium, phosphate homeostasis and bone formation. Consequently, deficiency of vitamin D affects more than 70% of the United States general population, and has been found to be associated with worsening of many inflammatory conditions [7–9].

Even more important to brain health, vitamin D binds receptors in brain cells and helps to produce heat shock proteins (HSP), which act as chaperone proteins that make the cells more resistant to stress [10, 11]. Heat shock proteins help brain cell proteins maintain their 3-D shape/conformation during stress, ischemia, hyperthermia, hypothermia, hyperglycemia, hypoglycemia, hypertension, and hypotension. Loss of 3-D protein shape by neuronal cells results in loss of cellular function, which predisposes the brain cells to apoptosis and cell death [12]. All cells in the human body are capable of producing HSP. Therefore, low vitamin D levels may be associated with lower levels of HSP. Thus, vitamin D deficient neuronal cells are less likely to survive a stressful event, such as trauma or ischemia to the brain. HSP has anti-apoptotic (prevents programmed brain cell death) and anti-inflammatory properties, which also decreases cerebral edema [13, 14]. Heat shock protein plays a very important and central role in brain cell survival and resiliency after a traumatic brain injury.

Recent research has shown that progesterone is a neuroprotectant that works synergistically with vitamin D in protecting the nerve cells from injury. Progesterone has been shown to protect the brain from traumatic injury and is now in Phase III clinical trials. However, studies have shown that progesterone's beneficial effects can be ameliorated in vitamin D deficient patients. Vitamin D can modulate neuronal apoptosis, trophic

factors, inflammation, oxidative stress, excitotoxicity, and myelin and axon repair. Low dose vitamin D hormone plus progesterone has been demonstrated by Hua et al. to improve performance in acquisition, more effectively than progesterone alone, suggesting that a lower dose of activated vitamin D may be optimal for combination therapy. Their data support that the combination of progesterone and vitamin D is more effective than progesterone alone in preserving spatial and reference memory [15].

According to the CDC, up to 80% of the United States population is omega-3 fatty acid deficient. As 30% of human brain tissue is made up of omega-3 fatty acid, emerging evidence suggests that supplementing TBI patients with omega-3 fatty acid may help the injured brain to repair itself. This makes omega-3 fatty acid a very essential adjunct in the treatment of severe TBI. A broken brick wall is repaired with bricks and not straw. The same analogy applies to the brain. It needs omega-3 fatty acid to heal properly. Also, omega-3 fatty acids are anti-inflammatory and works very well with vitamin D3 in down-regulating inflammation, which counteracts cerebral edema and swelling.

Thus, vitamin D deficiency and omega-3 fatty acids deficiency may work synergistically to worsen outcome in patients with TBI. As both are very prevalent in the general US population and even more pronounced in critically ill patients with TBI, in our opinion, at-risk patients should be routinely supplemented with vitamin D and omega-3 fatty acids. In fact, vitamin D levels less than 17.8 ng/mL is shown to be associated with a 28% increased all-causes risk of premature death [6]. Equally important, omega-3 fatty acid deficiency is associated with over 96,000 preventable deaths in the US annually according to a recent report from the CDC. Therefore, nutritional deficiencies of these two supplements can potentially have a grave impact on the clinical outcomes of TBI patients.

On the other hand, glutamine is a non-essential amino acid that becomes a conditionally essential amino acid during periods of stress. Glutamine is the most abundant amino acid and in human skeletal muscle. During stress, glutamine is used as the primary energy source for rapidly dividing cells and is used by the liver to make glucose via gluconeogenesis to supply glucose to the brain, red blood cells, enterocytes of the small bowel, and the cell of the immune system. Glutamine also works synergistically with vitamin D3 to increase HSP70 [16, 17]. Thus, adequate levels of glutamine and vitamin D3 are needed to produce a optimal concentration of HSP70 in brain cells, which potentially work together to protect the injured brain from ongoing insult or injury.

Of note, there were no side effects or complications from treating these three patients with our NATBI therapeutic regimen using the combination of supplements as noted above. Increasing data suggests that each supplement in the NATBI protocol is essential to obtaining optimal clinical outcomes in severe TBI patients. This novel approach (NATBI protocol) to treating TBI patients works by down-regulating multiple inflammatory response pathways which produces

cerebral edema, upregulating HSP which helps injured brain cells survive stress of any kind, and by helping the brain to repair itself with omega-3 fatty acid.

We have reported a case series of three patients with very severe TBI's who were managed with vitamin D3, progesterone, omega-3 fatty acids, and glutamine. All three patients were presented in a coma, and had very poor and grave prognosis based on their CT scan and neurosurgical consultation/recommendations. They are now well adjusted and have returned to their mental baselines with minimal long-term affects of TBI, other than short-term memory loss which is rapidly improving.

## CONCLUSION

Our group is the first to report in literature the multi-component therapeutic regimen of vitamin D3, progesterone, omega-3 fatty acids, and glutamine as a combination therapy for moderate and severe traumatic brain injury treatment, which we have termed neuroceutical augmentation for TBI (NATBI). The potential for improving clinical outcomes and potentially decreasing healthcare costs associated with TBI patients is limitless. A large clinical study trial using these four supplements together is warranted.

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## Author Contributions

Leslie R Matthews – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Omar K Danner – Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Y A Ahmed – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

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Ed W Childs – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Kenneth L Wilson – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

### Guarantor

The corresponding author is the guarantor of submission.

### Conflict of Interest

Authors declare no conflict of interest.

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