

REVIEW

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## Neurotrauma and Repair Research: Traumatic Brain Injury (TBI) and its Treatments

Hanna Algattas and Jason H. Huang

University of Rochester Medical Center, Department of Neurosurgery, Rochester, NY, USA.

Corresponding authors email: [hanna\\_algattas@urmc.rochester.edu](mailto:hanna_algattas@urmc.rochester.edu); [jason\\_huang@urmc.rochester.edu](mailto:jason_huang@urmc.rochester.edu)

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**Abstract:** Traumatic brain injury (TBI) affects a growing portion of the population and continues to take national spotlight with advances in imaging technology and understanding of long-term effects. However, there is large variance in TBI treatment protocols due to injury variability and lack of both mechanistic understanding and strong treatment recommendations. Recent practice suggests three disparate treatment approaches, all which aim at promoting neuroprotection after TBI, show promise: immediate hypothermia, hyperbaric oxygen, and progesterone supplementation. The research is controversial at times, yet there are abundant opportunities to develop the technology behind hypothermia and hyperbaric oxygen treatments which would surely aid in aligning the current data. Additionally, while progesterone has already been packaged in nanoparticle form it may benefit from continued formulation and administration research. The treatments and the avenues for improvement are reviewed in the present paper.

**Keywords:** TBI, treatment, hypothermia, hyperbaric, progesterone

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## Introduction

Traumatic brain injury (TBI) afflicts approximately 1.7 million individuals annually in the United States and a third of all injury-related deaths in the US list TBI as a contributing cause.<sup>1</sup> Despite such a resounding influence in health, TBI treatments are lacking. Currently, more than ever, national spotlight has been placed on TBI whether in sport, combat, or everyday living. The current guidelines for severe TBI management, as detailed by the Brain Trauma Foundation, contain few level I recommendations and most level II suggestions are prophylactic measures aimed at reducing the risk of secondary complications, including intracranial pressure (ICP) and cerebral perfusion pressure (CPP) monitoring as well as antibiotic treatment.<sup>2</sup> One strong level I measure is to avoid administration of high dose steroids, such as methylprednisolone, which are linked to increased mortality among TBI patients.<sup>3</sup> In fact, ICU treatment protocols for TBI are frequently deviated from and may produce extra-cranial complications, as described in a prospective study by Schirmer-Mikalsen et al,<sup>4</sup> further displaying the disagreement upon treatment options.

One difficulty for treatment efforts is the lack of effective pharmacotherapy in the acute injury phase. A comprehensive review of randomized controlled trials (RCTs) showed that the majority of acute pharmacological treatments had no beneficial or adverse effects on TBI outcomes, suggesting other acute interventions may be more advantageous.<sup>5</sup> A likely explanation for the lack of effective pharmacotherapy is the absence of an accurate and complete mechanism for TBI. TBI encompasses a heterogeneous collection of injuries which vary in severity and localization, often either focal or diffuse, thus justifying many treatment options. These novel treatments provide research avenues for the biomedical engineering community aimed at enhancing the current technology and techniques to better personalize treatment protocols to both the patient and injury type.

The goal of the present review will be to describe immediate hypothermia, hyperbaric oxygen, and progesterone treatment for TBI of all severities and in all ages as well as the areas which may be improved upon. The treatments selected do not represent the full breadth of therapeutic options but do

represent areas where potential improvements may be introduced.

## Immediate Hypothermia Treatment

Induction of hypothermia after TBI as a treatment has been used for decades. Yet data has both supported and undermined its establishment as routine treatment; the current POLAR-RCT in Australia and New Zealand aims to confirm its prophylactic benefit. Immediately after brain injury, many biological reactions take place leading to cell death including pathological neuroexcitation, inflammation, free radical generation, and opening of the blood-brain barrier (BBB). Earlier work using an *in vitro* serum deprivation model has displayed a reduction in such apoptotic pathways when hypothermia is induced.<sup>6</sup> Hypothermia's benefit may stem from diminishing cerebral metabolic rates and thus slowing the damage which occurs after TBI. Quantitatively, for every degree Celsius drop in temperature, brain oxygen consumption is capable of dropping 5%–7% which reduces energy expenditure in the brain while maintaining blood oxygenation levels.<sup>7</sup> Hypothermia serves to slow an ischemic cascade, reduce BBB breach, slow reactive oxygen species (ROS) generation, and lessen inflammation. Recent work found that children treated with hypothermia after TBI had reduced CSF levels of dimethylarginine.<sup>8</sup> Dimethylarginine is a nitric oxide synthase inhibitor, blocking production of the potent vasodilator nitric oxide. Thus, hypothermia acutely permits vasodilation and increased perfusion to cerebral tissues which may mitigate secondary damage of TBI. Mild hypothermia after severe TBI also lowers the critical brain tissue oxygenation threshold, reduces anaerobic metabolism, and decreases release of excitatory amino acids; however, in that same study, patients admitted with spontaneous hypothermia had worse outcomes with contradictory findings.<sup>9</sup> Thus, the clinical data is still controversial, partly due to the variation in cooling protocols techniques, and equipment in addition to the breadth of physiologic processes affected by hypothermia.

A large phase III clinical trial aimed at studying hypothermia's benefit provided early insight into protocols for hypothermia. 392 patients who suffered TBI-induced coma were admitted to a hospital where half underwent a surface cooling treatment technique. On average, gradual cooling occurred between 4.1



and 8.3 hours post-admission, was maintained for 48 hours, and then the re-warming phase was slower. Patients who were cooled did not fare better than the normothermic group.<sup>10</sup> The authors attributed the result to inherent individual variation concerning treatment strategies. However, re-analysis of data demonstrated that patients who arrived at the hospital already hypothermic had significantly better outcomes.<sup>10</sup> Together, the results suggested the expediency of hypothermia induction was vital. Curiously however, recent work by Rubiano et al<sup>11</sup> in the Pennsylvania Trauma Outcome Study (PTOS) found that TBI patients admitted with spontaneous hypothermia were 1.7 times more likely to die compared to those admitted with hypothermia. Additionally, the National Acute Brain Injury Study: Hypothermia II (NABIS: H II) was terminated due to futility and could not confirm the utility of early hypothermia (within 2.5 hours) in patients with severe TBI.<sup>12</sup> Furthermore, pediatrics patients with severe TBI that were treated with hypothermia within eight hours post-injury were at an elevated risk for adverse outcomes (RR = 1.41) and death (RR = 1.40).<sup>13</sup> Overall, these works suggest the presence of many confounding variables in the clinical setting such as the degree of initial hypothermia, the rate of cooling, the severity of TBI, and even age.

Plenty of recent literature suggests benefits to controlled hypothermia and stresses the importance of time-course of treatment. Mild-induced hypothermia (MIH) (32 °C–35 °C) in the acute and subacute phases is used as a prophylactic treatment to prevent brain edema.<sup>14</sup> Additionally, late phase MIH has proven effective in maintaining a reduced ICP, reduced mortality, and better Glasgow Outcome Scale (GOS) outcomes.<sup>15–18</sup> Yet, as is seen in a number of studies, technologies and protocols must become more consistent. The incredible variation inherent in cooling protocols makes it difficult to assess whether hypothermia is indeed beneficial. What has become clear is the need for rapid, controlled-induction of cooling followed by a gradual re-warming phase.

Harris et al<sup>19</sup> and Urbano and Oddo<sup>14</sup> advocate the generation of algorithms to manage cooling while limiting potential side effects such as shivering, infection, electrolyte disturbance, arrhythmia, and reduced cardiac output. Traditionally, two general cooling technologies have been utilized: surface (either whole

body or head-localized cooling) and vascular. Such a comparison exemplifies the variation in hypothermia treatment as they each pose unique risks and benefits which hinder comparison of hypothermia studies. For instance, surface cooling technologies run the risk of skin lesions,<sup>14</sup> whereas intravascular cooling devices are associated with risk of venous thrombosis.<sup>20</sup> A systematic review by Harris et al<sup>19</sup> found nasal coolants and liquid cooling helmets to be more effective cooling techniques, capable of reducing temperature by  $>1$  °C/hr. The rate of cooling is especially important because work suggests the optimal window for initiating cooling is 90 minutes post-injury and that hypothermia should last 48 hours.<sup>21,22</sup> Nevertheless, quantitative thermal modeling may benefit the future research in the field. Implementation of the Pennes Bioheat equation and the study of bioheat transfer have gleaned insight into routes for improvement. In their review, Diller and Zhu<sup>7</sup> suggest that the development of technologies aimed at reducing body temperature by 2 °C within 90 minutes may be an effective treatment advancement.

### **Hyperbaric Oxygen Therapy**

Hyperbaric oxygen therapy (HBOT) entails the inhalation of 100% oxygen at environmental pressures greater than one atmosphere. The central tenet of HBOT is to increase the partial pressure of oxygen in the blood, independently of red blood cells (RBCs), so it reaches the brain to reduce tissue loss to ischemia and hypoxia.<sup>23</sup> Thus, HBOT is theoretically similar to hypothermia, rather than decreasing energy requirements of the brain HBOT increases energy content reaching the tissues. Controversy concerning HBOT's benefits still persists; however, there is data supporting its use. In severe TBI, patients HBOT has increased  $P_{O_2}$ , decreased lactate/pyruvate, increased cerebral blood flow and cerebral metabolic rate of oxygen, and decreased ICP post-treatment.<sup>24</sup> A meta-analysis involving seven HBOT studies and over 500 patients found HBOT to be associated with a decrease in unfavorable outcomes one month after treatment using the Glasgow Coma Scale (GCS). The same study revealed the relative risk of death with HBOT was 0.69 (NNT = 7) compared to normal treated controls.<sup>25</sup> Still, the authors concede there was a high risk of bias in some of the analyzed studies; for instance, patient drop-out, lack of blinding, and



selection bias introduces a level of skepticism. One concern of HBOT are the side effects of dwelling in a pressurized room. Yet, in military service members with combat-related mild TBI there was no increase in major adverse side effects with HBOT compared to standard treatment; however, there were increased mild side effects, albeit at a very low absolute probability of occurrence.<sup>26</sup>

Monitoring brain tissue oxygenation plays an instrumental role in proper HBOT, or even normobaric, therapy for TBI. Maintaining the balance between hyperoxia and hypoxia is critical in effective HBOT management. It is possible that more consistent, accurate measurement methods would align the HBOT literature and support the case for its use.

Monitoring technologies involve the placement of a catheter into the brain parenchyma in one of two manners. The first are Clark-based catheters which contain two metallic electrodes surrounded by electrolytes and a permeable membrane that allows oxygen to pass, become reduced, and detected by a gold polarographic cathode.<sup>27</sup> An electrical current is produced, which is proportional to the oxygen concentration in the parenchyma. An example of such a device is the Licox probe (Integra Neurosciences-Plainsboro, NJ), which also boasts minimal procedural complications including hematoma, infection, and dislodgement.<sup>28</sup> The alternative utilizes optical sensors and wavelength analysis to quantify oxygen concentrations via a photochemical reaction visualized by indicator compounds.<sup>27</sup> In contrast to the Clark-based devices, these optical sensors do not utilize oxygen in the measurement process.

Other methods aimed at intracranial monitoring should be noted as well, particularly of ICP. The current gold standard for ICP measurement is the external ventricular drain (EVD). However, other options are used when the EVD is contraindicated due to limiting ventricular anatomy, for instance intraparenchymal (or 'Bolt') monitors, subdural, and extradural monitors.<sup>29</sup> ICP spectral waveform analysis, which measures heart rate, slow vasogenic waves, and respiratory waves, has also been utilized. Farahvar et al<sup>29</sup> provided a call to bioengineers to improve the computational analysis involved to allow more sophisticated use of the spectral software. An added benefit would be that the improved waveform analysis may subsequently provide insight into the pathophysiology of TBI.

Technologies capable of identifying ICP and brain oxygenation with high resolution would offer the clinician the ability to prevent an elevated ICP and carefully monitor the balance between hypoxia and detrimental hyperoxia in patients. Thus both immediate hypothermia and HBOT display promise, yet, varied treatment and measurement technologies introduce difficulty in comparing studies; more uniform, accurate techniques would hopefully abolish this issue.

## Progesterone Treatment

Many of the present TBI pharmacotherapies have utilized drugs which act on single pathways. In a perspectives piece, Stein<sup>30</sup> argues that a pleiotropic hormone capable of acting on genomic, proteomic, and metabolic mediators may confer increased neuroprotection compared to single target drugs. Stein names progesterone as a candidate and current research lends credibility to this notion.<sup>30</sup> The membrane bound progesterone receptor (mPR $\alpha$ ) is expressed in neurons throughout the mouse brain, but not in glia. However, upon induction of TBI, mPR $\alpha$  drastically increases in oligodendrocytes, astrocytes, and reactive microglia, suggesting a neuroprotective role of progesterone signaling.<sup>31</sup> Progesterone at low doses even promotes cell proliferation, the innate immune response, blood vessel remodeling, and is anti-apoptotic.<sup>32</sup> Furthermore, the union of data from three studies examining progesterone for the treatment of acute TBI revealed lower relative risks for mortality (RR = 0.61; 0.4–0.93 CI) and severe disability (RR = 0.77; CI 0.62–0.96) after follow-up compared to controls.<sup>33–36</sup> Interestingly, the effectiveness of progesterone treatment is enhanced with vitamin D supplementation. Patients who suffered brain trauma and were administered intramuscular progesterone within 8 hours of injury along with vitamin D displayed higher recovery rates, more favorable GOS outcomes, and lower mortality.<sup>37</sup> Overall, progesterone treatment appears to be well received, yet the hormone has proven difficult to administer at both high dose and low volume due to its lipophilicity and ability to crystallize. Exploration into the use of nanoparticle drug formulations in a preclinical study has shown preliminary success in combating these troubles. For example, Figueroa et al<sup>38</sup> used Flash NanoPrecipitation in the production of 300 nm progesterone-loaded

nanoparticles with dissolved rather than crystallized hormone. The authors suggest this formulation would be beneficial in the emergency treatment of TBI where progesterone may be rapidly administered. Currently underway is the phase 3 SyNAPSe clinical trial which aims at determining whether IV progesterone given within 8 hours of severe TBI for 120 hours will enhance patient recovery. The study is a randomized, double-blind, placebo-controlled trial which may further support progesterone administration.

## Conclusion

This paper examined the current literature on induced-hypothermia, hyperbaric oxygen, and progesterone for the treatment of TBI. The brief description represents a limited view of the entire breadth of therapies, and since TBI entails a wide variety of damages it comes to no surprise that treatments differ based on the patient's present situation. For instance, other treatment options not presently discussed include osmotic therapy, decompressive craniectomy, and pharmacotherapy; of particular note is the ongoing clinical trial examining the effects of erythropoietin post-TBI. Indeed the majority of damage comes at the moment of injury, making mitigation of secondary insults a primary treatment goal. As has become evident, there are opportunities to expand upon the treatments of TBI, including reducing the cons of specific cooling techniques, standardizing and optimizing brain oxygen monitoring, and improving formulations and routes of administration of progesterone. Additionally, the continued elucidation of the pathophysiology of TBI will both supplement and provide further prospects for development in the field.

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ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

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