

## Brain Injury: On the Verge of a Breakthrough

By David Durham, M.D., M.P.H.

Before the wars in Iraq and Afghanistan, the topic of brain injury was primarily a discussion among physicians and ancillary rehabilitative therapists who treat brain injuries. Today, it has become one of medicine's obsessions, and one of the most common topics for news stories. More compelling than the myriad of statistics being compiled by numerous civilian and governmental organizations, are the subtleties of how our brain cells react immediately after an injury as well as the months and even years after an injury.

I would submit that medicine has probably been most enlightened by knowledge of what occurs months and years after an injury, specifically how the brain attempts to adapt at the cellular level, and the constellation of neuropsychiatric symptoms associated with specific anatomical regions of the brain. Today, TBI's mortality (cause of death) and morbidity (cause of significant physiological impairment) is more than 50 percent. It is the largest cause of death and disability in young persons under forty years old. This includes not just the many brain injuries in the war zones but brain injuries resulting from car accidents and other traumatic events.

Until only recently, there were few, if any, options to slow or arrest the propagation of cellular injury that occurs rapidly after trauma to the brain. The dilemma is a logical one: injured brain tissue swells from both the breaking open of cells and blood vessels and the body's emergent response to the injury, causing a net decrease in the amount of blood delivered to the area, and thus a net decrease in the amount of oxygen. Damaged and non-damaged cells in the immediate and surrounding areas subjected to the reduction in oxygen delivery are further damaged. Many die.

For physicians, time is never on our side. It is the enemy of the nearly 80% of the brain injured patients that die from cerebral ischemia (reduced oxygen to the brain). Those that survive an ischemic event most often fared much more poorly in their rehabilitation, and thereafter in their daily lives. The solution is a logical one as well: either (1) increase the pressure delivering the blood to the damaged area (cerebral perfusion pressure) thereby delivering more oxygen as a result, or (2) deliver more oxygen by altering the body's internal and external pressure (e.g. hyperbaric oxygen chamber) or (3) deliver oxygen to the area via another mechanism.

It is the third which has recently become potentially the greatest medical breakthrough for treating brain injuries to date: increasing dissolved oxygen levels in the blood, and thus the brain, by using perfluorocarbons (PFCs).

Because oxygen is dissolved into PFCs, and not tightly bound as it is in hemoglobin, PFCs can deliver oxygen at twice the rate of our own hemoglobin. Furthermore, PFCs have been now shown to enhance the ability of nearby blood cells (erythrocytes) to unload their oxygen by improving diffusion capacity (a measurement of a tissue's ability to transfer gases like oxygen and carbon monoxide). This has been shown to occur even in low blood-flow states (e.g. as in injured tissue that is swollen). A PFC particle is about  $1/35^{\text{th}}$  –  $1/40^{\text{th}}$  the size of an average blood cell.

PFCs, carrying oxygen, are much more effective at penetrating into constricted capillaries too small for red blood cells. When a PFC reaches its delivery area, its extremely small surface area makes for a massive increase in surface area available for gas exchange. The net benefits of PFCs are crystal clear: they deliver oxygen at twice the rate of our own blood, they deliver more oxygen than our own blood cells, and they positively alter the oxygen/gas – exchange process by making it more efficient, thereby helping nearby red cells “unload” their

oxygen faster. PFCs have been shown to specifically benefit brain tissue that is more prone to ischemic injury. Namely, the Hippocampus – the brain’s storage depot for memories. Cellular death in the Hippocampus is the most detrimental injury to a brain injury patient’s memory.

The most costly damage most often occurs as a ‘secondary injury’ long after the event itself. It slows rehabilitation and is almost always permanent to a great extent. It dramatically increased the risk of Alzheimer’s-type and Vascular dementia. PFCs have been proven to have a ‘neuroprotective’ effect on cells in the brain’s Hippocampus thereby improving recovery of the brain’s ability to process, manage and retrieve memories. The benefits of PFCs to treat brain injuries is clear, but what are the risks considering other available treatments verses no treatment?

PFCs, like all medicines, have side effects. But a comprehensive review of the more than three decades of research, as well as the FDA’s own on-going investigation, indicate the new generation of PFCs, which are currently proposed to be used for treatment, are relatively safe. When compared to the existing treatments and then including no treatment at all, there really isn’t an argument whether to use PFCs. There is only the question: why haven’t we yet? PFCs can cause a drop in blood Platelets (called thrombocytopenia), which are important for blood clotting and contribute to the volume of blood, thereby stabilizing pressure within the arteries and veins of the body.

The new generation of PFCs (specifically, Oxycyte, being studied right now at Virginia Commonwealth University) do not appear to significantly cause more thrombocytopenia than what already occurs in brain injury patients (who are already at significant risk for thrombocytopenia from their injury). Brain injury patients, like all critically injured patients, are at an increased risk for infection, especially ‘nosocomial’ (hospital-based) infections. Analysis of the data from the past three decades of using PFCs experimentally, and most specifically, from initial data from a 9-patient trial at Virginia Commonwealth University (VCU) seems to indicate PFCs increase the global risk of infection.

When one, however, compares this risk with the existing risk of infection inherent to TBI patients (found to increase linearly with the severity of injury), the risk is modestly increased. When the infection rate is compared to recent findings, primarily from the VCU study, there doesn’t appear to be much of a difference. In fact, when one includes the incidence of infection one year after suffering a traumatic brain injury, and completion of neurological rehabilitation, PFCs might even have lowered the infection rate in the VCU study.

There have been a number of gifted and dedicated physicians and scientists over the years who have attempted to tackle the seemingly impossible task of increasing oxygen delivery to injured brain tissue within the critical window immediately after an injury. Many have brought highly compelling results of their proposed therapies before the Federal Drug Administration, only to be caught in the quagmire of beauracy and endless ‘hearings’. Public records indicate most of the questions and discussions instigated by the FDA as a result of the proposed use of a ‘blood substitute’ have focused almost entirely on the proposed drug’s physiological effects (e.g. causing anemia and other adverse effects) but not the comparative risks verses benefits of a proposed drug and other available treatments (essentially none) and that of not receiving any treatment.

The public is now more aware of both the beneficial work of the FDA, and their weaknesses which are a growing concern to both American medicine and the American public. The greatest risk, at present, that appears to confront patients suffering from severe traumatic brain injuries – to absolutely include our soldiers, marines and sailors – is our own government. It is my solemn hope that this risk will be quickly overcome, for the sake of those whose enemy is time.

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