Traumatic Brain Injury (TBI)—A Brief Review of the Role of DMSO.

by Stan Jacob, Jack de la Torre, Colette Cozean

Two thirds of the injuries sustained in the Iraq war are traumatic brain injuries (TBI).

By contrast, the percentage of TBI during prior wars was only 20%. This dramatic increase is primarily due to improvised explosive devices and a decrease in other injuries resulting from the use of improved body armor. The Veterans Administration is gearing up to treat 10,000 patients with clinical sequellae of brain injuries resulting from the Iraqi war. Traumatic brain injuries, both closed and penetrating, result in the loss of life, permanent physical and mental impairment, and long term treatment requirements, but also affect every member of a military family.

In terms of human suffering, medical expenses, and lost productivity, head injury is one of the major health care problems in the United States.

Apart from the casualties sustained in the Iraq war, 1 million people are estimated to incur traumatic brain injuries every year in the US. Vehicular accidents, falls (primarily children and seniors) and athletic injuries are the main causes of these brain injuries. Of the 1 million TBI events, 230,000 result in hospitalization with 50,000 annual deaths (Center for Disease Control statistics). About 60,000 per year sustain severe, closed head injuries, defined as blunt, non-penetrating trauma to the brain causing an altered state of consciousness with possible permanent impairment of mental, physical and emotional functioning. Of these 60,000 patients hospitalized annually for severe, closed head injuries, approximately 39,600 (66%) will die shortly following injury, regardless of whether they are treated in a major trauma center or a small community hospital. This high mortality rate reflects the lack of a genuinely effective treatment for TBI. To add to these catastrophic statistics, the majority of the survivors sustaining severe TBI will endure neurological disability for the remainder of their lives.

TBI Equates with Staggering Healthcare Costs

The cost of TBI in the United States is estimated at $48.3 billion dollars annually, with hospitalization accounting for $31.7 billion. These figures do not include the recent rise in military expenditures to treat TBI. Such expenditures places TBI as one of the key targets to reduce the burden of healthcare that is currently compromising the U.S. economy. DMSO provides a scientifically & economically valid means to reduce mortality, morbidity & healthcare costs associated with TBI.

Other Agents in Current Use for TBI Do Not Optimize Outcome

Primary concerns after TBI include insuring proper oxygen supply to the brain and the body, maintaining adequate brain blood flow, controlling blood pressure, and controlling intracranial pressure. The latter frequently is accomplished via major neurosurgery and involves removing a portion of the skull. Standard treatments now in use include **osmotic diuretic agents**, such as urea and mannitol for the control of intracranial pressure (ICP).[1] Osmotic diuretics also lower blood viscosity which can be higher in brain traumatized patients. Mannitol is commonly administered to lower ICP but repeated doses are known to induce hyperosmolar states that render it ineffective and

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Pathological Targets of DMSO

Pathologic Event	DMSO Action
Calcium influx	Attenuates
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Cerebral hypoperfusion (ischemia)	Increases flow
Free radical formation	Scavenges
Glutamate excitotoxic death	Prevents
Inflammatory activity	Suppresses
Intracranial pressure increase	Reduces
Na^+ channel activation	Blocks
Neurologic disability	Reduces
NMDA-AMPA channel activation	Suppresses

ially dangerous as result of inducing renal failure.[2] onally, high doses mannitol can result rebound effect ICP becomes than before ment .

ds were used widely past to treat head but many studies shown these agents ineffective in ng ICP or improving me.[3-8] The use of tirilazad, a non-glucocorticoid-21-amino steroid, showed great potential during animal experiments as a strong anti-oxidant and inhibitor of lipid peroxidation-induced free radicals.[9] However, tirilazad was not demonstrated to be effective in human TBI trials.[10] Another highly promising anti-oxidant, **polyethylene-glycol conjugated superoxide dismutase** (PEG-SOD), was reported to be ineffective in a multi-center trial for severe head injury.[11]

Barbiturate therapy was originally suggested as a possible treatment for reducing ICP.[12,13] However, subsequent prospective studies reported no improvement in outcome and a dangerous tendency of this agent to provoke hypotension, thus reducing cerebral perfusion pressure[14] and worsening cardiovascular compromise, a condition likely to be fatal in geriatric patients.[15] **Dexanabinol**, a non-psychotropic cannabinoid NMDA receptor antagonist, also showed no efficacy in a clinical trial involving over 800 TBI patients. Other pharmacological agents that have been proposed as possible treatments for head injury include **calcium channel blockers, prostaglandin metabolites** and **anti-inflammatory compounds**. However, none of these treatments have shown consistent clinical efficacy.[16-18]

DMSO Pre-clinical Studies in TBI

Dimethyl sulfoxide (DMSO) has been shown to be a powerful free radical scavenger,[30,31-33,34,35] with antiinflammatory and cell membrane stabilizing activity.[36-38] DMSO has also been shown to decrease cerebral edema in rhesus monkeys and in humans.[26,27,39-41] DMSO has the ability to increase cerebral blood flow (CBF) following a variety of cerebral insults, possibly as a result of reducing tissue edema and lowering cerebrovascular resistance.[21-23,34,40] DMSO has been reported to improve neurologic and functional outcome after induced brain ischemia in animals, including non-human primates.[42-47]

In addition, dimethyl sulfoxide has been shown to be a sodium channel blocker.[28,29] Drugs that block voltage-dependent Na^+ channels have been shown to exhibit strong neuroprotective activity in animal models of brain ischemia/hypoxia. A number of clinical trials are currently in progress to test this class of drugs when cerebral ischemia is present.[48-51]

DMSO given at clinical concentrations suppresses, in a reversible manner, excessive calcium influx into cells and channeling of the ionotropic receptors D- and α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA) which are known to be activated by glutamate during metabolic or oxidative stress.[32] This "excitotoxic" process by glutamate, which can damage or kill neurons, has been recently reported to be blocked by DMSO.[32] The Na^+, NMDA, AMPA and calcium channel blocking activity by dimethyl sulfoxide.[28,29,32] could in part explain its beneficial effect when administered to patients presenting with high ICP secondary to severe, closed head injuries [26,27] or in the presence of cerebral bleeding resulting in clinically elevated ICP.[22]

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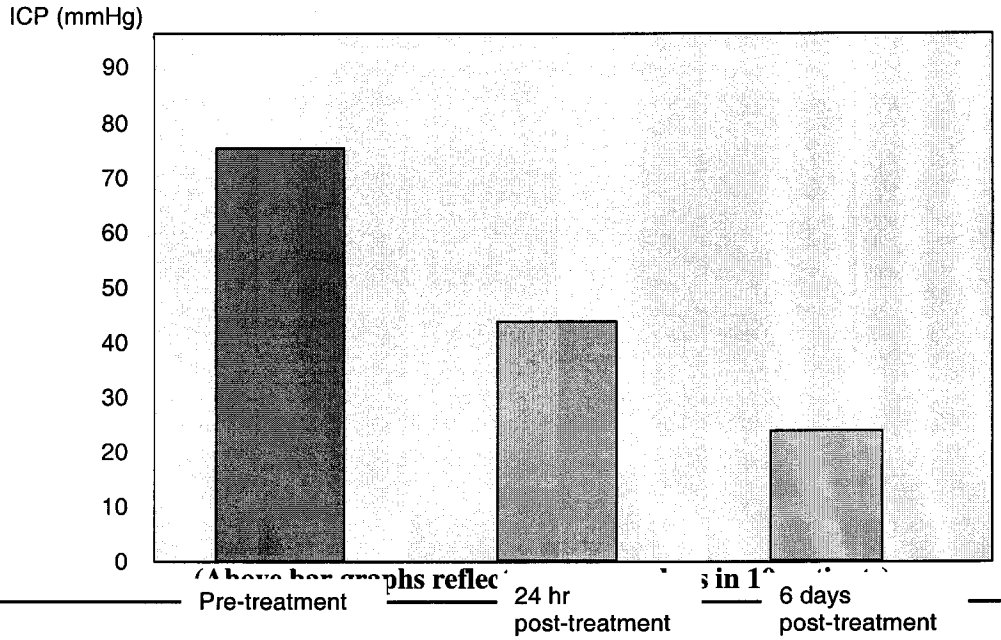
DMSO Clinical Studies in TBI

Due to the consistent safety and efficacy demonstrated by DMSO (dimethyl sulfoxide) in dozens of animal experiments,[52] a preparation containing sterile, pharmaceutical grade 28% DMSO was given every 6 hours intravenously (1 gm/Kg) or as needed to reduce ICP for a mean period of 7 days to 20 patients presenting with raised ICP secondary to severe closed head injury. All twenty patients had a Glasgow Coma Scale (GCS) of 8 or less and all showed a reduction of ICP quickly after treatment with dimethyl sulfoxide.[26,27] ICP pressures ranging from 40-127 mm Hg were reduced to normal within 6 days of treatment with DMSO.

Reduction in Intracranial Pressure with DMSO
Karaca et al.[27]



GCS returned to normal (15) or near normal (13) in all but 3 patients.[26,27] No changes in cardiac output, blood pressure or serum glucose were seen in the treated patients. No adverse events were attributable to DMSO treatment and DMSO was well tolerated in this patient population. Of the 20 patients treated, 5 died (25%) and 2 (10%) had severe disability; **75% survived**. Neurologic assessment 3 months after discharge from the hospital using the Glasgow Outcome Score showed a rate of favorable outcome (good recovery or mild disability) in 13 patients (65%).[26,27] Historically, mortality after severe closed head injury ranges ranges from 60-70% and the rate of favorable outcome in the survivors ranges from 20-30%, i.e. ***historically, approximately 8% of all patients with TBI have a good recovery v. 65% in this study***. The excellent results reported in this European clinical trial were statistically significant.

DMSO U.S. Clinical Studies in Preparation

DMSO is presently ready for human clinical trials for the treatment of severe head injury in 30 patients at three sites. Abela Pharmaceuticals has been granted an IND (Investigational New Drug, NR 39,262) by the FDA and *Orphan Drug Product status* (NR 94-813). Oregon Health and Science University has been selected as one of the three sites. DMSO has also been given ***"fast-track"*** designation by the FDA since:

- DMSO is aimed at a "life threatening" condition of major prevalence.
- Early clinical results demonstrated significant improvement in patients.
- There has been no significant improvement in pharmacologic treatment of TBI for decades.

Fast track review can considerably reduce clinical testing expenses and shorten the timeframe to market approval since it essentially eliminates phase III and reduces the total number of subjects required during clinical testing. In addition, the FDA's position (FDA Consumer Special Report, January, 1995) on orphan drugs such as DMSO is that they are typically *reviewed* and *approved faster* than other products because they require less data to prove their safety and effectiveness.

DMSO in TBI: Funding Proposal

Oregon Health and Science University (OHSU) has led the research on DMSO for more than 40 years. Stanley Jacob, Professor in the Department of Surgery at OHSU and formerly of Harvard Medical School, discovered the clinical uses of DMSO. Dr. Jacob has published numerous books and articles on the clinical applications of DMSO. Based on the OHSU work, the University has been selected along with Cornell in New York and a third center (to be selected) as the sites to perform human trials of i.v. DMSO in the treatment of TBI. The funding of this multi-study trial would primarily support the work at OHSU, with smaller amounts to the other Universities to confirm OHSU's results. The details of the grant proposal are to be found in Appendix A. If early results confirm the findings of the previously published studies of Kulah et al & Karaca et al, then Dr. Rich Mullins, a Captain in the Navy Reserve who served a tour in the Iraq war in 2003, would be available to travel to Iraq to train neurosurgeons in the use of DMSO to reduce intracranial pressure in trauma situations. **Therefore, financial support for this proposal could translate into a near immediate impact on the survivability of our men and women in Iraq and Afghanistan as well as their long term neurological viability and functional progress.**

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Appendix A
Funding Proposal
TBI Clinical Trial

		Total
Clinical Sites		
	OHSU research fellow	$75,000
	OHSU clinical coordinator	$50,000
	Cornell fellow	$75,000
	Third center fellow	$75,000
		$275,000
Supplies		
	DMSO sterile and pyrogen-free	$120,000
	Ventilators	$12,000
	Misc. (masks, O_2 filter)	$36,000
		$168,000
Clinical Monitoring		
	Clinical monitoring	$100,000
	Medical monitoring	$60,000
	Clerk for data entry	$24,000
	Monitoring supplies	$16,000
		$200,000
Travel		
	Trips to clinical sites (6)	$27,000
	Presentation of results at scientific meetings	$5,000
	Iraq trip and salary for Dr. Mullins	$23,000
		$55,000
Total		$698,000
OHSU Overhead - 33%		$230,340
Grand Total		$928,340

Assumptions:
Phase 1 30 patients (1/2 control) at 3 sites
Phase 2 (partial) 30 patients