Past, Present, and Future of Traumatic Brain Injury Research

Gregory W.J. Hawryluk, MD, PhD[a], M. Ross Bullock, MD, PhD[b,*]

KEYWORDS

• Traumatic brain injury (TBI) • Research • Secondary injury • Clinical trials • Trends • History • Big data

KEY POINTS

- Traumatic brain injury (TBI) is the greatest cause of death and severe disability in young adults; its incidence is increasing in the elderly and in the developing world.
- Mortality rates have decreased from more than 80% for severe TBI in the 1940s to about 20% currently in well-resourced hospitals, largely as a result of improvements in trauma systems and supportive critical care.
- Recognition of secondary injury and secondary insults has led to novel basic science and clinical approaches aimed at improving outcomes from TBI.
- Over 30 late-phase clinical trials have failed to translate a therapeutic agent for clinical use and numerous explanations for this failure have been postulated.
- New research is armed with lessons from past trials, new scientific advances, as well as improved research infrastructure and funding; there is great hope that an effective therapeutic for TBI will be translated to clinical use in the coming years.

INTRODUCTION

Traumatic brain injury (TBI) of any severity has the potential to devastate the lives of patients over minutes or hours. An intracranial hematoma can transform an active life to a vegetative state, death, or severe disability more dramatically than almost any other consequence of trauma. The evolution of trauma care systems, rapid delivery of imaging, neurocritical care, and rehabilitation has improved outcomes.[1] In contrast, despite 8 decades of research aimed at developing targeted "neuroprotective" drug therapies for severe TBI, none has been successfully translated. Although the same holds true for occlusive stroke, multiple sclerosis has, in contrast, been transformed by new drugs.[2] TBI scientists have revealed many pathologic molecular processes that cause progressive brain damage after the initial injury, suggesting a therapeutic window and multiple potential drug targets. Paralleling this basic science advancement is recognition of the methodologic shortcomings of the approximately 35 phase III TBI trials undertaken to date, which likely contributed to their failure.[3] There is thus great optimism that victims of TBI may soon benefit from novel and efficacious therapeutics that have been long elusive. In this article, we aim to provide an overview of TBI research to date, both successes and failures, with a particular focus on putative reasons for the failure to translate preclinical findings into clinical trial success (**Table 1**).

[a] Department of Neurosurgery, University of Utah, 175 North Medical Drive East, Salt Lake City, UT 84132, USA;
[b] Neurotrauma, Department of Neurosurgery, Miller School of Medicine, Lois Pope LIFE Center, University of Miami, 1095 NW 14th Terrace, Miami, FL 33136, USA
* Corresponding author.
E-mail address: rbullock@med.miami.edu

Neurosurg Clin N Am 27 (2016) 375–396
http://dx.doi.org/10.1016/j.nec.2016.05.002

Table 1
Themes in the advancement of the traumatic brain injury field: past, present, and future

	Basic Science Advancement	Advance in Clinical Management	Major Research Efforts
Past	Recognition of secondary injury and secondary insults	Birth of clinical practice guidelines and efforts to standardize care; treatment thresholds for physiologic parameters (ICP, CPP, Pco_2, etc)	Numerous clinical trials of neuroprotective agents
Present	Introspection relating to trial failures of the past; increased focus on mild/repetitive TBI, chronic traumatic encephalopathy; increasingly robust preclinical data (Operation Brain Trauma Therapy); cell therapies and early regenerative medicine strategies	Recognition of the importance of cerebrovascular autoregulation; the IMPACT model and improved prognostication; development of common data elements; maturation and expansion of guidelines efforts; scrutiny of the role of conventional treatment (ICP monitoring and decompressive craniectomy)	Novel trial and analytical methodologies (more sensitive statistics, comparative effectiveness research)
Future	Novel neuroprotectants and regeneration-stimulating agents	Shift from routine implementation of guidelines to "personalized medicine" accounting for patients' unique physiology and physiologic states	Big data in research efforts and in care of individual patients, improved classification scheme for TBI; greater use of genomic and proteomic data; studies of combinations of agents; more sensitive outcome measures

Abbreviations: CPP, cerebral perfusion pressure; ICP, intracranial pressure; TBI, traumatic brain injury.

EPIDEMIOLOGY

TBI is changing demographically. Economic growth in developing nations such as Brazil, China, and India has led to an increase in motor vehicle use and a significant increase in TBI in these countries.[4,5] Additionally, in the United States, Europe, and Japan an increasing proportion of TBI is being seen in the elderly as a result of falls.[6] TBI remains, however, the leading cause of death in young adults under the age of 45 in the United States and is believed to cost society more than $60 billion annually.[7] Fortunately, only 10% of the 500,000 people admitted to hospital for TBI each year sustain a severe injury.[8] One-third who sustain severe TBI die and survivors frequently have lasting deficits of motor, sensory, and cognitive functions.[8] Despite the increase in incidence, the outcome after TBI is improving though these outcomes depend on the quality of care provided.[1,5] An analysis of survival in placebo groups in major head injury trials has noted progressive improvement since the mid 1980s: contemporary mortality rates are now less than one-half of what they were 3 decades ago.[9]

Almost one-third of Americans will sustain a mild TBI, or concussion in their lifetime, and increasing evidence suggests that cumulative concussions, or concussion in vulnerable individuals may progress to dementia, a potential future public health and "social engineering" dilemma of massive proportions, that is covered elsewhere in this issue. Likewise, penetrating TBI owing to gunshot and explosive shrapnel injuries has increased significantly in the United States.

TRAUMATIC BRAIN INJURY RESEARCH METRICS

Meaningful TBI outcomes and demographic research was not possible until the advent of the Glasgow Coma Scale (GCS) in 1974.[10] This scale