Comparative effectiveness research in neurotrauma

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Comparative effectiveness research (CER) is emerging as a commonly applied technique to determine the usefulness of medical interventions. Such research aims to compare various treatments for specific disease entities for overall effectiveness and potential for harm. According to the Centers for Disease Control, an estimated 1.7 million patients sustain a traumatic brain injury (TBI) annually in the US. In this review the authors examine the existence of CER reports in the area of neurotrauma to date and consider the context in which clinical research and evidence-based guidelines have and will continue to inform such analyses, with special attention to TBI.

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The use of comparative effectiveness research in neurotrauma is newly emerging but with deep roots in the history of neurotrauma research, particularly in the area of TBI. A plethora of basic science research into TBI has demonstrated diverse pathophysiological processes involved in secondary injury and has described many of their effects on outcome. Clinical research into the efficacy of various interventions has yielded advances when focused issues have been addressed and alternative research methodologies have been used. Improvements in outcome have been demonstrated by the utilization of standardized evidence-based treatment protocols. However, several large-scale prospective randomized controlled trials have yielded few meaningful results. Because CER aims to demonstrate the effects of two or more interventions on outcome, clinical researchers must conceptualize future studies in innovative ways if meaningful comparisons are to be made. While SCI (affecting an estimated 12,000–20,000 people annually in the US) and peripheral nerve injury affect far fewer individuals, the impact on lifelong functionality is great. To date few studies have addressed CER in neurotrauma despite the widespread incidence, potentially devastating impact, and massive financial burden associated with injuries to the nervous system.

Abbreviations used in this paper: AHRQ = Agency for Healthcare Research and Quality; CER = comparative effectiveness research; EBM = evidence-based medicine; EPC = Evidence-Based Practice Center; EU = European Union; NIH = National Institutes of Health; SCI = spinal cord injury; TBI = traumatic brain injury.

Evidence-Based Medicine

Since ancient civilization, physicians have been wrestling with questions of prognostication after TBI. The Egyptian physician(s) who described various forms of brain injury between 3000 BC and 1700 BC in the Edwin Smith Papyrus divided cases of brain trauma into those thought to be treatable and those that were “not to be treated.” Since the early efforts at organized research into TBI outcomes in this century, functional outcome has taken center stage. Even in those early studies addressing questions of mortality, the specter of the surviving but neurologically devastated patient loomed large and has remained at the forefront of research and clinical decision making in this area—in part because decisions affecting survival must be made in very short time frames, with incomplete information, and often without the participation of family so that clinicians are required to act on the patient’s behalf. Furthermore, a cascade of complex physiological processes that affect the degree of secondary injury continues to influence patient outcome and is susceptible to variable circumstances, including the presence or absence of other injuries, patient age, mechanism of injury, comorbidities, rapidity of transport and intervention, experience of caregivers, resources for care, and environment of care. We are only beginning to scratch the surface of our understanding of genetic and other biological influences on outcome. Appropriately, the focus has been on improving mortality after moderate and severe TBI in recent decades, which has largely been successful. Attention to resuscitative efforts to avoid hypoten-
sion and hypoxia can significantly reduce mortality.\textsuperscript{14,15} Many studies have shown various functional improvements with selected management protocols.\textsuperscript{22} However, we stand at a crossroads where we must now address issues of improving ultimate outcomes in survivors so that we can optimize the quality of their lives as well as that of their families, who often shoulder the burden of lifelong debility or a very long and arduous recovery to ultimate community reintegration.

Evidence-based medicine has been used to inform decision making in TBI for almost 2 decades now, since the publication of the first neurosurgical EBM guidelines in 1996.\textsuperscript{23} Despite this relatively long history, including 2 revisions, in 2000\textsuperscript{13} and 2007,\textsuperscript{6} many questions remain regarding the effectiveness of various treatments for TBI. These guidelines were the first to address a neurosurgical problem and were variously embraced and implemented or met with skepticism and controversy. Many practitioners were reticent to accept guidelines that were thought to be prescriptive in nature. However, the emphasis of the practice guidelines has remained on identifying the best evidence for various treatments and improving the existing body of literature by raising important questions for future research. Other documents have followed, including evidence-based guidelines for pediatric TBI in 2003\textsuperscript{2} and 2012,\textsuperscript{24} prehospital management of severe TBI in 2000\textsuperscript{21} and 2008,\textsuperscript{4} surgical management of TBI in 2006\textsuperscript{7}–\textsuperscript{11} field management of combat-related head trauma in 2006,\textsuperscript{22} and management of penetrating brain injury in 2001.\textsuperscript{1} Many questions of efficacy remain for patients with specific types of injuries as well as for populations at large.

**Challenges in Assessing Clinical Effectiveness**

For clinical effectiveness to be demonstrated, it is important to describe the methodologies by which practitioner decision making can be guided by the best available therapeutic options. Once a TBI has been sustained, myriad circumstances will affect the ultimate outcome, ranging from the manner and context in which care is delivered to the many medical and surgical interventions that will be used over a patient’s lifetime. While decision analysis has sought to incorporate available evidence for TBI management, many challenges have been identified.

In the initial phases of treatment, the volume of clinical parameters being monitored in a continuous fashion, the influence of events and physiological states on said parameters, an abundance of detailed imaging data, and fluctuating physical examination status and sedation requirements that obscure the examination contribute to critical care complexity in patients with TBI. Further complicating this scenario are care delivery models that incorporate teams of individuals who frequently must sign out care to other team members and who come from different medical specialties and must co-manage injuries and medical issues related to various organ systems. Coordination and communication by care teams makes decision analysis difficult over the critical care epoch.

Sophisticated computer technology exists to aid practitioners by integrating patient data into heads-up visual displays and incorporating the data into treatment algorithms. However, limited availability of these expensive multimodal monitoring technologies makes bedside decision tree analysis intellectually difficult and labor intensive. Consequences of the complex organization of care delivery can include the overutilization of diagnostic modalities, such as repeat brain imaging; underutilization of neuromonitoring, such as intracranial pressure monitoring and brain tissue oxygenation monitoring; and overuse or underuse of various therapeutic options, such as nutritional support, seizure prophylaxis, temperature and glucose control, hyperosmolar therapy, and others.

The social fabric and economic well-being of a patient’s family dramatically impacts the effectiveness of treatment for TBI. Also affecting outcome is the geopolitical environment in which the trauma system has evolved and the patient is injured, that is, availability of services for prehospital transport, the degree of prehospital provider training and familiarity with brain injury, the standardization of airway management and resuscitation in the field, the distance and time from the scene of injury to the hospital where the patient is taken, and the trauma center status and practitioner expertise at the hospital where the patient is taken.

Many interventions can impact the effectiveness of other interventions in the treatment cascade, including those in the prehospital, hospital, rehabilitative, and community settings. Mitigating all of this variability must be a primary goal of CER.

**Comparative Effectiveness Research**

Comparative effectiveness research should have the following characteristics: research must be relevant and timely as well as objective and scientifically rigorous and should include public participation. Particular challenges for TBI research are present in each of these domains.

While all efficacy research aims to be relevant and timely, the number of patients with similar injury patterns required to generate statistical significance in TBI trials has frequently resulted in significant lag time between inception of the study and publication of the results. For example, the DECRA trial,\textsuperscript{18} in which authors studied decompressive craniectomy in diffuse TBI, enrolled patients from 2002 to 2010, and the results were published in 2011. The RESCUEicp trial (Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intra-cranial Pressure), a multinational multisite study assessing the value of hemicraniectomy, has been enrolling patients since 2006 and is still underway. The COBRIT trial (Study of Citicoline for the Treatment of Traumatic Brain Injury), a multicenter randomized prospective trial assessing the effects of CDP-choline in complicated mild, moderate, and severe TBI, enrolled patients from 2007 to 2011, and the results are currently pending publication.\textsuperscript{18} Most of the neuroprotection randomized controlled trials have been multicenter studies to accrue sufficient study populations to address the clinical question at hand. Center differences in outcome have repeatedly been observed even in the controlled settings of multicenter clinical trials, as illustrated most recently in the National Acute Brain Injury Study: Hypothermia...
II and the Pilot Data Project of the NIH-sponsored TBI Clinical Trials Network. Whether these differences in outcome are attributable to clinical decision-making processes, demographic or epidemiological differences, disparities in resources or trauma systems issues remains unclear. If a trial eventually provides evidence of neuroprotective or neurorestorative properties of agents or strategies for TBI, generalizing results to general practice may prove difficult.

Finally, unless very specific questions are asked, research in this area does not particularly lend itself to the comparison of two or more treatments.

It is not surprising, given the challenges outlined here-in, that TBI has not been an early focus of CER. However, some early efforts by the AHRQ have been made to address TBI and SCI.

**Current Status**

*Agency for Healthcare Research and Quality*

The AHRQ is one of 12 agencies in the Department of Health and Human Services. Its mission is to “improve the quality, safety, efficiency, and effectiveness of health care for all Americans” (http://www.ahrq.gov/).

**Evidence-Based Practice Centers.** The AHRQ has 14 EPCs, which work under 5-year contracts conducting reviews for the agency. Five of these centers specialize in technology assessments for the Centers for Medicare and Medicaid Services (Duke University, ECRI Institute, McMaster University, Tufts–New England Medical Center, and the University of Alberta). One supports the US Preventive Services Task Force (Oregon Evidence-based Practice Center). The other 8 currently active centers include the following: Blue Cross and Blue Shield Association, Technology Evaluation Center; Johns Hopkins University; Minnesota Evidence-based Practice Center; RTI International–University of North Carolina; Southern California Evidence-based Practice Center–RAND Corporation; University of Connecticut; University of Ottawa; and Vanderbilt University. Stanford University is a previous EPC no long under active contract.

The purpose of the EPCs is to assess the comparative effectiveness and harm of interventions by conducting research, performing literature reviews, and producing summary documents for various stakeholders, including the public. Since the program’s inception in 1997, the AHRQ EPCs have generated 17 published technical reviews (primarily methodological in nature) and 204 evidence reports. Topics are mostly tangential to the treatment of injuries to the central and peripheral nervous systems. Of those reviews on topics related to the treatment of patients with neurotrauma, however, the most directly relevant are archived reports related to SCI.

The AHRQ archives consists of reports “that have not been updated within the past 5 years and are therefore no longer considered current” (http://www.ahrq.gov/). The AHRQ cites reasons for not updating a report, including “the amount of new literature, potential changes to practice and policy, partner interest, available funding, and new nominations.” They go on to state that “if a partner nominates one of the archived topics for a new report, it is considered along with other topic nominations.” Partners include various medical specialty organizations, advocacy groups, and educational institutions.


One relevant prevention program assessment has been performed: Preventing Violence and Related Health-Risking Social Behaviors in Adolescents (2004). Care delivery topics related to the treatment of neurotrauma patients include Nurse Staffing and Quality of Patient Care (2007), Training of Hospital Staff to Respond to a Mass Casualty Incident (2004), and Community-Based Participatory Research (2004).

The paucity of reviews related to neurotrauma stands in notable contrast to 11 recent reviews assessing the impact of omega-3 fatty acids on various aspects of health.

**Effective Health Care Program.** The Effective Health Care Program is another arm of the AHRQ that is more directly concerned with comparative effectiveness assessments (http://www.effectivehealthcare.ahrq.gov/). The program is relatively new, initiated in 2003 to fund and conduct research focusing on CER and to disseminate the findings widely. The first funding appropriation was received in 2005. Research summaries are conducted on topics suggested by the public and may include 1) research reviews (comparative effectiveness and effectiveness reviews or technical briefs); 2) original research; or 3) research summaries designed for clinicians, consumers, or policymakers.

An interactive web search for research summaries, reviews, and reports was conducted for activities relevant to neurotrauma. The search engine for health conditions lists the following brain and nerve conditions: atypical antipsychotics, epilepsy, migraine headache, restless leg syndrome, and dementia. A search for “all brain and nerve conditions” with the key word “injury” yields reports on
“Effectiveness and Safety of Antiepileptic Medications in Patients with Epilepsy,” discovered due to a relationship with “secondary seizure injury,” and “Comparative Effectiveness of Preventive Pharmacological Treatments for Migraine.” A search of “all brain and nervous conditions” with the key word “trauma” yields the same report on epilepsy.

This group recently conducted a review of TBI and depression (http://www.ahrq.gov) and found the prevalence of depression after TBI to range widely from 12.2% to 76.7%. Even in studies incorporating only the Structured Clinical Interview for DSM-IV or something similar, the range was still quite wide, from 12.2% to 54.0%, with a weighted average for a prevalence of 31%. No pattern of peak prevalence or natural history was discovered, and the relationship to the biology of the TBI as an etiological factor was unclear. No specific recommendation for time frame or tools for screening emerged from the literature. The role of coexisting conditions, such as posttraumatic stress disorder, was highlighted. The summary cited a “concerning lack of high-quality evidence to inform clinical decision making for the 1 to 2 million individuals in the United States who experience traumatic brain injury each year” and asserted that “a priority on promoting high-quality research in the United States is imperative.”

The effectiveness of postacute rehabilitation for TBI is also being addressed by the Effective Health Care Program in 2011 (http://www.effectivehealthcare.ahrq.gov/). This study cites community reintegration as the most relevant outcome for postacute rehabilitation after moderate or severe TBI and aims to answer questions of timing, setting, intensity, duration, and composition of rehabilitation programs.

There is currently an open comment period regarding prophylaxis for deep vein thrombosis and venous thromboembolism in special populations. A specific question is, “What is the optimal timing of initiation and duration of pharmacologic prophylaxis to prevent venous thromboembolism in hospitalized patients with traumatic brain injury?”

Given that TBI is such a pervasive societal problem, it may be considered surprising that it hasn’t gained more attention in these government agencies. Examining the manner in which topics are chosen for consideration is somewhat instructive.

Congress recently asked the Institute of Medicine to recommend national CER priorities for funding support from the American Recovery and Reinvestment Act of 2009. This act designated $1.1 billion for such research to be attributed to the NIH ($400 million), the AHRQ ($300 million), and the Office of the Secretary of Health and Human Services ($400 million). In their initial report, the Institute of Medicine developed a list of 100 priorities for this national research agenda. None of these priorities related to TBI or other neurotrauma topics. A related priority was to “compare the effectiveness of diverse models of transition support services for adults with complex health care needs (e.g., the elderly, homeless, mentally challenged) after hospital discharge,” which could loosely be considered to include patients with brain and spinal cord injuries, although that does not appear to be the intent. Most of the priorities relate to various aspects of chronic disease management. Certainly survivors of TBI and SCI also suffer from chronic “diseases” that require long-term medical, social, and financial support. However, priorities were in part selected with public input, suggesting that despite recent advances in public education and the media attention to TBI in particular, such injuries may not be seen as a societal priority. Possible contributors are conceptualizations of trauma as an event rather than a “disease” or an inability of survivors and overwhelmed caregivers to participate in public forums. Advocacy groups will continue to aid in raising public awareness and formulating support for studies in neurotrauma, and the research community must continue to pursue work in this area. The Institute of Medicine also considered the prevalence of the medical problem, mortality rates, morbidity, and variability of available data in setting priorities. Certainly, future work that highlights the epidemiological, social, and financial impact of TBI, SCI, and peripheral nerve injury may influence priorities.

Comparative Effectiveness Research in the Neurosurgical Literature

Given the difficulty in controlling the variables inherent in TBI management, it should not be surprising that early CER efforts have focused on the utility of imaging modalities. Although these analyses cover only a fraction of the patients with neurotrauma, they have provided a framework for effective decision management in the choice of imaging modalities in these patients. Several studies have compared diagnostic modalities, for example, for cervical spine clearance and blunt vascular injury. Aiming to create evidence-based guidelines for treatment, a few meta-analyses have addressed the effectiveness of specific rehabilitative therapies after TBI, such as physical therapy interventions for gait and balance as well as cognitive rehabilitation interventions. However, literature searches for CER in various neurotrauma conditions otherwise yield little data, in part because of the relatively new use of this term. Certainly, the literature is rife with studies of various aspects of treatment for brain, spinal cord, spinal column, and peripheral nerve injuries. It remains for us to place this vast body of literature into the context of CER by performing the types of rigorous analyses that formulated the basis of the EBM guidelines and are being used for CER in other areas of interest.

Undoubtedly, CER will play an important part in the evolution of evidence-based guidelines for TBI. Past guidelines assessments have include comparisons of intracranial pressure monitoring technology, anticonvulsant agents for seizure prevention, and types of nutritional replacement following TBI. Logical areas to explore in the future include optimal sedative agents for reducing agitation and intracranial pressure; anticonvulsant agents for prophylaxis against early posttraumatic seizures; agents for deep venous thrombosis chemoprophylaxis; therapies to improve brain tissue oxygenation in the wake of TBI; and dose, route, and timing of hyperosmolar therapeutic regimens. It is especially important to consider these topics as new agents become available in the critical care treatment of these patients.
Comparative effectiveness research in neurotrauma

In 2010, a working group organized by the Directorate-General for Research and Innovation of the European Commission and the National Institute of Neurological Disorders and Stroke of the US NIH met to address CER in TBI. The goals of this workshop were to 1) perform a critical reappraisal of approaches to clinical research in TBI, 2) identify the greatest unmet needs from a clinical perspective, 3) discuss the potential of CER in the field of TBI, and 4) explore the possibility and added value of a joint EU-US effort in this field.

The findings of this workshop highlighted the use of alternative forms of clinical research in TBI, such as observational studies, utilization of registries, and systems biology approaches. Recommendations for further research included promotion of translational research and large-scale data capture, integration of acute care and post–acute care research, development of new classification schemas and prediction models, improvement of outcomes measurements, exploration of the biological bases of outcomes differences, and a host of measures aimed at assessment of outcomes in high-variability settings. Progress toward this goal is being made through the development of common data elements for TBI research, a project sponsored by the NIH. The “proposed process of standardization will facilitate comparative effectiveness research and encourage high-quality meta-analysis of individual patient data.”

Conclusions

Perhaps nowhere in medicine is the assessment of effectiveness more difficult to achieve than in the setting of severe TBI. Coupled with an already heterogeneous population in terms of structural brain injury, genetic and physiological backgrounds, mechanisms of injury, and polytrauma injury patterns, poorly controlled research conditions with multiple treatment variables make comparisons of any two treatments difficult. However, it is imperative that the TBI research community embraces this new framework. By designing innovative trials to address specific questions, developing high-quality registries, and maintaining robust data sets for longitudinal follow-up, our community will be able to provide ever more useful information for clinical decision making.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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