REVIEW OPEN

Global neurotrauma research challenges and opportunities

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Traumatic injury to the brain or spinal cord is one of the most serious public health problems worldwide. The devastating impact of 'trauma', a term used to define the global burden of disease related to all injuries, is the leading cause of loss of human potential across the globe, especially in low- and middle-income countries. Enormous challenges must be met to significantly advance neurotrauma research around the world, specifically in underserved and austere environments. Neurotrauma research at the global level needs to be contextualized: different regions have their own needs and obstacles. Interventions that are not considered a priority in some regions could be a priority for others. The introduction of inexpensive and innovative interventions, including mobile technologies and e-health applications, focused on policy management improvement are essential and should be applicable to the needs of the local environment. The simple transfer of a clinical question from resource-rich environments to those of low- and middle-income countries that lack sophisticated interventions may not be the best strategy to address these countries' needs. Emphasis on promoting the design of true 'ecological' studies that include the evaluation of human factors in relation to the process of care, analytical descriptions of health systems, and how leadership is best applied in medical communities and society as a whole will become crucial.

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The global burden of disease (GBD) related to all injuries or 'trauma' is the leading cause of loss of human potential around the world especially in low- and middle-income countries (LMICs). According to the 2010 report of the GBD study 89% of trauma-related deaths occur in LMICs. Nearly 6 million people die each year as a result of trauma, accounting for 10% of the world's deaths — 32% more than the number of fatalities from malaria, tuberculosis and HIV/AIDS combined[1].

Within the spectrum of trauma-related injuries, traumatic brain injury (TBI) and spinal cord injury (SCI) are the largest causes of death and disability, leading to suffering by, and costs to, the individual, their family and society. Social costs include changes to the family care structure owing to cognitive, emotional and/or physical disabilities in addition to economic costs and reduced productivity. The incidence of central nervous system (CNS) injuries varies between regions, with estimates ranging from 200 to 600 injuries per 100,000 people. The data are sparse and the true incidence of both TBI and SCI may be considerably underestimated[2].

Efforts to quantify the magnitude of TBI are hindered by several factors, the most common of which is related to the lack of consistent data recording where this occurs[3–5]. For example, the absence of formal injury surveillance or reporting systems (trauma registries) in some high-income countries as well as in LMICs, leads to an underestimate of the true magnitude of CNS burden of disease worldwide. Despite 89% of the trauma population being in LMICs, pre-hospital mortality for CNS injuries is not systematically recorded in research that originates in these countries. Even fewer LMICs have formally implemented a data-specific registry for neurotrauma. In addition, most patients with TBI have mild to moderate injury and are therefore often not reported[6,7]. CNS injuries in patients with multiple trauma, especially as a result of military or civilian conflicts, may be recorded under other causes of death or injury statistical codes.

EPIDEMIOLOGY AND GLOBAL RESEARCH IN TBI

Although high-quality worldwide data of TBI incidence and prevalence are difficult to find, neurotrauma registries from high-income countries indicate that around 5.3 million people in the United States and nearly 7.7 million people in Europe are living with TBI-related disability. The 2010 GBD study[8] shows that in high-income countries an important cause of TBI is motor vehicle accidents, and that there has been a shift in the age of the affected population towards older groups. In LMICs, those with TBI are generally young adult pedestrians, cyclists or motorcyclists. In regions where the prevalence of armed violence is higher (Central America, the Middle East and Central Africa), assault and gunshot injuries are important causes of TBI[9]. Deficits associated with TBI, including impaired attention, poor executive function, depression, impulsivity, poor decision-making and aggressive behaviour, have particularly striking social and economic consequences for individuals, families and the development of societies as a whole[10,11]. An example of the heterogeneity of the data in international epidemiological research in TBI is shown in Supplementary Table 1.

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Basic and clinical research in TBI have been focused on understanding the biological process of the disease, developing advanced diagnostic tools, minimizing secondary brain injury and improving treatment guidelines. Unfortunately, the evidence generated from neurotrauma studies carried out in high-income countries does not always translate to LMICs, where the health infrastructure (including providers and facilities) is limited, creating a different context for care practice[12–14]. Recently published consensus statements, established in high-income countries, do not take into account the unique challenges that neurotrauma researchers may face in LMICs. Most of these evidence-based recommendations are best applied in well-funded and well-equipped neurosurgical or neurotrauma centres[15–17]. The recent Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST Trip) trial was based on standard recommendations for randomized clinical trials in high-income countries[18–22]. Results were far from expected because advanced monitoring tools used to guide treatments in high-income countries were not as successful in LMICs, and discussion within the global neurotrauma scientific community emerged after the publication of this study[23–27]. The interpretation and implications of the study for the neurotrauma field in high-income countries and LMICs are still being analysed[28]. The applicability of high-income-country clinical research standards in LMICs is an important topic for future international research.

Research will focus on new trends for TBI care, including, but not limited to, the use of hyperosmolar fluids, blood components for early resuscitation and other strategies aimed at improving resuscitation in patients with multiple injuries, including TBI[29–31]. Additional aspects that are more applicable to LMICs, such as the importance of data collection (neurotrauma registries), capacity building for advanced education in neurotrauma-care provision and research, and integration of teams within a trauma-care system have been recently proposed[32,33]. Treatment strategies such as prophylactic hypothermia have also been considered as therapies with the potential for further research in LMICs. However, this would require organizational effort by the health-care systems to obtain reliable evidence. Multicentre collaborative approaches towards data collection are already in place in high-income countries; such endeavours may also be an efficient and productive strategy for TBI research in LMICs. Alcohol and substance misuse associated with TBI is a further key topic that needs to be addressed in LMICs. Poorer outcomes have been associated with alcohol and substance misuse in high-income countries, but the findings were mixed and further research is required in different contexts[34].

EPIDEMIOLOGY AND GLOBAL RESEARCH IN SCI

In 2013, the World Health Organization (WHO) and the International Spinal Cord Society (ISCoS) joined together to report SCIs worldwide[35,36]. Unsurprisingly, similar to TBI, information in epidemiological studies from LMICs was limited. Since 2000, at least 7 papers have reviewed the epidemiology of SCI around the world[37–43] and 2 papers have focused on the epidemiology of SCI in LMICs[44,45]. Common conclusions relate to the lack of information available in LMICs owing to the absence of SCI registries — paradoxically, these are regions where incidence of the disease is high according to observational studies. Reported incidence ranged from 12 to close to 60 cases per million inhabitants in different countries (see Supplementary Table 2). It is difficult to compare the data owing to the heterogeneity of the studies, which had diverse methods for reporting and classifying the disease.

SCI registries from high-income countries and meta-analysis of studies reporting incidence of the disease allow us to estimate that worldwide, every year nearly 250,000 to 500,000 people sustain an SCI[46,47]. Historically, around 90% of SCIs have been associated with trauma; however, in an analysis of high-income-country registries, non-traumatic SCI has recently increased to beyond 10%. The traumatic SCI population is young, especially in LMICs. Underestimation of SCIs is common and with the exception of a few countries that have countrywide registries (Finland, Canada and the United States), incidence estimates are extrapolated from city or regional data that may not be representative of the countries as a whole[45].

The three most common causes of SCI across the world are road traffic accidents, falls and violence. Because of the low quality of data, especially in LMICs, there may be country-level variation in the causes or the context of injury, especially in areas with higher levels of social violence (Central America, the Middle East and Central Africa). In studies from Africa, transportation-related events account for nearly 70% of cases; in countries affected by war such as Afghanistan, around 60% of all SCI cases are related to violence. It has been estimated that work-related injuries contribute to at least 15% of all traumatic SCIs. There are consistently higher incidence rates in adult males, and the two groups most likely to have an SCI are young and elderly males. Life expectancy for patients with an SCI is shorter than the average in LMICs, as well as in comparison with patients with an SCI from high-income countries[48].

In a similar way to TBIs, most SCI research is carried out in high-income countries, and focused on the basic science of the biological process of the disease, helping to develop treatment guidelines and the application of advanced technology for nerve reconstruction, sophisticated prosthesis and advanced rehabilitation. Many of these studies are not feasible in LMICs where basic science resources are scarce and advanced rehabilitation is almost non-existent. Recommendations by researchers from high-income countries for designing SCI clinical trials have been published, but the applicability of these recommendations to the LMIC context has yet to be determined[49]. Organization of neurotrauma-care systems and capacity building for neurotrauma and SCI registries may have an effect in LMICs, but they are not priorities for researchers from high-income countries. Crucial aspects, such as the relationship between pre-hospital care and outcomes for patients with SCI are difficult to analyse in LMICs because pre-hospital care is not widely available[50]. An example of the difficulties in SCI research owing to a lack of data is presented in a review about pressure ulcers as a complication in patients with SCI in LMICs[51]. Over the past few years, researchers in China have been making important steps towards evaluating cellular therapies and improving the quality of life of those with SCI. Registries are now available to improve epidemiological data collection within the country[52].

Lessons learned from clinical neurotrauma research

In this section, we present examples of active neurotrauma research groups from LMICs.

Latin America. The three examples from Latin America draw upon our direct experience of working in Argentina, Bolivia, Colombia and Ecuador.

Between 2008 and 2011 a randomized controlled trial of intracranial-pressure (ICP) monitoring in patients with TBI, which compared the management of patients with severe TBI that was based on information from ICP monitoring with treatment that was based on imaging and clinical examination without ICP information, was performed in Bolivia and Ecuador. The study reported no difference in outcomes between these groups. The study is considered to be class 1 — it has high internal validity. Thus, for LMICs, the study provided concrete information on which to base resource-allocation decisions, and documented the clinical success of a treatment approach that is sustainable in low-resource environments. Sufficiently skilled clinical staff with a better organized protocol of care could produce good recovery results in the intensive care unit (ICU) without data from an ICP monitor by using clinical assessment to manage intracranial hypertension[53–56].

A multicentre randomized controlled trial of post-discharge care of paediatric traumatic brain injury in Argentina aimed to develop, introduce and test a family-provided, post-discharge intervention for children with complicated mild, moderate and severe TBI. Multiple research methods were used, beginning with focus groups with children who had sustained a TBI, as well as with their parents, physicians, nurses and social workers. The focus group experience was one of the most important aspects of this project. It gave the high-income-country research team an appreciation of the realities of TBI in these communities, and allowed for an ecologically relevant approach to developing an intervention. The participating hospitals elected to maintain the intervention, and said that the protocol improved overall quality of care for the children and their families. An unexpected finding was that despite reports that paediatric TBI is a serious problem in Latin America[57], hospitals in this study saw, on average, fewer than one child with TBI per month.

In another study, a standardized trauma-care protocol decreased in-hospital mortality of patients with severe TBI in a LMIC teaching hospital[58]. The standardized trauma-care protocol was based on generally accepted best practices; damage-control resuscitation strategies were proposed based on military protocols from war scenarios in the Middle East. With the knowledge that most hospitals in LMICs have financial or logistical limitations in building evidence-based protocols and do not have a pre-existing trauma registry, an administrative electronic database was adapted to capture clinical information about adults with TBI[59]. Adherence to the protocol was limited — around 60%. Surprisingly, the barriers to adherence were not associated with resources or technology, but with human factors related to changing established practices. How to create motivational interventions to change practice is an important research question for LMICs.

China. Here we summarize studies of the use of decompressive craniectomy and hypothermia in the treatment of severe TBI conducted in China.

In a study of decompressive craniectomy, the influence of a standard, larger, unilateral frontotemporoparietal bone flap (a standard trauma craniectomy) was compared with a limited, smaller temporoparietal bone flap (a limited craniectomy) based on a 6-month Glasgow Outcome Scale (GOS) score and complications. The investigators found significantly greater mortality in patients with a limited craniectomy[60]. A second study in China compared 1-month mortality, complications and the 1-year GOS score of larger unilateral decompressive craniectomy with routine unilateral temporoparietal decompressive craniectomy. One-month survival and one-year GOS scores were significantly better in the larger unilateral decompressive craniectomy group; however, they had a higher rate of complications[61]. These findings contribute important information for LMIC environments where decompressive craniectomy may be the only treatment option available for a quick resolution of ICP.

Similar to decompressive craniectomy, prophylactic hypothermia for the treatment of ICP is a relatively low-technology option available in LMICs. However, its influence on patient outcome is yet to be clearly demonstrated. In a comparison of a longer course of mild hypothermia (33–35°C for 3–14 days) with normothermia, mortality was found to be lower and 1-year GOS scores were better for the hypothermia group[62]. A subsequent study that compared short-term (1–3 days) and long-term (4–6 days) mild hypothermia found that patients given a course of hypothermia for 5 days had significantly better 6-month GOS scores than those given a 2-day course[63]. Finally, patients who received systemic cooling (full body) were compared with those who received selective brain cooling (head only) and normothermia. Pneumonia rates were lowest and 2-year GOS scores were highest in patients who received selective cooling[64]. Although the results of these studies are promising, the findings are tempered by contradictory findings from similar studies conducted in other countries. What is important for research in LMICs is the question of how to manage a crucial aspect of TBI, ICP, in the absence of technological resources.

India and Nepal. Recent studies from India and Nepal describe the experience of creating surveillance and research infrastructures in extremely austere conditions.

In India, the WHO's Standards for Surveillance of Neurotrauma were used to design and build a simple data collection instrument, and an observational study of TBI was conducted in a rural teaching hospital. Over 6 months, data on 414 patients were collected and descriptive statistics about a sample were reported. Logistical difficulties, including a lack of closely managed data collection and entry, inconsistent coding and missing data were recorded[65]. In an epidemiological study of trauma in a hospital in the Eastern region of Nepal, data on 6,793 patients over 1 year were collected, and a subset of TBI cases was reported on. This is the first study in Nepal that collected comprehensive patient profiles and reported outcomes in detail[66]. The authors concluded that trauma-related injury significantly contributes to morbidity and mortality and is the third leading cause of death in the region.

The examples from Latin America, China, and India and Nepal illustrate the vast differences in the spectrum of neurotrauma research across LMICs. Neurotrauma research at the global level needs to be contextualized — different regions have their own needs and challenges during the research process. Certain interventions may be high priority in one country, but low priority in another.

Research priorities, opportunities and challenges

Although CNS injury is important, we must acknowledge that an isolated brain or spinal cord injury represents a small fraction of the burden of trauma as a disease, but they occur frequently in the context of the multiple-injury patient. From a mechanistic viewpoint, isolated CNS trauma is the best model to understand the pathophysiology of brain or spinal injury, but it is naive to ignore the fact that patients with multiple trauma injuries have a conglomerate of systemic events that affect the brain. We must, therefore, study CNS injury in the setting in which it most commonly occurs: the patient with multiple injuries. This context needs to be part of the research portfolio in global health, especially in LMICs where it is difficult to measure the interactions of different interventions in the same patient. Assessment could, however, improve with better organization of the existing resources.

The impact of new resuscitation techniques, early use of blood products and early evaluation of coagulopathy in patients with TBI or SCI could be key in areas where violence is an important cause of injury and transport times to hospital are long. The impact of non-invasive intracerebral blood detectors, advanced airway management by non-physicians, and pre-hospital resuscitation fluids could be a priority in areas where organized trauma systems do not exist. Most LMICs do not have organized pre-hospital care. If it exists, it is not consistent and there are no evidence-based transport protocols. There is little training for ambulance staff, which may or may not include a physician. If physicians are present, often they are not trained in emergency medicine. It is possible that in LMICs the most important area of research is within the public health system in order to demonstrate the benefits of an organized pre-hospital care system to improve patient outcomes, and to reduce costs both in hospital and post-discharge. Establishing systematic surveillance systems to accurately identify incidence, prevalence, processes of care and outcomes following TBI and SCI are essential priorities for research in areas where these systems do not exist.

Capacity-building priorities and opportunities

Countries where TBI and SCI are a significant burden of disease are also those with substantial gaps in services that affect the entire spectrum of trauma care, including prevention, pre-hospital care, specialized neurotrauma care, rehabilitation, quality control and research. As daunting as it may seem to propose capacity-building activities in all these areas, the comprehensive management of TBI and SCI will require human resources, infrastructure and research training aimed at enhancing capacity in all these components. Because resources are limited, the next fundamental question is how to establish priorities so that these areas can advance in parallel. Research training grants and collaborative research between partners in LMICs and high-income countries should include the creation of multidisciplinary teams of health-care professionals that work in prevention, pre-hospital care, clinical care and clinical epidemiology to expand overall human-resource capacity. At the same time, basic training in provision of care is gravely needed, as is research training. The capacity-building curriculum for different parts of the health system will differ, but they must all introduce the concepts that are inherent to the creation of a comprehensive trauma system.

Specific capacity-building activities should address the design and feasibility of using modular theme-based trainee curricula that employ enabling technologies such as e-learning and teleconferencing; low-tech clinical simulation training that emphasizes early life-saving interventions or procedures; and team-training techniques to accentuate the collaborative nature of neurotrauma care. Strengthened capacity to use information and communication technologies to support research and research-training programmes is also needed.

CONCLUSION

Enormous challenges must be met to significantly advance neurotrauma research worldwide, particularly in underserved areas and austere environments. Experts beyond clinical practitioners and basic science researchers will need to participate in order to meet these challenges. The introduction of inexpensive and innovative interventions, including communication technologies, mobile-health applications and policy management approaches that meet the needs of a particular local environment is the ultimate goal. Simply transferring a clinical question from a resource-rich environment to that of a LMIC which lacks sophisticated interventions may not be the best strategy to address the needs of LMICs. Furthermore, the findings of studies conducted in resource-rich environments may not necessarily result in evidence-based guidelines that can be implemented in health-care scenarios with more-limited resources.

A new context for capacity building in neurotrauma should include broad international collaborations and global-health opportunities directed at creating not only advanced researchers, but also health leaders who work in field research and health-policy development and implementation. Fundamental questions in research that are relevant to LMICs need to go beyond health-care facilities and medical schools. Emphasis on promoting the design of true 'ecological' studies that include evaluation of human factors in relation to the process of care, analytical descriptions of health systems, and how leadership is applied in the medical community and society as a whole will be crucial.

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ADDITIONAL INFORMATION