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A retrospective cross-sectional study of the prevalence of generalized convulsive status epilepticus in traumatic brain injury: United States 2002–2010

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ABSTRACT

Purpose: To determine the incidence, predictors, and outcomes of generalized convulsive status epilepticus (GCSE) in traumatic brain injury (TBI) patients.
Methods: We conducted a retrospective cross-sectional study of adult patients with acute TBI using the 2002–2010 Nationwide Inpatient Sample (NIS) database of USA. We used multivariable logistic regression analyses to identify independent predictors of GCSE in patients with TBI and to determine the impact of GCSE on outcomes (in-hospital mortality, length of stay, total hospital charges, and discharge disposition).
Results: Among 1,457,869 patients hospitalized with TBI, 2315 (0.16%) had GCSE. In-hospital mortality was significantly higher in patients with GCSE (32.5% vs. 9.6%; unadjusted OR 4.54, 95% CI 4.16–4.96; $p < 0.001$; adjusted OR 3.41; 95% CI 3.09–3.76 $p < 0.001$). Patients with GCSE had longer length of stay (17.3 ± 21.9 vs. 6.8 ± 11.1 days; $p < 0.001$), higher total hospital charges ($\$147{,}415 \pm 162{,}319$ vs. $\$54{,}041 \pm 90{,}524$; $p < 0.001$), and were less likely to be discharged home (19.8% vs. 52.7%; $p < 0.001$). Using multivariable logistic regression analysis, age >35 years (OR 2.15; 95% CI 1.87–2.47), CNS infections (OR 4.86; 95% CI 3.70–6.38), anoxic brain injury (OR 9.54; 95% CI 8.10–11.22), and acute ischemic stroke (OR 4.09; 95% CI 3.41–4.87) were independent predictors of GCSE in TBI patients. Epilepsy was an independent negative predictor of GCSE (OR 0.74; 95% CI 0.55–0.99).
Conclusion: Despite its low incidence, GCSE in TBI patients was associated with worse outcomes with threefold higher in-hospital mortality, prolonged hospitalization, higher hospital charges, and worse discharge disposition. Surprisingly, epilepsy is a negative predictor of GCSE in this population.
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1. Introduction

Traumatic brain injury (TBI) is among the leading causes of disability, morbidity, and mortality in the United States (US) and other developed countries. Recent estimates in the US indicate that 235,000 patients are hospitalized for nonfatal TBI per year, of which 50,000 die and 43.3% of them have residual disability 1 year after injury [1]. Patients with TBI were found to have 1.5 times higher mortality as compared to the general population [2]. Although evidence based protocols have resulted in significant reduction in mortality, TBI continues to be among the leading causes of death and it is associated with a high economic burden to the society [3]. In the US, the financial impact of TBI in 2010 alone was estimated to be $76.5 billion, including $11.5 billion in direct medical costs [4].

TBI is also associated with increased risk for seizures, and the development of post-traumatic epilepsy [5]. The pathophysiology of acute seizures after traumatic brain injury may be related to increased intracranial pressure as well as elevated lactate–pyruvate ratio suggestive of prolonged metabolic distress [6]. In a large population based study from Denmark, the risk of seizures following traumatic brain injury is estimated to be 2.2–7.4 times higher depending on severity of injury; and this risk remains high even after 10 years of injury [7]. In another retrospective cohort study from the US, patients with TBI were 22 times more likely to die from seizures as compared to an age and sex matched general population [2]. The incidence of generalized convulsive status epilepticus (GCSE) in patients with TBI, however, is poorly

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characterized and is only described in small population studies ranging from 1.8 to 8% [8–12]. Most of these studies report on non-convulsive status epilepticus using continuous EEG in moderate to severe cases of TBI. In a study by Vespa et al., non-convulsive status epilepticus was associated with 100% mortality in patients with TBI [12].

GCSE is a medical emergency, with an estimated in-hospital mortality of up to 21% [13,14]. Approximately 19% of patients die within the first 30 days of new onset status epilepticus [15], while survivors develop significant neurological complications [16]. The annual direct cost for inpatient admissions from status epilepticus in the US is estimated to be around $4 billion, which is high compared to other major conditions such as acute myocardial infarction and congestive heart failure [17]. Predictors of GCSE mortality and morbidity in specific settings have been studied in several retrospective cross-sectional studies [18,19]. The predictors of GCSE in the population of TBI patients and its impact on disease progression and mortality are unknown. Using a large US nationwide cohort of hospitalized patients we aim to determine the incidence, predictors and outcomes of GCSE in acute TBI patients.

2. Methods

2.1. Data source

Data for the study was derived from the Nationwide Inpatient Sample (NIS) from the United States for the years 2002–2010. The NIS is the largest all-payer administrative database maintained as part of the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ) [20]. HCUP is the family of databases, which brings together the data collected by state-based organizations, hospital associations, and the federal government. AHRQ is an agency of the US Department of Health and Human Services focused on research of healthcare quality, costs, outcomes, and patient safety. The NIS contains discharge-level information from approximately 8 million hospital stays from about 1000 non-federal hospitals and represents approximately 20% stratified sample of all hospitals in the United States. It contains the discharge level information for each patient including admission day, admission source, patient and hospital characteristics, discharge destination and healthcare cost, and up to 15 diagnosis and procedures. Discharge weight was provided for each discharge record, and was used to obtain a national estimate of the total number of patients admitted with acute TBI from 2002 to 2010 in the United States.

2.2. Study population

We identified all patients 18 years of age or older who were admitted with the principal diagnosis of acute TBI using the HCUP Clinical Classification Software (CCS) code 233. CCS code 233 includes all TBI codes (Fracture of the vault or base of the skull with intracranial injury, 800.1–801.9; Other and unqualified multiple fractures of the skull or facial bones with intracranial injury, 803.1–804.9; Intracranial injury, including concussion, contusion, laceration, and hemorrhage, 850.0–854.1) in accordance to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Diagnosis Related Group (DRG) [21,22]. Diagnosis code of V1552 (history of traumatic brain injury) was excluded to ensure all cases of TBI were acute onset. Patients with diagnoses and conditions that were previously reported and could independently cause GCSE (tumors, non-traumatic intracranial hemorrhage, and subarachnoid hemorrhage, hemangioma, brain metastasis, arteriovenous malformations) were excluded (Supplemental data Table e-1). Patients with GCSE were then identified using ICD-9-CM code 345.3.

2.3. Patient and hospital characteristics

Baseline patient demographics (age, sex, race, primary expected payer) and hospital characteristics such as hospital location (rural vs. urban), bed size (small, medium or large) and teaching status of the hospital were included. We also compared incidence of in-hospital procedures (craniotomy and craniectomy, hematoma drainage, ventriculostomy, intracranial pressure (ICP) monitor insertion, intubation and mechanical ventilation, tracheostomy, and percutaneous endoscopic gastrostomy (PEG) – tube placement) in TBI patients with and without GCSE. A list of ICD-9-CM codes used to identify relevant comorbid conditions and in-hospital procedures is provided in supplemental data Table e-2. We did not have access to individual patient information regarding the etiology of TBI, duration of GCSE and the medical care provided such as antiepileptic drugs (AED).

Previous studies in patients with ischemic stroke, non-traumatic subarachnoid hemorrhages identified certain conditions to be strongly associated with occurrence of GCSE [18,19]. We identified the following co-variates based on the previous reports which included: alcohol abuse, coagulopathy, drug abuse, diabetes mellitus, epilepsy, hypertension, liver disease, chronic renal failure, sodium imbalance, acute ischemic stroke (AIS), anoxic brain injury, and central nervous system (CNS) infections.

2.4. Outcome measures

We initially examined the independent predictors of GCSE in patients with TBI. Our primary outcome of interest was in-hospital mortality. Secondary outcomes studied were length of stay, total hospital charges, and discharge disposition among the survivors. Discharge disposition was identified as death, home, short-term hospital, transfer to a skilled nursing or other facility (including rehabilitation and intermediate care facility), and others (home health care, against medical advice) using the HCUP defined DISPUniform variable.

2.5. Statistical analysis

We first compared the demographics, comorbidities, and hospital characteristics between TBI patients with and without GCSE using Student's *t*-test for continuous variables and Pearson's χ^2 test for categorical variables to detect any significant univariate associations. We stratified age into 3 groups; 18–35 years, 36–65 years and, >65 years. Next, we used multivariable logistic regression analysis to identify independent predictors of GCSE in patients with TBI. Variables entered in the regression model included age (stratified into 3 age groups: 18–35 (reference as used in regression model), 36–65, and >65 years), sex, and relevant comorbid conditions (alcohol abuse, coagulopathy, drug abuse, diabetes mellitus, epilepsy, hypertension, liver disease, chronic renal failure, sodium imbalance, AIS, anoxic brain injury, and CNS infections). Multivariable logistic regression analysis was also used to compare risk-adjusted in-hospital mortality between TBI patients with and without GCSE. The regression model adjusted for demographics (age, sex, and primary expected payer), hospital characteristics, 29 Elixhauser comorbidities, and other clinically relevant comorbidities (epilepsy, sodium imbalance, AIS, anoxic brain injury, and CNS infections).

Statistical analysis was performed using IBM SPSS Statistics 20.0 (IBM Corp., Armonk, NY). For all analyses, we used a 2-sided p value of <0.05 to assess for statistical significance. Categorical variables are expressed as percentage and continuous variables as mean ± standard deviation. Odds ratio (OR) and 95% confidence interval (CI) were used to report the results of logistic regression analysis.

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