Neurobiology of Sleep and Circadian Rhythms 2 (2017) 85–93

Contents lists available at ScienceDirect

Neurobiology of Sleep and Circadian Rhythms

journal homepage: www.elsevier.com/locate/nbscr

Research paper

# Circadian variability of the initial Glasgow Coma Scale score in traumatic brain injury patients

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A R T I C L E  I N F O

*Keywords:*
Circadian
Emergency department
Glasgow Coma Scale
Hospital admission
Neurologic deficit
Traumatic brain injury

A B S T R A C T

*Introduction:* The Glasgow Coma Scale (GCS) score is the primary method of assessing consciousness after traumatic brain injury (TBI), and the clinical standard for classifying TBI severity. There is scant literature discerning the influence of circadian rhythms or emergency department (ED) arrival hour on this important clinical tool.

*Methods:* Retrospective cohort analysis of adult patients suffering blunt TBI using the National Sample Program of the National Trauma Data Bank, years 2003–2006. ED arrival GCS score was characterized by midday (10 a.m.–4 p.m.) and midnight (12 a.m.–6 a.m.) cohorts (N=24548). Proportions and standard errors are reported for descriptive data. Multivariable regressions using odds ratios (OR), mean differences (*B*), and their associated 95% confidence intervals [CI] were performed to assess associations between ED arrival hour and GCS score. Statistical significance was assessed at $p < 0.05$.

*Results:* Patients were 42.48 ± 0.13-years-old and 69.5% male. GCS score was 12.68 ± 0.13 (77.2% mild, 5.2% moderate, 17.6% severe-TBI). Overall, patients were injured primarily via motor vehicle accidents (52.2%) and falls (24.2%), and 85.7% were admitted to hospital (33.5% ICU). Injury severity score did not differ between day and nighttime admissions.

Nighttime admissions associated with decreased systemic comorbidities ($p < 0.001$) and increased likelihood of alcohol abuse and drug intoxication ($p < 0.001$). GCS score demonstrated circadian rhythmicity with peak at 12 p.m. (13.03 ± 0.08) and nadir at 4am (12.12 ± 0.12). Midnight patients demonstrated lower GCS (12 a.m.–6 a.m.: 12.23 ± 0.04; 10 a.m.–4 p.m.: 12.95 ± 0.03, $p < 0.001$). Multivariable regression adjusted for demographic and injury factors confirmed that midnight-hours independently associated with decreased GCS (*B*=−0.29 [−0.40, −0.19]).

In patients who did not die in ED or go directly to surgery (N=21862), midnight-hours (multivariable OR 1.73 [1.30–2.31]) associated with increased likelihood of ICU admission; increasing GCS score (per-unit OR 0.82 [0.80–0.83]) associated with decreased odds. Notably, the interaction factor ED GCS score*ED arrival hour independently demonstrated OR 0.96 [0.94–0.98], suggesting that the influence of GCS score on ICU admission odds is less important at night than during the day.

*Conclusions:* Nighttime TBI patients present with decreased GCS scores and are admitted to ICU at higher rates, yet have fewer prior comorbidities and similar systemic injuries. The interaction between

*Abbreviations:* CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRSD, circadian rhythm sleep disorder; ED, emergency department; GABA, gamma-aminobutyric acid; GCS, Glasgow Coma Scale; ICD-9, International Classification of Diseases, 9th Revision; ICU, intensive care unit; IQR, interquartile range; ISS, injury severity score; MVA, motor vehicle accident; NSP, National Sample Program; NTDB, National Trauma Data Bank; OR, odds ratio; REM, rapid eye movement; RHT, reticulohypothalamic tract; SCN, suprachiasmatic nucleus; SD, standard deviation; SE, standard error; TBI, traumatic brain injury

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http://dx.doi.org/10.1016/j.nbscr.2016.09.002
Received 15 June 2016; Received in revised form 13 September 2016; Accepted 29 September 2016
Available online 11 October 2016
2451-9944/

nighttime hours and decreased GCS score on ICU admissions has important implications for clinical assessment/triage.

## 1. Introduction

Traumatic brain injury (TBI), defined as an alteration in brain function or other evidence of brain pathology following trauma, is a debilitating disease and public health burden (Manley and Maas, 2013). The incidence of TBI in the USA is at least 1.7 million annually, and 5.3 million people are currently living with TBI-related disability (Faul et al., 2010; Langlois et al., 2006). The Glasgow Coma Scale (GCS), designed as a standardized method for healthcare practitioners to evaluate and describe TBI severity, is the primary method of assessing level of consciousness after TBI. The GCS score comprises three subcategories: eye opening (score of 1–4), verbal response (score of 1–5) and motor response (score of 1–6), with a sum score of 15. It is the current clinical standard for subdividing patients into mild (13–15), moderate (9–12), and severe (3–8) TBI (Maas et al., 2008; McNett, 2007; Saatman et al., 2008; Teasdale et al., 2014).

Accordingly, the GCS score forms the basis for clinical management decisions following TBI, such as the need for computed tomography (CT) scan, serial neurologic exams, medical management and/or surgical intervention (Fischer et al., 2001). A GCS score of less than 15 is an indicator of neurologic deficit and a strong predictor of the need for emergency intervention (e.g. surgery) in TBI patients (Hong et al., 2016). There is an approximately linear relationship between decreasing total GCS scores and increasing mortality following moderate and severe TBI (Reith et al., 2016). The GCS score has also been shown to be a predictor for hospital admission following trauma. One study showed abnormal GCS (score of 13 ± 4) to be the only parameter associated with increased relative risk for hospitalization following motor vehicle accidents (MVA) (Norwood et al., 2002).

Circadian rhythmicity is an endogenous oscillation of alertness/consciousness across a 24-hour period regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus (Leproult and Van Cauter, 2010). The SCN receives input from photosensitive retinal ganglion cells via the reticulohypothalamic tract (RHT); the SCN both self-regulates circadian cycles through gene transcription and sends signals to the pineal gland as well as other hypothalamic nuclei for melatonin and cortisol secretion (Leproult and Van Cauter, 2010). In addition to dysregulation of serotonergic and noradrenergic neurotransmitter circuits (Pappius, 1991; Kawa et al., 2015), studies have demonstrated that circadian rhythm of melatonin production is disrupted following both TBI and ICU admission following trauma (Paul and Lemmer, 2007). Hence it is not unreasonable to extrapolate that nighttime hours may be associated with reduced levels of alertness; indeed, one study of traumatic insults in children found an association between reduced GCS score and admission to the ICU (Onita et al., 2015). However, these admissions were onto both trauma and/or medicine services, and did not extend to adults.

The literature associates TBI with persistent circadian rhythm sleep disorders (CRSD). Schekleton and colleagues report a correlation between melatonin secretion and rapid eye movement (REM) sleep; accordingly, patients with a history of TBI demonstrate lower evening melatonin production compared to controls, and suffer from increased sleep disturbances and higher anxiety and depressive symptoms (Shekleton et al., 2010). Ayalon and colleagues discuss the development of CRSD, e.g. delayed sleep phase syndrome and irregular sleep-wake patterns, following even mild TBI (Ayalon et al., 2007). While most patients exhibit a 24-h rhythmicity of melatonin secretion, patients who have suffered mild TBI experience a 1–2 h delay of the peak (3:40 a.m. -vs - 5:39 a.m.) and 2–3 h delay of the nadir (5:00 a.m. - vs - 7:59 a.m.) compared to controls, associating with increased fatigue and loss of productivity (Ayalon et al., 2007).

There is scant literature discerning the potential influence of circadian rhythms and/or ED arrival hour on the GCS score at the time of injury, and no study exists for adults in the TBI setting. The National Sample Program (NSP) of the National Trauma Data Bank (NTDB) is a prospectively enrolled registry with a purpose of informing trauma care and outcomes in the USA, and draws from a sample size of 100 hospitals to represent the nationwide patient distribution (American College of Surgeons, 2009). Here, we use the NSP to evaluate the effects of emergency department (ED) arrival hour on ED GCS score following blunt TBI in adult patients – controlling for demographics, medical comorbidities, and injury severity factors. We hypothesized that ED arrival hour would associate with GCS score as well as ICU admission. Our data indicate that there is a circadian distribution of GCS score across ED arrival hours, that ED arrival hour is independently associated with GCS score, and that nighttime ED admissions are associated with an increased likelihood of ICU admission.

## 2. Methods

In this study, we used the NSP of the NTDB from arrival years 2003–2006. The NSP for each year consists of a stratified sample of 100 NTDB participating hospitals based on U.S. census region, trauma care designation, and NTDB reporting status (Aarabi and Bizhan, 2003). Hospitals were drawn by the NTDB from the sampling universe of 453 Level I or II trauma centers, and the sample size of 100 hospitals was determined by prior review indicating it can be extrapolated to represent the national patient distribution (Schoenfeld et al., 2013). Detailed data qualification, selection, cleaning and standardization algorithms have been previously reported (Schoenfeld et al., 2013). As the NSP of the NTDB is a fully de-identified dataset without the 18 federal Health Insurance Portability and Accountability Act (HIPAA) identifiers, the current study was classified as exempt from institutional review board (IRB) review.

The NSP years 2003–2006 were selected because they are the only NSP years in the public domain with the variable “edarrtime” which represents the time of patient arrival to the ED on a 24-h clock. A total of 89541 incidents sustaining TBI were extracted from NSP years 2003–2006 using the International Classification of Diseases, 9th Revision (ICD-9) codes 800-801.99, 803-804.99 and 850-854.19 as previously described (Bekelis et al., 2015; Bowman et al., 2007; Majidi et al., 2013). Adult patients (variable name “age” ≥18, n=72,015) with known hour of arrival (n=58,937), ED GCS (variable name “edgcstotal”, n=55,109), gender (variable name “gender”, n=55,083), blunt TBI (variable name “injurytype”=blunt, n=52,782; variable name “mech_cdc” ≭ “drowningsubmersion”, “cutpierce”, “firearm”, “fireburn”, “poisoning”, “suffocation”, n=52,645) in stepwise fashion. The 52,645 qualifying patients were analyzed for circadian trends, showing a clear peak in ED GCS score during ED arrival hours of 10 a.m.–4 p.m. (n=13,501) and a clear nadir during arrival hours of 12 a.m.–6 a.m. (n=11,047), with comparable sample sizes between both groups. As the objective of this manuscript was to discern whether circadian variability existed in the initial ED GCS score, these times windows were determined empirically. Accordingly, these two groups were extracted for targeted analysis as mid-day and mid-night circadian cohorts, for a combined subgroup n of 24548 patients (Fig. 1).

Demographic and clinical variables of interest were extracted for multivariable analysis to include age, prior medical history, mechanism of injury, whether injury was work-related, hypotension in the ED (ED