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Glasgow Coma Scale Scores and Impact of Delirium on Intubated Seizure Patients Treated with Phenytoin and Lacosamide: Retrospective Analysis and Literature Review

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Abstract

Studies have shown that decrease in time intubated is associated with better prognosis. Delirium is associated with increased duration of mechanical ventilation and Intensive Care Unit (ICU) length of stay. However, there is limited report on delirium in intubated seizure patients. As per report, low Glasgow Coma Scale (GCS) increased the risk of delirium and thus increasing ICU length of stay. Information on delirium and outcome in intubated seizure patients receiving lacosamide versus phenytoin is limited. Our retrospective pilot study aimed to assess the GCS scores and impact of delirium in intubated seizure patients who were treated with phenytoin and lacosamide. In this retrospective pilot study, review was conducted via chart review of hospitalized, intubated seizure patients on Phenytoin or Lacosamide at Loyola University Medical Center Neurology ICU from 2018 to 2020. Endotracheal intubation was identified by ICD 10, ICD-10-PCS 0BH17EZ, (Z99.11), and Delirium

diagnosis was identified using delirium ICD codes 10 F05, R41. 82 R41.0, ICD 9: 293, 780.97, and 298.2. Hospital and ICU patient admit and discharge dates and Glasgow Coma Scale scores were extracted. This pilot study investigated qualitative variables. The patient age at admission was an average of 65 years. A total of 20 charts were included in the final analysis. 50% of phenytoin group experienced delirium (4/8), 50% of the lacosamide group also experienced delirium (6/12). Number of Days Intubated in Delirium: 2.0 days, no delirium: 1.5 days, number of Days in ICU in Delirium: 5.6 days, no delirium: 3.3 days, number of days in hospital in delirium: 13.7 days, no delirium: 8.5 day. Patients with delirium had longer ICU stays (5.6 days vs. 3.3) and hospital stays (13.7 days vs. 8.5). Patients with GCS less than 10 were much more likely to experience delirium, with 8 out of 11 (73%) patients experiencing delirium versus 2 out of 9 (22%) for patients with GCS greater than 10. Low GCS score at ICU admission could predict emerging delirium in intubated seizure patients. Studies are required to see if early treatment of delirium can decrease the ICU length of stay. Our pilot study highlighted that GCS scores are a key component of assessment of functioning over hospital admission. Prospective and larger studies are required to determine the impact of delirium and relationship between GCS scores and delirium in intubated seizure patients.

Keywords
Status epilepticus; intubation; seizure; delirium; anticonvulsants; Glasgow Coma Scale score

1. Background

Delirium in critically-ill patients is a frequent hospital diagnosis in the ICU setting; increased morbidity and mortality of these patients is an often-cited finding in the medical literature [1]. Common conditions encountered in neurocritical care serve as risk factors for delirium, including traumatic brain injury (TBI), alcohol-withdrawal seizures, and brain hemorrhage. Additionally, postictal delirium following status epilepticus (SE) is frequent, with a 2020 retrospective study demonstrating its incidence in fifty-five percent of patients following status epilepticus termination [1, 2]. SE is historically defined as a single epileptic seizure that is longer than a 30 minute duration, or several seizures without a return to baseline within a 30 minute duration [2]. Status epilepticus is a neurological emergency that requires prompt treatment. SE frequently requires intubation as well. Delirium as a comorbid hospital diagnosis has been found to increase the length of stay in SE patients. Delirium incidence is reported to be the highest in the ICU setting, with up to 80% of intubated patients having delirium [3]. Delirium is common in epilepsy [4, 5]. Delirium is independently associated with long-term cognitive impairment [6]. Delirium is associated with mortality [7].

However, there is a limited report on delirium for intubated seizure patients. When refractory status epilepticus (RSE) has not responded to benzodiazepines, it requires second-line Phenytoin or third-line Lacosamide [8]. Intubated SE had higher overall mortality [9]. Status epilepticus patients required mechanical ventilation for a medium length of four days and is associated with an increased risk of no return to premorbid function [10].

It has been well-established that endotracheal intubation in severely ill patients is a known risk factor for systemic complications such as ventilator-associated pneumonia, pulmonary infections, and sepsis [11]. Therefore, reduced duration of intubation and shorter Intensive Care Unit (ICU) stays are associated with better patient outcomes. A study reviewing 35,232 patients from 2002–2014 indicated that the average time patients remain intubated on a mechanical ventilator was 7.1 ± 11.3 days, and the mean ventilation-free (spontaneous respiration) days was 19.5 ± 11.9 days [12]. The average ICU length of stay in this study was 11.7 ± 13.8 days. 56.4% of patients in this study had traumatic brain injury (TBI). Per report, one-third of patients requiring mechanical ventilation will die [13]. In patients requiring prolonged mechanical ventilation, one-third receives tracheostomy [14-16].

1.1 Glasgow Coma Scale (GCS) Score and Delirium

GCS score [17] is classified as, Severe, GCS 3 to 8, Moderate GCS 9 to 12 and Mild, GCS 13 to 15 in TBI [18]. Low admission GCS in seizures is related to poor outcome [19]. Delirium is associated with duration of mechanical ventilation and ICU length of stay. As per report, Glasgow Coma Scale (GCS) score significantly predicted delirium, decreased GCS score increased the risk of delirium and thus increasing ICU length of stay [20]. Delirium group had a greater duration of mechanical ventilation, and delirium severity was higher among patients on a ventilator and had been on mechanical ventilation for 6 days or more [20-22]. Studies report relationship between GCS and the incidence of delirium and GCS influences the onset of delirium [20, 23]. Disorders of consciousness causes delirium [24] and risk for delirium increases with decreasing GCS scores [25].

Treatment of status epilepticus is urgent and time sensitive. A small study investigating the utility of creating a “status epilepticus alert” similar to a “stroke code” to make SE treatment more efficient found that the administration of a nonbenzodiazepine antiseizure medication was reduced from 58 minutes to 22 minutes [26]. Typically, benzodiazepines are the first-line treatment for SE because they quickly control seizures, and intravenous antiseizure medications besides benzodiazepines are given as second-line treatments as well as to prevent recurrence [27], even if the SE has already stopped. Initial therapy of benzodiazepines only has been proven to not be sufficient as it does not properly prevent recurrence of the seizures [28].

The nonbenzodiazepine medications used to prevent SE recurrence include levetiracetam, phenytoin, or valproate. The Established Status Epilepticus Treatment Trial showed that these three are equally effective [29]. Typically, choice of medication is guided through evaluating the patient’s other chronic antiseizure medications, if any, and choosing a different medication if the patient is at a therapeutic level of their respective home medication.

Phenobarbital and lacosamide are two other antiseizure medications that may also be used, but are typically third-line when patients are refractory. There is evidence that lacosamide may have similar efficacy as other antiseizure medications in treating refractory SE [30]; one study showed that it was similarly effective to phenytoin specifically in treating refractory nonconvulsive seizures [31]. Studies have been published comparing lacosamide versus phenytoin [32-35].

One study focused on treatment failure and safety as assessed by liver function tests, blood pressure, heart rate and ECG while comparing both medications [32]. Similarly, other studies compared efficacy and safety of lacosamide versus phenytoin for seizure prophylaxis [33], comparable efficacy in seizure control in patients with SE [34], Lacosamide and PHT was similar in

efficacy for treatment of SE [35]. The studies have compared clinical efficacy of lacosamide versus phenytoin and the side effects compared were mostly physical side effects. Information on delirium and outcome in intubated seizure patients receiving lacosamide versus phenytoin are lacking.

There are multiple lines of treatment utilized for management of refractory SE, and are known to successfully reduce recurrence of seizures [36, 37]. Given the increased mortality, morbidity, and length of hospital stay of postictal delirium patients in intubated patients in the critical care setting, investigation of patient outcomes after experiencing delirium and after utilizing these treatments is needed to further explore how we may decrease complications of intubation and increased stay in such patients.

1.2 Hypothesis/Objectives

This pilot study assessed the impact of delirium in intubated seizure patients who were treated with Phenytoin and Lacosamide.

This pilot study aimed to assess hospital stay variables included: length of intubation, length of stay and GCS in intubated seizure patients who were treated with an antiepileptic medication other than levetiracetam, such as phenytoin or lacosamide.

This study was conducted to understand about the potential relationship between delirium and GCS. The goal of this pilot study was to evaluate the GCS scores and hospital course of intubated seizure patients with and without delirium.

2. Methods

This is a pilot study. Institutional Review Board approval was obtained for this retrospective analysis. Charts were identified by ICD-10 codes and extracted through supercomputer. Review was conducted via chart review of hospitalized, intubated seizure patients on Phenytoin or Lacosamide at Loyola University Medical Center Neurological ICU from 2018 to 2020. Endotracheal intubation identified by ICD 10, ICD-10-PCS 0BH17EZ, (Z99.11), Delirium diagnosis was identified using delirium ICD codes 10 F05, R41. 82 R41.0, ICD 9: 293, 780.97, and 298.2. Hospital and ICU patient admit and discharge date**s** and Glasgow Coma Scale scores were extracted. The following exclusions were applied: No documented intubation, and use of levetiracetam. Deceased patients were excluded, as were patients not receiving phenytoin or lacosamide, and patients receiving both medications. Participants who received tracheostomy were excluded.

After extracting the relevant patient charts, number of patients intubated, date and time patients were intubated, extubation date, Number of Days Intubated, Number of Days in ICU and hospital were extracted. Number of intubated patients started on phenytoin and lacosamide, date of phenytoin and lacosamide initiation and discontinuation, number of intubated patients started on phenytoin and lacosamide who received diagnosis of delirium, their extubations dates, ICU and hospital discharge date, GCS scores at hospital, during ICU admission, during intubation and extubation, and at discharge were extracted.

3. Results

3.1 Patient Demographics

The patient age at admission was an average of 65 years.

3.2 Sample Characteristics

A total of 20 charts were included in the final analysis. Eight patients received phenytoin, and 12 received lacosamide.

Given the low number of patients that are given an antiepileptic medication other than levetiracetam, our study sample was low, limiting statistical power and confidence in our findings. Thus, this pilot study will look at qualitative variables to assist in determining if such a relationship exists and warrants further study.

50% of phenytoin group experienced delirium (4/8), 50% of the lacosamide group also experienced delirium (6/12), thus showing no difference between the medication groups.

3.2.1 Delirium and Hospital Stay Variables (Table 1)

Number of Days Intubated in Delirium: 2.0 days, no delirium: 1.5 days
Number of Days in ICU in Delirium: 5.6 days, no delirium: 3.3 days
Number of Days in Hospital in Delirium: 13.7 days, no delirium: 8.5 days
Patients with delirium had longer ICU stays (5.6 days vs. 3.3) and hospital stays (13.7 days vs. 8.5).

Table 1 Delirium versus no Delirium in relation to number of days Intubated, Length of ICU and Hospital stay.

	Number of Days Intubated	Number of Days in ICU	Number of Days in Hospital
Delirium	2.0	5.6	13.7
No Delirium	1.5	3.3	8.5

The delirum group had higher lengths of stay and intubation. Thus, further exploration of these variables is warranted through a larger retrospective chart review.

When classifying GCS severity (9-15) vs. (1-8), individuals with GCS less than 10 were much more likely to experience delirium, with 8 out of 11 (73%) patients experiencing delirium versus 2 out of 9 (22%) for individuals with GCS greater than 10 (Table 2) (Figure 1).

Table 2 GCS of Patients Experiencing Delirium.

	Delirium	No Delirium
GCS greater than 10	2 patients	7 patients
GCS less than 10	8 patients	3 patients

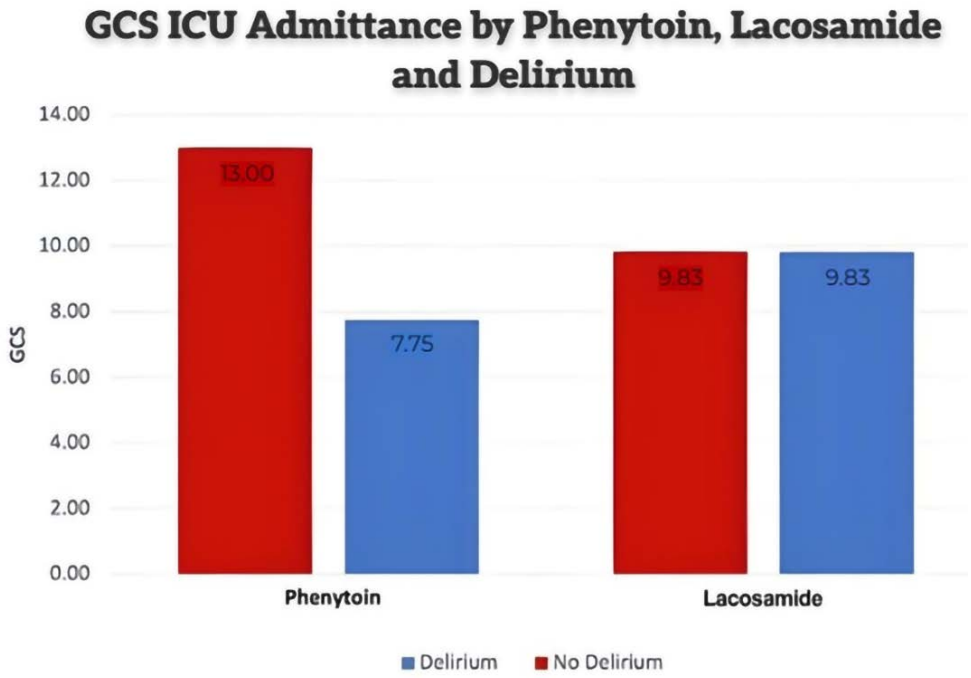

Figure 1 GCS at admission in relation to delirium versus no delirium. X axis is Delirium vs no delirium and Y axis is GCS. In Phenytoin group, patients with GCS mean score of 7.75 developed delirium. In the Lacosamide group, patients with GCS mean score of 9.83 developed delirium.

For all patients (delirium and no delirium), GCS scores at ICU admission ranged from 5 to 15, with a median of 8 and mean of 10.05

For all patients, GCS scores at ICU discharge ranged 6 to 15 with a median of 15 and mean of 13.95

For all patients treated with only lacosamide, GCS scores at ICU admission ranged from 5 to 15, with a median of 8 and mean of 10. GCS scores at ICU discharge ranged 6 to 15 with a median of 15 and mean of 13.3 (Table 3)

For all patients treated with only phenytoin, GCS scores at ICU admission ranged from 7 to 15, with a median of 9.5 and mean of 10.00. GCS scores at ICU discharge ranged from 14 to 15 with a median of 15 and mean of 14.8 (Table 3).

In Phenytoin delirium group, GCS mean score: 7.75 (Table 4 and Figure 1)

In Phenytoin delirium group, GCS mean score improved from 7.75 to 15.00 (Table 4 and Figure 2)

In the Lacosamide delirium group, GCS mean score: 9.83 (Table 4 and Figure 1)

In the Lacosamide delirium group, GCS mean score improved from 9.83 to 13.17 (Table 4 and Figure 2)

Low GCS sores at ICU admission indicates the severity of the patient status requiring intubation and developing delirium. GCS scores increases at ICU discharge.

With respect to the potential relationship between GCS and incidence of delirium to determine if this warrants further exploration, we found the following:

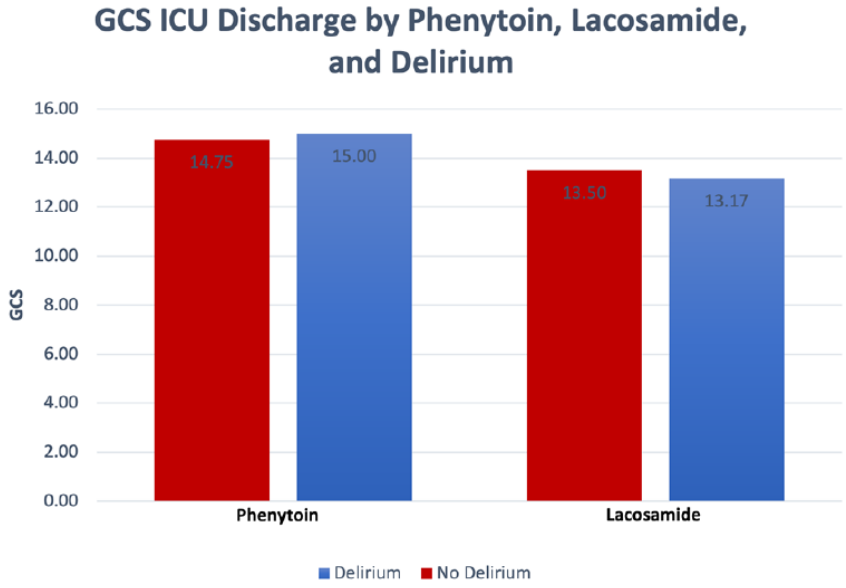

Figure 2 GCS score of Delirium and no delirium patients at discharge from ICU. X axis is Delirium vs no delirium and Y axis is GCS. In Phenytoin delirium group, GCS mean score improved from 7.75 to 15.00. In the Lacosamide delirium group, GCS mean score improved from 9.83 to 13.17.

Table 3 GCS of all Patients (delirium and no delirium) Treated with Phenytoin versus Lacosamide.

	ICU Admission GCS of all patients	ICU Discharge GCS of all patients	GCS Change
Phenytoin (n = 8)	10.00 (GCS of patients treated with Phenytoin at ICU admission)	14.8 (GCS of patients treated with Phenytoin at ICU discharge)	4.8 (Phenytoin)
Lacosamide (n = 12)	10.00 (GCS of patients treated with Lacosamide at ICU admission)	13.33 (GCS of patients treated with Lacosamide at ICU discharge)	3.3 (Lacosamide)

Table 4 GCS of Delirium patients treated with Phenytoin versus Lacosamide.

	ICU Admission GCS of Delirium patients	ICU Discharge GCS of delirium patients	GCS Change in delirium patients
Phenytoin (n = 4)	7.75 (GCS of patients treated with Phenytoin at ICU admission)	15.00 (GCS of patients treated with Phenytoin at ICU discharge)	7.25 (Phenytoin)
Lacosamide (n = 6)	9.83 (GCS of patients treated with Lacosamide at ICU admission)	13.17 (GCS of patients treated with Lacosamide at ICU discharge)	3.34 (Lacosamide)

4. Discussion

In this small pilot retrospective chart review, low GCS score during ICU admission in intubated seizure patients co-relate with delirium, and these patients had longer ICU and hospital stays. Seizures can have grave effects on neuropsychiatric functioning, but the use of anti- seizure medications (ASM) in acute management may mitigate outcomes. Studies evaluating phenytoin and lacosamide in this setting suggest significant effects on prevention of early post-traumatic seizure [36, 37]. Postictal delirium is additionally known to cause an increase in duration of intubation, ICU stay, and hospital stay, ultimately resulting in a worsening prognosis.

Our aim with this study was to conduct a retrospective study on the impact of delirium on intubated seizure patients by analyzing their duration of hospital stay, duration of intubation, and GCS, and understand possible correlations between these factors.

To our knowledge, our preliminary pilot study is of the first to investigate delirium and hospital outcomes specifically on intubated post-status epilepticus patients receiving phenytoin and lacosamide. Utilizing intubation status when evaluating status epilepticus patients is significant in that it is an objective measure of patients' critically ill state, rather than identifying their ICU stay as a determinant alone. This is because within the ICU, there may be large variations in how critical patients are. Some patients may also be admitted to the ICU for observation over 24 hours or hourly neurological exams.

When we reviewed GCS score severity and delirium, we found that individuals with a GCS below 10 were much more likely to experience delirium. Those patients with delirium additionally had longer ICU and overall hospital stays. Our overall goal is to understand how to predict delirium early, improve prognosis and outcomes in these patients. Delirium is associated with negative outcomes [38, 39]. Larger and prospective studies are required to see if low GCS score is a risk factor for delirium in intubated seizure patients. Prospective studies are needed to see if low GCS score during ICU admission in intubated seizure patients could predict delirium so that intervention can be provided. Additionally, studies are needed to see the long term prognosis of low GCS score patients and see if GCS scores had significant correlations with prognosis.

Shorter duration of intubation and ICU stay is associated with better outcomes. More data is needed to better understand GCS scores and what interventions may be used to improve neurocognitive function in intubated seizure patients.

Several studies show phenytoin's efficacy as compared to levetiracetam among other ASMs, including for management of status epilepticus [40]. One study comparing levetiracetam and phenytoin in preventing early posttraumatic seizures revealed equal efficacy, but found levetiracetam to be associated with higher incidence of abnormal EEG findings and increased seizure tendency on EEG [41]. A meta-analysis conducted in 2016 of 1614 patients to assess seizure-related outcomes in brain injury patients found that levetiracetam was not superior to phenytoin in early seizure prophylaxis [41]. Prospective studies are needed to see if neuroprotective effect is playing a positive role in extubation in seizures.

The results of this small retrospective pilot study identifies delirium increasing length of stay and a possible relationship between GCS and delirium in intubated seizure patients on phenytoin and lacosamide; prospective studies are needed on other ASMs. While long-term effects on cognition may be difficult to predict at the time of hospitalization, GCS are a key component in the assessment of functioning over the course of admission.

The utility of GCS scores may extend beyond the course of admission, as evidence suggests an association between GCS at ICU discharge and patient outcomes at 1-year follow-up [42]. These findings support the approximation of ICU discharge GCS with prognosis. While GCS scores are an appropriate metric for cognitive functioning during hospitalization, more data is needed to understand if they provide significant prognostic value for long-term cognitive functioning in status epilepticus, posttraumatic seizure and delirium patients. The potential to significantly improve both acute and long-term recovery from status epilepticus and should prompt further studies investigating the impact of anti-epileptic medications on prognosis. We suggest also evaluating GCS scores and the impact of delirium on patients who were treated with antiepileptic drugs for seizure prophylaxis after traumatic brain injury, which is a frequent underlying cause of seizures and status epilepticus.

Cognitive impairment is common in patients with epilepsy [43]. GCS score is classified as Severe 3 to 8, Moderate 9 to 12 and Mild 13 to 15 in TBI [18]. As low admission GCS in seizures is related to poor outcome [19] could ICU GCS is one among many parameters predict long term neuropsychiatric outcomes? Intubated seizure patients after hospital discharge may be encountering neuropsychiatric complications. Prospective studies are required to see if low GCS and delirium at ICU admission lead to long term effects. This information will be valuable and assist the outpatient neuropsychiatry providers while they manage these patients.

4.1 Limitation

This study was limited by its smaller n, design, as retrospective chart review constrained the ability to control for variables and analyze additional outcomes of interest.

The evaluation of cognitive outcomes associated with postictal delirium in this study was limited to GCS scores, a measure that introduces subjectivity and potential measurement bias into the results. Multiple other factors could have also influenced extubation in this retrospective study, including the effect of other medications, comorbidities, and effect of other medications like dexmedetomidine [44]. Smaller sample size was also a limitation in our data collection; extracting more charts for review and access to different databases may improve our sample size to increase the power of our data. Prospective studies are needed comparing extubation time to other antiepileptics.

5. Conclusion

Low GCS score at ICU admission could predict emerging delirium in intubated seizure patients. Studies are needed to see if early treatment of delirium in can decrease the ICU length of stay. Our pilot study highlighted that GCS scores are a key component of assessment of functioning over hospital admission, and may be predictive of postictal delirium after a seizure. Patients with a GCS score less than 9 were more likely to experience postictal delirium. Prospective and larger studies are needed to determine impact of delirium and relationship between GCS scores and delirium in intubated seizure patients receiving phenytoin and lacosamide in addition to understanding their antiepileptic effect. Similar studies are required in patients receiving other ASMs.

Author Contributions

Sara Alattar, Muhammad Nouman, Edwin Meresh - project development, data collection, manuscript writing, reviewed literature, revised and edited the manuscript. Chidozie Onyiuke, Conrad Stasieluk - manuscript writing, background information, review of literature, provided feedback.

Competing Interests

The authors have declared that no competing interests exist.

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