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Intubation for Psychogenic Non-Epileptic Attacks: Frequency, Risk Factors, and Impact on Outcome

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ABSTRACT

Purpose: Patients with psychogenic non-epileptic attacks (PNEA) sometimes receive aggressive treatment leading to endotracheal intubation. We sought to identify the frequency, risk factors, and impact on outcome of intubation for PNEA.

Methods: We retrospectively reviewed all PNEA patients admitted via the emergency department (ED) who had an episode of PNEA documented by continuous video electroencephalography (vEEG) at Henry Ford Hospital between January 2012 and October 2017. Patients with comorbid epilepsy were excluded. Clinical features, treatments, and vEEG reports were compared between intubated and non-intubated patients.

Results: Of 80 patients who were admitted via the ED and had PNEA documented by vEEG, 12 (15%) were intubated. Compared with non-intubated PNEA patients, intubated patients had longer duration of convulsive symptoms (25 [IQR 7-53] vs 2 [IQR 1-9] minutes, P = 0.01), were less likely to have a normal Glasgow Coma Scale score of 15 (33% vs 94%, P < 0.001), received higher doses of benzodiazepines (30 [IQR 16-45] vs 10 [IQR 5-20] mg of diazepam equivalents, P = 0.004), and were treated with more antiepileptic drugs (AEDs, 2 [IQR 1-3] vs 1 [IQR 1-2], P = 0.01). Hospital length of stay was longer (3 [IQR 3-5] vs 2 [IQR 2-3], P = 0.001), and the rate of complications (25% vs 4%, P = 0.04) and re-hospitalization from a recurrent episode of PNEA within 30 days was higher among intubated PNEA patients (17% vs 0%, P = 0.02).

Conclusion: Fifteen percent of patients hospitalized for vEEG-documented PNEA were intubated. Intubated patients had longer length of stay, more in-hospital complications, and a high rate of re-hospitalization from recurrent PNEA symptoms. Prolonged duration of convulsive symptoms, depressed level of consciousness, and aggressive treatment with benzodiazepines were associated with intubation for PNEA.

1. INTRODUCTION

Psychogenic non-epileptic attacks (PNEA) are defined as paroxysmal movements or abnormal behaviors that resemble epileptic seizures, are not accompanied by epileptiform activity, and are often associated with psychogenic factors. [1,2]. Documented clinical signs of PNEA without accompanying epileptiform activity on video electroencephalography (vEEG) is typically required to definitively confirm the diagnosis of PNEA. [1–3] Approximately 30% of hospitalized patients who undergo elective vEEG monitoring in epilepsy referral centers are diagnosed with PNEA.[4,5] We used the term “psychogenic nonepileptic attacks (PNEA)” instead of the term “psychogenic nonepileptic seizures (PNES)” or “dissociative seizures” because we want to make a clear differentiation of these events from epileptic seizures.

An older study found that recurrent hospital admissions for PNEA-status occur in up to one-third of all patients with PNEA, regardless of the underlying psychiatric diagnosis. [6] Prolonged episodes of PNEA-status are sometimes mistaken for and inappropriately treated as status epilepticus, leading to aggressive antiepileptic treatment and endotracheal intubation, which can be fatal. [7–9] In this study we sought

Abbreviations: PNEA, Psychogenic non-epileptic attacks; EEG, electroencephalography; cEEG, continuous electroencephalography; ED, emergency department; EMU, epilepsy monitoring unit; AEDs, antiepileptic drugs; CIV-AEDs, continuous infusion antiepileptic drugs; GCS, Glasgow Coma Scale; ICU, intensive care unit; BZPs, benzodiazepines; HFH, Henry Ford Hospital

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to identify the frequency of, risk factors for, and clinical outcomes associated with intubation for PNEA.

2. METHODS

We retrospectively reviewed our electronic medical record (www.epic.com) of all adult patients (age ≥ 18 years) who underwent video continuous vEEG monitoring at Henry Ford Hospital from January 2012 to October 2017. Patients who had a discharge diagnosis of "non-epileptic" or "psychogenic" seizures or spells, "pseudoseizures," or "PNEA" were identified; in all cases the diagnosis of PNEA was re-confirmed by retrospective chart review performed by the study team according to current proposed diagnostic criteria. [2] All patients had clinical signs of PNEA witnessed by the attending neurologist at our institution during admission, or by an epileptologist on review of vEEG without epileptiform activity. Patients who had comorbid epilepsy or who did not have PNEA documented by cEEG were excluded. Our study was limited to patients admitted via the emergency department (ED) of either our hospital or a transferring hospital; patients directly admitted to the floor or epilepsy monitoring unit (EMU) were excluded. Demographics, clinical features, treatments given in the ED, and vEEG reports were abstracted and recorded in a Research Electronic Data Capture (REDCap) database (www.project-redcap.org). [10] Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed, and this study was approved by the Henry Ford Institutional Review Board. As the study was retrospective and posed no significant risks, the requirement for written informed consent was waived.

2.1. Clinical Data Collection

Clinical data that we collected included demographics; documented history of PNEA prior to admission; documented psychiatric conditions including major depressive disorder, posttraumatic stress disorder, generalized anxiety disorder, schizophrenia, and bipolar disorder; source of hospital admission; location of intubation; convulsive and postictal symptoms prior to intubation; duration of convulsive symptoms; antiepileptic drugs (AEDs) and continuous infusion antiepileptic drugs (cIV-AEDs) drugs and dosages administered in the ED; endotracheal intubation and vasopressor initiation in the ED; Glasgow Coma Scale (GCS) scores on admission (first recorded score) and discharge; and whether the patient was admitted to an intensive care unit (ICU).

We did not have access to data regarding the use of benzodiazepines (BZPs) in the prehospital setting. Data on BZPs given in the ED included only bolus intravenous or intramuscular administration of lorazepam, diazepam or midazolam. Dosage of BZPs used in the ED were calculated as diazepam equivalents, with 5 mg of diazepam being equivalent to 1 mg of lorazepam and 2 mg of midazolam (dosage of continuous infusion midazolam was not included).[11,12] Continuous infusion of midazolam, propofol, pentobarbital, and ketamine were classified as cIV-AEDs.

2.2. Continuous Video Electroencephalography

All cEEG was performed using 32-channel digital EEG machines with video monitoring for at least 12 hours. Information from vEEG reports were extracted and classified according to the American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology 2012. [13] Ictal characteristics of PNEA [2,14–17] and post-episode symptoms were abstracted from EEG reports. PNEA-status was defined as continuous or repeated episodes of ictal or convulsive features suggesting PNEA for at least 30 minutes without returning to baseline during vEEG monitoring and no associated epileptiform activity.[6,18] Time from admission to the start of vEEG, total vEEG duration, time from the start of vEEG to PNEA detection, and duration of PNEA were recorded.

2.3. Outcome Assessment

Outcome assessments included survival and Glasgow Coma Scale (GCS) at hospital discharge; in-hospital complications included hypotension requiring vasopressors and nosocomial infections; and re-hospitalization within 30 days of discharge at any EPIC Care Everywhere Network hospital in Southeast Michigan, which includes the Henry Ford Health System.

2.4. Statistical Analysis

To identify factors associated with endotracheal intubation we compared demographics, clinical characteristics, treatments and outcomes between PNEA patients who were intubated and those who were not. Continuous data were described using means, standard deviations, medians, and interquartile range as appropriate, while categorical data were described using counts and column percentages. Univariate two-group comparisons were carried out using independent t-tests for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed continuous variables, Pearson's chi-square tests for categorical variables with expected cell counts > 5, and Fisher's exact tests for categorical variables with expected cell counts < 5. Multivariate analysis was not performed due to the small sample size. Statistical significance is set at $p < 0.05$. All analyses were performed using PASW Statistics version 18. [19]

3. RESULTS

Of 1,735 patients who underwent cEEG monitoring at Henry Ford Hospital (HFH) between January 2012 and October 2017, 144 patients had PNEA as the confirmed principal diagnosis in the discharge summary. 22 patients who were directly admitted to the EMU and 42 patients who had comorbid epilepsy or who did not have PNEA documented by cEEG were excluded, leaving 80 PNEA patients who had PNEA documented by cEEG and were admitted via the ED in the final analysis. Twelve of these PNEA patients (15%) were intubated (Fig. 1). Of the 12 intubated patients, 11 (92%) were intubated in an outlying ED before transfer to HFH, and one (8%) was intubated on the HFH neurology ward by a covering non-neurologist shortly after admission.

3.1. Baseline Characteristics

Median age of all PNEA patients was 33 [interquartile range, IQR 25-41] years and 74% were female. Overall a prior diagnosis of a psychiatric disorder was reported in 73% and PNEA in 6%. There was no significant difference in age, gender, race, or prior history of psychiatric disorder or PNEA between intubated and non-intubated patients (Table 1).

3.2. Clinical Features

Intubated PNEA patients had substantially longer convulsive symptoms than those who were not (25 [IQR 7-53] vs 2 [IQR 1-9] minutes, $P = 0.01$). Post-episode confusion was not significantly different between the two groups. Intubated patients were less likely to have GCS of 15 on hospital admission (33% vs 94%, $P < 0.001$). All intubated patients were admitted to ICU, whereas only 13% of non-intubated PNEA patients required ICU admission (Table 1).

3.3. Treatments in the ED

Data on treatment in the ED was available in 59 of 80 patients (74%). Compared with non-intubated patients, intubated PNEA patients were more frequently treated with AEDs (100% vs 65%,

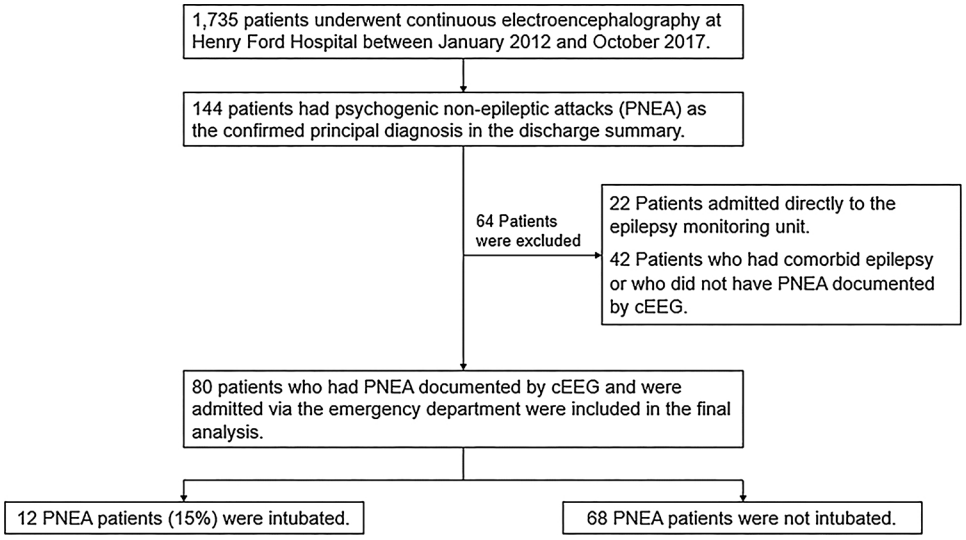

Fig. 1. Patient Population.

Table 1
Baseline Characteristics.

Characteristics	Intubated PNEA (N = 12)	Non-intubated PNEA (N = 68)	P Value
Demographics			
Age, years	37 [27-44]	32 [25-40]	0.26
Female	7 (58)	52 (77)	0.28
White	10 (91)	35 (61)	0.08
African-American	1 (9)	20 (35)	0.15
Documented comorbid diseases prior to admission			
PNEA	2 (17)	3 (4)	0.16
Psychiatric disorders	11 (92)	47 (69)	0.16
Admission sources			0.44
HFH emergency department	1 (8)	16 (24)	
Transferred from other hospital	11 (92)	52 (77)	
Clinical features			
Duration of convulsions in the ED[a], minutes	25 [7-53]	2 [1–9]	**0.01**
Post-episode confusion	3 (25)	11 (16)	0.43
Patients with GCS of 15 on admission	4 (33)	64 (94)	< **0.001**
ICU admission	12 (100)	9 (13)	< **0.001**

Data are n (% of total available data within each column) or median [IQR].
PNEA = psychogenic non-epileptic attacks; GCS = Glasgow Coma Scale; ED = emergency department;
IQR = inter-quartile range.
[a] Data are available for 42 patients (4 intubated and 38 non-intubated patients).

P = 0.02) and received multiple AEDs (median 2 [IQR 1-3] vs 1 [IQR 1-2], P = 0.01; Table 2). Overall, intravenous BZPs were the most common AED class used in the ED (66%), followed by levetiracetam (24%), phenytoin (20%) and lacosamide (3%). Of patients treated with bolus BZPs, 82% received lorazepam, 26% received midazolam, and 3% received diazepam. Compared with non-intubated patients, intubated PNEA patients were more often treated with BZPs (100% vs 58%, P = 0.01) and were treated with three times the amount of BZPs (30 [IQR 16-45] vs 10 [IQR 5-20] mg of diazepam equivalents, P = 0.004). CIV-AEDs was used more frequently in intubated patients (46% vs 6%, P = 0.004), mostly after intubation (Table 2). Propofol was the most common CIV-AEDs administered (14%), followed by midazolam (10%), and ketamine (2%).

Table 2
Treatment in the Emergency Department.

	Intubated PNEA (n = 11)[a]	Non-intubated PNEA (n = 48)[a]	P Value
Antiepileptic treatment in the ED	11 (100)	31 (65)	**0.02**
Numbers of AEDs used in the ED	2 [1-3]	1 [1-2]	**0.01**
Benzodiazepines administered	11 (100)	28 (58)	**0.01**
Dosage of benzodiazepines[b], mg of diazepam equivalents	30 [16-45]	10 [5-20]	**0.004**
CIV-AEDs used in the ED	5 (46)	3 (6)	**0.004**

Data are n (% of total available data within each column) or median [IQR]
PNEA = psychogenic non-epileptic attacks; ED = emergency department; AEDs = antiepileptic drugs; CIV-AEDs = continuous intravenous infusion antiepileptic drugs; IQR = inter-quartile range.
[a] Data are available for 11 of 12 intubated and 48 of 68 non-intubated patients.
[b] Calculated as diazepam-equivalent dose with 5 mg of diazepam being equivalent to 1 mg of lorazepam and 2 mg of midazolam[9,10] Data are available for 7 intubated patients and 25 non-intubated patients.

3.4. Continuous Electroencephalography

Overall median time from admission to the start of cEEG was 1 [IQR 0-1] day, and total duration of monitoring was 22 [IQR 20-25] hours. Diffuse background slowing was found in 8% of overall PNEA patients, and rhythmic or periodic patterns were uncommon (Supplemental Table 1). There was no significant difference in the frequency of any EEG abnormality, or of any of 24 different motor phenomena or other symptoms documented on video-cEEG, between intubated and non-intubated patients (Supplemental Tables 1 and 2).

3.5. Outcomes

There was no mortality and the discharge GCS score was 15 in all patients. Hospital length of stay was longer in intubated patients than non-intubated patients (3 [IQR 3-5 vs 2 [IQR 2-3] days, P = 0.001). The rate of overall in-hospital complications (25% vs 4%, P = 0.04) and re-hospitalization from a recurrent episode of PNEA within 30 days (17% vs 0%, P = 0.02) were significantly higher in intubated PNEA patients (Table 3).

Table 3
Outcomes.

	Intubated PNEA (N = 12)	Non-intubate PNEA (N = 68)	P Value
Hospital length of stay, days	3 [3–5]	2 [2–3]	**0.001**
In-hospital complications	3 (25)	3 (4)	**0.04**
Hypotension requiring vasopressors	2 (17)	1 (2)	0.06
Nosocomial infection	1 (8)	2 (3)	0.39
Re-hospitalization within 30 days	2 (17)	1 (2)	0.057
Re-hospitalization from a recurrent episode of PNEA within 30 days	2 (17)	0 (0)	**0.02**

Data are n (% of total available data within each column) or median [IQR].
PNEA = psychogenic non-epileptic attacks; IQR = inter-quartile range.

4. DISCUSSION

In this study, 15% of EEG-documented PNEA patients who presented to the ED were intubated. Intubation occurred more frequently in patients who had longer duration of convulsive symptoms and depressed level of consciousness. Perhaps most importantly, intubated PNEA patients received benzodiazepines more often and at much higher doses, suggesting that in some cases the intubation may have been iatrogenic.

Little data exists regarding the frequency of intubation for PNEA. In a post-hoc study of RAMPART, a randomized clinical trial that compared the use of intramuscular midazolam to intravenous lorazepam for the treatment of prehospital seizures, 83 of 1,023 patients (8%) were ultimately diagnosed with a non-epileptic spells, and only two of them (2%) were intubated. [20] In the Established Status Epilepticus Treatment Trial (ESETT), a randomized trial of therapies for benzodiazepine-refractory status epilepticus in the emergency department, 10% of enrolled patients were determined to have psychogenic seizures [21].

The large discrepancy in the frequency of intubation for PNEA between our study and RAMPART is most likely explained by differing selection criteria, since RAMPART included all patients with suspected seizures in the prehospital setting, [20] whereas our study was limited to patients admitted via the ED who had PNEA documented by cEEG monitoring. Although utilization of video-cEEG is the best strategy to confirm the diagnosis of PNEA, this may have led to inflation of the observed rate of intubation due to exclusion of patients with milder symptoms and a well-established diagnosis. However, a small prior study reported a 22% frequency of intubation (2 of 9 PNEA patients) among patients with prolonged PNEA, [22] which is slightly higher than our observed rate of 15%.

The predominance of women and young adults in our study cohort are consistent with previous PNEA studies. [22–26] It is also noteworthy that the majority (92%) of intubated PNEA patients were transferred from an outside hospital for escalation of care.

A prior diagnosis of a psychiatric disorder or PNEA was not different between patients who were intubated and those who were not. Our results also demonstrated a high frequency (73%) of comorbid psychiatric disorders in PNEA patients; many other studies support this finding. [27–29]

PNEA patients who were intubated had longer convulsive symptoms and more frequently had depressed level of consciousness than those who were not intubated. Since we did not have data on pre-hospital treatment, it is unclear if the higher frequency of altered consciousness in those who were eventually intubated was due to different inherent clinical features or greater BZP use. Regardless, intubated patients were loaded with significantly higher doses of BZPs and were more frequently treated with multiple AEDs after ED admission. This suggests that in some patients the need for intubation was a direct consequence of the sedative effects of BZPs and AED therapy, although in some cases BZPs may have merely been used to facilitate intubation. Prior studies have confirmed that episodes of PNEA usually last longer than epileptic seizures. [6] One study comparing 9 patients with PNEA-status with 10 cases of refractory generalized convulsive status epilepticus (RGCSE) found that the PNEA-status patients received significantly higher doses of BZPs than RGCSE patients (72 vs 29 mg of diazepam equivalents, respectively). [22]

Not surprisingly, subsequent video-cEEG monitoring showed no differences in electrographic abnormalities or clinical signs of PNEA between intubated and non-intubated patients. Motor phenomena and other PNEA symptoms documented on video-cEEG in our cohort were consistent with reports from previous studies. [14,15,30–34], The diffuse background slowing that was found in 8% overall can be explained by the effects of benzodiazepines or other AEDs.

None of the PNEA patients in our cohort died and all were discharged with normal level of consciousness. In one report a PNEA patient who was intubated eventually died from anaphylaxis from a neuromuscular blocking agent used to facilitate mechanical ventilation. [8]

PNEA patients in our study who were intubated were more likely to have recurrent PNEA symptoms leading to rehospitalization within 30 days of discharge. This most likely reflects more severe PNEA symptomatology in patients who are intubated, and highlights the need for close follow-up immediately after discharge, since early psychological intervention might prevent a recurrent episode of PNEA and re-hospitalization. [35–37]

Our data also demonstrate that besides unnecessary intubation, a variety of other serious complications can occur in hospitalized PNEA patients, including hypotension requiring pressor support and nosocomial infections. The rate of these complications in intubated PNEA patients (25%) is comparable to that reported in status epilepticus (28%), [38] and was six times higher than among non-intubated PNEA patients.

There are some limitations of this study. First, this study included patients admitted to a single tertiary referral center in the Midwest United States, which may limit generalizability. Second, PNEA semiology occurring in the ED leading to intubation was not recorded; thus, the epileptic nature of some of these events could not be completely excluded. Third, we could not perform multivariate analysis to identify independent risk factors for endotracheal intubation because of the small sample size. Fourth, the 17% 30-day readmission rate that we found among intubated PNEA patients is most likely an underestimate, since approximately only three of the six major healthcare systems in Southeast Michigan participate in EPIC Care Everywhere. Finally, we did not evaluate clinical outcome and quality of life after discharge.

In summary, fifteen percent of PNEA patients admitted via the ED to our hospital were intubated, and these patients had longer length of stay, higher rates of in-hospital complications, and more frequent re-hospitalization for recurrent PNEA symptoms. Early clinical recognition of PNEA, awareness of the tendency of PNEA-status to be prolonged, and mindfulness of the potential harm of BZP overtreatment would seem to be the most effective ways to reduce harm in this patient population. Increased use of rapid-response EEG may also help reduce benzodiazepine overuse. Close follow-up and early psychological intervention after discharge may reduce the high risk of re-hospitalization in these patients.

Author Contributions

TV performed data collection, statistical analysis and interpretation, drafted and revised the manuscript. NP performed data collection, analysis and interpretation, assisted drafting and revised the manuscript. GO performed data collection, data review and interpretation, assisted drafting and critically reviewed the manuscript. NOA assisted collecting data. VSW and GB assisted interpreted the data and critically reviewed the manuscript. SAM designed the study and data analysis, performed data review and interpretation, drafted and revised the

manuscript. All authors have read and approved the final manuscript, and agree to be accountable for all aspects of the work.

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Declaration of Competing Interest

S.A.M. has received consulting fees from UCB Pharma. The remaining authors have no conflicts of interest.

Data Sharing Statement

Anonymized data not published within this article are available from the corresponding author on reasonable request.

Ethics Approval

This study was approved by the Henry Ford Institutional Review Board. As the study was retrospective and posed no significant risks, the requirement for written informed consent was waived.

The authors declare no competing financial interest.

Transparency document

The Transparency document associated with this article can be found in the online version.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2019.12.025.

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