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The safety and efficacy of modifying the admission protocol to the epilepsy monitoring unit in response to the COVID-19 pandemic



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ABSTRACT

Purpose: The coronavirus disease 2019 (COVID-19) pandemic has impacted admission to epilepsy monitoring units (EMUs) for classification and presurgical evaluation of patients with refractory epilepsy. We modified the EMU admission protocol via anti-seizure medications (ASM) withdrawal implemented one day before admission; thus, we aimed to evaluate the efficacy and safety of this modified protocol. *Methods:* In January 2021, we initiated ASM tapering 24 h before—rather than on the first day after—EMU admission, contrasting with the previous protocol. We retrospectively reviewed EMU admissions between January and April of 2018, 2019, and 2021, and identified the time required to record the first seizure, and EMU yield to confirm or change the epilepsy classification. We also evaluated the safety of the modified protocol, by monitoring the seizure frequency for up to 5 months after the discharge from the hospital.

Results: One hundred four patients were included (mean age: 30 years, men: 43%); excluding a longer disease duration and abundance of normal routine electro-encephalogram (EEG) in patients admitted before the pandemic, no differences were observed in patients' characteristics. On average, it took 41 h and 21 h to record the first seizure using the standard and modified protocols, respectively (p < 0.001, 95% CI: 10–30). Other characteristics were investigated both before and after the COVID-19 pandemic, and epilepsy classifications were confirmed twice using the modified protocol (OR = 2.4, p = 0.04, 95% CI: 1.1–5.5). Multivariate regression analysis confirmed the shorter time to record the first seizure using the modified admission protocol (23 h less, p < 0.001; 95% CI: 12–34). Finally, 36 (86%) patients admitted during the pandemic exhibited no increase in seizure frequency after the discharge from the hospital. *Conclusions:* Initiating ASM withdrawal one day before EMU admission was deemed to be an efficient and safe way to confirm epilepsy classification and significantly decrease the length of hospital stay. Ultimately, this will shorten the long waiting list for EMU admission created by the COVID-19 pandemic.

1. Introduction

Admission to the epilepsy monitoring unit (EMU) is a crucial step in identifying the seizure generator in drug-resistant epilepsy, as well as classifying epilepsy and other spells [1-3]. Along with other hospital procedures, elective admissions were significantly minimized due to the COVID-19 pandemic [4-6], leading to a dras-

tic increase in the already long waiting time for admission to the EMU in our hospital.

Withdrawal of anti-seizure medications (ASM)—the standard approach in all epilepsy centers upon admission to the EMU—helps to record seizures, identify seizure onset zone (SOZ), classify seizure type, ensure patient safety, and minimize complications related to seizures [7,8]. EMU admission protocols have various ASM withdrawal methods that are gradually initiated following admission to the unit; the average length of EMU stay to achieve the goal of admission is generally less than a week [9,10], despite the speed of the withdrawal [11]. The time to record the first seizure remains unknown; however, the exact time required to reach the admission objective is always uncertain.



Abbreviations: ASM, anti-seizure medication; COVID-19, coronavirus disease 2019; EMU, epilepsy monitoring unit; PWE, patients with epilepsy; SOZ, seizure onset zone.

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Facing the long waiting list following the reopening of elective hospital admissions in late 2020, and in response to the COVID-19 pandemic, we modified the ASM withdrawal protocol in adult patients scheduled for EMU admission in our hospital. Starting in January 2021, ASM withdrawal was initiated one day before admission, but other admission measures remained unchanged. In this study, we aimed to evaluate whether our modified admission protocol would safely aid in recording seizures earlier than during the pre-COVID-19 era, impact the yield of EMU to confirm or add new knowledge of epilepsy classification, and identify SOZ.

2. Materials and methods

2.1. Patients and data acquisition

We reviewed patients admitted to the EMU in our hospital between January and April of 2018, 2019, and 2021; 2020 was excluded, since EMU admissions were paused in mid-March of that year. Inclusion criteria were: an age > 13 years, known or suspected cases of epilepsy, who are on at least one ASM. We excluded patients admitted for the classification of psychogenic nonepileptic seizures. In 2018 and 2019, the admission protocol included initiating withdrawal of ASM the second day after admission to the EMU, by 50% reduction of all medications, and withholding all medications in day three. Starting in January 2021, we initiated ASM withdrawal from home, one day before admission, where patients were requested to reduce the morning doses of all medications by 50%, and to hold all the evening medications the night before admission. For those who were reluctant to reduce their ASM from home, we requested them to hold all the evening medications the night before admission. We considered patients admitted in 2018 and 2019 as the "pre-CVOID" group and those admitted in 2021 as the "post-COVID" group, ensuring that no ASMs were administered following EMU admission for patients in the post-COVID group. In addition to early ASM withdrawal, we followed similar EMU admission protocols in both groups, and encouraged sleep deprivation. According to standard procedure, rescue therapy was used after the occurrence of three or more seizures, or status epilepticus [12]. Since July 2020, all patients and their companions were required to undergo a COVID-19 test within 72 h before admission; only those with negative COVID-19 PCR results were admitted to the unit. We collected patients' data, including basic demographics, epilepsy classifications, disease duration, number of ASMs, seizure frequency, longest seizure freedom, and the last seizure recorded before EMU admission. We also determined the number of seizures recorded and use of rescue therapy in EMU. We assessed the EMU yield of both groups to determine whether EMU admission confirmed the pre-EMU hypothesis on the seizure generator, or added new knowledge to identify the seizure generator. We also assessed whether EMU admission failed to add any knowledge related to identifying the SOZ.

2.2. Study outcomes and safety

We determined the time required to record the first seizure, the frequency of rescue therapy use, the number of seizures recorded, and seizure-related complications in both groups. To further assess the safety of the modified EMU admission protocol, we identified seizure patterns and frequencies up to 5 months after EMU discharge in the post-COVID group. The hospital stay was determined once enough seizures were recorded to establish a satisfactory knowledge about the seizure generator in each patient. We determined that recording three seizures will be considered satisfactory to classify epilepsy and identify SOZ [13]. Yet, we managed each patient on an individual basis, in order to achieve the goal of

EMU admission. Our EMU admission protocol suggests seven days of "length of stay" in our hospital, based on in-hospital withdrawal of ASM. This study was approved by our institutional Review Board (IRB) and informed consent was waived because of the nature of the study.

2.3. Statistical analysis

We used R studio for data analysis [14]. We used the mean, median, standard deviation, and range to describe numerical data, and percentages to describe categorical variables. We performed Student's *t*-test, analysis of variance (ANOVA), and Chi-squared test for binary statistical analyses, and multiple linear and logistic regression analyses for multivariable analysis. We calculated the 95% confidence intervals, and interpreted the p-values according to the American statistical association guidelines [15].

3. Results

During the study period, 131 patients were admitted between January and April 2018, 2019, and 2021; only 104 patients met the study criteria and were included in the analysis. Sixty-two patients were admitted during the pre-COVID period, and 42 during the post-COVID period. There were 45 (43%) men, the mean age

Table 1

Patients' basic characteristics.

	Pre-COVID	Post-COVID	P value
	(N = 62)	(N = 42)	
Men (%)	24 (39%)	21 (50%)	0.3
Age (SD) [‡]	31 (11 years)	28 (8 years)	0.1
Age at diagnosis	14 (10 years)	15 (9 years)	0.5
Disease duration in years (SD)	17 (11 years)	13 (9 years)	0.03
Number of ASMs [§]	2	2	0.6
The presence of risk factor(s)	25 (40%)	20 (48%)	0.5
Diagnosis			
TLE	19 (31%)	14 (33%)	0.9
FLE	12 (19%)	13 (31%)	0.3
Posterior neocortical epilepsy	5 (9%)	5 (12%)	0.9
Multifocal epilepsy	4 (6%)	2 (5%)	0.7
Unclassified epilepsy	13 (21%)	6 (14%)	0.6
Primary generalized epilepsy	8 (13%)	2 (5%)	0.3
Seizure frequency			
Daily	4 (6%)	4 (10%)	0.7
2–4 seizures a month	39 (63%)	25 (60%)	0.8
Once every 3–6 months	14 (23%)	10 (24%)	0.9
Once every 12–18 months	4 (6%)	3 (7%)	0.9
Longest seizure freedom (months)	6 (15 years)	5 (10 years)	0.6
Last seizure prior to admission to EMU**			
Within a month	41 (66%)	31 (74%)	0.5
More than a month	21 (34%)	11 (26%)	
Baseline EEG			
Normal or no IEDs ^{††}	34 (55%)	12 (29%)	0.02
Focal IDEs	22 (35%)	23 (55%)	0.9
Multifocal IEDs	5 (8%)	6 (14%)	0.8
Generalized IEDs	1 (2%)	1 (2%)	0.9
MRI brain findings			
Normal	24 (39%)	13 (31%)	0.9
MTS ^{‡‡}	14 (23%)	12 (29%)	0.8
MCD ^{§§}	3 (5%)	7 (17%)	0.3
Vascular lesion	3 (5%)	1 (2%)	0.8
Tumor	3 (5%)	3 (7%)	0.3
Encephalomalacia	4 (6%)	2 (5%)	0.9
Other	11 (18%)	4 (10%)	0.5

[‡]Standard deviation.

§Anti-seizure medications.

**Epilepsy monitoring unit.

^{††}Interictal epileptic discharges.

^{‡‡}Mesial temporal sclerosis.

§§Malformation of cortical development.

and disease duration of the cohort were 30 years (SD = 10 years; range: 14–54 years) and 14 years (SD = 11 years; range: 6 months-48 years), respectively. Table 1 summarizes the patient demographics. Apart from the differences in disease duration and frequency of normal or - no interictal discharges - in routine EEG between the two groups, similar characteristics were observed in both groups. Eighty-one patients (78%) developed seizures during their hospital stay, lasting between 12 h and 10 days: 45 (73%) in the pre-COVID group, and 36 (86%) in the post-COVID group (p = 0.1). A total of 475 seizures were recorded, of which slightly more than half (240 seizures) were in the post-COVID group (18 (29%) and 15 (36%) patients in the pre-COVID and post-COVID groups, respectively (p = 0.6)). Similarly, there was no difference in the distribution of focal to bilateral tonic-clonic seizures (44% vs. 60%; p = 0.2), or median number of seizures between the two groups (4 vs. 6: p = 0.1). Conversely, rescue therapy with either lorazepam or diazepam was used in both groups in no particular distribution (35% vs. 21%, respectively; p = 0.2). One patient in each group developed shoulder dislocation; however, no patient in either group developed status epilepticus requiring intravenous loading of ASMs, a transfer to the intensive care unit (ICU), or anesthesia. None of the patients in post-COVID group developed seizures while tapering ASM at home.

3.1. Time to record the first seizure

Seizures during the first 24 h were recorded eight times more frequently in the post-COVID group than in the pre-COVID group (adjusted OR = 8.4, p < 0.001, 95% CI: 2.7–30.2); on average, the first seizure was also recorded 20 h sooner in the post-COVID group (21 vs. 41 h, p < 0.001, 95% CI: 10–30; Fig. 1). Multivariate regression analysis confirmed these results, adjusted for clinical, radiological, and EEG findings (11 vs. 30 h, p < 0.01, 95% CI: 8–31). After excluding patients admitted with no seizures recorded, sensitivity analysis revealed a significant difference between the pre-COVID and post-COVID groups (50 vs. 31 h, p < 0.001, 95% CI: 11–31). This significant difference in the time to record the first seizure demonstrates that the post-COVID-19 EMU admission protocol appears to facilitate the utilization of EMU to document the first seizure, which could ultimately assist in identified SOZ. The

time to record the first seizure remained relatively short during the post-COVID period, irrespective of seizure frequency, recorded seizure type, or how early seizures were recorded before EMU admission (Fig. 2). Furthermore, there was no difference in the median number of seizures recorded before and after the modified admission protocol (4 vs. 6 seizures, respectively; p = 0.13). The observation mentioned above was reassuring, as the modified EMU admission protocol appeared safe, demonstrating no increase in the frequency of seizures recorded in EMU.

3.2. EMU yield

We were able to confirm the classification of epilepsy in up to three times more cases in the post-COVID group than in the pre-COVID group (unadjusted OR = 2.4, p = 0.04, 95% CI: 1.1–5.5), even when adjusted for age, sex, length of stay, number of ASMs, and the last seizure before admission to EMU (adjusted OR = 3.4, p-value = 0.02, 95% CI: 1.2–10.4; Fig. 3). We could also lateralize and localize the SOZ two-fold in the post-COVID group; however, this was not statistically significant (OR = 2, p = 0.08, 95% CI: 0.9–4.5). Therefore, confirming epilepsy classification was significantly enhanced after using the modified EMU protocol. Gaining a new knowledge on the pre-EMU hypothesis for epilepsy type was equally observed in both groups, as well as failing to identify the SOZ (Fig. 3).

3.3. Length of hospital stay

The average length of stay in the post-COVID group was approximately 3 days, compared with 5 days in the pre-COVID group (p < 0.01, 95% CI: 1–2.2). The modified EMU admission protocol led to a significantly shorter hospital stay, which can be considered an effective way to minimize unnecessary hospital-acquired infections, including COVID-19.

3.4. Seizure patterns following hospital discharge

The patients in the post-COVID group were followed up for 1– 5 months after discharge from the hospital, during which we inquired regarding seizure patterns. Among the 42 patients in this



Fig. 1. Kaplan-Meier curve showing the time to record the first seizure before and after COVID-19 modified admission protocol.



Fig. 2. The time (hours) required to record first seizure according to patient's characteristics (TCs: tonic-clonic seizure, Fs: focal seizures, Fs to bi-TCs: focal to bilateral tonicclonic seizures).

group, 21 (50%) reported no change in seizure frequency, and 15 (36%) reported less frequent seizures. Only 6 (14%) patients reported an increase in seizure frequency; therefore, about 85% of the post-COVID group exhibited no increase in seizure frequency when using the modified EMU admission protocol. We also found that up to 38% of patients remained seizure free after discharge from the hospital. Finally, there was no association between seizure recurrence after hospital discharge and the use of rescue therapy during EMU admission (OR = 5.9, p = 0.1, 95% CI: 0.9–11.5). The presence of seizures within a month before EMU admission was also not associated with seizure recurrence after EMU discharge (OR = 1.1, p = 0.9, 95% CI: 0.2–4.2).

4. Discussion

Undoubtedly, the COVID-19 pandemic caused an unprecedented disruption of the continuum of care for those with chronic physical and mental disorders worldwide, altering the delivery of standard care and adding more challenges to those in need. This encouraged care providers to implement further action, monitor these challenges, and develop an action plan that ensures adequate care [6,16–19]. Some conditions are considerably affected by various aspects; for example, anxiety, depression, sleep disturbances, and seizures are increased in patients with epilepsy (PWE) [20– 23]. Epilepsy surgery was therefore also impacted by this health



Fig. 3. The yield of EMU before and after COVID-19 modified admission protocol (LT-LC: lateralized but not localized, LT + LC: lateralize and localize, Not LT nor LC: not lateralized nor localized.).

crisis [24], as many PWE feared contracting the infection and thus avoided attending hospital procedures.

By contrast, the management of PWE through telemedicine has dramatically evolved during the pandemic, leading to outstanding and efficient management with minimal compromise of patient care [24,25]. Reports also demonstrate the cost-effectiveness of managing PWE via telemedicine during the pandemic [26–28]. A rather creative approach to managing PWE evolved early during the pandemic, with the notion of facing the unknown regarding the duration and overall magnitude of the COVID-19 pandemic's impact on healthcare [29,30].

Elective epilepsy-related procedures and admissions encountered more challenges, since hospitals were in lockdown and unseen cancelations of these procedures occurred. For instance, EEG was restricted to patients with acute seizures, and for the diagnosis and prognosis of the critically ill. The COVID-19 pandemic also significantly impacted the use of continuous EEG monitoring, and the invasive EEG recording for the pre-surgical cases with epilepsy [31,32]. Some experts recommended avoiding outpatient EEGs during the pandemic [33]. On the other hand, guidelines were also proposed, by different neurophysiology societies, in order to prioritize EEG use, protect patients and healthcare professionals, and to maintain a high-quality EEG recording. These recommendations should guide clinicians to safely utilize EEG, and other neurophysiological procedures, during the pandemic [34-36]. EMU admissions were panned in most epilepsy centers, with no strategy to cope with the pandemic other than canceling admissions to the unit. We blocked our EMU and epilepsy surgeries from mid-March 2020, and slowly recommenced in early July 2020. Our waiting list surpassed 400 days, which caused frustration for both patients and epileptologists in our institute. As a result of the service halt, we modified our EMU admission protocol and initiated ASM withdrawal from home; following admission, this was found to record seizures earlier, effectively shorten length of hospital stay, and significantly increase yield to confirm epilepsy classification.

Although no protocols or strategies exist regarding when or how to initiate the stepwise lowering of ASMs in EMU, the consensus is to individually taper medication, considering the patient and medication factors [37,38]. Epileptologists tend to initiate ASM tapering in most patients within 24 h of admission, with recent reports showing an association between the seizure type recorded, and the percentage reduction in ASM dose during the first 24 h [39]. In our study, we found no differences in the seizure types recorded between the pre-COVID and post-COVID groups. In previous studies, the time to record the first seizure with hospital tapering was similar to ours when using the standard admission protocol [39]. This confirmed that a shorter time to record the first seizure was obtained using our modified admission protocol, rather than our standard protocol or that of previous studies. Thus, with ASM withdrawal, seizures will likely be recorded during a defined period to confirm the preadmission hypothesis or goals, with a shorter hospital stay [40].

To the best of our knowledge, our results are the first to explore the effects of the pandemic on the effective and safe use of EMU. We were able to safely record significantly more seizures within the first 24 h of admission, than the admissions during 2018 and 2019 combined. Confirming epilepsy classification more than three times added another advantage to our modified admission protocol. Additionally, we achieved the goals of admission to EMU in a shorter amount of time than the standard EMU admission protocol, which should minimize the patient's risk for hospital-acquired infections during the pandemic. Moreover, our modified protocol was a cost-effective approach from a quality point of view, although this was not the aim of this study. Researchers in the Netherlands initiated home tapering of ASMs up to 4 weeks before EMU admission, with less than 2% risk of status epilepticus demonstrated in that group, and high efficacy to record seizures [41]. Similar to our modified protocol, the Dutch approach was safe and effective. An increase in seizure frequency was not induced during or after our modified EMU admission, for up to 5 months. Likewise, the use of rescue medications remained similar to the pre-COVID-19 era. Thus, we recommend initiating ASM withdrawal from home in adult patients admitted to the EMU for epilepsy classification and presurgical evaluation.

Our study had some limitations; although we provided robust findings regarding the time to record the first seizure following home ASM withdrawal, we admitted a relatively small number of participants during the COVID-19 pandemic. This may be related to the short study duration; thus, further studies on a larger scale may replicate our observations. We also faced difficulties regarding patients' refusal of admission during the pandemic. Hypothetically, this could influence the demographics of patients enrolled in 2021, compared with those admitted in 2018 and 2019, as desperate patients, with frequent seizures, or those awaiting epilepsy surgery, would be more eager to be admitted, and may overlook the risk of acquiring COVID-19 during the elective EMU admission. Additionally, excluding patients infected with COVID-19 during the preadmission screening may also have had an impact on the population studied. The modified protocol should be applied following the end of the pandemic to address these concerns when all eligible PWE are admissible to the EMU.

5. Conclusions

EMU admission remains a safe investigative tool for evaluating PWE [8]; however, ASM withdrawal is the ultimate step toward recording seizures during EMU stay. Amid the pandemic, our modified EMU admission protocol added more value in utilizing EMU efficiently and safely, with a shorter hospital stay and higher yield to confirm epilepsy classification in PWE.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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