Role of Progesterone in Lennox-Gastaut Syndrome and Refractory Epilepsies: A Pilot Study

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Abstract

Introduction: Most patients with LGS and refractory epilepsies, despite multiple anti-epileptic drugs (AEDs) use, often achieve unsatisfactory seizure activity control. Previous studies have shown that neurosteroids (progesterone in this study) can improve seizure control but the effects on patients with LGS have not been well studied.

Method: This was a prospective open-labeled pilot study conducted in Phramongkutklao Hospital from January 1 to December 31, 2020. We selected patients with LGS and adults with refractory epilepsies who were receiving at least 2 AEDs and still experiencing at least 5 epileptic attacks a month. The patients were assigned progesterone 400 mg/day. Seizure frequency and seizure type were recorded at baseline and every month for 3 months. The primary outcome was seizure frequency. Adverse drug reactions were observed as a secondary outcome.

Results: Total of 6 patients were enrolled. There were 3 LGS and 3 adults with refractory epilepsy. In LGS group, the median overall seizure frequency (times/month) were 197 for visit baseline and 200 for visit 3 months. In adults with refractory epilepsy group, the median overall seizure frequency (times/month) were 4 for visit baseline and 3 for visit 3 months. There were 2 adverse events detected which were mild headache (1 subject, 20%), and depression (1 subject, 20%). There were no serious adverse reactions.

Conclusions: From our small-scale study, after receiving progesterone 400 mg/day for 3 months, seizure frequency in patients with LGS and refractory epilepsy was not reduced from baseline. No serious adverse event was noticed. Further studies with proper dosage or longer duration of use would need to be conducted for demonstrating a clearer effect.

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Introduction

Lennox-Gastuat syndrome[1,2] (LGS) is one of severe childhood epileptic encephalopathies which consists of multiple seizure types that often leads to unsatisfactory seizure activity control in spite of multiple AED use. Refractory epilepsy[3] in adults is also one of conditions that has similar disease activity. The inadequate seizure control often leads to multiple complications effecting the quality of lives to both patients and care-takers.

Neurosteroids[4] are endogenous steroids synthesized within the central nervous system (CNS) that have rapid effects on neuronal excitability. Allopregnanolone, one of the prototypes of neurosteroids, enhances the function of both synaptic and extrasynaptic GABA-A receptors, which promotes maximal inhibition in the brain. Previous studies have shown that neurosteroids can improve seizure control in various types of epilepsies[5-7] for instance catamenial epilepsy, status epilepticus, infantile spasms, fragile x syndrome, but the effects on patients with LGS and adults with refractory epilepsy have not been well studied.

In this study we are interested in whether using oral progesterone which has been proven to be converted to allopregnanolone in vivo, is beneficial in controlling seizure activities in patients with LGS and refractory epilepsy (RE).

Objectives

1. To study the efficacy of progesterone in reducing seizure frequency in patients with LGS and refractory epilepsy.
2. To study the safety of progesterone used in patients with LGS and refractory epilepsy

Material and Methods

Study design

This was a prospective open-labeled pilot study conducted in Phramongkutklao Hospital from January 1, 2020 to December 31, 2020.

Characteristics of study samples

We selected the patients with LGS and adults with refractory epilepsies from the pediatric epilepsy clinic and adult epilepsy clinic of Phramongkutklao hospital who were receiving at least 2 different AEDs and still experiencing at least 5 epileptic attacks a month. As this was a pilot study, we planned on studying in 6 patients (3/group).

Study intervention

The patients were assigned Utrogestran® (progesterone 400 mg/day, 200 mg twice a day) for 3 months. The patients maintained their current AEDs at the same dosage while taking progesterone. We followed the patients monthly for 3 months. Each patient was given a seizure diary. In The diaries the patients or care-takes were assigned to record seizure frequency for each day as well as seizure types. The possible seizure types were generalized tonic-clonic seizure (GTC), drop attack (atonic seizure), tonic seizure, simple partial seizure (SPS), and others which are not compatible with the given seizure types are classified as unclassified. Seizure frequency and seizure types were recorded at baseline (Visit-0), 1 month (visit-1), 2 months (visit-2), and 3 months (visit-3). Each visit the patients were interviewed about their experiences using the medication. Possible side effects and adverse reactions were reported at any points of time during the study period by the patients and/or the care-takers.

Outcomes

The primary outcome measurement was seizure frequency in patient with LGS and refractory epilepsy after receiving progesterone 400 mg/day for 3 months

The secondary outcome was the adverse drug reactions such as drug eruptions, headache, nausea and vomiting, depressive episodes.

Statistical methods

The statistical analysis was performed by using SPSS 24.0 statistical software. Demographic data were described in number and percentage, mean, SD, and median (for non-parametric data). Seizure frequencies at visit 0 (baseline) to visit 3 (times/month) were compared.

Results

Total of 6 patients were enrolled in the study. The mean age was 29.8 years-old (SD 14.1), 4 patients were male (83%), and 2 patients were female. There were 3 LGS and 3 adults with refractory focal epilepsy (RE).

The number of AEDs used in the studied patients varied from 2 to 9 medications. The minimal number of AED use was 2 in 1 patient (16.7%), the maximal number of AED use was 9 in 1 patient (16.7%). The average number of AEDs used in the study group was 5 medications. A total of 13 different AEDs were used in the patients which were perampanel (66.7%), clonazepam (66.7%), sodium valproate (50%), topiramate (50%), levitiracetam (50%), lamotrigine (50%), carbamazepine (50%), phenytoin (33.3%), lacosamide (33.3%), clobazam (33.3%), zonisamide (33.3%), phenobarbital (16.7%), and rufinamide (16.7%). Demographic data were shown in Table 1.

Throughout the study, 4 out of 6 patients had completed the 3 month-period. One patient from the LGS group withdrew after 4 doses of medication due to an unspecified reason, the other from the refractory epilepsy group withdrew after 2 months due to intolerable adverse drug reaction which was depressive episodes.

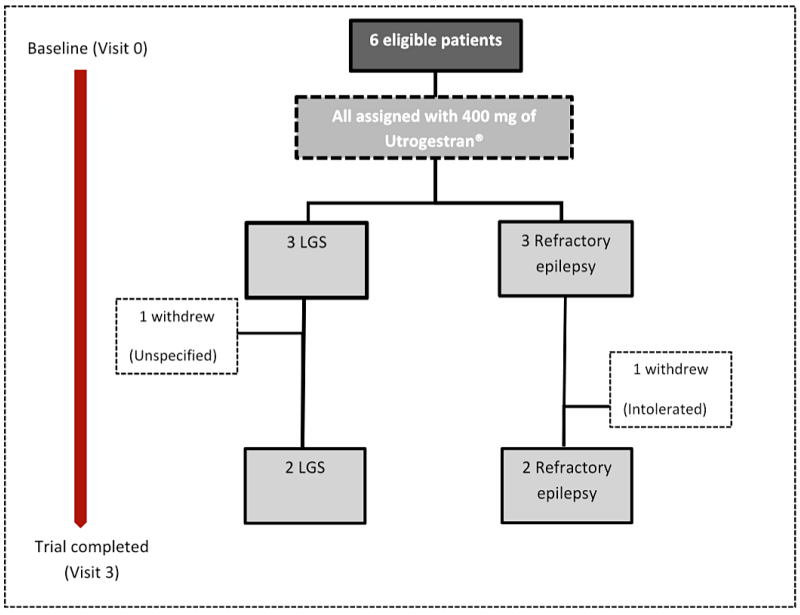

Figure 1 Flow chart of clinical study

Median baseline seizure frequency was 4.5 time/month in both groups, according to Table 2. In LGS group, baseline seizure frequency was 197/ month. After taking oral progesterone, the median seizure frequency had changed over the time to 253, 216, and 200 in visit 1-month, 2-month and 3-month respectively. While in refractory epilepsy group, baseline seizure frequency was 4/month and changed to 7, 3 and 3 in visit 1-month, 2-month and 3-month respectively

Table 1 Demographic data (n = 6)

Variables	Total number (%)
Age: year, mean ± SD	29.8 ± 14.1
Male	4 (83.3)
Total number of AEDs	
2 AEDs	1 (16.7)
3 AEDs	1 (16.7)
5 AEDs	1 (16.7)
7 AEDs:	2 (33.3)
9 AEDs:	1 (16.7)
Mean AEDs = 5	
Types of AEDs	
Carbamazepine	3 (50)
Clobazam	2 (33.3)
Clonazepam	4 (66.7)
Lacosamide	2 (33.3)
Lamotrigine	3 (50)
Levetiracetam	3 (50)
Perampanel	4 (66.7)
Phenobarbital	1 (16.7)
Phenytoin	2 (33.3)
Rufinamide	1 (16.7)
Sodium valproate	3 (50)
Topiramate	3 (50)
Zonisamide	2 (33.3)

Table 2 Monthly seizure frequency from baseline to 3 months

		Seizure frequency (times/month)		
Pt. Group / Visit		Total	LGS	RE
Baseline (median)	Total	4.5	197	4
1-month (median)	Total	11	253	7
2-month (median)	Total	5	216	3
3-month (median)	Total	98	200	3

There were 2 adverse drug reactions reported from 2 patients, both were from the adult refractory focal epilepsy group, as shown in Table 3. One male patient developed mild headache (Pain score of 3-4/10) occurring 21 days during the 3 month-period. The headache didn't interfere with his daily activities and didn't require any rescue medications. Another side effect reported was depressive symptom. One female patient experienced depressive symptom 3-4 times a week, but no suicidal ideation, causing discontinuation from the trial after the visit 2 months. The symptoms began to resolve after 2 days of discontinuation and completely vanished by the end of the second week. There were no skin eruptions, abnormal vital signs, or any signs that indicated organ dysfunction or life-threatening adverse drug reactions. There were no adverse drug reactions reported from the LGS group.

Table 3 Adverse events throughout the study period

Reported adverse reactions	Total (n=5)	LGS (n=3)	RE (n=3)
Headache: number (%)	1 (20)	0	1 (33.3)
Nausea/vomiting: number (%)	0 (0)	0	0
Depression: number (%)	1 (20)	0	1 (33.3)
Total: number (%)	2 (40)	0	2 (66.7)

Discussion

Progesterone 400 mg/day orally, did not show evidence of seizure frequency reduction in the patient in both LGS and adult refractory epilepsy groups. This would be due to the effect of small sample size and also severe symptoms of LGS which was very difficult to control. LGS requires numerous AEDs and yet poorly response to the treatment given which makes the disease one of the refractory or drug-resistant epilepsies. The same result applied for the refractory epilepsy group, which was also an extremely difficult and challenging condition to manage and achieve seizure free or even reduction.

Throughout the study, very minor adverse drug reactions were reported in the adult with refractory epilepsy group and no adverse drug reactions reported at all from the LGS group. However, one depression developed in one patient.

Despite the unsatisfactory results in reducing seizure frequency in both LGS and adult refractory epilepsy groups, this study demonstrated the satisfying safety outcomes especially in those with LGS who didn't experience any serious adverse effects at all. The fact that oral progesterone is well tolerated in the patients with minor side effects reported makes it a promising medication in managing patients with this group of epilepsies.

The weaknesses of our study were a very small sample size, single dosage use, and single center. Therefore, further studies, with larger sample size, multicenter, higher dosage range as well as a longer duration, would need to be demonstrated a better effect of oral progesterone in managing the patients with LGS and adult refractory epilepsy.

Conclusion

The oral Utrogestran® (progesterone) 400 mg/day didn't reduce seizure frequency in both LGS

and adult refractory focal epilepsy groups. No serious adverse event was noticed except one depressive symptom in refractory epilepsy group.

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