

Adjunctive use of electroconvulsive therapy in patients with Lennox-Gastaut syndrome and drug-resistant epilepsy: A pilot study

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Abstract

Background: Lennox-Gastaut syndrome (LGS) is an epileptic encephalopathy, characterized by drug-resistant multiple seizure types. The aim of this study was to determine if the adjunctive use of electroconvulsive therapy (ECT) in patients with LGS and drug-resistant epilepsy is efficacious in decreasing their seizure frequency and also to investigate its safety and tolerability.

Methods: This was an open-label pilot study with convenience sampling from one center. Bitemporal electrode placement was selected. ECT was administered three times per week for four weeks (considered as the induction phase), and then once a week for two months (considered as the maintenance phase). Follow-up visits were scheduled at 2, 3, 4, and 6 months to determine the seizure types and counts and also to determine the safety and tolerability of adjunctive use of ECT in these patients. All patients and / or their caregivers consented in writing to their participation.

Results: Seven patients were studied. Just one patient experienced more than 50% reduction in seizure frequency. One patient experienced more than 50% seizure increase with ECT. In three patients, there was an increase in aggressive behavior after receiving ECT. Two patients experienced mild and transient ataxia with ECT. One patient experienced mutism with ECT, which was transient and resolved with the termination of the procedure.

Conclusion: In this small study, adjunctive use of an intensive ECT program in patients with LGS was not efficacious in decreasing their seizure frequency. However, the safety profile was acceptable, and patients tolerated the adjunctive use of ECT very well. This finding can pave the road for future investigations.

Keywords: Lennox-Gastaut syndrome, Treatment, Electroconvulsive therapy, Epilepsy, Safety.

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Introduction

Lennox-Gastaut syndrome (LGS) is an epileptic encephalopathy, characterized by intractable, multiple seizure types and an interictal electroencephalogram (EEG) showing bursts of slow spike-and-wave complexes, generalized paroxysmal fast activity, and a slow background (1,2). LGS accounts for approximately 1-10% of all childhood epilepsies. It is notoriously re-

sistant to medical and even surgical treatments (1,3). When these patients become adults, most continue to experience seizures, as well as cognitive, psychiatric, and behavioral problems (4). Therefore, the disorder has a devastating impact on the patients' quality of life (5).

Electroconvulsive therapy (ECT) has been successfully employed as a treatment for refractory epilepsy and status epilepti-

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cus (SE), after exhausting therapy with antiepileptic drugs (AEDs), in a few anecdotal reports (6-8). Early studies showed that the threshold for seizures is increased in patients undergoing convulsive treatment, and it was proposed that ECT might be useful in the management of patients with epilepsy (6-8). The exact mechanism for ECT to anticonvulsive effect is not clear. Electroconvulsive therapy can be safely and effectively administered to patients treated with various AEDs. No severe adverse effects or complications are reported (9). For most patients, adequate seizures can be obtained during ECT despite concomitant treatment with AEDs (9). Finally, it should be mentioned that ECT has not been found to cause epilepsy (10).

This study was conducted to determine if adjunctive use of electroconvulsive therapy (ECT) in patients with Lennox-Gastaut syndrome (LGS) and drug-resistant epilepsy is efficacious in decreasing their seizure frequency. We also investigated the safety and tolerability of adjunctive use of ECT in patients with LGS and drug-resistant epilepsy.

Methods

This was an open-label pilot study with convenience sampling from one center (outpatient epilepsy clinic at Shiraz University of Medical Sciences). Inclusion criteria were: male/female patients, age of eight years and older; diagnosis of LGS made on the basis of electro-clinical findings; drug-resistant disabling seizures defined as failure of two or more AEDs at maximal tolerated doses and one or more disabling seizures (e.g., generalized tonic-clonic seizures and/or drop attacks) per week. They had stable medication regimen for four weeks before entry. Exclusion criteria were: patients with progressive neurological conditions; patients with a history of non-compliance for seizure diary completion or frequent clinic visits; having any serious medical (particularly, cardiac) illness or major psychiatric disorder or history of psychogenic non-epileptic seizures.

In the first visit, informed consent was taken, enrollment and registration was performed, history and physical examination was taken, baseline blood pressure (BP) was determined, and electrocardiography (EKG) was done. The care-givers of the patients were instructed to keep a diary of the most disabling seizures (i.e., generalized tonic-clonic seizures and drop attacks). In the second visit (30 days baseline), seizure types and seizure count was determined. After this visit, the patients were referred for ECT to our psychiatry center.

For anesthetic management, standard noninvasive monitors were used during the ECT and patients received titrated dose of thiopental for induction of anesthesia, followed by succinylcholine (0.3mg/kg) as a muscle relaxant. The airway was secured and managed with a face mask and reusable airway circuit. Bitemporal electrode placement was selected to produce the most generalized seizure, given the lack of a clear seizure focus in these patients and considering previous corpus callosotomy in four patients. ECT parameters were adjusted individually and as needed, based on standard protocols at our ECT center at Hafez Hospital, Shiraz University of Medical Sciences. Electroconvulsive therapy was administered three times per week for four weeks (considered as the induction phase), and then once a week for two months (considered as the maintenance phase). Follow-up visits were scheduled at 2, 3, 4 (end of the ECT period), and 6 months to determine the seizure types and seizure count and also to determine the safety and tolerability of adjunctive use of ECT in these patients. All patients received free ECT and were offered free visits and free EKGs during the study period.

This study was conducted in accordance with local ethical regulations with approval by Shiraz University of Medical Sciences Review Board and Ethics Committee (IRCT # 2014062111778N2 and grant # 92-01-34-6910). Electroconvulsive therapy has been employed as a treatment for epi-

lepsy in the pediatric population before (7). All our patients (both children and adults) had severe intellectual handicap and their care-givers consented in writing to their participation, after the scope of the study was explained in a form understandable to them. All patients and their caregivers were advised that ECT was not an approved therapy for epilepsy. The collected data were kept confidential through codes

Demographic variables and relevant clinical variables were summarized descriptively to characterize the study population. The proportion of responders, that is, patients with more than 50% reduction in seizure (e.g., generalized tonic-clonic seizures and/or drop attacks) frequency from baseline, was tabulated. Mann-Whitney test was used for statistical analysis. P value less than 0.05 was considered as significant.

Results

Seven patients were studied. The characteristics of the patients and their clinical variables are summarized in Table 1. Four patients (57%) had previously undergone corpus callosotomy, without any beneficial responses. Three patients (43%) declined the offer for such an operation. Electroconvulsive therapy induced seizures during 126 out of 140 sessions (90%) that it was delivered to all seven patients. In one patient ECT failed to induce a seizure in 5 out of 20 sessions. In others, ECT failed to induce seizures less frequently. Habitual seizure frequency changes in response to ECT in these seven patients are shown in Table 2. Habitual seizure frequency increased in three and decreased in four patients. Just one patient experienced more than 50% reduction in seizure frequency (patient number 5). One patient experienced more than

Table 1. Characteristics of the patients studied

Patients	Age (yrs)	Age at onset	Seizure type 1	Seizure type 2	Seizure type 3	Etiology	EEG	MRI	Drugs	CC	Duration of the induced seizures during ECT
1	32	Neonate	GTCS, 5 per day	Astatic, 5 per day	Myoclonic, daily	HIE	SSW and GPFA	Atrophy	VPA 1400mg/day & CLO 40mg/day TPM 200mg/day & LEV 1500mg/day	Failed	11 ± 7 seconds
2	16	3 years	GTCS, 5 per week	Myoclonic, daily	Tonic, daily	Unknown	SSW and GPFA	Normal	VPA 1000mg/day & TPM 200mg/day ZNS 200mg/day and LEV 1500mg/day	Failed	18 ± 7 seconds
3	19	Neonate	GTCS, 3 per day	Tonic, 2 per day	Absences, daily	HIE	SSW and Multifocal sharp waves SSW	Atrophy	VPA 900mg/day & LEV 1500mg/day	NP	22 ± 10 seconds
4	11	Neonate	Tonic, 3 per day	Clonic, 2 per year	-	HIE	SSW	Atrophy	VPA 800mg/day & CLO 20mg/day VPA 1500mg/day & PRM 750mg/day	NP	31 ± 6 seconds
5	9	3 years	Atonic, 2 per day	Absences, daily	Tonic, daily	Developmental	SSW and GPFA	Pachygyria	VPA 900mg/day & LEV 1500mg/day	Failed	35 ± 19 seconds
6	15	6 months	Tonic, 2 per day	Myoclonic, daily	GTCS, once a year	Unknown	SSW and GPFA	Atrophy	VPA 800mg/day & CLO 20mg/day VPA 1500mg/day & PRM 750mg/day	Failed	7 ± 5 seconds
7	20	11 years	Tonic, 3 per day	Atonic, 1 per week	-	Unknown	SSW and GPFA	Normal	VPA 1500mg/day & PRM 750mg/day	NP	18 ± 7 seconds

CC: corpus callosotomy; ECT: electro-convulsive therapy; GTCS: generalized tonic-clonic seizure; HIE: hypoxic-ischemic encephalopathy; SSW: slow spike-waves; GPFA: generalized paroxysmal fast activity; VPA: valproate; LEV: levetiracetam; CLO: clobazam; ZNS: zonisamide; TPM: topiramate; PRM: primidone; NP: not performed

*Seizure frequencies are according to the history provided by the guardians and subject to recall bias

Table 2. Seizure frequency before ECT, during induction phase and in maintenance period of electro-convulsive therapy.

Patients	Seizure count before ECT (in 30 days)	Seizure count during induction phase (30 days)	Seizure count during the first month of maintenance	Seizure count during the second month of maintenance
1	401	207	419	692
2	106	80	75	82
3	167	149	88	86
4	139	170	165	164
5	624	290	123	208
6	124	152	153	163
7	16	61	36	10

ECT: electro-convulsive therapy

*Seizure frequencies are according to the seizure diary

Table 3. Seizure days before ECT, during induction phase & maintenance period, and in the follow-up.

Patients	Number of days with seizure(s)				
	Before ECT (30 day)	Induction phase (30 day)	First month of maintenance	Second month of maintenance	Follow-up
1	30	30	30	30	25
2	30	28	27	28	24
3	30	30	30	28	30
4	30	30	30	30	30
5	29	23	24	30	30
6	30	30	30	30	30
7	14	17	22	10	18

ECT: electro-convulsive therapy

50% seizure increase with ECT (patient number 1). Both these patients had failed corpus callosotomy before (Table 1). In none of these patients, days with seizures in each month changed significantly. Days with seizure(s) before starting ECT, during the induction phase, during the maintenance period of ECT and in the follow-up (i.e., month 1-2 after ECT termination) in these seven patients are shown in Table 3. In none of the patients, days with or without a seizure(s) changed significantly (more than 50%). In three patients, there was an increase in aggressive behavior after receiving ECT. In one patient, aggression needed therapy with risperidone, but in others, it was mild and transient (i.e., only during the induction phase). Two patients experienced mild and transient ataxia (i.e., for a couple of weeks and at the end of induction phase) with ECT. One patient experienced mutism with ECT, which was transient and resolved with the termination of the procedure. We compared patients with previous callosotomy (4 patients) with those without (3 patients). Mean of change in seizure frequency from baseline to the follow-up period was not statistically different between these two groups (-27 ± 292 (in callosotomy patients) vs. -20 ± 54 (in

medical therapy alone patients) seizures per month; $p=0.8$).

Discussion

For many years, investigators and physicians have addressed the problem of medically-refractory epilepsy by investigating and developing new AEDs (11). However, no study has demonstrated that the new AEDs have greater potency than more established AEDs. Therefore, it would be desirable to explore novel methods in hoping of developing more effective ways to treat epilepsy. Electroconvulsive therapy (ECT) has been proposed as a treatment option for refractory epilepsy in a few anecdotal reports (6-8). However, in this small pilot clinical trial adjunctive use of an intensive ECT program in patients with Lennox-Gastaut syndrome (LGS) and drug-resistant seizures was not efficacious in decreasing their seizure frequency. In contrast to previous suggestions, we did not observe any short-term or long-term benefits after delivering ECT to patients with LGS, with regard to seizure reduction; repeated induced-seizures given over several days did not have any beneficial effects. None of the patients showed any clear and meaningful improvement. Of course, this negative

study cannot rule out the possible benefits of ECT in all patients with epilepsy and the findings cannot be extrapolated to the whole population of patients. Epilepsy is a family of neurological disorders, not a single disorder. Considering the previous anecdotal reports, it is possible that ECT plays a role in seizure reduction in other syndromes of epilepsy with less severe seizures. This needs further investigation. One important finding of our study was the absence of any significant adverse effects after such an intensive ECT program. The safety profile was acceptable, and these seven patients tolerated the adjunctive use of ECT very well. This finding is in concordance with previous reports (9,10). We also noticed that previous corpus callosotomy did not have any influence on the results. We could not find any papers in the literature to compare this novel finding with.

Conclusion

In this small study, adjunctive use of an intensive ECT program in patients with LGS was not efficacious in decreasing their seizure frequency. However, the safety profile was acceptable, and patients tolerated the adjunctive use of ECT very well. This finding can pave the road for future investigations.

Limitations

This study included a small sample size, and it was a one-center, open label, and non-placebo controlled study. Besides, our patients had a severe intellectual handicap and any cognitive or memory problems as a result of ECT would be extremely difficult to detect in this patient population.

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Conflict of interest

None of the authors has any conflict of interest to disclose.

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