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Review article

Treatment of refractory status epilepticus with electroconvulsive therapy: Need for future clinical studies

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ABSTRACT

Status epilepticus (SE) is a serious medical emergency. Refractory-SE non-responsive to anesthetic medication is a life threatening condition with very high mortality rate. Proper management of those cases is a big medical challenge. Over the last two decades there are anecdotal reports of successful management of such cases with electroconvulsive therapy (ECT) in 12 patients of different age group with variable pattern of seizures and different etiology. However, there is no systematic research about it. ECT is a well-known safe, easy- to-administer, low-cost therapeutic modality in the field of neuro-psychiatry. Thus its potential to treat refractory-SE which essentially lacks effective management should be evaluated in future research. The objectives of this article are to do a thorough literature review on use of ECT in refractory-SE; mechanism of action of ECT in refractory-SE; and finally formulate a working protocol for future study of using ECT in patients of refractory-SE.

Contents

1. Introduction

Electroconvulsive therapy (ECT) was introduced in 1938 for treating psychotic illnesses. Quite interestingly, in the initial decades after introduction it was also used in treatment of epilepsy. Apart from use in controlling episodic aggression and psychosis in epileptic patients during “epileptic twilight states”, ECT was also successfully used in reducing the spontaneous seizure rates in intractable epilepsy.[1,2,3] Subsequently from 1950s to 1980s, there was no report of such use probably because of serial emergence of antiepileptic drugs (AEDs). After 1990, case reports of use of ECT in refractory status-epilepticus (SE) again started reappearing. Till date there are 9 reports of 12 cases regarding use of ECT in refractory-SE patients; of them eight are summarized in a review article.[4] In most of the cases SE was prolonged and refractory to anesthetic medications and outcome of ECT was satisfactory. But apart from those anecdotal reports there is no systematic research regarding this. None of those reports provided in-depth discussion on how ECT can be effective in refractory-SE. Interestingly the American Psychiatric Association task force

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Table 1
Findings of case reports where ECT was used to treat SE.

Report No.	Article	Patient	Clinical Condition	ECT Electrode	ECT Session	Concurrent Antiepileptic with ECT	Charge (mC)	Outcome
1	Viparelli and Viparelli, 1992	19 year Female Duration of SE: 12 hour	Continuing Partial seizures (46 in 12 hr)- nonresponsive on- IV PHT, DZP	Bi-temporal	2 in 48- hour interval	Nil – Only Curare, DZP	Not known	On 1st ECT frequency reduced; Seizures free by 2nd. Subsequently seizure-free in 7 years on CBZ
2	Gonzalez et al. 1997	25 year Male Duration of SE: 40 days	Post-head injury SE- nonresponsive-over 40 days on PHT CBZ, DZP PHB and 1 attempt of PBT coma	Not known	6 in 2-weeks	All pre-ECT AED –dosage- Not known	Not known	Cessation of SE
3	Griesemer et al., 1997	13 year Male Duration of SE: 30 days	Microgyria- Clusters of Partial seizure, Drop attacks, Tonic seizure- 10 seizures in 18 h. Nonresponsive- on- PHB PHT ACT CLZ VPA GBP LTG FBM. – After 1 year NCSE. Recurrence of Clusters again after 8 month.	Fronto-central	4 in 9 days; After 1 year 3 in 3 days; After 8 months 8 in 15 days	AED Withdrawn	64–217; After 1 year - 201–302; After 8 months - 201–403	Reduction in frequency and duration of seizures.After 1 year - Cessation of NCSE;After 8 months - Reduction in seizures with–no untoward effects
		10 year Female Duration of SE: Not Known	Microcephaly –Microgyria Clusters of GTCS-nonresponsive – PHB PHT CBZ VPA FBM GBP LOR KD	Fronto-central	6 in 15 days	Only VPA GBP continued With reduction of dosage	180–576	Reduction in seizures
4	Lisanby et al., 2001	36 year Male Duration of SE: 26 days	Cortical dysplasia- NCSE for 26 days following surgery for Subdural hematoma on VGB, PHB, NZP, PHT MDZ and finally PF PBT coma	Right Fronto-temporal And left Parietal	5 in 5 days	PBT PF withdrawn-All AED continued- dosage unknown	1152–3379	Cessation of seizure in EEG but remained comatose even after 1 month and developed DIC. Final outcome not known.
5	Morales et al., 2004	8 year Female Duration of SE: Not Known	Ceroidolipofuscinos Repeated episodes of SE Nonresponsive PHB ZNS LEV- PBT coma and rTMS	Not known	5 in 5 days	All AED along with PBT coma	192–1536	No cessation of SE- Final outcome Death
6	Cline and Ross, 2007	39 year Male Duration of SE: 103 days	Viral Encephalitis –Persistent SE for 3.5 months – Multiple AED- fosPHT VPA LEV OXC TPM LOR FBM and PBT coma	Bifronto-temporal	9 in 3 days	All pre-ECT AED, except PBT–dosage unknown.	576	Cessation of SE – regaining of consciousness- maintaining awake for next 16 months with residual cognitive decline and focal seizures
7	Kamel et al., 2010	32 year Female Duration of SE: 30 days	Viral Encephalitis SE- Nonresponsive to Multiple AEDs – VPA PHT PHB LEV TPM and 3 trials of PBT coma over 6 weeks	Bifronto-temporal	13 in 5 days	All pre-ECT AED– dosage unknown. MDZ PF maintained burst suppression in between sessions	505	Cessation of SE –regaining alertness with short-term amnesia resolving over time.
		41 year Female Duration of SE: 30 days	Viral Encephalitis – SE- Nonresponsive to Similar protocol with fosPHT LEV VPA PBT KT over 4 weeks	Bifronto-temporal	20 in 5 days	Pre-ECT AED and continuing PBT coma	Not known	Cessation of seizure in EEG but remained comatose. Nosocomial pneumonia Acute renal failure Death
		26 year Female Duration of SE: 70 days	Viral encephalitis – SE – Nonresponsive to Multiple AEDs PHT VPA LEV TPM PHB KT MDZ and trials of PBT coma with IF over 8 weeks	Bifronto-temporal	8 in 10 days	All Pre-ECT AED- MDZ withdrawn when ECT failed to induce seizure in first two sessions	Not known	Cessation of SE after 8 sessions. ECT not continued. Seizures continued with reduced frequency and mild cognitive decline
8	Shin et al., 2011	7 year Female Duration of SE: 14 days	Bilateral Polymicrogyria-NCSE- for 14 days- despite VPA LEV CLB LOR PHB MDZ FEN TPM KD steroid and finally PBT KT coma	Bi-temporal	4/8 days	All Pre-ECT AED- Flumazenil was given prior to ECT session	Not known	Cessation of SE Improvement of mental Status.
9	Incecik et al.,2015	16 year Female Duration	Cerebral palsy-cortical atrophy- Unconscious with 10–20 seizures/day in ventilator.	Not known	5/9 days	AED reduced LEV PHT TPM CLB continued	Not known	Significant reduction of seizure, Conscious, Ventilator withdrawn by 5 days. 4 AED continued at

Table 1 (*Continued*)

Report No.	Article	Patient	Clinical Condition	ECT Electrode	ECT Session	Concurrent Antiepileptic with ECT	Charge (mC)	Outcome
		of SE: 105 days	VPA, LEV, TPM, PHT, VGB, CLB, MDZ, KD, KT, PBT, ST, IVIG, Plasma exchange			PBT withdrawn MDZ continued		discharge. Seizure free at 1 month follow up

AED anti-epileptic drug; ACT, acetazolamine; CLB, clobazam; CLZ, clonazepam; CBZ, carbamazepine DZM, diazepam;DIC disse minated intravascular coagulation; EEG electroencephalogram; FEN, fentanyl; FBM, felbamate; GBP, gabapentin; GTCS generalized tonic clonic seizure; IF isoflurane;IVIG intravenous immunoglobulin; KD, ketogenic diet; KT, ketamine; LTG, lamotrigine; LEV, levetiracetam; LOR, lorazepam; mC millae coulomb; MDZ, midazolam; NZP, nitrazepam; NCSE nonconvulsive status epilepticus; OXC, oxcarbazepine; PHB phenobarbital; PF, propofol; PGB, pregabalin; PHT, phenytoin; PBT, pentobarbital; rTMS repetitive transcranial magnetic stimulation; SE status epilepticus ST steroid; TPM, topiramate; VGB, vigabatrin; VPA sodium valproate; ZNS, zonisamide.

report on ECT[5] mentioned regarding successful use of ECT in intractable epilepsy and SE but without any suggestion regarding proper indication, schedule and dosage. However, refractory- SE is still a big medical challenge with no optimum management.[6] Whether ECT holds out some promise in this regard is really a matter of interest which should be addressed in future systematic research.

1.1. Objectives

This article would like to do a thorough literature review on use of ECT in SE; probable mechanism of action of ECT in SE; justification of future study regarding ECT in refractory-SE; and finally formulate a working protocol for such future study.

2. Methods

Literature search was done through search-engine like Google and PubMed using key-words like status epilepticus – refractory; pathophysiology; epidemiology; management; anesthesia; ECT-status epilepticus; anticonvulsant action. Some articles were selected from the cross reference of some major review articles on 'ECT in refractory SE';[4] 'SE-pathophysiology and management'[6]; and 'anticonvulsant hypothesis of the mechanism of action of ECT'.[7] Articles on non-convulsive SE were also included under SE. No exclusion of any particular clinical condition was done. Minor descriptive statistics was generated regarding reports of ECT in refractory-SE.

3. Reports on use of ECT in SE

In Table 1, findings of nine case reports on use of ECT in SE have been summarized. In this list of 12 cases, patients were heterogeneous with no uniform selection criteria, variable aetiologies and duration of SE but the overall outcome of ECT was quite encouraging. Most of the cases were refractory to anesthetic drugs and even pentobarbital (PBT) coma. Mean duration of SE before starting ECT was 44.85 days. Still SE could be terminated with regaining of consciousness in 9(75%) cases. In 2 cases (Report 4,7) there were electrical cessation of SE but patient remained in coma. In only 1case (Report 5) there was no cessation of SE. In those 3 unsuccessful cases there was grave underlying cerebral pathology. Moreover factors like continued PBT coma during ECT (Report 5,7) and unconventional electrode placement due to neurosurgical skull defect (Report 4) also probably interfered with the action of ECT in the unsuccessful cases.

Regarding safety there was no untoward incident during ECT in any of the cases despite serious underlying cerebral pathology, frequent ECT sessions (up to 3–4 in a day) (Report 6,7) and very high electrical charge (1500–3300 mC) (Report 4,5). Two patients (Report 5,7) out of those 3 unsuccessful cases ultimately succumbed to medical complications of prolonged SE.

However, there is a chance of bias in this review[4] of anecdotal reports where only patients treated successfully are reported.

4. Probable mechanism of action of ECT in refractory-SE

Before discussing the mechanism of action of ECT, we should first look into the pathogenesis of refractory-SE in a nutshell. After an intense seizure if the cerebral mechanisms required for seizure termination fail particularly through impairment of GABA mechanisms, it facilitates continuing seizure activity and leads to SE.[6] In refractory SE a progressive and time-dependent pharmacoresistance to anti-epileptic-drugs (AED) develop probably because of progressive changes at GABA/Glutamate receptor levels and the ionic environment at the neuronal synapses.[8] When SE becomes self-sustaining multiple other sets of phenomena also develop in brains, like down-regulation of inhibitory neuropeptides (neuropeptide-Y, somatostatin, galanin,); up-regulation of proconvulsant peptides tachykinins, substance-p in hippocampus[9,10]; kindling phenomenon in hippocampal dentate granule cells resulting neuronal loss[11]; and finally there may be long-term changes in gene expression, inhibition in brain protein synthesis and neuronal plasticity.[12] In an ongoing SE and NCSE the electrical synchrony in brain gets completely disrupted thus the final resort of treatment is often burst suppression through prolonged anesthetic coma to cause electrical cessation of the seizures.[6,13]

Regarding mechanism of action of ECT in refractory-SE, previous case reports have only highlighted the GABAergic action of ECT. But both human and animal researches provide much more important clues which have been summarized by Sackeim, HA[7]as anticonvulsant hypothesis of the mechanism of action of ECT Table 2.

5. Justification of future clinical studies on ECT in refractory-SE

Refractory-SE is a life threatening condition and still a big medical challenge. The incidence of status epilepticus was 41 per 100,000 individuals per year in USA Richmond[29] but was highly skewed towards elderly (>60-year) going up to 86 per 100,000 per year with mortality of 38%. There is no exact statistics regarding refractory-SE but mortality is likely to go much higher in those cases. This appears quite alarming as the world progressively approaching towards an ageing society and identification of optimum treatments for refractory-SE still remaining elusive. Apart from elderly, children with different developmental anomalies and epileptic syndromes are also prone to refractory seizures and SE.[30] Till date the accepted management for refractory-SE is prolonged anesthetic infusion or anesthetic (PBT) coma as last resort.[6] This ensures electrical cessation of seizure better than the AEDs through 'burst-suppression' of cortical activity, but final outcome is still guarded due to risk of intercurrent infection, multiorgan disturbances like renal and cardiac failure, consumptive coagulopathy.[6,31] Some patients may die out of these complications before regaining consciousness even

Table 2
Studies showing probable anticonvulsant actions of ECT.

Probable Anticonvulsant actions	Studies	
	Authors	Findings
I.**GABA**-ergic Action	Lloyd et al. 1985[14]	Repeated electroconvulsive-stimulations (ECS) in rats result in rise in GABA synthesis, concentration and receptor density in brain.
	Green et al. 1982[15]	Repeated ECS in rats have shown increased seizure threshold against substances which causes seizures by antagonism of GABAergic transmission like bicuculline, pentylenetetrazol, isopropylbicyclophosphate
II. Enhancement of **Inhibitory Neuropeptides**	Wahlestedt et al 1990[16]	Repeated ECS in rats cause increase in Neuropeptide-Y and Somatostatin in selected areas of frontal cortex, occipital cortex and hippocampus with largest increase in the dentate gyrus.
	Kragh et al. 1994[17]	There was significant elevation of Neuropeptide-Y, Somatostatin and Endothelin in the CSF samples of drug-free depressed patients 5–10 days after completion of ECT course.
	Mathe et al. 1996[18]	
III. EEG changes- **Burst Suppression**	Weiner 1982[19]	During an individual ECT session hypersynchronous polyspikes and slow wave complexes during the ictus gradually slow down to delta waves before termination and are often abruptly replaced by EEG flattening- 'postictal suppression' or 'burst suppression' lasting upto 90 s that progressively merges into the pre-seizure rhythms by about 20 to 30 min after seizure termination.
	Weiner 1980[20]	After a course of 6–8 ECT-sessions there remains a persistence of electrical slowing in EEG up-to 8–12 weeks depending on the number of sessions which is more generalized in case of bilateral ECT.
	Suppes et al. 1996[21] Krystal et al. 1997[22]	Degree and generalization (versus lateralized) of post-ictal 'burst suppression' and subsequent electrical slowing are associated with therapeutic efficacy of ECT.
IV. **Anti-kindling** action	Handforth 1982[23]	In animal study, after a course of ECS administered before amygdala kindling, kindling gets completely blocked for next few days.
	Post et al. 1984[24]	
V. Long term **plasticity**	Vaidya et al. 1999[25]	Course of ECS results new cell formation and mossy fibre sprouting in dentate gyrus of hippocampus in rats, as compared to untreated animals.
	Scott et al. 2000[26]	
	Duman 1997[27]	After a course of ECS, there is rapid rise of Brain Derived Neurotropic Factor (BDNF-mRNA) through phosphorylation of different proteins, including CREB (cAMP response element binding protein). This correlates with degree of post-ictal cortical slowing.
	Krystal and Weiner 1999[28]	

after electrical cessation of seizure, as in report 5 and 7 in Table 1 who were in continuous PBT-coma even during ECT.

On the other hand the anticonvulsant potential of ECT at least theoretically encompasses multiple mode of actions as demonstrated through various animal studies (Table 2). In clinical practice, despite chance of bias, anecdotal reports (Table 1) have shown satisfactory positive response of ECT on refractory-SE. Moreover, ECT is a non-invasive, low-cost, and easy- to- administer therapeutic modality with unequivocal records of safety particularly in the elderly population in depression with multiple medical comorbidities.[5] Thus, in the background of those case reports (Table 1) and animal studies (Table 2), there should be future clinical study on ECT in refractory-SE as the optimum treatment in this field is still elusive.

6. Protocol for future clinical studies on ECT in refractory-SE

If we discuss this protocol Fig. 1 in detail first important point is sample selection. Refractory-SE may be defined as an ongoing SE not terminating on two intravenous AEDs of different categories used in adequate dosage.[6] Standard management protocol for these patients is general anesthesia (GA). But there are patients where SE fails to terminate on prolonged infusion of anesthetic drugs for days. Such cases of SE with various seizure patterns as-well-as NCSE would be included for this study with proper informed consent from the guardians and assessment of anesthetic fitness for muscle relaxation during ECT. Institutional ethical clearance would be ensured beforehand. Regarding exclusion, symptomatic epilepsy with increased intracranial tension, though not an absolute contraindication, should have precaution due to probable risk of brain herniation during ECT. SE with only SPS also to be excluded in initial study as there is no such report and ECT has very little potential of navigation. Regarding age, ECT does not have much experience with young children in psychiatric patients.[5] But, refractory SE is quite common in children with different developmental cerebral anomalies and epileptic syndromes and there were 5 such cases of age <16 year among 12 reported cases in Table 1. But the lowest age being 7 year in that table, the lower age limit would be 5 year for this study. This study would be an open label experimental study where nobody would remain blind about the intervention. If there is success in the initial study, ECT can be controlled with PBT-coma in later studies. Since there is no exact epidemiology for GA-refactory-SE, target sample number is difficult to predict beforehand. The duration of study would be 2 year may be over multiple centres with proper neuro-critical-care set-up for adequate enrolment of samples. However, the entry point into the study regarding duration of SE may vary. The mean time interval before initiation of ECT was 44.85 days in the 12 cases of SE in Table 1. However, earlier the intervention better should be the result, as there would be less down-regulation of the inhibitory system of brain and less excitotoxic damage to the brain and entire body. During prolonged GA or PBT-coma there is high chance of intercurrent infection and multi-organ disturbance[6] so the time interval should not be beyond 1–2 week even if ECT is applied after PBT-coma. Authors of Report 7(Table 1) insisted that ECT should be applied only after failure of two attempts of PBT-coma. But that appears debatable as it would definitely worsen the outcome result for ECT. Moreover ECT is a much easier and safer treatment option than PBT-coma. Regarding ECT parameters, the apparatus should be brief-pulse with EEG monitoring software to quantitatively monitor ictal and post-ictal suppression and slowing during ECT. The apparatus should be high charge delivering (up to 1000–1500 mC) as the charge required in SE is higher due to concomitant use of AEDs. In most of the cases (Table 1) baseline was around 200–300 mC and went higher in subsequent sessions due to rising seizure threshold. ECT electrode placement should be bitemporal as that is the most commonly employed electrode placement and causes better generalization and burst suppression effect.[32] ECT frequency in SE is much higher than in usual psychiatric practice. In the reported cases the frequency was very heterogeneous to get any proper guide. It can be planned as mentioned in the flowchart with the principle that the frequency may be more in the beginning

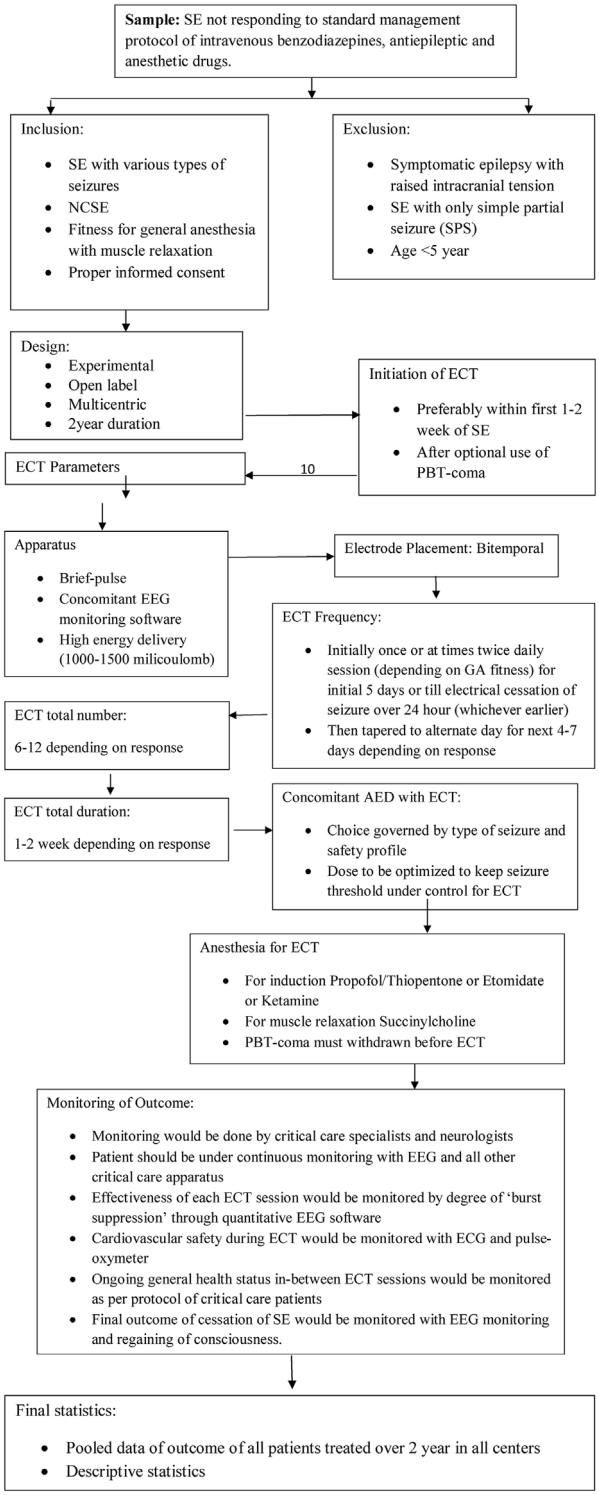

Fig. 1. Flowchart of the study protocol.

and then tapered. Course to end either with regaining of consciousness or plateau of response in clinical and electrical parameters. In Table 1, mean number of total sessions was 7.15 ± 4.83 applied over 3–15 days. But in our study minimum number of sessions should be kept around 6, as the previous human and animal studies[22,24] have suggested that an adequate and sustainable post-ictal bio-suppression with anti-kindling effect can only be generated after a course 5–6 ECT/ECS not in few isolated sessions. Another important question is whether continuation or maintenance ECT to be attempted for preventing recurrence of SE. This can only be addressed after success of initial trial. Use of AEDs during ECT should be judicious rather than exhaustive. Dosage and number of concomitant AED during ECT should be optimized to keep the seizure threshold under control. All efforts are to be done to prevent the ECT-charge going too high in consideration of future cognitive outcome.[33] For anesthetic induction during ECT, ketamine and etomidate[34] may be used in place of propofol because propofol raises the seizure threshold. During ECT, PBT-coma and Midazolam infusion must be withdrawn as they interfere with the electrical convulsion. Final aspect of this protocol is the monitoring of outcome. Foremost important thing of monitoring would be safety of the patients. Repeated use of succinylcholine in critically ill patients within short interval is a major concern. Cardiovascular safety during ECT would be monitored by anesthetists. Fluid-electrolyte balance, renal clearance, cell count, creatinine phospokinase, blood sugar, coagulation profile, liver and other relevant organ functions are to be regularly monitored by critical care specialists. Therapeutic outcome of ECT would be monitored by neurologists with continuous EEG-recoding in terms of degree of post-ECT burst suppression and slowing, electrical cessation of seizure and no recurrence over 24–48 h. When there would be cessation of electrical seizure with no recurrence over 24 h ECT would be tapered to alternate day. Final clinical outcome regarding regaining of consciousness would be monitored with Glasgo-coma-scale.[35] Unless there is any serious deterioration in cardiovascular and general medical status, ECT would be continued for at least 6 sessions. There would be no abrupt discontinuation but gradual tapering after regaining of consciousness or plateau of response in clinical and electrical parameters. Maximum number of sessions should be kept around 12 with some flexibility. Final statistical outcome of the study would be generated by pooling together results of all patients treated over 2-year period in different centres.

7. Conclusion

Systematic clinical studies should be conducted in future to evaluate the potential of ECT to treat refractory-SE.

Conflict of interest

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