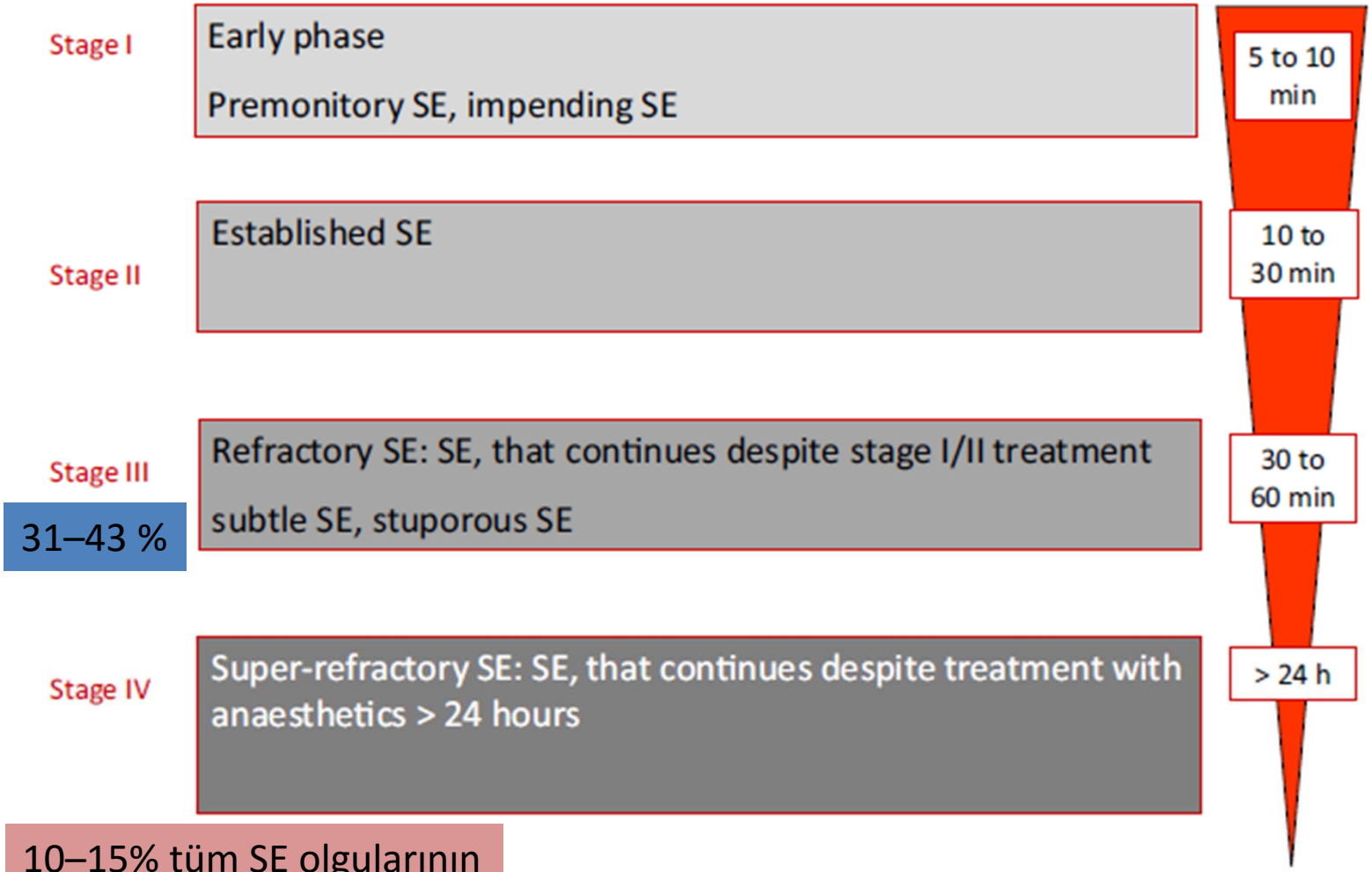
Dirençli SE ve Süperdirençli SE Tedavisi- Dünyadaki ve Bizdeki Durum

Yard. Doç. Dr. Ayşe GÜLER
Ege Üniversitesi Tıp Fakültesi Nöroloji Anabilim Dalı

Medscape


Stage I
Early phase
Premonitory SE, impending SE
5 to 10 min
Stage II
Established SE
10 to 30 min
Stage III
Refractory SE: SE, that continues despite stage I/II treatment
subtle SE, stuporous SE
30 to 60 min
31–43 %
Stage IV
Super-refractory SE: SE, that continues despite treatment with anaesthetics > 24 hours
> 24 h
10–15% tüm SE olgularının

REVIEW ARTICLE

Status Epilepticus: A Review, With Emphasis on Refractory Cases

Gary Hunter, G. Bryan Young

Can J Neurol Sci. 2012; 39: 157-169

neurocritical care society Neurocrit Care (2012) 17:3–23
DOI 10.1007/s12028-012-9695-z

REVIEW

Guidelines for the Evaluation and Management of Status Epilepticus

Gretchen M. Brophy · Rodney Bell · Jan Claassen · Brian Alldredge · Thomas P. Bleck · Tracy Glauser · Suzette M. LaRoche · James J. Riviello Jr. · Lori Shutter · Michael R. Sperling · David M. Treiman · Paul M. Vespa · Neurocritical Care Society Status Epilepticus Guideline Writing Committee

- Nöbet 30 dakikadan uzun devam ederse mortalite oranı 19%
- Refrakter vakalarda ise mortalite 23-61%
- Refrakter vakaların 90% kadarında nbt relapsı izlenir.

Refrakter SE

- Mortalite %30-50
  - Status tipi
  - Yaş
  - Epilepsi öyküsü
  - Status süresi
  - APACHE-2 skorları
  - Kullanılan anestezik ajan

Klinik outcome için etkili değil

  - Etiyoloji
  - Kardiopulmoner komplikasyon
  - Uzun süreli anestezi

Kötü prognoz ile ilişkili

Clinical Neurology and Neurosurgery 139 (2015) 96–99

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Status epilepticus severity score (STESS): A useful tool to predict outcome of status epilepticus

Manoj Kumar Goyal [a], Sudheer Chakravarthi [a], Manish Modi [a,*], Ashish Bhalla [b], Vivek Lal [a]

Status epilepticus severity score (STESS).

Variable	Feature	Score
Level of consciousness	Alert or somnolent or confused	0
	Stuporous or comatose	1
Type of SE	Simple partial, complex partial, myoclonic, absence	0
	Generalized convulsive	1
	Non convulsive SE in coma	2
Age in years	<65	0
	≥65	2
Past history of seizures	Yes	0

Table 4
Predictive value STESS >3.

Parameter		STESS >3	STESS <3	Negative predictive value (95% CI of NPV)	Positive predictive value (95% CI of PPV)	*p* Value
Mortality	Yes	3	1	96.9% (83.7–99.5%)	25% (5.9–57.2%)	0.05
	No	9	31			
Final outcome at discharge	Poor	6	1	96.7% (83.7–99.5%)	50% (21.2–78.8%)	0.001
	Good	6	31			
Control of SE within 1 h of treatment	Yes	10	6	81.3% (63.5–92.7%)	83.3% (51.6–97.4%)	0.0001
	No	2	26			
Coma induction	Yes	3	31	96.7% (83.7–99.5%)	75% (42.8–94.2%)	0.0001
	No	9	1			

- Yatakbaşı kullanım için uygun ve kolay
- STESS<3 kötü prognoz açısından mükemmel negatif prediktif değere sahip
- STESS düşük hastalarda başlangıçta anestezi başlanması geciktirilebilir.
- Tedavi öncesi SE süresinin de hesaplamaya dahil edilmesi ile prediktif değeri arttırılabilir.

J Neurol (2016) 263:485–491
DOI 10.1007/s00415-015-7992-0

ORIGINAL COMMUNICATION

Association of seizure duration and outcome in refractory status epilepticus

Dominik Madžar[1] · Anna Geyer[1] · Ruben U. Knappe[1] · Stephanie Gollwitzer[1] · Joji B. Kuramatsu[1] · Stefan T. Gerner[1] · Hajo M. Hamer[1] · Hagen B. Huttner[1]

Table 2 Multivariable model for prediction of long-term functional outcome as well as in-hospital mortality

	Odds ratio	95% confidence interval	*p* value
A. Poor long-term outcome			
STESS ≥ 3	**11.56**	**1.88–71.04**	**0.008**
Duration of RSE	**1.11**	**1.01–1.22**	**0.033**
Sepsis	**10.40**	**1.24–87.40**	**0.031**
C-reactive protein	1.01	0.99–1.04	0.393
B. In-hospital mortality			
STESS ≥ 3	*4.99*	*0.90–27.10*	*0.066*
Mechanical ventilation	7.98	0.61–103.57	0.112
Use of vasopressors	1.87	0.23–14.90	0.831

STESS Status Epilepticus Severity Score, *RSE* refractory status epilepticus

Parameters significantly ($p < 0.05$) associated with poor long-term outcome or in-hospital mortality are expressed in bold, parameters showing a statistical trend ($p < 0.1$) are expressed in italics

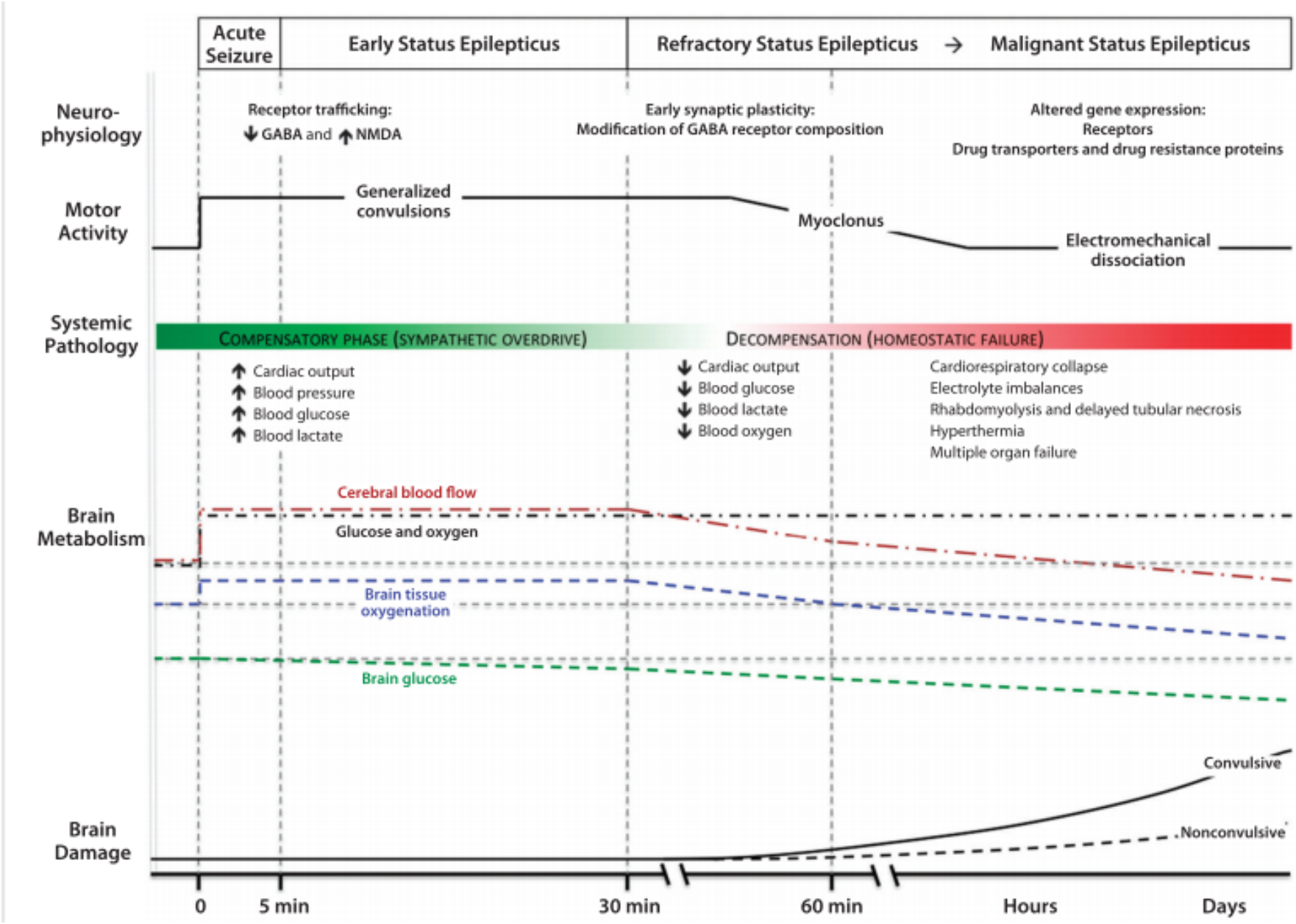
TABLE 12-7 Summary and Comparison of Available Guidelines for the Management of Status Epilepticus *(continued)*

[redacted]nt	2010 European Federation of Neurological Societies Guidelines[a]		2012 Neurocritical Care Society Guidelines[b]	
	Recommendations	**Evidence**	**Recommendations**	**Strength/Evidence**
Initial (emergent/ urgent) treatment for generalized convulsive status epilepticus and nonconvulsive status epilepticus	IV lorazepam *or* IV diazepam plus IV fosphenytoin/ phenytoin	Level A Level A	Benzodiazepines are the treatment of choice: IV lorazepam *or* IM midazolam *or* Rectal diazepam	SR-HQ I-A I-A IIa-A
	If possible, prehospital treatment should be administered	Level A	Followed by an IV AED: fosphenytoin/phenytoin *or* valproate *or* phenobarbital *or* levetiracetam *or* midazolam (continuous)	SR-MQ IIa-B IIa-A IIb-C IIb-C IIb-B

- Hastane öncesi tdv çalışmalarında 2-4 mg lorazepam %60, 5-10 mg diazepam %40 nbt kontrolü sağlandığı saptanmış.
- Solunum depresyonu yapıcı etkileri benzer.
- IV fenitoin ve fenobarbital ile karşılaştırıldığında IV lorazepam %65 oranında nbt kontrolü sağlar.

Response Rates for Subsequent Agents in Each Arm of the Veterans Affairs Cooperative Study (Overt Status Epilepticus Patients Only)[a]

Drug	Response Rate (%)
Initial agent: lorazepam	
Lorazepam	64.9
Phenytoin	7.2
Phenobarbital	2.1
Initial agent: phenobarbital	
Phenobarbital	58.2
Phenytoin	3.3
Lorazepam	2.2
Initial agent: diazepam plus phenytoin	
Diazepam and phenytoin	55.8
Lorazepam	3.2
Phenobarbital	2.1
Initial agent: phenytoin	
Phenytoin	43.5
Lorazepam	13.9
Phenobarbital	3.0


Acute Seizure
Early Status Epilepticus
Refractory Status Epilepticus → Malignant Status Epilepticus
Neuro-physiology
Receptor trafficking:
↓ GABA and ↑ NMDA
Early synaptic plasticity:
Modification of GABA receptor composition
Altered gene expression:
Receptors
Drug transporters and drug resistance proteins
Motor Activity
Generalized convulsions
Myoclonus
Electromechanical dissociation
Systemic Pathology
COMPENSATORY PHASE (SYMPATHETIC OVERDRIVE)
DECOMPENSATION (HOMEOSTATIC FAILURE)
↑ Cardiac output
↑ Blood pressure
↑ Blood glucose
↑ Blood lactate
↓ Cardiac output
↓ Blood glucose
↓ Blood lactate
↓ Blood oxygen
Cardiorespiratory collapse
Electrolyte imbalances
Rhabdomyolysis and delayed tubular necrosis
Hyperthermia
Multiple organ failure
Brain Metabolism
Cerebral blood flow
Glucose and oxygen
Brain tissue oxygenation
Brain glucose
Brain Damage
Convulsive
Nonconvulsive
0
5 min
30 min
60 min
Hours
Days

Drug	Loading Dose	Maintenance Dose	Level	Mechanism(s) of Action
Second-Line Agents				
Phenytoin	18–20 mg/kg IV up to 50 mg/min (25 mg/min in older patients or patients with cardiovascular instability)	5–7 mg/kg/d orally/IV, divided every 8 h	Total: 15–20 μg/mL Free: 1.5–2.5 μg/mL	Sodium channel modulation
Fosphenytoin	18–20 phenytoin equivalents/kg IV up to 150 mg/min	5–7 phenytoin equivalents/kg/d/IV, divided every 8 h	n/a	Sodium channel modulation
Valproate	20–40 mg/kg IV up to 3 mg/kg/min (probably safe up to 6 mg/kg/min)	30–60 mg/kg/d, divided every 6 h	80–140 μg/mL	Multiple, including sodium channel modulation, GABA potentiation and glutamate/NMDA inhibition
Levetiracetam	2500–4000 mg IV up to 500 mg/min	2–12 g/d orally/IV, divided up to every 6 h	25–60 mg/L	Synaptic vesicle protein 2A
Lacosamide	400 mg IV over 5 min	400–600 mg/d IV, divided every 12 h	Unknown	Sodium channel modulation
Phenobarbital	20 mg/kg IV up to 60 mg/min	1–4 mg/kg/d orally/IV, divided every 6–8 h	20–50 mg/mL	GABA potentiation

INVITED REVIEW

Are Newer AEDs Better Than the Classic Ones in the Treatment of Status Epilepticus?

Andrea O. Rossetti

(*J Clin Neurophysiol* 2016;33: 18–21)

TABLE 1. Overview of Classic and Newer Antiepileptic Drugs and Recent Developments in the Treatment of SE, Stratified After the Conventional 3 Treatment Lines

Treatment Line	Classic Compounds	Newer Compounds	Evidence Favoring Newer compounds	Emerging Compounds
First	Lorazepam, diazepam, midazolam, clonazepam	Levetiracetam	No	Midazolam
Second	(fosph-)phenytoin, phenobarbital, valproate	Levetiracetam, lacosamide, topiramate, pregabalin	No	Valproate
Third	Barbiturates, midazolam, propofol	No	No	None
Beyond the lines	All previously mentioned agents, several general anesthetics	No	No	Ketamine, ketogenic diet

Treatment of refractory generalized convulsive status epilepticus and subtle status epilepticus	Admission to intensive care unit (ICU)	GPP	Management in an ICU that can provide cEEG	SR-VLQ
	Continuous IV propofol, thiopental or midazolam	GPP	Additional treatment (switch to or start a new AED) preferred over rebolus of AED used initially	SR-LQ
	Titrate to burst suppression (propofol or thiopental) or seizure suppression (midazolam)	GPP	Continuous IV midazolam, propofol, or pentobarbital +/− intermittent boluses *or* Intermittent IV AED in nonintubated patients	SR-VLQ SR-VLQ
	Simultaneous initiation of chronic medication	GPP	Use maintenance AEDs for the transition from continuous IV.	SR-VLQ WR-VLQ
	If intubation/ artificial ventilation is not justified, further nonanesthetizing agents may be tried	GPP	Titrate to seizure suppression or burst suppression	WR-VLQ
			Electrographic control for 24–48 h before weaning	
			In case of status epilepticus refractory to continuous IV anesthetics, alternative therapies can be considered but the patient should be transferred to an ICU that specializes in the treatment of status epilepticus and can provide cEEG monitoring	WR-VLQ

[redacted] Drugs Used for Definitive Treatment of Status Epilepticus

Agent	Loading Dose	Maintenance Dose	Adverse Effects	Comments
Midazolam[21]	0.2 mg/kg over 5 min	0.2 mg/kg/h to 2.0 mg/kg/h	Hypoventilation, hypotension	Tachyphylaxis occurs rapidly.
Propofol	1 mg/kg to 5 mg/kg (depending on blood pressure and other drugs used) over 5 min to 10 min	Up to 15 mg/kg/h (increasing risk of propofol infusion syndrome above 5 mg/kg/h)	Propofol infusion syndrome (acidosis, rhabdomyolysis), hypotension, immune suppression	Lipid vehicle is a substantial calorie source.
Pentobarbital	5 mg/kg to 10 mg/kg at 50 mg/min; slow infusion for hypotension	0.5 mg/kg/h to 5 mg/kg/h	Acidosis from glycols in vehicle, hypotension, immune suppression, prominent negative inotrope at higher doses	May become unavailable; substitute phenobarbital at a loading dose of 20 mg/kg.
Ketamine[22]	1 mg/kg to 3 mg/kg over 2 min to 5 min	0.5 mg/kg/h to 10 mg/kg/h	Hypotension may develop in patients who have exhausted their intravascular catecholamine stores	Raises blood pressure in about 70% of cases. Increased intracranial pressure reported in the past was a consequence of carbon dioxide retention, not an issue with controlled ventilation.
Isoflurane or desflurane[23]	Requires assistance of an anesthesiologist			Newer delivery devices may facilitate intensive care unit use.

Neuroritical Care Society-2012

- Klinik ve elektrofizyolojik nbt hızlı tedavisi
- Lorazepam IV, Midazolam IM, Rectal Diazepam ilk basamak ilaç
- IV fenitoin, VPA, LEV ikinci basamak ilaç
- Anestezikler EEG'de burst-supresyon ya da izoelektrik EEG elde edilene kadar titre edilmeli
- Tedavi 24-48 saat devam, ek AED idamesi sağlanmalı
- ***Nörolojik yoğunbakım ünitesine deneyimli yaklaşım ve tedavi düzenlenmesi için transferi uygundur!!!!***

[redacted] **Common Medications Used in Status Epilepticus** (*continued*)

Drug	Loading Dose	Maintenance Dose	Level	Mechanism(s) of Action
Felbamate	400 mg every 8 h orally	Up to 1200 mg every 8 h orally	40–100 μg/mL	GABA potentiation and glutamate/NMDA inhibition
Magnesium sulfate	2–4 g IV over 2 h	2 g IV every 8 h or 0.5–2 g/h continuous IV	>2.0 mEq/L (up to 7.0 mEq/L)	Glutamate/NMDA inhibition and calcium channel modulation
Immune Therapies	**Starting Dose**	**Maintenance Dose**	**Level**	**Mechanism(s) of Action**
Methylprednisolone	1 g/d during 3 d	1 mg/kg/d then taper	n/a	Renal
IV immunoglobulin	0.4 g/kg/d for 5 d	NA	n/a	n/a
Plasmapheresis	1 session every other day for 5 to 7 d	Unknown	n/a	n/a

IV = intravenous; n/a = not applicable; IM = intramuscular; NMDA = *N*-methyl-D-aspartate.
[a] Doses up to 1200–1600 mg have been used and are recommended in the Neurocritical Care Society guidelines.

Nonpharmacologic Approaches Used in Status Epilepticus

Nonpharmacologic Approaches	Dose	Duration	Mechanism(s) of Action	Interactions	Adverse Reactions/ Comments
Electroconvulsive therapy	1 session daily for 3–8 d	Unknown, but up to 2 wk	Unknown	None, although doses of anticonvulsants should be decreased prior to electroconvulsive therapy for optimal response	Adverse reactions attributable to a short general anesthesia; memory loss and mood effect difficult to ascertain in patients with status epilepticus; requires lowering of the dose of current anticonvulsant drugs.
Hypothermia	n/a	Unknown, but usually 24 h	Decrease brain metabolism which is theoretically neuroprotective	None	Acid, base, and electrolyte disturbances; coagulation disorders and thrombosis; infections; cardiac arrhythmia; bowel ischemia; paralytic ileus
Resective surgery	n/a	n/a	n/a	None	
Ketogenic diet	n/a	n/a	n/a	None	Acidosis, immunosuppression, nephrolithiasis

n/a = not applicable.

doi:10.1093/brain/

BRAI
A JOURNAL OF NEUR

REVIEW

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Simon Shorvo

Table 1 The published literature on treatment outcomes

Therapy	Number of published papers reporting outcome data	Number of published cases in which outcome data are provided
Pentobarbital/thiopental	23	192
Propofol	24	143
Midazolam	20	585
Ketamine	7	17
Inhalational anaesthetics	7	27
Hypothermia	4	9
Magnesium	2	3
Pyridoxine	2	2
Immunotherapy	8	21
Ketogenic diet	4	14
Vagal nerve stimulation	4	4
Deep brain stimulation	1	1
ECT	6	8
Emergency neurosurgery	15	36
CSF drainage	1	2
Topiramate	10	60
Levetiracetam	8	35
Pregabalin	1	2
Lacosamide	2	10

All patients had received more than one therapy, but we have included in this table only the therapies highlighted in individual papers. The anaesthetic reports include patients with refractory and super-refractory status epilepticus.

Table 2 **Overall outcome of anaesthetic therapy**

Outcome	Thiopental/pentobarbital (*n* = 192)	Midazolam (*n* = 585)	Propofol (*n* = 143)
Control	64% (123/192)	78% (458/585)	68% (97/143)
No control ever achieved[a]	5% (9/192)	16% (93/585)	11% (16/143)
Breakthrough seizures	0% (0/192)	3% (19/585)	1% (2/143)
Withdrawal seizures	9% (18/192)	<1% (2/585)	6% (8/143)
Therapy failure because of side-effects	3% (5/192)	<1% (1/585)	6% (8/143)
Death during therapy	19% (37/192)	2% (12/585)	8% (12/143)

- **Potansiyel bias!!!**
- **Midazolam- barbitürat etkinliği ? Barbitürat etkinliğini gösteren çalışmalar ICU pratiğinin başlarında!!**
- **Breakthrough seizures; Başlangıçtaki nbt kontrolünün ardından nbt lerin tekrar başlaması ve başka bir anestezik ajana değişim gereksinimi**

3% midazolam,

1.3% propofol

0% barbiturate

RSE ve SRSE TEDAVİ ALGORİTMASI ÖNERİLERİ

- İlk basamak tedaviler
  - Anestezikler(24-48 saat aralıklarla doz azaltımı denemeleri, nbt izlenirse tekrar üst doz çıkımı ve

- the longer the seizures persist the worse

the functional outcome

    - Sık AED değişiminden yan etki, rebound nbt, allerjik reaks riski nedeni ile kaçınılmalı
    - İlaç seçimi klinik tabloya göre belirlenmeli

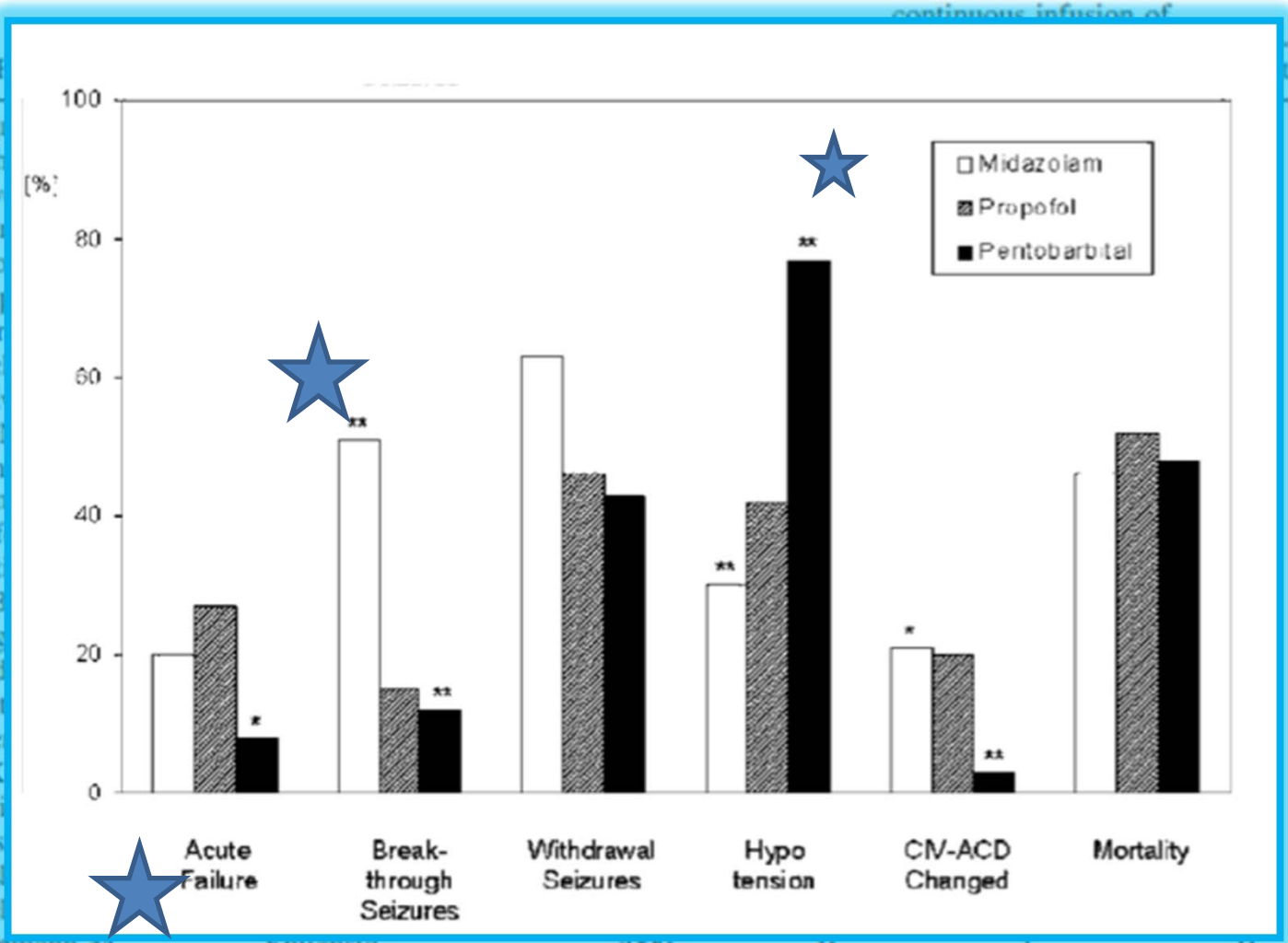
Epilepsia
Official Journal of the International League Against Epilepsy

Epilepsia, **43**(2):146–153, 2002
Blackwell Publishing, Inc.

Treatment of Refractory Status Epilepticus with Pentobarbital, Propofol, or Midazolam: A Systematic Review

- **Barbitüratlar, midazolam ve propofolden daha etkin.**
- **Erken mortalite açısından aralarında fark yok.**
- **ZR supresyonunun, nbt supresyonuna göre**
  - **Nöbet tekrarını önlediği,**
  - **Ancak hipotansiyon etkisinin daha belirgin olduğu**
  - **Mortaliteye etkisi yok**

TABLE 1. *Studies included in the systemic review*



			RSE patients treated with continuous infusion of		
Naritoku DK	*Neurology*	2000	2	0	0
Prasasad A[a]	*Epilepsia*	2001	7	13	0
Claassen J[a]	*Neurology*	2001	33	0	8
Total			54	33	106

Epilepsy Research (2011) 94, 53–60

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journal homepage: www.elsevier.com/locate/epilepsyres

Propofol treatment in adult refractory status epilepticus. Mortality risk and outcome

Kjersti Nesheim Power[a,c,*], Hans Flaatten[b,d], Nils Erik Gilhus[a,c], Bernt A. Engelsen[a,c]

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[b] Department of Anaesthesiology, University Hospital, Bergen, Norway
[c] Department of Clinical Medicine, Section for Neurology, University of Bergen, Norway
[d] Department of Surgical Sciences, University of Bergen, Norway

- 18 hastada, 27 RSE tablosu için propofol kullanılmış.
- 16 hastada anestezi başlanmasından önce en az 2 saattir devam eden SE mevcut.
- 8 hastada doz azaltımı sırasında nbt tekrarı(+)
- 17 RSE tablosunda komplikasyon gelişmiş, en sık pnömoni.
- 1 hastada PRIS(propofol infüzyon sendromu)
- 8/18 sekelsiz iyilemiş.

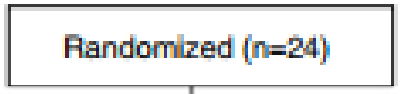


Table 2 Outcome data

	Propofol	BBT	*P*	Test
Patients	14	9		
Efficacy				
RSE controlled with first course of study drug	6 (43%)	2 (22%)	0.40	Fisher
RSE treated subsequently	4/8 (50%)	5/7 (71%)	1.00	Fisher
Functional outcome at 3 weeks (returned to baseline)	5 (36%)	3 (33%)	1.00	Fisher
Functional outcome at 3 months (returned to baseline)	5 (36%)	4 (44%)	1.00	Fisher
Mortality	6 (43%)	3 (33%)	1.00	Fisher
Tolerability				
Thrombotic/embolic complication	0	0	1.00	Fisher
Infections requiring antibiotics	7 (50%)	6 (66%)	0.67	Fisher
Hypotension requiring specific treatment	7 (50%)	5 (55%)	1.00	Fisher
Other severe complications	1 (7%)[a]	1 (11%)[b]	1.00	Fisher
Study drug administration (days, median, range)	2.5 (0–7)	2 (0–4)	0.45	*U*
Intubation time in survivors (days, median, range)	4 (2–28)	13.5 (8–70)	0.03	*U*

Propofol infusion syndrome in patients with refractory status epilepticus: An 11-year clinical experience*

Table 1. Definitions of propofol infusion syndrome traits

Propofol Infusion Syndrome Trait	Definition
Arrhythmias	Increased premature ventricular contractions, new left or right bundle branch block, prolonged QTc, Brugada-like electrocardiographic features, bradycardia (heart rate <55 beats/min or decrease in HR >30 beats/min), ventricular tachycardia/fibrillation, new heart blocks
Renal changes	Renal failure, anuria, oliguria, hyperkalemia

- **6% mortalite hızı**
- **10% Kardiorespiratuar arrest=> PRIS nedenli**
- **39% hastada PRIS semptomlarının bir veya daha fazlası izlenmiş.**

Table 4. Propofol dosing and laboratory values in the propofol infusion syndrome (PRIS) versus non-PRIS group

PROPOFOL

Characteristics	(Other Than Cardiac Arrest)[a] (n = 11)	Non-PRIS Group (n = 17)	p
Peak creatine kinase levels, median (range)		(1241–1833)	.28
Lowest pH, median (range)		(6.92–7.42)	.89
Days of intravenous antiepilept median (range)		(2–29)	.13
No. of intravenous antiepilepti median (range)		(1–5)	.89
Propofol dosing, median (rang			
Peak rate, μg/kg/min		(19–175)	.005
Total cumulative dose, mg		(336–43,870)	.001
Total infusion time, hours	92 (36–391)	36 (2–169)	.006
Infusion rate μg/kg/min,	57 (10–118)	30 (10–85)	.007

- **Pik infüzyon hızı**
- **Total kümülatif doz**
- **Total infüzyon süresi**

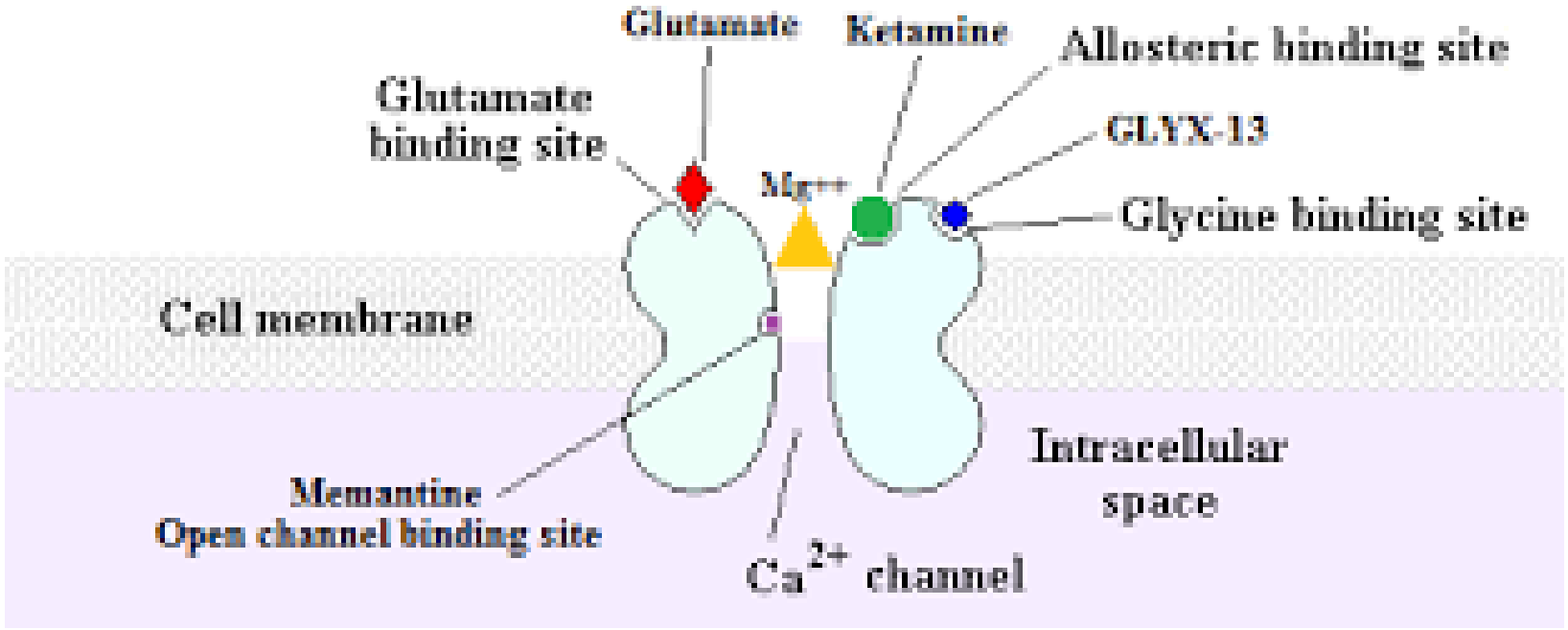
Thiopental/ pentobarbital	Advantages: strong antiepileptic action; long clinical experience; tendency to lower core temperature; and theoretical neuroprotective effects. Disadvantages: problematic pharmacokinetics—zero-order kinetics, profound tendency to accumulation, long recovery time, hepatic metabolism, autoinduction, drug–drug interactions; hypotension, cardio-respiratory depression; and pancreatic and hepatic toxicity.
Midazolam	Advantages: antiepileptic action; and only benzodiazepine with pharmacokinetic properties suitable for prolonged infusion without accumulation. Disadvantages: may be less effective than other anaesthetics; hypotension, cardio-respiratory depression; risk of hepatic and renal impairment; and risk of tolerance and breakthrough seizures (probably overestimated).
Propofol	Advantages: excellent pharmacokinetic properties including very rapid onset and recovery even after prolonged infusion allowing ease of control of anaesthesia; no drug interactions; and less hypotension and cardio-respiratory depression than barbiturate or midazolam anaesthesia. Disadvantages: propofol infusion syndrome, especially in children; pain at the injection site; and difficulty in differentiating drug-induced involuntary movements and seizures.
Ketamine	Advantages: no cardiodepressant or hypotensive action; and anti-glutaminergic action. Disadvantages: very limited published experience; and possible neurotoxicity.

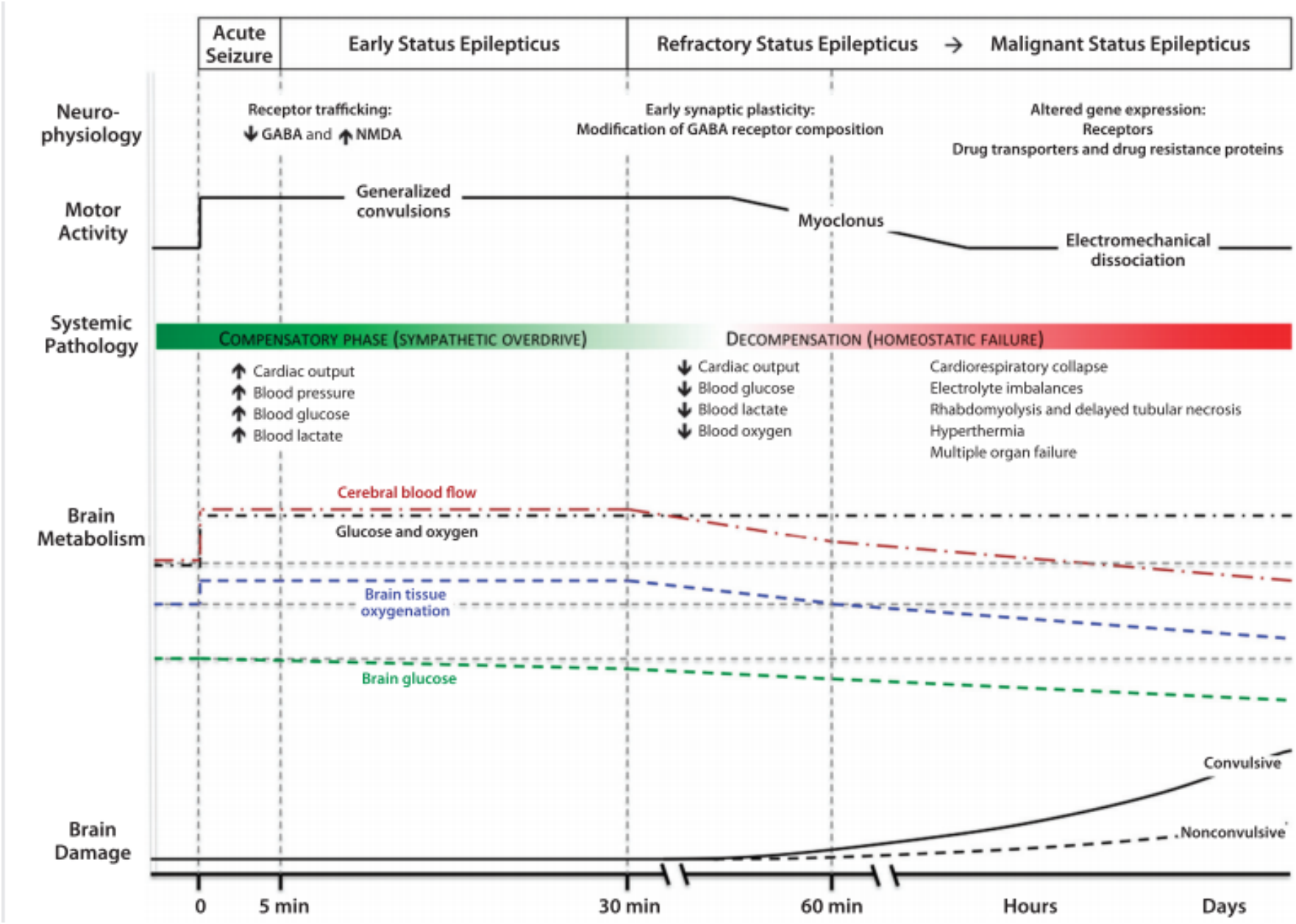
Table 5 Recommendation for anaesthetic use in refractory and super-refractory status epilepticus (adults)

Anaesthetic	Dose	Recommendations
Thiopental/ pentobarbital	Thiopental: Loading dose: 2–3 mg/kg Maintenance dose: 3–5 mg/kg/h Pentobarbital: Loading dose: 5–15 mg/kg Maintenance dose: 0.5–3 mg/kg/h	First-line therapy in severe cases. Avoid in situations where pharmacokinetic interactions would be detrimental. Avoid in hepatic disease, myasthenia gravis, porphyria, severe haemorrhage or burns, cardiovascular disease, adrenocortical insufficiency.
Midazolam	Loading dose: 0.1–0.2 mg/kg Maintenance dose: 0.1–0.4 mg/kg/h	First-line therapy in most cases. Avoid in hepatic or renal disease, myasthenia gravis, porphyria.
Propofol	Loading dose: 3–5 mg/kg Maintenance dose: 5–10 mg/kg/h	First-line therapy in complex cases where ease of use and pharmacokinetic properties are important. Use where other drugs cause problematic hypotension. Avoid prolonged infusion (>48 h) especially at high doses and in children. Caution with concurrent steroid or catecholamine therapy.
Ketamine	Loading dose: 1–3 mg/kg Maintenance dose: up to 5 mg/kg/h	Second-line therapy especially where hypotension or cardiorespiratory depression is problematic.

The doses reflect our clinical practice, but higher doses are sometimes quoted in the literature, for instance midazolam 0.2–0.6 mg/kg/h and ketamine up to 7.5 mg/kg/h (Rossetti and Lowenstein, 2011).

NMDAR


Glutamate
Ketamine
Allosteric binding site
Glutamate binding site
GLYX-13
Mg++
Glycine binding site
Cell membrane
Intracellular space
Memantine
Open channel binding site
Ca2+ channel


Acute Seizure
Early Status Epilepticus
Refractory Status Epilepticus → Malignant Status Epilepticus
Neuro-physiology
Receptor trafficking:
↓ GABA and ↑ NMDA
Early synaptic plasticity:
Modification of GABA receptor composition
Altered gene expression:
Receptors
Drug transporters and drug resistance proteins
Motor Activity
Generalized convulsions
Myoclonus
Electromechanical dissociation
Systemic Pathology
COMPENSATORY PHASE (SYMPATHETIC OVERDRIVE)
DECOMPENSATION (HOMEOSTATIC FAILURE)
↑ Cardiac output
↑ Blood pressure
↑ Blood glucose
↑ Blood lactate
↓ Cardiac output
↓ Blood glucose
↓ Blood lactate
↓ Blood oxygen
Cardiorespiratory collapse
Electrolyte imbalances
Rhabdomyolysis and delayed tubular necrosis
Hyperthermia
Multiple organ failure
Brain Metabolism
Cerebral blood flow
Glucose and oxygen
Brain tissue oxygenation
Brain glucose
Brain Damage
Convulsive
Nonconvulsive
0
5 min
30 min
60 min
Hours
Days

- 7.5 mg/kg/gün gibi yüksek dozda 14 gün süre ile uygulamalar.
- 10mg/kg/gün 27 gün, mortalite ve komplikasyon oranlarında artış saptanmamış.
- Ketamin erken dönemde başlandığında SE kontrol oranlarının daha yüksek olduğu saptanmış.
- 3. veya 4. tedavi seçeneği olarak kullanıldığında 60% oranında SE kontrolü sağlamaktadır.
- SE başlangıcından 1 hafta sonrasında ketamin tdv başlandığında veya 7 AED başlanması sonrası başlandığında benzer oranda etkili tedavi yanıtı alınamamaktadır.

Table 2. Determinants of ketamine efficacy (N = 60 episodes)

	Likely response (N = 7)	Possible response (N = 12)	Likely or possible response (N = 19)	No response (N = 41)	p-Value (univ.)[$]	p-Value (multiv.)
Latency to ketamine; median (range)	12 h (6 h–7 d)	5 d (18 h–30 d)	4.5 d (6 h–30 d)	10 d (12 h–122 d)	0.0053	NS
Number of previously failed drugs; median (range)	4 (3–7)	6 (3–11)	6 (3–11)	8 (3–16)	0.0012	<0.01
Etiology						
Unknown (N = 34)	1	7	8	26	<0.001	NS
Anoxic (N = 7)	4	0	4	3		
Acute nonanoxic (N = 13)	2	2	4	9		
Remote (N = 6)	0	3	3	3		
SE classification						
Generalized c					NS	–
Generalized n						
Focal convuls						
Focal noncon						
Infantile spasn						
Maximum infusi median (range)[a]					NS	–
Loading dose administered[b]	6/6 (100%)	5/8 (63%)	11/14 (79%)	23/32 (72%)	NS	–
Duration of administration	1 (0–2)	3 (0–10)	2 (0–10)	5 (0–27)	<0.001	NS
Number of concurrent drugs	3 (1–5)	5 (1–11)	4 (1–11)	6 (1–10)	<0.001	NS
Number of concurrent anesthetic drugs[c]	1 (0–1)	1 (1–3)	1 (0–3)	2 (1–3)	<0.001	NS

- Uygulama süresi
- Kullanılmakta olan AED sayısı
- Eş zamanlı kullanılan anesteziklerin sayısı

Seizure 30 (2015) 14–20

- Plasma proteinlerine düşük oranda bağlanır
- Kan beyin bariyerini hızlıca geçer
-IV uygulama sonrası Tmax 1-5 dk
-Oral alım sonrası Tmax 15-30 dk

Year	Number of patients	Administration	Dosages							Outcome
			Bolus							
2014	1	Intravenous	2 bolus of 2 mg						eizures	SE reappeared and died
2013	58	Intravenous	Median 1.5 mg/ (max 5 mg/kg)							Good outcome (5%); mortality (45%)
2013	11	Intravenous	1–2 mg/kg						esolved	Home/rehabilitation (5); need nursing (4); died (2)
2013	2	Intravenous	0						esolved	Rehabilitation (2)
2013	1	Intravenous	1.5 mg/kg	1.2–3.75 mg/kg/h	0	12d	hours; Within 30 min Unknown	Within 3d	Completely resolved	Rehabilitation

Usage of ketamine for the treatment of RSE.

Administration	Indication	Contraindications [ ]	Dosages		Onset time [52]
			Adults	Children (0–18 y)	
Oral	After 5–6 ADEs failed	Allergic Severe hypertension	1500–2000 mg/d [34]	1.5 mg/kg/d in two divided doses [27]	15–30 min
Bolus and infusion	After 5–6 ADEs failed	Allergic Severe hypertension	Bolus: 1–5 mg/kg Infusion: 0.45–10 mg/kg/h [25,30]	Bolus × 2: 2–3 mg/kg Infusion: 2.4 mg/kg/h (range 0.6–3.6 mg/kg/h) [26]	1–5 min
Infusion	After 5–6 ADEs failed	Allergic Severe hypertension	0.6–15 mg/kg/h [31,56]	1.95 mg/kg/h (range 0.6–3.6 mg/kg/h) [57]	1–5 min

Ketamine
Seizure
Status epilepticus (SE)

to treat RSE. To improve the prognosis of SE, we present a narrative review of ketamine for the treatment of RSE in the extant literature. We draw the conclusion that ketamine appears to be effective and relatively safe for the control of multidrug-resistant RSE in children and adults.

FDA ÖNERİLERİ

- İnfüzyon hızı düşük olarak başlanmalı ve daha yavaş olarak arttırılmalıdır;
  - Yüksek doz=>psikiatrik semptomlar, solunum depresyonu, apne
- Nbt kontrolü amacı ile başlanırken solunum depresyonu etkileri göz önüne alınarak mekanik ventilasyon uygulanmalıdır.
- İntrakraniyal hipertansiyona yol açabilecek intrakraniyal lezyon varlığını ekarte etmek için kraniyal görüntüleme(BT,MRI) yapılmalıdır.
- Yaşlı populasyonda mümkün olan en düşük doz uygulanmalıdır.
- İskelet kas tonusunu arttırabilir ve bu tablo tonik-klonik nöbetlerden ayırt edilmelidir.

neurocritical care society Neurocrit Care (2014) 20:502–513
DOI 10.1007/s12028-013-9939-6

REVIEW ARTICLE

NMDA Antagonists for Refractory Seizures

F. A. Zeiler · J. Teitelbaum · L. M. Gillman · M. West

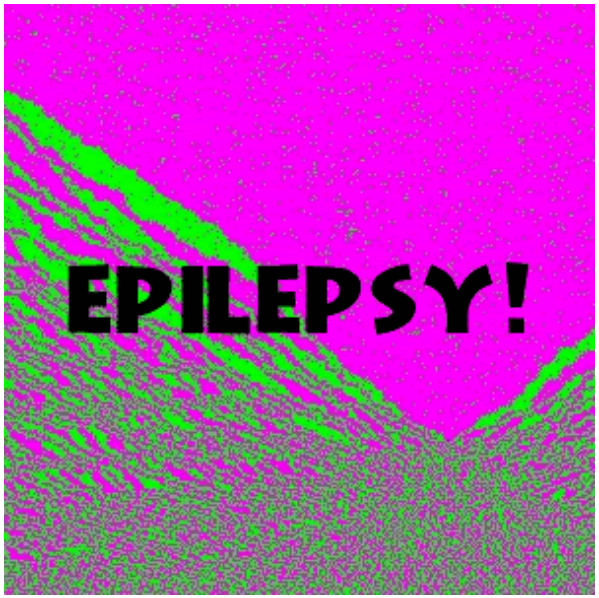
- 162 hasta(110 yetişkin)
- Retrospektif vaka serileri, 3 propektif kohort çalışması
- RSE da 56.5% elektrografik nbt kontrolü
- Yan etki insidansı düşük

the studies available. The lack of RCT on the use of ketamine in the control of seizures prevents a high level of evidence for this treatment. Thus, based on this review, we can currently provide Oxford level 4, GRADE C recommendations for the use of ketamine for RSE.

- Genel anestezik kullanımı sırasında;
  - Endotrakeal entübasyon ve mekanik ventilasyon
  - cEEG
  - Vazopressör ve inotropik ajan
  - Poikilotermi
  - Enteral beslenme(ileus? PN)
  - Enfeksiyon

- Ne kadar süre ile anestezik kullanılabilir?

- Genel anestezik kullanımında doz hedefi?
  - EEG’ de burst supresyon (nbt tekrarının önlemede yetersiz!!)
  - ESAS HEDEF=>
    - Belirli bir süre(12-24 saat) tam nöbet kontrolü sağlanması
    - Ardından ilaç dozunun azaltılması ve
    - Bu sırada klinik ve cEEG ile nöbet tekrarının takibi



- Diğer SE tipleri için genel anestezik kullanımı?
  - Epilepsia parsialis kontünia
  - Absans SE
  - Kompleks parsiel SE
  - Non-konvulziv SE

- Anestezik gazlar SSS nin lipofilik yapısına kolay giriş gösterir. MAC ile etkinlik takibi.
- EEG yanıtına göre kolayca doz titrasyonu sağlanır.
- NMDA İsoflurane >90% yanıt elde edildiği vaka

CONCLUSIONS

There currently is Oxford level 4, GRADE D evidence to potentially support the use of isoflurane to achieve burst suppression for RSE in the adult and pediatric populations. Further prospective study of inhalational anesthetics in RSE is warranted.

- Metabolizmaları sonucu ortaya çıkan ürünler CO2 moleküllerine bağlanarak, toksik bileşimler oç.
- Kardiyovaskuler YE.

SHORT COMMUNICATION

CNS Drugs 2012; 26 (9): 761-772
1172-7047/12/0009-0761/$49.95/0

Topiramate as an Adjunctive Treatment in Patients with Refractory Status Epilepticus

An Observational Cohort Study

Annalena Hottinger,[1*] *Raoul Sutter*,[2,3*] *Stephan Marsch*[2] and *Stephan Rüegg*[4]

Topiramate (Enteral)

- Çeşitli etki mekanizmaları olan geniş spekturumlu AED
- İonotropik glutamaterjik AMPA reseptör blokajı da(+)
- IV formulasyon yok, enteral yükleme
- 2 -25 mg/kg/gün çocuk
- 1600 mg/gün erişkinlerde
- Nbt kontrolü 71 %, 9% olguda yükleme sonrası 24 h içinde nbt kontrolü, geri kalan 62% de 72 h içinde nbt kontrolü
- Metabolik asidoz en sık yan etki. VPA ile kombinasyonda hiperamonyemi!

RSE ve SRSE TEDAVİ ALGORİTMASI ÖNERİLERİ

- İkinci basamak tedaviler
  - Hipotermi
  - Magnezyum ve piridoksin infüzyonu
  - İmmunolojik tedaviler
  - Ketojenik diyet
  - Acil cerrahi

neurocritical care society Neurocrit Care (2008) 9:189–197
DOI 10.1007/s12028-008-9092-9

ORIGINAL ARTICLE

Hypothermia for Refractory Status Epilepticus

Jesse J. Corry · Rajat Dhar · Theresa Murphy ·

-Hipotermi elektroserebral sessizlik sağlar

- **4 olgu;**
  - **Anestezik ajanların infüzyonu sırasında uygulama**
  - **3 midazolam, 1 thiopental**
  - **Hedef vücut ısısı 31-35°C**
  - **EEG de burst-supresyon**
- **Hipotermi uygulanamayacak hastalar; İmmunsuprese, hemodinamik olarak unstabil, hamile, aktif enfeksiyonu olan, koagülopatisi olan(INR > 2 veya tromb < 75,000),**

- Super refrakter SE tedavisinde bazı merkezlerde rutin olarak uygulanmakta.

Seizure 32 (2015) 100–108

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

- N-methyl D-aspartate (NMDA) reseptör inhibisyonu ile

- IV yükleme dozu 3-6 g, ardından sürekli infüzyon 0.75- 6 g/h,

- Ortalama 2-7 gün süresince.

5. Conclusions

Oxford level 4, GRADE D evidence exists to suggest a trend towards improved seizure control with the use of intravenous $MgSO_4$ for non-eclamptic RSE. Routine use of IV $MgSO_4$ in non-eclamptic SE/RSE cannot be recommended at this time. Further prospective study of this drug is required in order to determine its efficacy as an anti-epileptic in this setting.

PİRİDOKSİN iNFÜZYONU

- Piridoksin metabolizma bzkl olan yenidoğanlarda SE tedavisinde etkin.
- Piridoksin metabolizma bzkl olmadan da gençlerde süper dirençli SE tedavisinde etkin olabileceği düşünülerek uygulanmakta.
- Literatürde 2 olgu; gebe ve malnutrisyonlu, eş zamanlı başka AED kullanımı, etkinlik bias?
- 180–600 mg/gün

İMMUNOTERAPİ

- SE kontrolü literatürde 5%
- Pulse kortizon 1gr/gün,
- IVIG 0.4 g/kg/gün 5 gün ,
- Plazmaferez
- Yeterli kanıt olmamasına rağmen geniş olarak kullanılmakta.
- Teorik etki mekanizması;
  - 1. Kriptojenik RSE altta yatan otoimmun yada immunolojik süreç nedeni ile oç.
  - 2. Epileptik fokü̈steki epileptogeneze neden olan olası inflamatuar mekanizmaların kontrolü

New Onset Refractory Status Epilepticus: NORSE Syndrome

- Genç, öncesinde sağlıklı olan başağrısı ve ateş yüksekliği gibi viral enfeksiyon semptomları sonrası nöbet ve refrakter SE gelişimi
- Enfeksiyöz, non-enfeksiyöz ve otoimmun etyoloji
- Tanı diğer nedenlerin dışlanması ile
- Hastalar sıklıkla genç (ort 29), kadın ve nörogörüntüleme sıklıkla normal, nadiren küçük T2/FLAIR lezyonları
- BOS ılımlı lenfositik pleositoz
- EEG fokal, multifokal veya generalize epileptiform aktivite gösterir.
- Nbt birinci ve ikinci sıra tedavilere dirençli
- Otoimmun proçes? Steroid, IVIG, plazmaferez yanıtsız,

OLGU-1

- 20 yaş kadın
- 3 gün önce hafif ateş yüksekliği, boğaz ağrısı, mide bulantısı
- Bilinç kaybı ile AS başvurusu
- NM:
  - Bilinç uykulu,taktil uyarana göz açıyor.
  - Kooperasyon yok.Verbal yanıt yok.
  - Pupiller NIK,IR +/+.
  - Ağrılı uyaranı her iki üst ekstremite ile eşit lokalize ediyor.
  - Ense sertliği pozitif.
  - 4 ekstremitede rijidite mevcut.
  - Sağda babinski poziti

- LP de ise lökosit 20, prot 46 mg/dl
- Ampirik AB ve antiviral tedavi başlandı.
- Kr. MRG(diffüzyon, ADC, FLAIR kontrastlı seriler) normal
- JTKK geçirmeye başladı.
- EEG :Yaygın lateralizasyon ve lokalizasyon göstermeyen zemin ritmi yavaşlığı saptandı. Zemin ritmi zaman zaman suprese oluyordu. Periyodisite gösteren yavaş dalgalar görüldü.

- LEV+VPA yüklemesi ve idamesine rağmen devam eden nbt
- Midazolam bolus ve IV infüzyon 24 saat
- Uzun süreli cEEG ile monitorizasyon ve nbt aktivitesinin kontrolü
- Fenitoin sodyum ilave
- 48 saat sonunda extube ve nbt kontrolü sağlanmış durumda

- 2 gün sonrasında sık nbt geçiren ve arada bilinci hiç açılmayan hastaya tekrar midazolam inf açıldı.
- Yüksek doza rağmen nbt kontrolü sağlanamaması nedeni ile propofol inf a geçildi.
- TPM eklendi.
- Propofol ile 48 h süre ile nbt kontrolü sağlanabilip ardından tekrar nbt başladı.
- Tiopental inf başlandı.

- Kontrol EEG'de bioelektriki non-konvulsif status tablosu saptandı.Zemin ritminin tüm çekim boyunca jeneralize keskin veya diken dalgalardan oluştuğu bu deşarjların hemisfer ön bölümlerinde ve sağda daha belirgin olduğu ve sağda daha belirgin kısa süreli burst supresyon izlendi.
- Tiopental infüzyonuna rağmen non-konvulsif status tablosu devam eden hastaya Literatür'deki örnekler de gözönüne alınarak Ketamin infüzyonu başlanması planlandı.

- Bolus ardından doz titrasyon ile arttırıldı ve cEEG ile monitorize edildi. İnfüzyonun 36. saatinde EEG de nbt kontrolünün sağlandığı izlendi.
- LEV, VPA, Fenitoin, Tpm, Okskarazepin, Phenobarbital tedavide kullanıldı.
- Tüm geniş etiyolojik tarama(otoimmun panel, serolojik tarama, hematolojik tarama) neden?
- Multipl organ yetmezliği; ex, 1 ay sonunda

Rare causes of SRSE

Immunologic (Davis R, 2013)	Intracellular paraneoplastic: Hu, CV2/CRMP5, Ma2, Amphyphysin Cell surface: NMDA, LGII, Caspr2, GABA(B), AMPAR (GluR I/2), mGluR5, DPPX, GAD Unclear significance: AMPAR (GluR3), VGKC other than LGII/Caspr2, TPO
Mitochondrial disorders	Alpers, MELAS, Leigh, MERRF, NARP
Uncommon infections	Atypical bacteria, prion disease, fungal, viral
Drugs/Toxins	AEDs, antimicrobials/antiviral drugs, antipsychotics, contrast media, chemotherapeutics, toxins.
Genetic disorders	Chromosomal abnormalities, malformation of cortical development, neurocutaneous syndromes, channelopathies

Table 2: Diagnostic Evaluation of Refractory Status Epilepticus

Infectious (serum and CSF)	HSV, HIV, VZV, EBV, CMV, Adenovirus, Measles, West Nile Lyme, Syphilis (VDRL), Mycoplasma, Mycobacterium, Cryptococcal Ag
Autoimmune (serum)	ANA, dsDNA, Rheumatoid factor, ANCA, Anti-phospholipids, Anti-La, Anti-Ro, Thyroid peroxidase, Anti-thyroglobulin, Paraneoplastic panel*
Autoimmune (CSF)	Paraneoplastic panel* Additional Anti-neuronal Abs: NMDA, VGKC (LG1), GAD65, GABA, AMPA
Paraneoplastic- Other	Chest/Abdomen/Pelvis CT, Pelvic ultrasound, Body PET

*Standard paraneoplastic panel includes antibodies against ANNA 1-3, Purkinje cell 1-2, Amphiphysin, CRMP 5, Glial Nuclear, P/Q and N Type Ca++ channels, AChR,

Ketojenik Diyet

- Yüksek yağ, düşük karbonhidrat ve uygun protein düzeyinden oluşan diet
- 24 saat açlık sonrası başlanır.
- Kısa dönemde asidoz, hipoglisemi, kilo kaybı, GÖR yapar.
- Kan şekeri ilk 3 günde 3 saatte bir, ardından 6 saatte bir ölçülmelidir.
- KŞ 45 mg/dl altına düşerse glukoz verilmelidir.
- Ketoz oluşturulduğunda üriner keton ve serum B-hidroksibütirat günlük ölçülmelidir.
- Steroidler ketoz oluşumunu inhibe edeceği için kullanılmamalıdır.

Rezektif Cerrahi

- Literatürde 36 olgu
- Uzun süreli iyi outcome 75%.
- Cerrahi seçenekleri;
  - Focal resection,
  - multiple subpial transection,
  - corpus callosectomy
  - hemispherectory (bazen kombine).
- Acil cerrahi ancak kesin elektrografik foküs saptanabilir ise ikinci basamak tedavide yer alabilir. Sadece lezyon değil epileptik zon rezeke edilmelidir.

Etomidate (IV)

- Anestezik ajan
- Etki mekanizması?
- Hızlı sedasyon etkisi dışında yan etki profili düşük
- Reversibl kortizol inhibisyonu oluşur ve ıv infüzyon alan hastalarda hormon seviyelerine dikkat edilmelidir.

Epilepsia. 2013 September ; 54(0 6): 93–98. doi:10.1111/epi.12289.

Neuroactive Steroids for the Treatment of Status Epilepticus

Michael A. Rogawski[1], **Carlos M. Loya**[2], **Kiran Reddy**[2], **Dorota Zolkowska**[1], and **Christoph Lossin**[1]

[1]Department of Neurology, School of Medicine, University of California, Davis, Sacramento, California 95817, USA

[2]Sage Therapeutics, Cambridge, Massachusetts 02142, USA

Benzodiazepines are the current first-line standard-of-care treatment for status epilepticus but fail to terminate seizures in about one-third of cases. Synaptic $GABA_A$ receptors, which mediate phasic inhibition in central circuits, are the molecular target of benzodiazepines. As status epilepticus progresses, these receptors are internalized and become functionally inactivated, conferring bezodiazepine resistance, which is believed to be a major cause of treatment failure. $GABA_A$ receptor positive allosteric modulator neuroactive steroids, such as allopregnanolone, also potentiate synaptic $GABA_A$ receptors, but in addition they enhance extrasynaptic $GABA_A$ receptors that mediate tonic inhibition. Extrasynaptic $GABA_A$ receptors are not internalized and desensitization of these receptors does not occur during continuous seizures in status epilepticus models. Here we review the broad-spectrum antiseizure activity of allopregnanolone in animal seizure models and the evidence for its activity in models of status epilepticus. We also demonstrate that allopregnanolone inhibits ongoing behavioral and electrographic seizures in a model of status epilepticus, even when there is benzodiazepine resistance. Parenteral allopregnanolone may provide an improved treatment for refractory status epilepticus.

Epilepsia, 54(Suppl. 6):93–98, 2013
doi: 10.1111/epi.12289

STATUS EPILEPTICUS 2013

Neuroactive steroids for the treatment of status epilepticus

*Michael A. Rogawski, †Carlos M. Loya, †Kiran Reddy, *Dorota Zolkowska, and *Christoph Lossin

*Department of Neurology, School of Medicine, University of California, Davis, Sacramento, California, U.S.A.; and †Sage Therapeutics, Cambridge, Massachusetts, U.S.A.

-Allopregnanolone :GABAA receptor PAM neurosteroid.

-Over, adrenal bez ve beyinde sentezlenir.

A Study With SAGE-547 for Super-Refractory Status Epilepticus

This study is currently recruiting participants. (see Contacts and Locations)

Verified March 2016 by Sage Therapeutics

Sponsor:
Sage Therapeutics

Information provided by (Responsible Party):
Sage Therapeutics

ClinicalTrials.gov Identifier:
NCT02477618

First received: June 2, 2015
Last updated: March 30, 2016
Last verified: March 2016
History of Changes

Purpose

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in Super-Refractory **Status Epilepticus** (SRSE).

TREATMENT OF REFRACTORY STATUS EPILEPTICUS

Table 1: Medications and Dosages for Treatment of Acute Repetitive Seizures and Status Epilepticus

	Agent	Load	Maintenance
Home Management	Lorazepam	Oral: 1-2 mg, may repeat x1 (adult)	
		Buccal: 2 mg/ml, 1-2 ml (adult)	
	Diazepam	Rectal: 20 mg (adult), 0.2-0.5 mg/kg (peds)	
EMS/ED	Lorazepam	Up to 0.1 mg/kg IV	
	Diazepam	10-20 mg IV (adult)	
	Midazolam	10 mg IM (adult) 0.2 mg/kg (peds)	
Initial AED	Fosphenytoin	20 mg/kg PE IV	5 mg/kg/ day
	Valproate	20-40 mg/kg IV	30 mg/kg/day
Refractory SE – First line	Midazolam	0.2 mg/kg	0.1-2.5 mg/kg/hr
	Propofol	1-2 mg/kg	20-200 ug/kg/min
	Pentobarbital	5-15 mg/kg	0.5-5 mg/kg/hr
Refractory SE – Second Line	Ketamine	1.5 -4.5 mg/kg	1 mg/kg/hr
	Levetiracetam	2000 mg IV (adult)	3000-4000 mg/day (adult)
	Lacosamide	200-400 mg IV (adult)	400-600 mg/day (adult)
	Phenobarbital	20 mg/kg IV	1-3 mg/kg/day

Seizure 31 (2015) 41–48

Contents lists available at ScienceDirect

- Lidokain sınıf 1b antiaritmik ve lokal anestezik ajan

-Na kanal antagonisti

-Neonatal SE tedavisinde pediatrik literatürde

-Fenitoin kullanımı olan hastalarda da etkinlik(+), ilacın

5. Conclusions

There currently exists level 4, GRADE C evidence to support the consideration of lidocaine for SE and RSE in the adult population. This constitutes weak evidence to support the use of lidocaine in this context. Further prospective studies of lidocaine administration in this setting are warranted.

RSE ve SRSE TEDAVİ ALGORİTMASI ÖNERİLERİ

- Üçüncü basamak tedaviler
  - EKT
  - BOS drenajı
  - Vagal sinir stimulasyonu
  - Transmanyetik stimulasyon
  - Derin beyin stimulasyonu(caudal zona incerta)

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Review

Electroconvulsive therapy for refractory status epilepticus: A systematic review

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5. Conclusions

Oxford level 4, GRADE D evidence exists to suggest an improvement in seizure control with ECT application for RSE. Routine use of ECT cannot be recommended at this time. Further prospective study of this therapy is required in order to determine its efficacy in this setting.

J Neurol (2006) 253 : 1100–1101
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CSF-ai
for ph
status

- **25 ml BOS alınıp yerine 70 ml hava verilmesi**
- **Prosedür sonrası RSE sonlanıp, geçici iyilik süresinin ardından 1 hasta gibi sürede nbt sıklığı artmış**
- **Prosedürün tekrarlanması nbt kontrolü sağlamamış.**

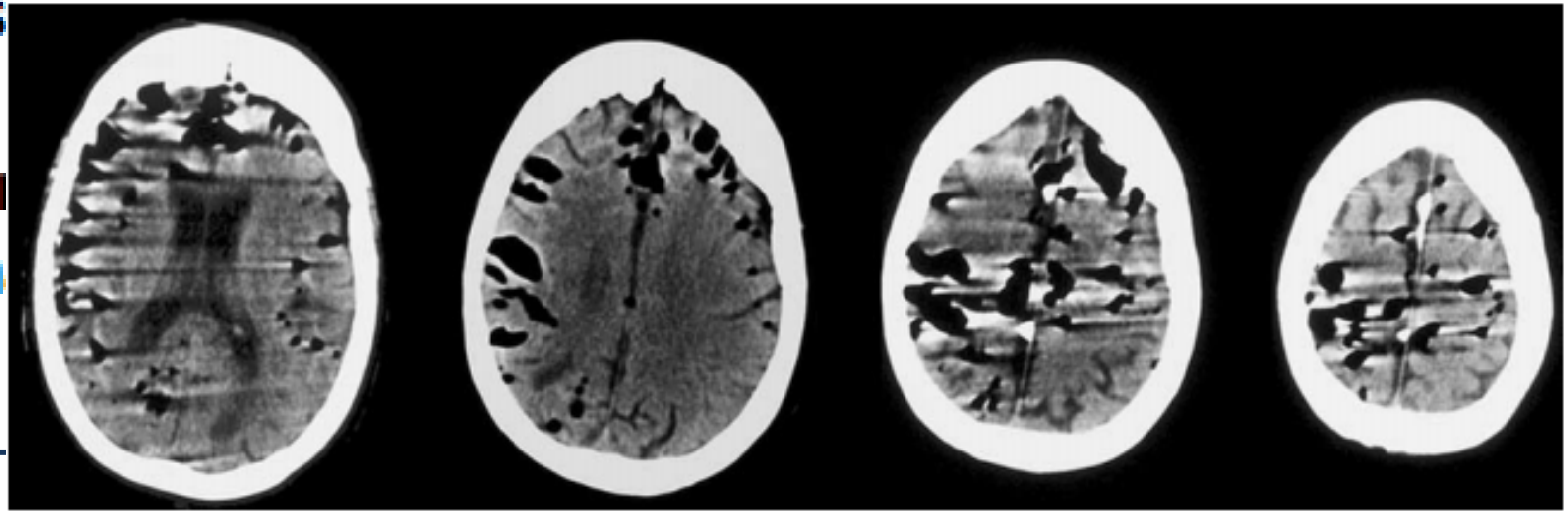

Fig. 1 CT-scan after the replacement of 25 ml of CSF with 70 ml of air

Epilepsy Research (2015) 112, 100–113

- **VNS Lennox—Gestaut syndrome level C evidence**
- **VNS vagal sinir C lifleri ile diffüz EEG değişiklikleri oluşturur, hipokampal artmış teta aktivitesi oç.**

Conclusions

We currently cannot recommend the use of VNS for RSE. There currently exists Oxford level 4, GRADE D evidence to suggest improvement in seizure control with the use of

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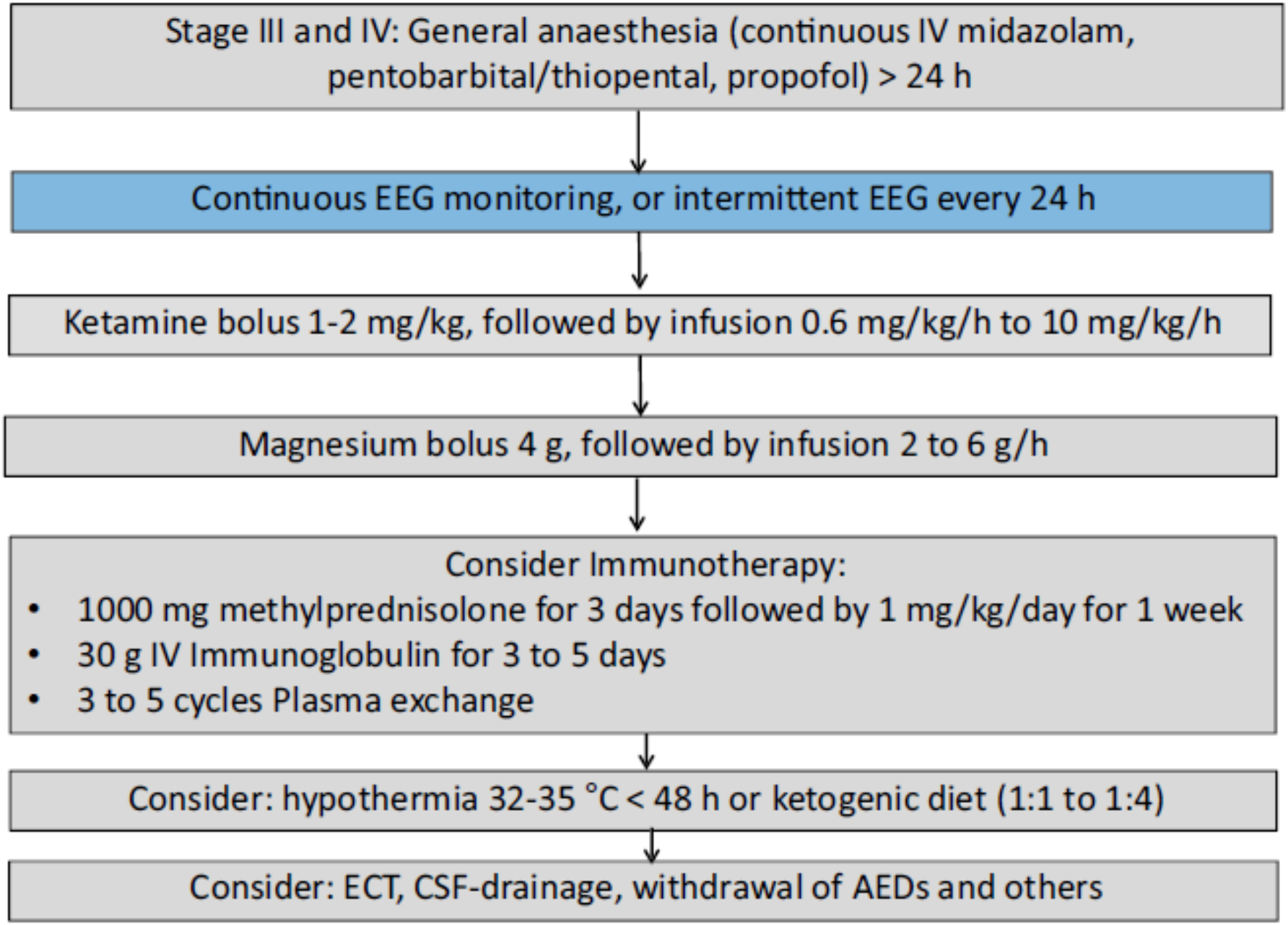
- **Nbt kontrolündeki gerçek etki mekanizması ?**
- **Nbt kontrolünde uzun dönemde etkisi;**

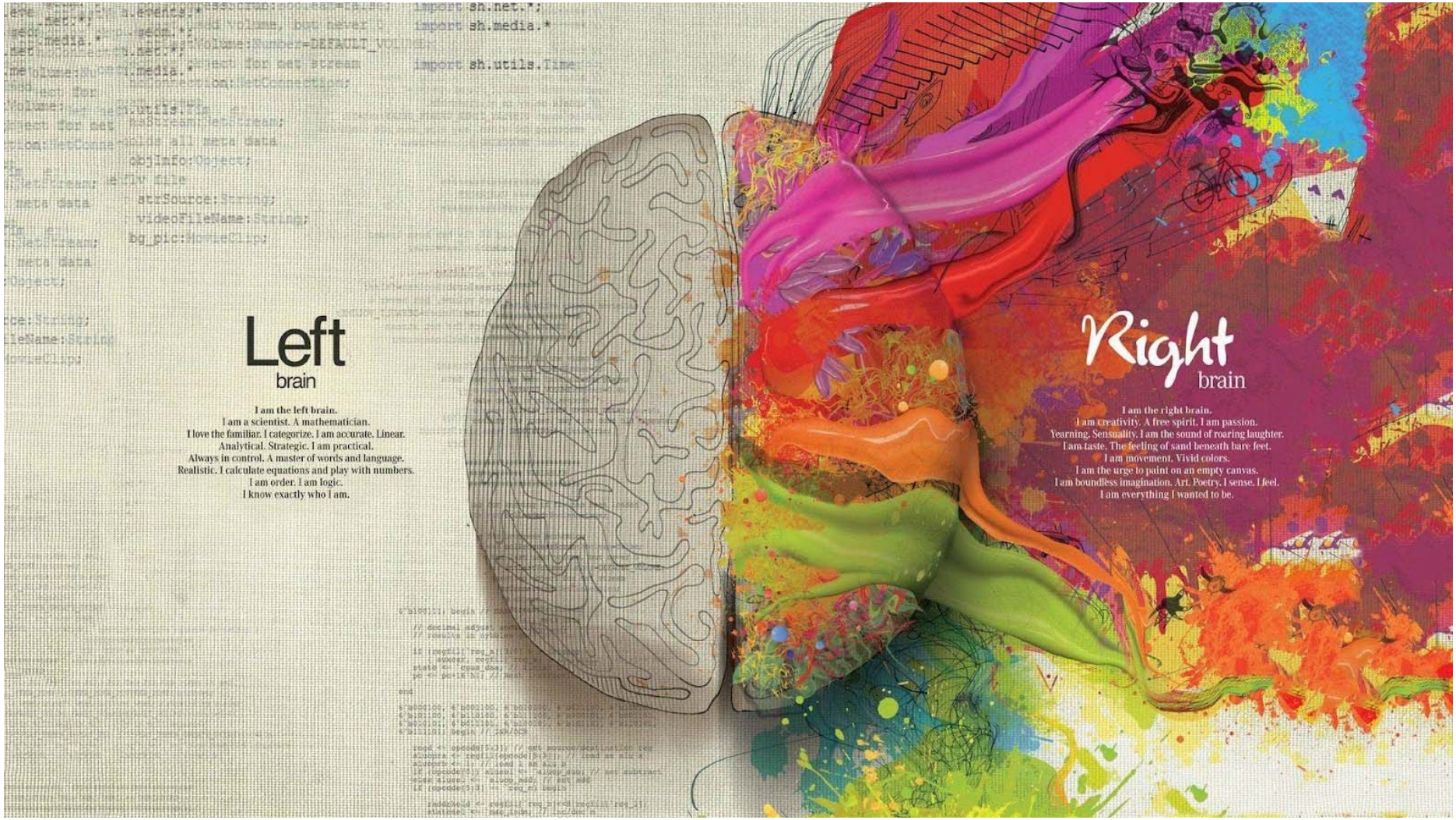
  kortikal eksitabilitede uzun süreli depresyon

5. Conclusions

Oxford level 4, GRADE D evidence exists to suggest a potential impact on seizure control with the use of rTMS for FSE and FRSE, though durability of the therapy is short-lived. Routine use of rTMS in this context cannot be recommended at this time. Further prospective study of this intervention is


Stage III and IV: General anaesthesia (continuous IV midazolam, pentobarbital/thiopental, propofol) > 24 h
Continuous EEG monitoring, or intermittent EEG every 24 h
Ketamine bolus 1-2 mg/kg, followed by infusion 0.6 mg/kg/h to 10 mg/kg/h
Magnesium bolus 4 g, followed by infusion 2 to 6 g/h
Consider Immunotherapy:
• 1000 mg methylprednisolone for 3 days followed by 1 mg/kg/day for 1 week
• 30 g IV Immunoglobulin for 3 to 5 days
• 3 to 5 cycles Plasma exchange
Consider: hypothermia 32-35 °C < 48 h or ketogenic diet (1:1 to 1:4)
Consider: ECT, CSF-drainage, withdrawal of AEDs and others

- Genel Anestezi(Midazolam, Tiopental, propofol sürekli infüzyonu) cEEG ya da 24 saat içinde aralıklı EEG
- Ketamin bolus 1-2mg/kg, ardından infüzyon 0.5-10mg/kg/saat
- İmmunoterapi(pulse kortizon, IVIG, TPE)
- Hipotermi(31-35’C) veya ketojenik diet
- Magnesyum bolus 4g, infüzyon 2-6 g/saat
- EKT, BOS drenajı, AED tedavinin gözden geçirilmesi



TEŞEKKÜRLER