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ORIGINAL RESEARCH ARTICLE

Intravenous Corticosteroids as an Adjunctive Treatment for Refractory and Super-Refractory Status Epilepticus: An Observational Cohort Study

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Abstract

Introduction Status epilepticus (SE) represents a neurological emergency that leads to considerable morbidity and mortality. Following failure of first-line therapy, usually with benzodiazepines, there is no clear evidence to guide treatment of refractory SE, although a wide variety of approaches has been described anecdotally.

Objective The aim of this study was to assess the clinical response to corticosteroids in adults with refractory and super-refractory SE, describing, to the best of our knowledge, the first adult SE cohort treated with corticosteroids.

Methods We retrospectively analysed our adult SE registry (2006–2017), identifying 15 out of 987 episodes (1.5%) in which corticosteroids were prescribed de novo as adjuvant therapy to a variety of antiepileptic drug regimens. We analysed incident episodes and defined clinical response as SE ceasing within 1 week of administration, without any other medical intervention.

Results Out of 987 SE episodes, 15 (1.5%) were treated with de novo corticosteroids, corresponding to 12 patients, with increasing prevalence as the SE became refractory (10/411; 2.4% of episodes) and super-refractory (5/108; 4.6% of episodes). One patient (a woman with Rasmussen encephalitis) presented with four SE episodes over a period of 3 years, so only her index SE episode was included in subsequent analyses. The episodes treated were predominantly of inflammatory origin (6/12), such as autoimmune or Rasmussen encephalitis. In five out of 12 (42%) of the considered incident episodes, SE resolved following corticosteroids (all within 3 days). The outcome was better in this responders group (for 2/5 episodes, patients did not have a new handicap at discharge, versus 0/7 in non-responders). In patients with inflammatory and acute symptomatic causes, global prognosis was better than in those with progressive or neurodegenerative aetiologies (6/8 vs. 4/4 had a new handicap at discharge or died).

Conclusions Our observations seem to support the use of corticosteroids, especially for acute SE of putative inflammatory origin; these compounds, however, were prescribed infrequently.

Key Points

There is no evidence guiding therapy in refractory status epilepticus (SE).

Despite current recommendations, corticosteroids are infrequently used, and have moderate efficacy.

Corticosteroids seem somewhat better in acute SE of putative inflammatory origin.

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1 Introduction

Status epilepticus (SE) represents a neurological emergency potentially leading to considerable morbidity and mortality [1]. Up to 33% of patients will not respond to first- and second-line therapy, thus fulfilling criteria of refractory SE (RSE), while in about 4% the seizure episode will persist after a first course of general anaesthesia, defining super-refractory SE (SRSE) [2, 3]. Following failure of first-line therapy, usually with benzodiazepines, there is no clear evidence to guide therapy in RSE and SRSE [4]. Several approaches have been described anecdotally, including multiple anticonvulsants, magnesium, ketogenic diet, vagus nerve stimulation, electroconvulsive therapy, transcranial brain stimulation, emergency neurosurgery, and corticosteroids, all with very weak evidence [4].

The recent recognition of autoimmune aetiologies in epilepsy and SE, and the observation that those patients tend to respond better to immunomodulatory therapies than to anticonvulsants [5, 6], seems to justify the prescription of immunomodulators in this setting. Immunomodulation is also interesting in the light of experimental observations of immunological mechanisms supporting epileptogenesis [7]. In the literature, however, corticosteroids have mostly been described in paediatric populations with refractory epilepsy, especially in the setting of West syndrome [8–10], while scarce observational data exist for SE in adults, with about 50 cases reported so far, in a general review of SRSE (obviously lacking details on the patients) [3] or in a previous report from our group completed 4 years ago, but focusing on diagnosis rather than on treatment [6]. Therefore, we aimed to assess the clinical response to corticosteroids in adults with RSE and SRSE, describing, to the best of our knowledge, the first adult SE cohort treated with corticosteroids.

2 Methods

2.1 Patients

In this cohort study, we retrospectively analysed our prospective adult SE registry [2, 11], focusing on the period between April 2006 and October 2017. Consultant neurologists established clinical SE diagnosis, defined as a continuous seizure that lasts 5 min or more; electroencephalogram (EEG) confirmation was required for non-convulsive SE forms, defined as a change in behaviour and/or mental processes from baseline associated with continuous (> 30 min) epileptiform discharges in the EEG. Post-anoxic SE was not included in view of the particularly poor prognosis. We restricted our analysis to patients for whom corticosteroids were prescribed de novo as adjuvant therapy to treat SE, not considering subjects already on corticosteroids or other chronic immunomodulatory treatment for other medical reasons (e.g. pre-existent autoimmune diseases, brain tumours). Inflammatory origin was defined as proven autoimmune, paraneoplastic or post-infectious aetiology with no concurrent infection or as chronic inflammatory disorders involving the brain, such as Rasmussen encephalitis.

2.2 Variables

Clinical variables, such as sex, age at SE onset, worst seizure type, SE aetiology, SE severity (summarized with the previously validated Status Epilepticus Severity Score (STESS) [12]), antiepileptic drugs (AEDs), timing, dose and duration of steroid therapy, SE control (see below) and outcome (mortality or new handicap at hospital discharge) were analysed from prospectively collected data. For the purpose of this study, we interpreted the response to treatment as probable if resolution of SE occurred within 1 week of administration, in analogy with neuroinflammatory conditions of the nervous system (like optic neuritis), without need of further AED escalation. The need for further AEDs was considered as an indication of no response. The primary outcome was SE cessation as an effect of steroid therapy. Secondary outcomes were mortality or new handicap at hospital discharge.

Given the relatively limited cohort size, without an identifiable control group, statistical analysis was performed using a descriptive approach using SPSS Statistics® (version 05-2017) and Excel software. We analysed the incident episodes identified in our search.

3 Results

Out of 987 SE episodes, 15 (1.5%) were treated with de novo corticosteroids, corresponding to 12 patients, with increasing prevalence as the SE became refractory (10/411; 2.4% of episodes) and super-refractory (5/108; 4.6% of episodes) (Table 1). One patient (a woman with Rasmussen encephalitis) presented with four SE episodes over a period of 3 years. The other causes of SE episodes treated with corticosteroids were also predominantly inflammatory (50% of all episodes), while acute brain lesions (stroke, post-operative scar of abscess drainage), neurodegenerative diseases (Creutzfeldt Jacob disease, vascular dementia) and episodes of unknown origin were evenly distributed for the remaining episodes. No episode of infectious aetiology treated de novo by corticosteroids was identified. Clinical characteristics of the SE episodes treated with corticosteroids are summarized in Table 2.

In all patients, intravenous methylprednisolone was prescribed, with marked heterogeneity in dosages, varying from 125 mg twice daily to 1000 mg daily for 5 days, with or without subsequent oral prednisone tapering. Time between SE onset and steroid initiation showed a median delay of 9 days (ranging between 1 and 31 days). With the exception of the patient with Rasmussen encephalitis, recurrently admitted for focal SE and receiving corticosteroids as second treatment line, in all of the other cases, corticosteroids were administered after several AED lines in patients with non-convulsive SE, following exclusion of infections (sixth median line of treatment, with a timing of treatment induction varying from the first to the 17th day of SE). Seizure type (focal or generalized) as well as STESS score were evenly distributed.

Table 1 Demographics of 15 SE episodes treated with corticosteroids divided into probable responders and non-responders. Four SE episodes refer to the same patient; thus only 12 index episodes are analysed

	Total index episodes	Probable responders	Non-responders
SE episodes (*n*)	12	5	7
RSE episodes (*n*)	7	4	3
SRSE episodes (*n*)	5	1	4
Age (years) (median, range)	47 (20–90)	59 (45–79)	47 (20–90)
Female gender (*n*)	7	2	5
Aetiology			
Inflammatory	6	3	3
Other (neurodegenerative, acute lesion, unknown, etc.)	6	2	4
Seizure type			
Generalized	8	2	6
Focal (with or without consciousness impairment)	4	3	1
STESS ≥ 3 (*n*)	9	3	6
Outcome			
Return to baseline	2	2	0
New handicap	8	3	5
Death	2	0	2

STESS score (0–2 related to favourable outcome, 3–6 unfavourable)

n number, *RSE* refractory SE, *SE* status epilepticus, *SRSE* super-refractory SE, *STESS* Status Epilepticus Severity Score

Because a single patient with Rasmussen encephalitis had four SE episodes in our cohort, we censored her data in further analyses, including only the index SE episode for each patient ($n = 12$). In five out of 12 of the incident episodes (42%), SE resolved within 3 days of corticosteroid administration (without any further AED: probable responders), regardless of the regimen modalities (methylprednisolone 500 or 1000 mg intravenously for 3 or 5 days). Three of these five responding episodes where of inflammatory origin, while the other two were related to acute brain lesions previously treated unsuccessfully with multiple lines of AEDs.

Among the remaining seven incident episodes (58%), in whom SE did not resolve within a week of corticosteroid administration (non-responders), in five, further AEDs were prescribed thereafter. Within this subgroup, three were clearly non-responders, while the other two received an adjuvant AED within a week from the immunomodulatory treatment and had their SE resolved within that week.

The median duration of SE after corticosteroid treatment in non-responders was 48 days (range 6–150 days) versus 2 days (1–3 days) in responders. Two subjects with progressive symptomatic SE (prion disease, vascular dementia) died in SE (17%). The outcome was better in this responders group (for 2/5 episodes, patients did not have a new handicap at discharge, versus 0/7 in non-responders). In patients with inflammatory and acute symptomatic causes, global prognosis was better than in those with progressive or neurodegenerative aetiologies (6/8 vs. 4/4 had a new handicap at discharge or died).

4 Discussion

In this observational study of adult SE, only 1.5% of episodes were treated with corticosteroids as adjuvant therapy, with a somewhat increasing prevalence as SE became refractory and super-refractory. This was associated with probable SE resolution in 42% of the treated patients, within a few days of administration. Although our observations are in agreement with what we know from paediatric studies on refractory epilepsy treated with corticosteroids (seizure reduction in up to 43%), one should bear in mind the inherent differences in brain development and aetiologies of SE in paediatric patients [8].

Conventional AED treatment is known to become less effective as the SE episode becomes more protracted (seizure control up to 55.5% with first administered therapy, while the second and third drug only have an extra 7.0% and 2.3% success rate, respectively) [13]; it is thus important to have a rationale for the use of alternative treatments. Responders in the present study had SE predominantly of inflammatory origin, while in progressive diseases, the SE course does not seem to have been modified. This observation may be related to inherent antiepileptic properties of corticosteroids, but be also indicative of the necessity to specifically treat the underlying condition [14]. The exact antiepileptic mechanism of corticosteroids is unknown, but several observations based on pilocarpine-induced rat models of SE suggest inhibition of corticotropic-releasing hormone peptide (CRH) expression in the temporal lobe, changes in serotonin turnover or γ-aminobutyric acid (GABA) uptake, and exertion of influence on voltage-dependent calcium channels [3, 10, 15]. Furthermore, animals treated with dexamethasone present fewer seizures and a decreased mortality [10]. Corticosteroids may also, at least in part, counteract inflammation, which can enhance epileptogenesis [7].

The present series highlights the variability in treatment initiation and the absence of a uniform administration protocol, reflecting major individual factors in the decision to treat. While methylprednisolone 1 g daily for 3 days followed by tapering has been recommended on the basis of case reports and small series [14], in our cohort,

Table 2 Detailed description of the 15 episodes of refractory and super-refractory SE treated with corticosteroids in 12 patients

Episode	Sex	Age	Diagnosis	Worst Sz type	AED	Corticosteroid regimen	Treatment line of corticosteroids	Corticosteroid intro (days)	Need for other AED	SE resolution (days)	STESS score	Handicap at discharge
1	F	25	NMDA encephalitis	GC	CLZ, LEV, CBZ, PHT	Methylprednisolone IV 500 mg 3×/day for 3 days then oral tapering	5th	15	TPM, PRO, KET, MDZ, VPA, PHB, PGB, LCM	77	2	1
2	M	79	Autoimmune encephalitis	SP	CLZ, LEV, LCM	Methylprednisolone IV 1 g/day for 5 days	4th	2	0	3	3	1
3	M	46	Post-infectious encephalitis	GC	CLZ, LEV, LCM, VPA, PRO, MDZ, PHT, THP, PGB	Methylprednisolone IV 1 g 3×/day for 3 days then oral tapering	11th	5	KET	12	4	1
4	M	59	SREAT	SP	OXC, LEV, VPA, PGB	Methylprednisolone IV 1 g 3×/day for 3 days then oral tapering	5th	3	0	4	0	0
5	F	44	Rasmussen encephalitis	SP	VNS, CLZ, LEV, PGB, LTG, LCM	Methylprednisolone IV 500 mg/day for 3 days	3rd	6	0	8	0	0
6	F	45	Rasmussen encephalitis	SP	VNS, CLZ, LEV, CLBZ, LTG, LCM	Methylprednisolone IV 1 g 3×/day for 3 days then oral tapering	6th	5	PGB	11	0	1
7	F	47	Rasmussen encephalitis	SP	VNS, CLZ, LEV, PGB, LCM	Methylprednisolone IV 500 mg/day for 3 days then oral tapering	2nd	8	PER	19	0	0
8	F	47	Rasmussen encephalitis	SP	VNS, CLZ, PGB, PER, LCM	Methylprednisolone IV 500 mg/day for 3 days then oral tapering	2nd	6	0	18	0	0
9	F	90	Creutzfeldt-Jacob disease	GC	CLZ, VPA, LEV, LCM, PGB	Methylprednisolone IV 500 mg/day for 3 days	6th	3	0	None	5	2

Table 2 (continued)

Episode	Sex	Age	Diagnosis	Worst Sz type	AED	Corticosteroid regimen	Treatment line of corticosteroids	Corticosteroid intro (days)	Need for other AED	SE resolution (days)	STESS score	Handicap at discharge
10	M	74	Acute stroke	GC	CLZ, LEV, PHT, LCM, PGB, TPM	Methylprednisolone IV 500 mg/day for 3 days then oral tapering	7th	13	0	15	5	1
11	F	76	Vascular dementia	PC	CLZ, VPA, LEV, LCM, PGB	Methylprednisolone IV 800 mg/day for 5 days	6th	17	PHT	None	3	2
12	F	55	Acute brain lesion (abscess)	GC	CLZ, LEV, LCM, VPA, PRO, MDZ, PER, PHT, KET, surgical resection	Methylprednisolone IV 1 g 3×/day for 3 days then oral tapering	10th	1	0	4	3	1
13	F	76	Post-infectious encephalitis	GC	CLZ, VPA, LEV, MDZ, PRO, PHT, LCM, TPM	Methylprednisolone IV 1 g 3×/day for 3 days then oral tapering	7th	12	0	25	5	1
14	F	20	Unknown	GC	CLZ, CLBZ, PHT, LEV, VPA, PRO, THP, ZNS, TPM	Methylprednisolone IV 125 mg 2×/day for 5 days	10th	5	PGB, KET	155	3	1
15	M	29	Unknown	GC	CLZ, VPA, MDZ, PRO, LEV, LCM, KET, THP, TPM	Methylprednisolone IV 1 g 3×/day for 3 days then oral tapering	10th	9	Ketogenic diet, PGB, PGB, PMT	16	3	1

STESS score (0–2 related to favourable outcome, 3–6 unfavourable)

Functional outcome at discharge: 0 for return in baseline, 1 for new handicap, 2 for death

Worst seizure type: *GC* generalized convulsive, *SP* focal without cognitive impairment, *PC* focal with cognitive impairment

AED antiepileptic drug, *CBZ* carbamazepine, *CLBZ* clobazam, *CLZ* clonazepam, *F* female, *IV* intravenously, *KET* ketamine, *LCM* lacosamide, *LEV* levetiracetam, *LTG* lamotrigine, *M* Male, *MDZ* midazolam, *OXC* oxcarbamazepine, *NMDA encephalitis* N-methyl-D-aspartate receptor antibody encephalitis, *PER* perampanel, *PGB* pregabalin, *PHB* phenobarbital, *PHT* phenytoin, *PMT* primidone, *PRO* propofol, *SE* status epilepticus, *SREAT* steroid-responsive encephalopathy associated with autoimmune thyroiditis, *STESS* Status Epilepticus Severity Score, *Sz* seizure, *THP* thiopental, *TPM* topiramate, *VNS* Vagus Nerve Stimulation, *VPA* valproic acid, *ZNS* zonisamide

the functional outcome in the responders group did not seem to differ between the smaller (500 mg) versus higher (1000 mg) doses. Seizure control was achieved rather shortly after steroid initiation (actually, within 3 days) in responders, apparently independently of the time to treatment.

New handicap at discharge was observed in 83.3% (incident episodes), although this might also reflect a more severe medical condition, and mortality occurred in 17% (patients), which correlates with figures reported in RSE and SRSE populations [1, 2].

This study has limitations. It is a retrospective analysis, and we cannot formally exclude underascertainment; however, in view of the uniform structure of the registry (which has been run by the same epileptologists since the beginning), this seems unlikely. We did not use a control group, given the difficulty in identifying a suitable profile in view of the marked heterogeneity of the described episodes. Corticosteroids were always administered with a combination of concomitant AEDs, and the steroid regimen was not adjusted to bodyweight, due to its unavailability in each case. The limited size of the sample prevents statistical analyses related to steroid efficacy. In view of what precedes, only associations and not causation can be inferred.

5 Conclusions

Corticosteroids seem currently to be applied infrequently in SE, with a moderate impact on prognosis. They should be considered in the treatment of SE of putative inflammatory origin, presenting as acute onset.

Compliance with Ethical Standards

Funding No funding was received for this study.

Conflict of interest Dr. Pantazou, Prof. Rossetti and Dr. Novy have no conflicts of interest to declare.

Ethical approval Our SE registry is approved by the local ethics commission.

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