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RESEARCH ARTICLE

Early timing of anesthesia in status epilepticus is associated with complete recovery: A 7-year retrospective two-center study

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Abstract

Objective: This study was undertaken to investigate the efficacy, tolerability, and outcome of different timing of anesthesia in adult patients with status epilepticus (SE).

Methods: Patients with anesthesia for SE from 2015 to 2021 at two Swiss academic medical centers were categorized as anesthetized as recommended third-line treatment, earlier (as first- or second-line treatment), and delayed (later as third-line treatment). Associations between timing of anesthesia and in-hospital outcomes were estimated by logistic regression.

Results: Of 762 patients, 246 received anesthesia; 21% were anesthetized as recommended, 55% earlier, and 24% delayed. Propofol was preferably used for earlier (86% vs. 55.5% for recommended/delayed anesthesia) and midazolam for later anesthesia (17.2% vs. 15.9% for earlier anesthesia). Earlier anesthesia was statistically significantly associated with fewer infections (17% vs. 32.7%), shorter median SE duration (.5 vs. 1.5 days), and more returns to premorbid neurologic function (52.9% vs. 35.5%). Multivariable analyses revealed decreasing odds for return to premorbid function with every additional nonanesthetic antiseizure medication given prior to anesthesia (odds ratio [OR] = .71, 95% confidence interval [CI] = .53–.94) independent of confounders. Subgroup analyses revealed decreased odds for return to premorbid function with increasing delay of anesthesia independent of the Status Epilepticus Severity Score (STESS; STESS = 1-2: OR = .45, 95% CI = .27–.74; STESS > 2: OR = .53, 95% CI = .34–.85), especially in patients without potentially fatal etiology (OR = .5, 95% CI = .35–.73) and in patients experiencing motor symptoms (OR = .67, 95% CI = .48–.93).

Pia De Stefano and Sira M. Baumann contributed equally as first authors.

Significance: In this SE cohort, anesthetics were administered as recommended third-line therapy in only every fifth patient and earlier in every second. Increasing delay of anesthesia was associated with decreased odds for return to premorbid function, especially in patients with motor symptoms and no potentially fatal etiology.

KEYWORDS
anesthesia, intensive care, neurocritical care, recovery, status epilepticus

1 | INTRODUCTION

Most patients with status epilepticus (SE) are treated in intensive care units (ICUs) due to the high case fatality rate.[1] International treatment guidelines recommend antiseizure treatment starting with benzodiazepines as first-line medication, followed by second-line antiseizure medication, such as levetiracetam, valproic acid, or phenytoin.[2–4] When SE is refractory to first- and second-line antiseizure drugs, treatment escalation with the induction of an artificial coma by continuously administered intravenous anesthetic drugs is recommended for 24–48 h with the aim of terminating seizures.[2–4] Although, at first glance, these recommendations seem justified, high-quality studies regarding the efficacy and tolerability of anesthesia at different stages of SE are scarce[5] and the induction of artificial coma has been associated with adverse effects,[6–10] complications during the course of SE[10,11] and the postictal phase,[12] and unfavorable outcomes in some studies.[10,11,13,14] This comes along with a large proportion of patients with SE in whom neither treatment start (with underdosing of benzodiazepines) nor escalation[15–17] adheres to the guidelines.[5,18]

Our research group demonstrated that early and direct coma induction after benzodiazepines was safe and efficacious in reducing SE length and in-hospital stay.[5] Given the limited cohort size of that study, deriving from a 2-year observation, we could not show an association with outcome of such procedure. Based on the current data deriving from the current larger cohort, we now aimed to investigate whether different timing of anesthesia in adult patients with SE was associated with better outcome and to identify specific patient subgroups who might benefit more or less from different timing of anesthesia.

Key Points

- Anesthetics were administered as recommended third-line therapy in only every fifth patient and earlier in every second
- Increasing delay of anesthesia was associated with decreased odds for return to premorbid function
- Early anesthesia was associated with better outcome, in particular in patients with motor symptoms and no potentially fatal etiology
- Early anesthesia was associated with shorter SE duration and fewer infections

2 | MATERIALS AND METHODS

2.1 | Research question and classification of level of evidence

The primary research question was to investigate the associations of the timing of anesthesia and short-term outcomes in adult patients with SE and specific patient subgroups. Our study provides class III evidence.

2.2 | Data assessment

This two-center observational cohort study was performed at the ICUs of two Swiss academic tertiary medical care centers, the University Hospital of Basel and the University Hospital of Geneva. The STROBE guidelines were followed to improve the quality of our study.[19]

Clinical data from all consecutive adult patients (i.e., ≥18 years of age) treated for SE from January 2015 to December 2021 in the two care centers were retrospectively assessed by two trained neurologists and epileptologists (P.D.S. and R.S.). Data from the Geneva University Hospital were collected in accordance with the data from the ongoing STEP UP (Status Epilepticus Unicenter Population) study (NCT04204863) at the University Hospital of Basel. Patients with SE following cardiorespiratory arrest (i.e., SE from hypoxic–ischemic encephalopathy) were excluded, as this etiology is associated with a high mortality independent of treatment.[20] Appendix S1 presents details regarding data assessment.

2.3 | Duration and types of SE

As previously described in our studies,[5,12,21] and according to the recent guidelines,[2] convulsive SE was defined as evidence of epileptic seizures lasting ≥5 min clinically, and all other types of SE as evidence of clinical symptoms or as detected by electroencephalography (EEG) lasting at least 10 min. Types of SE were assessed from the digital EEG databases. If EEG reports were not informative or not available, prehospital emergency medical service reports were consulted. SE was categorized into the following predefined types as recommended by the current guidelines of the International League Against Epilepsy (ILAE)[22]: focal nonconvulsive without coma (with or without altered consciousness and absences), with motor symptoms (myoclonic and convulsive), and nonconvulsive with coma.

SE duration was defined as the time period between the diagnosis of SE and the clinical and/or EEG evidence of seizure termination, as previously described.[17,23] Monitoring SE patients by either continuous EEG or spot EEG for ≥30 min every 12 h at both medical care centers leads to an approximation with a maximum inaccuracy of 12 h.

2.4 | Detailed assessment of the timing of anesthesia

The timing of administration of continuous anesthetic drugs, including propofol, midazolam, their combinations, phenobarbital, and thiopental, was noted in relation to the administration of nonanesthetic antiseizure medication (e.g., as first-, second-, third-, fourth-, or fifth-line treatment). This approach was chosen because the exact time of onset of SE in patients with unnoticed seizure onset is usually unknown, a limitation that cannot be overcome even in prospective studies. Patients were then categorized into three groups. The first group consisted of patients receiving anesthetics as recommended third-line treatment,[2,3] the second of patients treated with anesthetics earlier than third-line treatment (i.e., as first- or second-line treatment), and the third group of patients in whom anesthesia was delayed (i.e., as fourth- or fifth-line treatment).

2.5 | Outcomes

The primary endpoints were return to premorbid neurologic function at hospital discharge and in-hospital death. The timing of anesthesia in relation to administration of nonanesthetic antiseizure drugs, the emergence of complications during SE, and the duration of specific treatment measures (i.e., anesthesia, mechanical ventilation, and ICU and hospital stay) were considered secondary endpoints.

2.6 | Statistics

Patients were categorized into patients receiving anesthetics as recommended third-line treatment,[2–4] patients treated with anesthetics earlier than third-line (i.e., as first- or second-line) treatment, and patients in whom anesthesia was delayed (i.e., as fourth- or fifth-line treatment). Univariable comparisons of these three groups were performed by the Kruskal–Wallis test for continuous variables and by the χ^2 test or the Fisher exact test for categorical variables. To identify potential confounders for the associations with primary endpoints (outcomes), univariable comparisons between patients with and without these endpoints were performed using the Mann–Whitney *U*-test for continuous variables and the χ^2 test or the Fisher exact test for categorical variables. Subsequently, uni- and multivariable logistic regression models were performed to identify independent associations between the timing of anesthesia and other variables found to differ significantly among the groups defined above. The Hosmer–Lemeshow χ^2 goodness-of-fit tests were performed for multivariable logistic regression models, which provide summary measures of calibration based upon a comparison of observed and estimated outcomes.[24] We performed sensitivity analyses by further correcting the multivariable logistic regression model for each participating center and after excluding patients with care withdrawal. Finally, subgroup analyses were performed using logistic regression to assess the association of early anesthesia with the primary endpoints.

Two-sided *p*-values ≤ .05 were considered significant. Statistical analysis was performed with Stata 16.1 (StataCorp).

2.7 | Standard protocol approvals, registrations, and patient consents

The study protocol was reviewed and approved by the local ethics committees (Ethikkommission Nordwest- und Zentralschweiz 2019–00693 for Basel and CCER 2019–00836 for Geneva), and patients' consent was waived in compliance with the Declaration of Helsinki first published in 1964 and its following amendments.

3 | RESULTS

3.1 | Baseline characteristics and univariable comparisons

Among 809 adult patients treated for SE (371 at the University Hospital Geneva and 474 at the University Hospital Basel), 83 patients with hypoxic–ischemic encephalopathy were excluded. Of the remaining 762 patients, 246 received anesthesia to treat SE (Figure 1A). Of those, 21% were anesthetized as recommended with anesthetics administered as third-line treatment, 55% were anesthetized earlier, and 24% of patients received delayed anesthesia. Figure 1B,C presents the timing of anesthesia in relation to the administration of nonanesthetic antiseizure medication in the total cohort and in the subgroup of patients with specific types of SE.

Univariable comparisons of demographics and clinical characteristics of the three groups are presented in Table 1. SE types differed among the groups ($p < .001$), with fewer patients with focal nonconvulsive SE (NCSE) without coma receiving early anesthesia. More patients with motor symptoms received anesthesia earlier than recommended or delayed anesthesia (2.9% vs. 18.2%, and 83.8% vs. 55.5%). Univariable comparisons of treatment, course, and in-hospital outcomes are outlined in Table 2. Administered anesthetic drugs differed among the three groups ($p < .001$); propofol was preferably used for earlier anesthesia (86% vs. 55.5% for recommended/delayed anesthesia), and midazolam was mainly administered with or without propofol for later anesthesia (17.2% vs. 15.9% for earlier anesthesia).

None of our patients received ketamine as a sedative drug. Univariable analyses further revealed that earlier anesthesia was associated with fewer infections (17% vs. 32.7%), a shorter median duration of SE (.5 vs. 1.5 days), and more frequent return to premorbid neurologic function at hospital discharge (52.9% vs. 35.5%) as compared to anesthesia as third-line treatment as recommended or delayed. Further characteristics differing between patients with and without return to premorbid neurologic function at discharge are presented in Table 3, revealing that patients with return to premorbid function were younger, suffered less often from potentially fatal

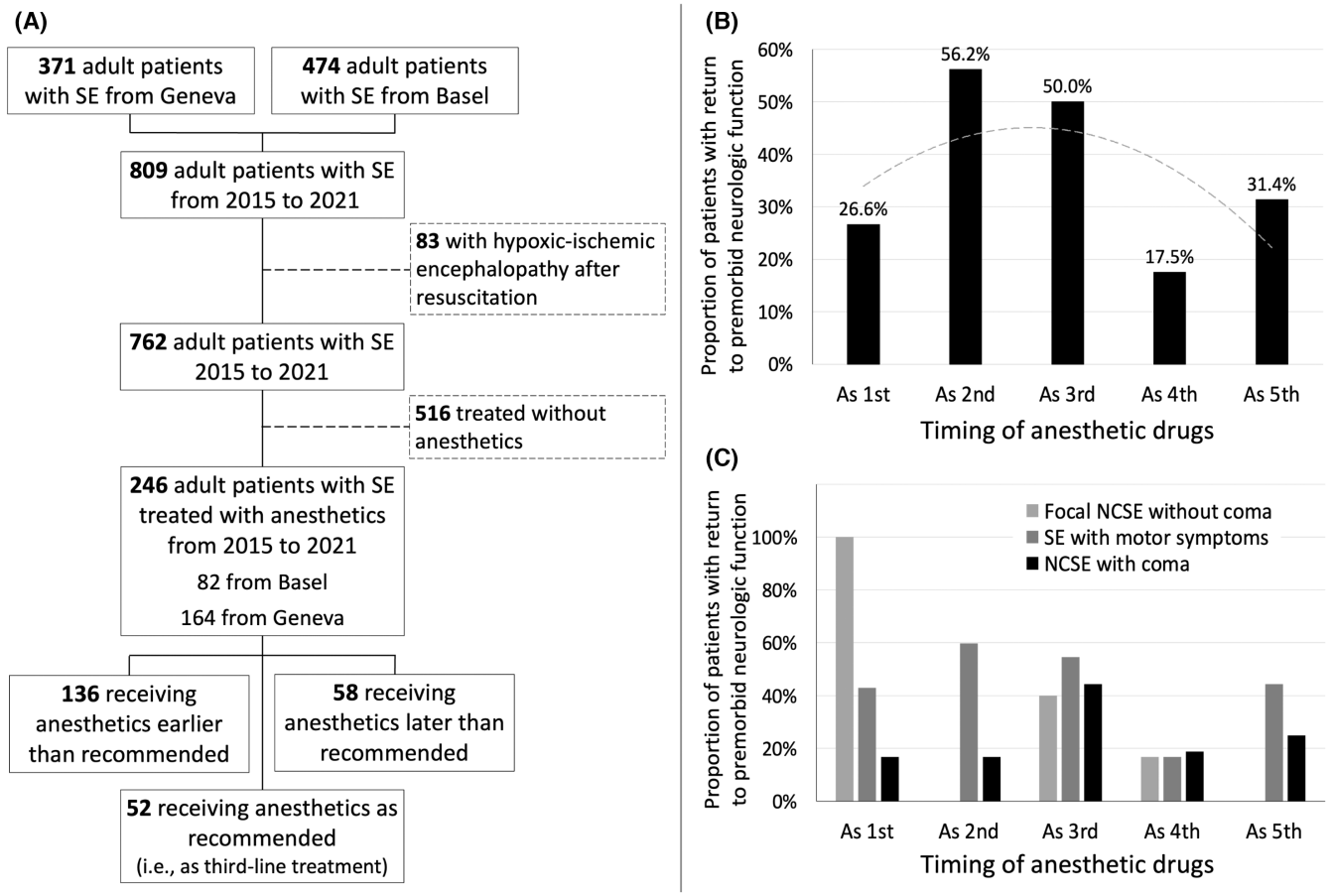

FIGURE 1 Flow chart (A) and proportion of patients with postictal return to premorbid neurologic function at hospital discharge and administration of anesthetics in relation to nonanesthetic antiseizure drugs in the total cohort (B) and categorized according to the type of status epilepticus (SE; C). NCSE, nonconvulsive SE.

TABLE 1 Univariable comparisons of demographics and clinical baseline characteristics of patients treated with anesthetics according to and not according to the guidelines ($n = 246$).

	Patients with anesthetics administered earlier than recommended, $n = 136$		Patients with anesthetics as third-line antiseizure treatment, $n = 52$		Patients with anesthetics administered later than recommended, $n = 58$		
Demographic and clinical characteristic	***n*/median**	**%/IQR**	***n*/median**	**%/IQR**	***n*/median**	**%/IQR**	***p***
Demographics							
Age, years, median, IQR	60	43–72	65	49–52	64	54–72	.227
Female, *n*, %	48	35.3	18	34.6	23	39.7	.817
GCS at SE onset, median, IQR	6	3–8	7	3–10	7	3–11	.070
SE etiology, *n*, %							
Potentially fatal etiology (not mutually exclusive)	31	22.8	16	30.8	15	25.9	.526
Acute intracranial hemorrhage	21	15.4	6	11.5	11	19.0	
Infectious (meningo-) encephalitis	5	3.7	4	7.7	5	8.6	
Acute severe traumatic brain injury	8	5.9	2	3.9	4	6.9	
Fast-growing brain tumors	12	8.8	5	9.6	6	10.3	
Acute ischemic stroke	5	3.7	1	1.9	1	1.7	
Acute autoimmune encephalitis	2	1.5	1	1.9	3	5.2	
No potentially fatal etiology	105	77.2	36	69.2	43	74.1	
Known epilepsy	50	36.8	17	22.7	24	41.4	
Unknown etiology	11	8.1	3	5.8	3	5.1	
SE type, *n*, %							
Focal NCSE without coma	4	2.9	10	19.2	10	17.2	**<.001**
With altered consciousness	3	2.2	8	15.4	7	12.1	
Without altered consciousness	1	.7	2	3.9	3	5.2	
SE with motor symptoms (convulsive or myoclonic)	114	83.8	33	63.5	28	48.3	**<.001**
Convulsive SE	104	76.5	30	57.7	16	27.6	
Myoclonic SE	10	7.4	3	5.8	12	20.7	
NCSE with coma	18	13.2	9	17.3	20	34.5	**.002**
NCSE with coma (nonsubtle)	14	10.3	6	11.5	11	19.0	
Subtle SE	4	2.9	3	5.8	11	19.0	

(Continues)

TABLE 1 (Continued)

Demographic and clinical characteristic	Patients with anesthetics administered earlier than recommended, $n=136$		Patients with anesthetics as third-line antiseizure treatment, $n=52$		Patients with anesthetics administered later than recommended, $n=58$		
	n/median	%/IQR	*n*/median	%/IQR	*n*/median	%/IQR	*p*
Illness severity, median, IQR							
STESS	3	2–4	3	2–4	3	1–4	.395
CCI	3	1–6	3	2–6	3	2–5	.604
SAPS II[a]	49	40–57	44	33–57	48	39–56	.398
APACHE II[a]	24	18–29	25	20-29	25	20–29	.314

Note: Bold font indicates statistical significance.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II (range 0–71); IQR, interquartile range[48]; GCS, Glasgow Outcome Score (range 3–15); SE, status epilepticus; NCSE, nonconvulsive status epilepticus[46]; SAPS II, Simplified Acute Physiology Score II (range 0–163)[47]; STESS, Status Epilepticus Severity Score (range 0–6)[44,45] Charlson Comorbidity Index (range 0–37).

[a]Data available in 174 patients (data incomplete for 72 patients).

etiologies, experienced NCSE more often, and had lower Status Epilepticus Severity Score (STESS) and Charlson Comorbidity Index scores.

3.2 | Multivariable logistic regression and subgroup analyses

Uni- and multivariable logistic regression analyses regarding the association between the timing of anesthesia and return to premorbid neurologic function at hospital discharge are presented in Table 4. Further analyses regarding the second primary endpoint (in-hospital death) were not performed due to the small sample sizes with this outcome. Multivariable analyses revealed decreasing odds for return to premorbid function with every additional nonanesthetic antiseizure drug given prior to anesthesia (i.e., with increasing delay of anesthesia) independent of confounders. The odds for the increasing delay of anesthetics remained decreased for no return to premorbid neurologic function at discharge after correcting the multivariable model for potential site bias (i.e., correcting the model for the participating medical care centers) and after excluding patients with care withdrawal (odds ratio [OR] = .71, 95% confidence interval [CI] = .51–.98, $p = .02$; with Hosmer–Lemeshow goodness-of-fit test remaining nonsignificant). After correcting our final model for the influence of the recent SARS-CoV-2 pandemic, the increasing delay of anesthesia remained associated with decreased odds for return to premorbid neurologic function (OR = .59, 95% CI = .40–.87, $p = .008$).

Subgroup analyses are presented in Figure 2, revealing decreased odds for return to premorbid function with increasing delay of anesthesia independent of the STESS in patients without potentially fatal etiology and in patients experiencing motor symptoms during SE.

Analyses for the subgroup of patients with SE with motor symptoms ($n=175$) revealed that the rank of administration delay of anesthetics (per increasing delay in relation to nonanesthetic antiseizure drugs) was associated with return to premorbid neurologic function in the univariable logistic regression analyses, with a decrease of odds for return to premorbid neurologic function with increasing delay of anesthetics (OR = .55, 95% CI = .37–.84, $p = .005$). This association remained significant after adjusting for the same potential confounders in the multivariable model, as in our previous multivariable analyses (Table 4; OR = .62, 95% CI = .39–1.00, $p = .050$).

Further subgroup analyses for patients with NCSE with coma ($n=47$) revealed that the rank of administration delay of anesthetics (per increasing delay in relation to nonanesthetic antiseizure drugs) was not associated with return to premorbid neurologic function in the univariable logistic regression analyses (OR per increasing delay in relation to nonanesthetic antiseizure drugs = 1.08, 95% CI = .51–2.30, $p = .838$). Multivariable analyses were not performed due to the limited sample size. For the same reason, subgroup analyses for patients with focal NCSE without coma ($n=24$) were not performed.

Additional subgroup analyses regarding patients with and without potentially fatal etiologies revealed that increasing administration delay of anesthesia was associated with decreased odds for return to premorbid neurologic function only in patients without fatal etiologies (without potentially fatal etiologies: univariable OR = .50, 95% CI = .35–.73, $p < .001$; multivariable adjusting for the confounders as in Table 4: OR = .58, 95% CI = .38–.89, $p = .012$; with potentially fatal etiologies: univariable OR = .66,

TABLE 2 Univariable comparisons of treatment characteristics, complications, and outcomes of patients treated with anesthetics according to and not according to the guidelines ($n = 246$).

Treatment characteristics, course, and outcomes	Patients with anesthetics administered earlier than recommended, $n = 136$		Patients with anesthetics as third-line antiseizure treatment, $n = 52$		Patients with anesthetics administered later than recommended, $n = 58$		
	n/median	%/IQR	*n*/median	%/IQR	*n*/median	%/IQR	*p*
Treatment characteristics							
In-hospital treatment, days, median, IQR	10	6–17	13	6–23	21	11–30	**<.001**
ICU treatment, days, median, IQR	3	2–5	4	2–8	10	4–17	**<.001**
Duration of mechanical ventilation, days, median, IQR	2	.5–3	2	2–6	6	2–12	**<.001**
Number of nonanesthetic antiseizure drugs, median, IQR	2	1–2	2	2–3	4	3–4	**<.001**
Anesthetics during SE, *n*, %							
Midazolam only	2	1.5	11	21.2	15	25.9	**<.001**
Propofol only	117	86.0	28	53.9	33	56.9	**<.001**
Midazolam and propofol	14	10.3	12	23.1	10	17.2	
Midazolam and/or propofol followed by barbiturates	3	2.2	1	1.9	0	.0	
Complications during SE, *n*, %							
Infections/sepsis	23	17.0	19	36.5	17	30.4	**.010**
Arterial hypotension requiring vasopressors	52	38.2	26	50.0	26	44.8	.311
Multiorgan failure	1	.7	0	.0	2	3.5	.253
SE duration, days, median, IQR	.5	.5–1	1	.5–2	2	1–4	**<.001**
SE duration (after excluding patients with care withdrawal), days, median, IQR)	.5	.5–1	1	.5–2	1.5	1–4	**<.001**
Care withdrawal, *n*, %	9	6.6	6	11.5	8	13.8	.241
Primary endpoints, *n*, %							
Return to premorbid neurologic function at discharge	72	52.9	27	51.9	12	20.7	**<.001**
Return to premorbid neurologic function at discharge (after excluding patients with care withdrawal)	72/127	56.7	27/46	58.7	11/50	22.0	**<.001**
In-hospital death	9	6.6	4	7.7	3	5.2	.884
In-hospital death (after excluding patients with care withdrawal)	1/127	.8	0/42	.0	0/50	.0	1.000

Note: Bold font indicates statistical significance.

Abbreviations: ICU, intensive care unit; IQR, interquartile range; SE, status epilepticus.

TABLE 3 Univariable comparisons of clinical baseline characteristics at SE onset between patients with and without return to premorbid neurologic function ($n = 246$).

Demographics and clinical characteristics	Return to premorbid neurologic function, $n = 111$		No return to premorbid neurologic function, $n = 135$		
	n/median	%/IQR	*n*/median	%/IQR	*p*
Demographics					
Age, years, median, IQR	55	40–68	66	54–74	**<.001**
Female, *n*, %	36	32.4	53	39.3	.267
GCS at SE onset, median, IQR	5	3–8	6	3–9	.244
SE etiology, *n*, %					
Potentially fatal etiology (not mutually exclusive)	13	11.7	49	36.3	**<.001**
SE type (*n*, %)					
Focal NCSE without coma	7	6.3	17	12.6	.098
With altered consciousness	2	1.8	3	2.2	
Without altered consciousness	5	4.5	14	10.4	
SE with motor symptoms (convulsive or myoclonic)	93	83.7	82	60.7	**<.001**
Convulsive SE	87	78.4	63	476.7	
Myoclonic SE	6	5.4	19	14.1	
NCSE with coma	11	9.9	36	26.7	**.001**
NCSE with coma (non-subtle)	6	5.4	23	17.0	
Subtle SE	5	4.5	13	9.6	
STESS, median, IQR	2	2–5	4	2–5	**<.001**
CCI, median, IQR	2	1–5	4	2–6	**<.001**

Note: Bold font indicates statistical significance.

Abbreviations: CCI, Charlson Comorbidity Index (range = 0–37)[46]; GCS, Glasgow Coma Scale; IQR, interquartile range; NCSE, nonconvulsive SE; SE, status epilepticus; STESS, Status Epilepticus Severity Score (range = 0–6).[44,45]

95% CI = .30–1.49, $p = .3211$; multivariable adjusting for the confounders as in Table 4: OR = .68, 95% CI = −.26 to −1.77, $p = .430$).

4 | DISCUSSION

In summary, this study investigated the efficacy and tolerability of the differences in timing of anesthesia in relation to nonanesthetic antiseizure drugs administered in adult patients with SE in the ICUs of two Swiss tertiary medical care centers. Our analyses revealed that in 79% of patients in our institutions, the administration of anesthetics does not adhere to the guidelines, with anesthesia being started earlier in more than half of our patients and being delayed in up to a quarter. Propofol was preferably used for earlier, and midazolam for later anesthesia, suggesting that the type of anesthetics may be an important contributor regarding outcome—a hypothesis that deserves to be studied more closely in future studies. Whereas earlier anesthesia was associated with fewer infections, a shorter median SE duration, and more frequent return to premorbid neurologic function in univariable analyses, our multivariable model revealed decreasing odds for return to premorbid function with every additional nonanesthetic antiseizure drug given prior to anesthesia, independent of potential confounders as identified in univariable comparisons.

Subgroup analyses revealed decreased odds for return to premorbid function with increasing delay of anesthesia independent of SE severity. In addition, subgroup analyses revealed that this association was persistently seen in the subgroup of patients without potentially fatal etiology, and in patients experiencing motor symptoms. Subgroup analyses for specific SE types revealed decreased odds for return to premorbid function with

TABLE 4 Uni- and multivariable logistic regression analyses regarding the association between the timing of anesthesia and return to premorbid neurologic function at hospital discharge.

Variables potentially associated with outcome (as identified in Tables 2 and 3)	Univariable model			Multivariable model		
	OR	95% CI	*p*	OR	95% CI	*p*[a]
Age (per increasing year)	.97	.95–.98	**<.001**	.98	.95–1.01	.111
Potentially fatal etiology	.23	.12–.46	**<.001**	.28	.13–.61	**.001**
SE with motor symptoms	3.34	1.81–6.16	**<.001**	1.89	.93–3.84	.077
STESS (per increasing unit)	.75	.63–.89	**.001**	.95	.73–1.23	.689
CCI (per increasing unit)	.84	.77–.93	**<.001**	.95	.83–1.09	.472
Rank of administration delay of anesthetics (per increasing delay in relation to nonanesthetic antiseizure drugs)[b]	.54	.39–.74	**<.001**	.71	.53–.94	**.018**

Note: Bold font indicates statistical significance.

Abbreviations: CCI, Charlson Comorbidity Index (range = 0–37)[46]; CI, confidence interval; OR, odds ratio; SE, status epilepticus; STESS, Status Epilepticus Severity Score (range = 0–6)[44,45].

[a]Hosmer–Lemeshow goodness-of-fit test, χ^2 4.72, $p = .787$ indicating adequate model fit.

[b]Rank of administration delay of anesthetics in relation to nonanesthetic antiseizure drug (i.e., anesthetics given as first-, second-, third-, fourth-, or fifth-line treatment).

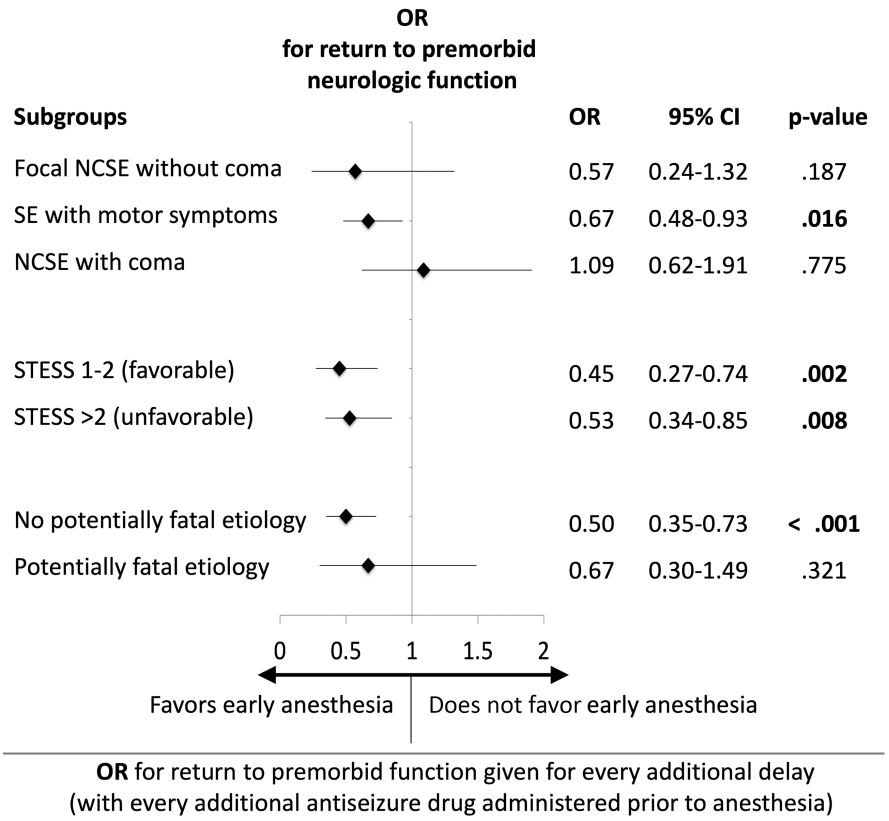

FIGURE 2 Subgroup analyses regarding the timing of anesthesia and the odds of return to premorbid neurologic function at hospital discharge (odds ratio [OR] is given for every additional delay of anesthesia expressed as additional nonanesthetic antiseizure drugs prior to anesthesia). CI, confidence interval; NCSE, nonconvulsive SE; SE, status epilepticus; STESS, Status Epilepticus Severity Score (range = 0–6)[44,45] Bold font indicates statistical significance.

increasing delay of anesthesia in patients with NCSE with motor symptoms after adjusting for potential confounders. In analyses for patients with NCSE with coma, these associations were insignificant. As the sizes of these subgroups were limited, multivariable analyses could not be performed.

Although a previous study in adult patients with SE already reported a similar deviation from treatment guidelines (in >60%)[18] with treatment delay, incorrect dosing, and incorrect medication sequences as the main reasons for such deviation, data regarding the specific timing of anesthesia and its association with outcomes were not analyzed.

Although detailed information regarding delayed anesthesia in patients was not assessable due to the retrospective nature of our study, some conclusions can nevertheless be drawn from our data in this regard. The finding that patients with focal NCSE without coma rarely received early anesthesia may reflect the reluctance of clinicians to anesthetize patients with preserved consciousness despite persistent SE. This is most likely explained by the fear of the possible complications from anesthesia, such as respiratory tract infections. Another explanation may be that treating physicians consider focal NCSE not to be as "severe" or "critical" as generalized SE or SE with convulsions, which is in line with prior studies revealing that focal NCSE without coma is considered a less severe form in illness severity scoring systems such as the STESS and therefore often treated with delay.[25] The association between earlier anesthesia and fewer infectious complications is likely explained by the duration of SE and mechanical ventilation being shortened, thereby reducing the risk of respiratory tract infection via aspiration of saliva. Moreover, a shorter duration of mechanical ventilation is associated with a lower rate of ventilator-associated pneumonia. A congruent result has also been shown in a prior SE cohort study.[12]

As especially in patients with potentially fatal etiologies, anesthesia can be started early for other reasons than controlling SE, such as for airway protection, our result of decreased odds for return to premorbid function with delayed anesthesia could be confounded by the underlying etiologies of SE. Our multivariable analyses, however, revealed decreasing odds for return to premorbid function with every additional nonanesthetic antiseizure drug given prior to anesthesia (i.e., with increasing delay of anesthesia) independent of confounders, including potentially fatal etiologies, increasing age, the types and severity of SE, and the Charlson Comorbidity Index. Furthermore, as characteristics other than SE that may sometimes be the reason for early anesthesia, such as potentially fatal etiologies, were associated with decreased odds for return to premorbid function, our finding of less chance of return to premorbid function with delayed anesthesia would be even more pronounced when excluding these patients. In addition, this finding held after correcting the model for the site of medical care and after excluding care withdrawal. The potential confounders were identified by the univariable comparisons of patients with early anesthesia, anesthesia as third-line treatment (as recommended), and delayed anesthesia, and by a comparison of patients with and without return to premorbid neurologic function at discharge. Such benefits from early anesthesia are in line with previous findings, showing that prolonged and uncontrolled SE is associated with unfavorable outcome[1,26–28] and our previous study revealing that treatment escalation with anesthesia as second-line treatment (i.e., after benzodiazepines were administered as first-line treatment) was not associated with an increase in complications but with shorter duration of SE, and ICU and hospital stay.[5] However, that previous study focused on anesthesia as second-line treatment and could not demonstrate a significant impact on primary outcomes.

Subgroup analyses of the current study revealed decreased odds for return to premorbid function with increasing delay of anesthesia independent of the STESS in patients without potentially fatal etiology and in patients experiencing motor symptoms during SE. The latter should be interpreted with caution, as the subgroups of patients with NCSE were small, which is reflected by the rather large CIs. However, the results of the subgroup analyses strongly suggest that anesthesia should not be delayed based on a low STESS, especially when the presumed underlying etiology is not potentially fatal. Delaying anesthesia based on the clinical context and the STESS indicating a low-severity type of SE may do more harm than good to patients. These findings should be seen as an important guide for future prospective studies.

The hypothesis that delayed anesthesia might be harmful is in line with the neuropathological mechanisms of SE, considering that the γ-aminobutyric acid (GABA)-responsive phase in SE lasts approximately 30 min from SE onset,[29] a time window after which changes in the GABA receptor composition and subsequently altered gene expression occurs. The ILAE operational definition of SE recommends initiating treatment at "t1" (the time point beyond which seizures should be regarded as "continuous," which is at 5 or 10 min, depending on the type of SE), when the seizure is likely to be prolonged, but it states in particular that treatment should be successful at "t2" (the time of ongoing seizures at 30 or >60 min, after which there is a presumed increased risk of long-term consequences) to prevent long-term consequences.[29]

Both propofol and midazolam act by increasing the activity of GABA neurotransmission. It is therefore not surprising that such medications are more effective when administered early or earlier than currently recommended. Delaying of administration of antiseizure drugs and anesthesia increases the risk of SE becoming less or

nonresponsive to antiseizure drugs and anesthetics, leading to prolonged anesthesia, mechanical ventilation, and ICU and in-hospital treatment, thereby increasing the risk of complications and unfavorable outcome—aspects to be considered in particular in patients in whom the exact time of onset of SE is unknown.

Patients with SE with motor symptoms and without potentially fatal etiology traditionally have better outcomes than comatose patients with potentially fatal etiologies; in SE with motor symptoms, excessive epileptic activity may play a role in the worsening of the brain damage itself and increasing systemic complications that may per se lead to brain injury (such as with desaturation following altered respiratory function following aspiration and/or impeded respiratory function due to altered function of respiratory muscles), whereas in SE emerging in comatose patients, the coma is mostly the result of proceeding brain damage, so the neuronal consequences from ongoing seizures play a less important role.[30,31] This could explain why delayed anesthesia impacts more the first category of patients.

4.1 | Limitations and strengths

Due to the observational nature of our study, the results do not prove causality. The generalizability of this study is limited by the retrospective two-center design and the restriction to Swiss care centers. The study design also limits the level of evidence of our results to class III. As treatment assignment was not randomized, we cannot exclude residual confounding. As the sample sizes of patients with focal NCSE without coma and patients with NCSE with coma were limited, which is also reflected by the rather large CIs in the respective subgroup analyses, it remains elusive to what extent more favorable outcomes may result from early coma induction in patients with these types of SE. NCSE moreover tends to be associated with worse outcomes than SE with motor symptoms, and this may represent a potential bias.

Propofol mainly administered earlier and midazolam for later anesthesia may have different safety and side effect profiles, and this could be a confounding factor.

Another limitation is the lack of information regarding timing of the administration of nonanesthetic antiseizure medication prior to anesthesia, calling for further studies.

Before we can adapt the current guidelines to recommend earlier induction of anesthesia, external independent validation of our findings in other SE cohorts is essential. Another important shortcoming is the potential underestimation of SE duration, especially with unwitnessed onset of seizures, which is likely the case with NCSE.[32,33] But the onset of SE may be undetermined even in patients with motor symptoms, as motor symptoms may emerge after an initial phase without motor signs with the spread of epileptic activity into the motor cortex. The exact onset of seizures can only be known in patients seizing during EEG, a scenario seen in very few patients. Moreover, SE duration was not a primary endpoint in our study and represents a limitation that cannot be excluded even in prospective studies.

Furthermore, the illness severity scoring systems Simplified Acute Physiology Score II (SAPS II) and Acute Physiology and Chronic Health Evaluation II (APACHE II) were unavailable for a substantial number of patients on the first day of SE, a shortcoming that is at least partially compensated for by correcting for the Charlson Comorbidity Index and the STESS, both well-established and validated scoring systems. In addition, although both the SAPS II and APACHE II facilitate benchmarking and comparisons of cohorts of severely ill patients, they offer no advantages over the STESS and the Glasgow Coma Scale regarding prediction of no return to baseline.[34] Finally, there may be an unrecognized selection bias from confounding factors or scenarios that may have led attending physicians to induce anesthesia early or to do the opposite (i.e., to avoid or postpone anesthesia in patients thought to be too critical for anesthesia), which we could not account for. Patients more suitable for continuous infusions may have received these sooner than patients in nonmonitored units or developing SE during their hospital stay outside the ICUs. In addition, especially SE patients already in comas and being intubated prior to the onset of SE and with stable respiratory and cardiac function may have received anesthesia earlier than those with preserved consciousness and focal SE. However, as the latter are likely to represent more critically ill patients than SE patients without initial coma and intubation prior to SE, we believe that such scenarios would strengthen our results. Although we carefully reviewed paramedic reports for indications of anesthesia, the retrospective study design does not exclude the possibility that artificial coma was induced for intubation and airway protection in some patients. However, because patients in whom paramedics reported administering anesthetics only for intubation to protect the airway were excluded (comparable numbers between the two centers), this limitation should not affect our results. In addition, intubation to maintain the airway that is at risk due to SE and intubation as a measure to secure the airway and ventilation after (over-)treatment with benzodiazepines may likely be surrogates for uncontrolled SE and thus the need for anesthesia.

Key characteristics of our cohort, such as age,[18,35–39] outcome,[18,35,36,40] etiologies,[18,36–40] severity[18,35–37,39] and types of SE,[39,40] and infectious complications,[41–43] are

similar compared to prior studies regarding SE. Another strength of the present study is the two-center design and the correction for the medical care centers and for care withdrawal, the latter being neglected in the vast majority of studies in this context.

5 | CONCLUSIONS

In this large SE cohort, anesthetics were administered as recommended third-line therapy in only every fifth patient and earlier in every second. Increasing delay of anesthesia was associated with decreased odds for return to premorbid function, especially in patients with motor symptoms and no potentially fatal etiology. Prospective trials are needed to confirm these results.

AUTHOR CONTRIBUTIONS

Pia De Stefano acquired and interpreted the data, planned and designed the study, and drafted the manuscript. Sira M. Baumann acquired and interpreted the data. Pascale Grzonka revised the manuscript and substantially contributed to the inaugural draft. Oana E. Sarbu acquired part of the data. Gian Marco De Marchis, Sabina Hunziker, Stephan Rüegg, Andreas Kleinschmidt, and Hervé Quintard revised the manuscript and substantially contributed to the inaugural draft. Stephan Marsch and Margitta Seeck interpreted the data, revised the manuscript, and substantially contributed to the inaugural draft. Raoul Sutter planned and designed the study, acquired and interpreted the data, performed the statistical analyses, and wrote most parts of the manuscript. All authors approved the final submitted version.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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