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Association between Sedation-Analgesia and Neurodevelopment Outcomes in Neonatal Hypoxic-ischemic Encephalopathy

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Abstract

Objective—To evaluate the association between sedation-analgesia (SA) during initial 72 hours and death/disability at 18 months of age in neonatal hypoxic-ischemic encephalopathy (HIE).

Design—This was a secondary analysis of the NICHD therapeutic hypothermia (TH) randomized controlled trial in moderate or severe HIE. Receipt of SA and anticonvulsant medications at 5 time points were considered: prior to and at baseline, 24, 48 and 72 hours of TH or normothermia. Disability was defined as mental developmental index <85, cerebral palsy, blindness, hearing impairment or Gross Motor Function Classification System 2-5.

Results—Of the 208 RCT participants, 38 (18%) infants had no exposure to SA or anticonvulsants at any of the 5 time points, 20 (10%) received SA agents only, 81 (39%) received anticonvulsants only and 69 (33%) received both SA and anticonvulsants. SA category drugs were not administered in 57% of infants while 18% received SA at ≥3 time points; 72% infants received anticonvulsants during 72 hours of intervention. At 18 months of age, disability among survivors and death/disability was more frequent in the groups receiving anticonvulsants, with (48 and 65%) or without (37 and 58%) SA, compared to groups with no exposure (14 and 34%) or SA (13 and

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32%) alone. Severe HIE (aOR 3.60; 1.59-8.13), anticonvulsant receipt (aOR 2.48; 1.05-5.88) and mechanical ventilation (aOR 7.36; 3.15-17.20) were independently associated with 18-month death/disability whereas TH (aOR 0.28; 0.13-0.60) was protective. SA exposure showed no association with outcome.

Conclusions—The risk-benefits of SA in HIE needs further investigation.

Introduction

Despite the significant benefits of therapeutic hypothermia (TH) for neonatal hypoxic-ischemic encephalopathy (HIE), death and disability remain considerable [1]. Infants with HIE are subjected to the stresses of an adverse perinatal event, resuscitation, TH itself and painful procedures. Whether use of medications for sedation/analgesia (SA) to mitigate the pain /stress response improves outcomes in HIE is unclear. Thoresen et al reported that mild hypothermia was not protective after hypoxia-ischemia in unsedated piglets but reduced the severity of brain damage in piglets receiving halothane or intravenous anesthesia [2, 3, 4]. However, neuroprotection with prolonged TH after hypoxia-ischemia has been consistently observed in unsedated fetal sheep and neonatal rodents [5, 6]. In adults, SA medications during TH are associated with earlier attainment and better maintenance of target temperatures [7]. Of the neonatal trials of TH, only the Neo-nEURO study treated all infants with morphine or an equivalent dose of fentanyl [8]. In the Total Body Hypothermia for Neonatal Encephalopathy trial, infants underwent sedation with morphine infusions or chloral hydrate if they “appeared to be distressed” [9]. In all other trials of TH for neonatal HIE, SA administration was provider-driven; there has not been an analysis of SA use from any of the randomized controlled trials (RCTs) [10–13].

SA used during TH for neonatal HIE may affect neuromonitoring of infants, duration of mechanical ventilation and hemodynamic status. TH, in turn, may alter drug pharmacokinetics and potentially increase their adverse effects. Roka and colleagues found serum morphine concentrations at 24 to 72 hours after birth to be higher in the 10 infants who underwent TH, compared to 6 normothermic infants, at similar morphine infusion rates and doses [14]. In addition to SA, infants with HIE may receive concomitant neuromuscular blocking agents and anticonvulsants, which may affect neurodevelopmental outcomes, either through an unclear causal pathway or because of altered systemic concentrations or as markers of global severity of illness. These effects have not been previously explored.

We sought to address this knowledge gap using data from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) TH RCT [10]. We describe patterns of use of SA, anticonvulsants and neuromuscular blocking agents during the initial days of life. Our primary hypothesis was that, among participants of the NICHD NRN whole body cooling RCT for neonatal HIE, SA administration during the 72 hours of TH or normothermia would be associated with an increased risk of death/moderate or severe disability at 18-22 months of age, after adjustment for center, HIE severity, TH, and clinical markers of severity of the infant’s underlying illness during the 72 hours.

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Methods

This was a secondary analysis of data from the NICHD NRN whole body cooling RCT for moderate or severe HIE in term or late preterm (gestational age ≥ 36 weeks) infants (10). Eligibility criteria for the original trial included cord blood or postnatal acidosis and/or clinical criteria (acute perinatal event and either a 10 minute Apgar score of 5 or less or assisted ventilation). Further, enrolled infants (n=208) had moderate or severe HIE on standardized neurologic examination or had seizures. Infants in the RCT were randomized to normothermia or TH to achieve an esophageal temperature of 33.5°C for 72 hours. The trial was approved by the Institutional Review Boards at all participating sites.

Prospectively collected data were available on SA administration and type at 5 time points, (each treated as a window from the previous): prior to baseline, baseline (defined as the time of initiation of TH when the cooling blanket was turned on or the time of randomization for the normothermic group of infants) and at 24, 48 and 72 hours of intervention (TH or normothermia). Included SA medications were morphine, fentanyl, chloral hydrate, midazolam and phenobarbital and other. Data on anticonvulsants were coded as phenobarbital, lorazepam, phenytoin, paraldehyde and other. In addition, data on neuromuscular blocking agent (pancuronium, vecuronium, rocuronium and other) administration were collected. For initial analyses, we classified infants into groups who received no SA or anticonvulsants, only SA, only anticonvulsants and both SA and anticonvulsant agents. Since SA use was the variable of interest, we further described degree of exposure to SA as a factor count by the number of SA agents and number of time points (0-5) at which they were administered. For example, receipt of 2 agents at 3 time points would give a count of 6.

Time to achieve target esophageal temperature and esophageal temperature fluctuations >2°C after 4 hours of cooling were noted for infants who underwent TH. Hypocarbia was defined as pCO_2 less than 35 mm Hg and hypercarbia as pCO_2 greater than 55 mmHg on blood gases (temperature-corrected in the TH group) obtained at 4, 8, 12, 24, 48 and 72 hours of intervention [15]. Demographic and birth characteristics and data on the use of pressors and neuromuscular blockers at the 5 time points through the 72 hour intervention, persistent encephalopathy, defined as moderate or severe encephalopathy without improvement on examinations at 24, 48 and 72 hours and anticonvulsants at discharge and outcomes at 18-22 months of age were compared between the 4 groups.

The primary outcome was death or moderate/severe disability at 18-22 months of age, defined as in the main RCT [10]. Neuromotor disability was defined on the basis of cerebral palsy (CP), and functional disability was graded according to the Gross Motor Function Classification System (GMFCS) [16]. Cognitive outcome was assessed with Bayley Scales of Infant Development (BSID-II), where the population mean (SD) scores were 100 (15) on the mental developmental index (MDI) and psychomotor developmental index (PDI). Severe disability was defined as any of the following: MDI score below 70, a GMFCS grade of level 3 to 5, hearing impairment requiring hearing aids for > 60 db testing, or bilateral blindness. Moderate disability was defined as MDI score 70 to 84 *in addition* to one or more

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of the following: a GMFCS grade of level 2, hearing impairment with no amplification, or a persistent seizure disorder.

Statistical Analysis

Descriptive statistics included median and inter-quartile (IQR) ranges for continuous variables and frequencies and proportions for categorical variables. ANOVA, Wilcoxon-Rank sum and chi-square tests were used, as appropriate, to compare infant characteristics and outcomes between the 4 groups of infants as defined. Logistic regression model for the association between SA exposure (factor count as a continuous variable) and death/disability at 18-22 months of age was developed, adjusting for severity of HIE, TH, anticonvulsant use through the 72 hours and center (as a random variable), in addition to clinical markers of severity of illness in the 72 hours of intervention (receipt of pressors through the 5 time points, mechanical ventilation at baseline, 24, 48 and 72 hours, and hypocarbia or hypercarbia at any time in the 72 hours). Adjusted odds ratios (ORs) and 95% C.I. were computed. All *P* values were based on 2-tailed tests and values < 0.05 were taken as significant. We decided a priori to evaluate the subgroups of cooled and normothermic infants separately, only if the p value for interaction test between SA and intervention (TH vs. normothermia) was < 0.1.

Results

Of the 208 RCT participants, 38 (18%) infants had no exposure to SA or anticonvulsants at any of the 5 time points, 20 (10%) received SA agents only, 81 (39%) received anticonvulsants only and 69 (33%) received both SA and anticonvulsant at some time point. Only two infants received phenobarbital as a sedative. There were no differences rates of TH in the 4 groups (55% in the no exposure, 50% in the SA only, 49% in the anticonvulsant only and 45% in those who received both classes; p=0.78). Table 1 is a comparison of demographic and birth characteristics of these 4 groups. Significant differences between groups were noted in the proportion of infants who were outborn, had severe HIE and received chest compressions in the delivery room (DR) and at 10 minutes and received resuscitation medications in the DR as well as in the median 1 and 5-minute Apgar score and cord pH. Infants who received anticonvulsants alone or along with SA had lower Apgar scores and cord pH, received chest compressions and had severe HIE more often. Table 2 is a detailed description of the receipt of SA, anticonvulsants, neuromuscular blocking agents and pressors at each time point. More than half (57%) the infants had no exposure to SA agents, with 18% receiving SA agents at 3 or more of the 5 time points. The commonly used drugs were morphine, fentanyl and midazolam (18-21% each). Anticonvulsants were administered to 72% of infants, with 46% receiving them for 3 or more time points.

Table 3 is a comparison of clinical characteristics during the 72 hours and outcomes in the 4 groups of infants. There were significant differences between groups in the receipt of neuromuscular blockers. Infants who had no exposure to SA or anticonvulsants had lower rates of unchanged HIE severity through the 72 hours, and had shorter durations of mechanical ventilation and supplemental oxygen. Mean length of hospital stay in survivors was significantly longer in the SA only group of infants, compared to the group without SA

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or anticonvulsant exposure. At 18 months of age, disability among survivors and death/disability was more frequent in the groups receiving anticonvulsants, with or without SA. Nineteen infants underwent one or more surgical procedures during hospitalization, the commonest being gastrostomy (n=9), gastrostomy and fundoplication (n=4), and ECMO (n=3). Surgical procedures were equally distributed between groups. Two infants had multiple surgeries, including fundoplication and unspecified surgery (n=1) and tracheostomy, fundoplication, and gastrostomy (n=1); one infant had “other” surgery.

Further analyses of exposure to SA were conducted using the factor count. Table 4 is a description of rates of death or disability in infants with varying exposure to SA, by the factor count. Rates of death/disability were 50%, 52% and 59% respectively for infants with no exposure to SA, a single agent at 1 time point and those with greater exposure.

Logistic regression on the association between level of SA exposure using factor count and the primary outcome, adjusting for severity of HIE, TH, center, anticonvulsant and pressor receipt and mechanical ventilation at all time points, and hypocarbia/hypercarbia at any time point with the adjusted OR and 95% C.I. for each included variable are shown (Table 5). The c-statistics for the models were 0.819 for death or disability. Severe HIE, anticonvulsant receipt and mechanical ventilation were independently associated with death or disability whereas TH was protective. SA exposure and hypocarbia or hypercarbia were not associated with death or disability.

Discussion

In this secondary analysis of data from the NICHD NRN whole body cooling RCT, 57% of infants received no SA drug; SA administration for prolonged durations was uncommon; SA administration did not significantly differ between cooled and normothermic infants. A greater proportion of infants who were administered anticonvulsants, alone or in combination with SA, at any of 5 time points during the 72 hours of trial intervention had severe HIE, lower median 1 and 5-minute Apgar scores and cord pH and required chest compressions. They also had higher rates of death/disability at 18 months and of disability alone. Infants without SA or anticonvulsant exposure had significantly less unchanged HIE severity, shorter durations of mechanical ventilation and supplemental oxygen. On logistic regression, severe HIE, TH and anticonvulsant receipt during the 72 hours were found to be associated with death or disability at 18 months of age, whereas degree of exposure to SA was not.

Current practice guidelines recommend SA and neuromuscular blocking administration during TH in *adult* comatose patients after cardiac arrest although variability in practice has been reported [17–19]. In the Therapeutic Hypothermia after Pediatric out-of-hospital cardiac arrest RCT, children were sedated and pharmacologically paralyzed during TH [20]. SA use in adults and older children is to prevent shivering during TH induction and maintenance, which may increase temperature if not suppressed. The newborn is distinctly different since non-shivering thermogenesis is the primary response to a cold stress.

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There are currently no data on the association between SA in the neonatal period and neurodevelopmental outcomes in term infants with HIE. In all except one RCT of TH in neonatal HIE, SA practices were heterogenous and determined by center and clinician preferences [8–13]. Despite this, the results from the trials have been remarkably similar. Our data underscore the complexity of examining the relationship between an important care practice such as SA associated with TH and outcomes. In the current data set, less than half the infants received SA agents during the intervention. While we did not find an association between level of SA exposure and death or disability at 18 months, whether SA affected other variables such as mechanical ventilation and anticonvulsant exposure which did show an association with outcome is unclear. Nonetheless, the results highlight the need for a careful approach when considering the risks/benefits of SA agents in infants with HIE. We statistically adjusted for severity of HIE and multiple other markers of acuity of illness in the logistic regression model; however, we may have adjusted for some variables intermediate in the causal pathway between SA exposure and outcome.

In other neonatal populations, there are no clear benefits of “routine” SA use. Among term neonates, longer duration or higher cumulative dose of SA in the neonatal period have been shown to adversely affect performance IQ and visual motor integration scores [21], and neuromuscular blockade to increase the risk of mortality [22]. Among mechanically ventilated preterm participants of the NEOPAIN RCT, pre-emptive morphine infusions did not reduce the frequency of brain injury or death, but intermittent open-label morphine was associated with an increased rate [23]. Other studies in preterm populations have not shown an effect of SA exposure on neurodevelopment [24–26].

The current data, while exploratory, suggest that careful, **rather than *routine* SA** administration in infants with HIE during the initial 72 hours of life, may not be harmful. Only 10% of infants received SA alone, making it difficult to ascertain their effects. Preclinical data are conflicting; neonatal morphine administration has been shown to induce apoptosis in microglial cells and behavioral changes have been demonstrated in some animal models [6, 27–29] and reduced survival but no significant differences in the volume of infarction, or behavioral outcomes in others [30].

We recognize the limitations of this exploratory secondary analysis. There were no defined protocols for SA in the NRN RCT and the categorization of levels of SA using a factor count, while designed to assess both number of agents and duration of exposure, was arbitrary. We attempted to account also for anticonvulsants and, neuromuscular blocking agents, which may be less driven by practice variation. However, we did not have indications for SA, doses or pain scores available, and could not discriminate the effect of each class of medication. The BSID-II has been shown to have systematic differences from the BSID-III current version. Our sample size precluded subgroup analysis of normothermic and cooled groups of infants separately and only 10% of the cohort received SA alone. Lastly, data on maternal education level which is a surrogate of socio-economic status and strongly influences outcome, was incomplete.

Nonetheless, the current study addresses a largely unstudied issue in a high-risk population of neonates and provides novel insights into potential associations of SA in the initial days

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of life among infants with HIE and neurodevelopmental outcomes. While it is difficult to unravel the relative contributions of the brain injury, the pain-stress of neurocritical care and SA administration on neurodevelopment, our data emphasize the need for further systematic investigation into the risk-benefits of SA in HIE, in an era when TH is widely disseminated.

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Table 1

Comparison of demographic and birth characteristics between groups of infants with SA and/or anticonvulsant (AC) receipt during the 72 hours of study intervention

Characteristic Mean ± SD or Median (IQR) or n(%)	No SA or AC N=38	Any SA without ACN=20	Any AC without SAN=81	Both SA and AC N=69	p-value
Outborn, n (%)	11 (29%)	4 (20%)	35 (43%)	43 (62%)	0.0005
Apgar scores at 1 min	1 (0-2)	2 (1-2)	1 (0-1)	0 (0-1)	0.0002
Apgar scores at 5 min	3 (2-4)	3.5 (3-5)	2 (0-4)	2 (0-4)	0.003
Apgar scores at 10 min	4 (3-6)	4 (3.5-6)	4 (2-4)	3 (2-5)	0.15
Birth weight (Grams)	3310 ± 666	3339 ± 763	3466 ± 649	3320 ± 541	0.45
Gestational age (Weeks)	38.7 ± 1.64	39.6 ± 1.76	38.9 ± 1.49	38.8 ± 1.63	0.25
Male sex, n (%)	20 (53%)	11 (55%)	43 (53%)	43 (62%)	0.67
Uterine rupture, n (%)	3 (8%)	1 (5%)	16 (20%)	9 (13%)	0.23
DR resuscitation, n (%)	38 (100%)	20 (100%)	81 (100%)	69 (100%)	N/A
Oxygen	38 (100%)	20 (100%)	81 (100%)	69 (100%)	N/A
Bag/mask	37 (97%)	18 (90%)	78 (96%)	66 (96%)	0.57
Chest compressions	18 (47%)	3 (15%)	50 (63%)	52 (75%)	<0.0001
Intubation	34 (89%)	18 (90%)	78 (96%)	65 (94%)	0.33
Drugs	18 (47%)	3 (15%)	44 (55%)	47 (68%)	0.0003
Continued resuscitation at 10 m, n (%)	34 (89%)	18 (90%)	76 (94%)	67 (97%)	0.31
Oxygen	33 (97%)	18 (100%)	75 (99%)	67 (100%)	0.58
Bag/mask	20 (59%)	6 (33%)	43 (57%)	41 (61%)	0.21
Chest compressions	8 (24%)	1 (6%)	26 (35%)	25 (37%)	0.03
Intubation	31 (91%)	16 (89%)	72 (95%)	58 (87%)	0.35
Drugs	10 (29%)	4 (22%)	26 (34%)	30 (45%)	0.23
Time to spontaneous respiration ≥10 m, n (%)	15 (42%)	10 (56%)	15 (20%)	17 (25%)	0.007

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Characteristic Mean ± SD or Median (IQR) or n(%)	No SA or AC N=38	Any SA without ACN=20	Any AC without SAN=81	Both SA and AC N=69	p-value
Cord pH	6.95 ± 0.22	6.95 ± 0.20	6.81 ± 0.19	6.82 ± 0.19	0.005
Cord base deficit (meq/L)	16.4 ± 8.09	16.6 ± 7.18	20.0 ± 7.68	20.9 ± 7.39	0.08
Postnatal gas pH	7.07 ± 0.22	7.05 ± 0.19	7.08 ± 0.22	7.01 ± 0.25	0.30
Postnatal gas base deficit (meq/L)	19.0 ± 6.60	16.8 ± 7.71	17.8 ± 8.06	18.1 ± 8.00	0.90
Encephalopathy at randomization:					0.008
Moderate	30 (79%)	17 (85%)	43 (53%)	44 (65%)	
Severe	8 (21%)	3 (15%)	38 (47%)	24 (35%)	
TH, n (%)	21 (55%)	10 (50%)	40 (49%)	31 (45%)	0.78
Time to target esophageal temp *	0.95 ± 0.48	1.17 ± 0.96	0.85 ± 0.39	0.81 ± 0.30	0.78
Temp fluctuations >2°, n (%) *	1 (5%)	3 (33%)	2 (5%)	3 (10%)	0.09

* Only among cooled infants in each group

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Table 2

Description of the receipt of SA, anticonvulsants, neuromuscular blocking agents and pressors at each time point.

Sedation-analgesia	**Any**	**Number of timepoints**					
		0	**1**	**2**	**3**	**4**	**5**
Any SA	89 (43%)	119 (57%)	29 (14%)	22 (11%)	19 (9%)	15 (7%)	4 (2%)
Specific drugs							
Morphine	38 (18%)	170 (82%)	23 (11%)	7 (3%)	5 (2%)	2 (1%)	1 (0%)
Fentanyl	44 (21%)	164 (79%)	11 (5%)	9 (4%)	15 (7%)	7 (3%)	2 (1%)
Chloral hydrate	1 (0%)	207 (100%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Midazolam	42 (20%)	166 (80%)	15 (7%)	10 (5%)	11 (5%)	4 (2%)	2 (1%)
Phenobarbital	2 (1%)	206 (99%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)
Other	5 (2%)	203 (98%)	3 (1%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Other Classes of Medications							
Medication Type	**Any**	**0**	**1**	**2**	**3**	**4**	**5**
Anticonvulsants	150(72%)	58 (28%)	33 (16%)	21 (10%)	32 (15%)	19 (9%)	45 (22%)
Neuromuscular blockage agents	32 (15%)	176 (85%)	14 (7%)	12 (6%)	3 (1%)	2 (1%)	1 (0%)
Pressors	116(56%)	92 (44%)	12 (6%)	22 (11%)	35 (17%)	15 (7%)	32 (15%)

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Table 3

Comparison of outcomes between groups of infants with SA and/or anticonvulsant exposure

Characteristic Mean ± SD or Median (IQR) or n(%)	No SA/AC N=38	SA without AC N=20	AC without SA N=81	SA and AC N=69	p-value
Pressors at all time points	2 (5%)	5 (25%)	11 (14%)	14 (20%)	0.10
AC at all time points	0 (0%)	0 (0%)	24 (30%)	21 (30%)	1.0*
Neuromuscular blocker at any time point	1 (3%)	6 (30%)	1 (1%)	24 (35%)	<0.0001
Unchanged HIE severity from randomization to:					
24 hrs (N=179)	10 (32%)	11 (69%)	50 (70%)	39 (64%)	0.003
48 hrs (N=175)	6 (19%)	12 (71%)	44 (64%)	34 (59%)	0.0001
72 hrs (N=170)	6 (20%)	8 (44%)	38 (55%)	27 (51%)	0.01
In-hospital death, n (%)	6 (16%)	4 (20%)	21 (26%)	18 (26%)	0.63
Days on ventilator	2.6 ± 2.3	9.1 ± 6.8	5.4 ± 5.8	6.9 ± 6.6	<0.0001
Days on oxygen	4.7 ± 7.5	11.2 ± 8.7	8.1 ± 12.7	9.0 ± 8.1	0.0001
Major surgery in NICU	1 (3%)	1 (5%)	11 (14%)	6 (9%)	0.26
Days of tube feedings	6.4 ± 13.2	6.4 ± 12.5	9.0 ± 14.1	8.0 ± 14.5	0.23
Age at full oral feeds, days	8.0 ± 10.1	13.2 ± 11.1	9.5 ± 16.3	10.8± 11.7	0.04
Length of stay, days **N=199**	**13.6 ± 13.3** **9 (7-15)**	**23.9 ± 22.1** **19 (9.5-26.5)**	**18.9 ± 17.3** **13 (9-22)**	**16.3 ± 15.8** **13 (7-20)**	**0.08** **0.07**
Length of stay in survivors **N=150**	**15.8 ± 13.4** **11 (8-17)**	**26.4 ± 23.4** **22 (10-26.5)**	**21.3 ± 15.2** **15.5(11-23)**	**20.4 ± 16.4** **14 (10-26)**	**0.04** **0.15**
Discharge gavage/gastrostomy feeds, n (%) (N=152)	3 (10%)	1 (6%)	18 (31%)	10 (21%)	0.051
Anticonvulsant at discharge, n (%) (N=152)	2 (6%)	0 (0%)	31 (53%)	26 (55%)	<0.0001
18 months outcomes					
Death (N=206)	9 (24%)	4 (21%)	26 (33%)	23 (33%)	0.61

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Characteristic Mean ± SD or Median (IQR) or n(%)	No SA/AC N=38	SA without AC N=20	AC without SA N=81	SA and AC N=69	p-value
Disability (N=144)	4 (14%)	2 (13%)	20 (37%)	22 (48%)	0.006
Death or disability (N=206)	13 (34%)	6 (32%)	46 (58%)	45 (65%)	0.003

*P-value only compares the latter two columns, since absence of anticonvulsants is part of the definition for the first two columns.

**Data unavailable in 9 infants who were transferred out before discharge

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Table 4

Description of number of infants in each SA factor count (range 0-15, for up to 5 time points and up to 3 drugs) group and corresponding rates of death/disability at 18 months of age

SA factor count	N (%)	Death or disability (N=206)
0	119 (57%)	59/118 (50%)
1	25 (12%)	13 (52%)
2	23 (11%)	15/22 (68%)
3	11 (5%)	8 (73%)
4	9 (4%)	4 (44%)
5	4 (2%)	2 (50%)
6	7 (3%)	3 (43%)
7	3 (1%)	1 (33%)
8	2 (1%)	2 (100%)
9	2 (1%)	2 (100%)
10	3 (1%)	1 (33%)
11-15	0 (0%)	110/206 (53%)

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Table 5

Adjusted logistic regression for association between SA exposure (factor count) and primary outcome at 18 months of age

Variable	AOR (95% CI)	P-value
SA factor count (0-15)	0.93 (0.79-1.10)	0.42
HIE severity	3.60 (1.59-8.13)	0.002
TH	0.28 (0.13-0.60)	0.001
Center (as random effect)	N/A	
Pressors at all 5 time points (prior to baseline, baseline, 24H, 48H, 72H)	0.43 (0.16-1.13)	0.09
Anticonvulsants at all 5 time points (prior to baseline, baseline, 24H, 48H, 72H)	2.48 (1.05-5.88)	0.04
Mechanical ventilation at all 4 time points (baseline, 24H, 48H, 72H)	7.36 (3.15-17.2)	<0.0001
Hypocarbia (PCO2 < 35) and/or hypercarbia (PC02 > 55) at any time point (baseline, 4H, 8H, 12H, 24H, 48H, 72H)	2.96 (0.82-10.7)	0.10