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First experience with amplitude-integrated electroencephalography (aEEG) for neuro-monitoring in newborns with suspected seizures in North Macedonia

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Introduction: Neonatal seizures (NS) occur commonly in newborns; however, their diagnosis is difficult due to atypical clinical presentation and variable electro-clinical correlation. The diagnosis of NS was further challenged in our settings due to the rooming-in concept of the neonatology ward, and the limited availability of conventional electroencephalography, particularly during the night shifts and weekends. The study presents the first experience of the usage of aEEG in the Republic of North Macedonia.

Material and methods: We enrolled both term and preterm newborns (term aged <28 days; preterm corrected gestational age ≤ 42 weeks) who underwent neuro-monitoring with aEEG since the implementation of the methodology in our country in 2023. Stratification was made as follows: group 1- patients with clinical suspicion of NS (seizures, seizure-like events, decreased activities, apnea or mental change) and group 2 - patients with increased risk seizures (Apgar score <7 in 5th minute, hypocalcemia, hypoglycemia, etc.). Data analysis included: demographics (gender, GA, BW), Apgar score, age at seizure onset, aEEG background pattern, presence of sleep-wake cycle (SWC), presence of epileptiform activity, and neurodevelopment outcome up to around 12 months postnatal age.

Results: A total of 48 newborns met the inclusion criteria, 52% were classified in group 1 and 48% in group 2. There was no significant difference between the groups for GA, BW, and Apgar score. Single or multiple electrographic seizures were observed in 16% of the group 2 patients. Neurodevelopment delay was present in 38.7% of the patients and 12% developed epilepsy. Predictors for unfavorable outcome were abnormal aEEG background pattern: OR: 9.62 (95% CI: 1.3776 to 67.2482, P = 0.0224), absence of developed SWC: OR: 3.20 (95% CI 0.4194 to 24.4180) and clinical manifestation of seizures or seizure-like events OR: 2.36 (95% CI: 0.7125 to 7.7986). Apgar score and presence of sole electrographic seizures were not associated with negative outcomes.

Conclusion: aEEG is an important neuro-monitoring tool for the evaluation of epileptiform activity and differentiation of NS from non-epileptic movements in newborns, but also in the prediction of the neurodevelopment outcome in infants with suspected NS.

None declared

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WITH 10 YEARS OF EXPERIENCE: THE ROLE OF ANTIEPILEPTIC TREATMENT AND LEVETIRACETAM IN VLBW INFANTS

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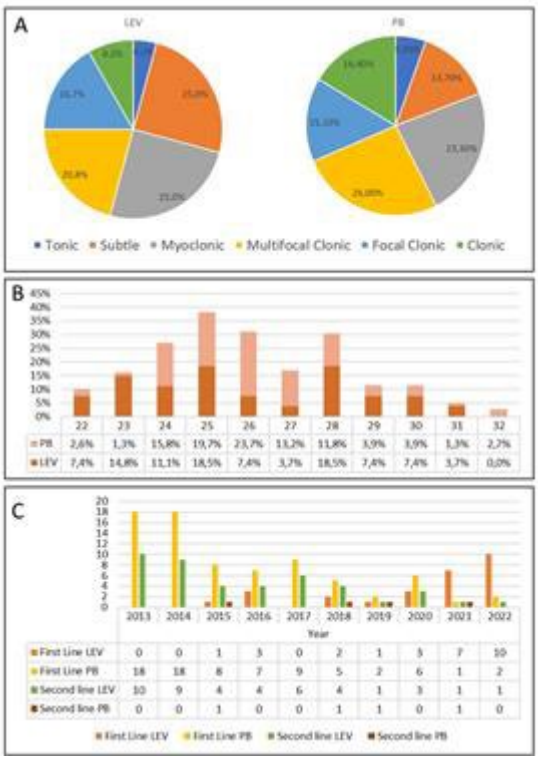
Objective:
Despite ongoing debates regarding optimal antiepileptic treatment strategies for Very Low Birth Weight (VLBW) infants, there is a notable lack of research concerning the efficacy of Levetiracetam (LEV) as a primary antiepileptic option. This study aims to compare the effectiveness of Phenobarbital (PB) and LEV in managing neonatal seizures in VLBW infants over the past decade, reflecting on changes in clinical practice and emerging preferences in neonatal care.

Methods:
This retrospective cohort study evaluated 103 VLBW infants treated for seizures in a neonatal intensive care unit. 27 infants received LEV, and 76 were treated with PB. We analyzed treatment outcomes relative to gestational ages, incidences of severe intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC), alongside response rates to initial antiepileptic treatment.

RESULTS:
The mean gestational age was 26.17±2.31 weeks, with no significant demographic or clinical differences between the groups. The LEV group included a higher proportion of infants under 24 weeks of gestation and showed a greater incidence of severe IVH and NEC, indicative of a more critically ill cohort. Nonetheless, the LEV group exhibited significantly lower rates of treatment unresponsiveness compared to the PB group (14.8% vs. 56.6%; $p<0.001$). Factors such as low gestational age and the presence of respiratory distress syndrome (RDS) were associated with PB treatment unresponsiveness. All non-responding infants in the LEV group were micropremies, and one exhibited congenital brain malformation.

Conclusion:
This study supports LEV as a more successful first-line agent for clinical seizure control compared to PB in VLBW infants, particularly in very small prematures. With its promising safety profile and efficacy, LEV could potentially be recommended in clinical algorithms as the preferred initial treatment for neonatal seizures in VLBW infants. The findings advocate for a shift in clinical practice, reflecting an increasing preference for LEV over PB. Future randomized controlled prospective studies are needed to confirm these results and support the inclusion of LEV as a primary treatment option, thereby enhancing personalized care and potentially improving outcomes in this vulnerable population.
None declared



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	First-line drug: Phenobarbital (N=76)	First line drug: Levetiracetam (N=27)	P-Value
Birth weight (gr.)	810.76 ± 244.958	853.0 ± 302,140	0,510
Gestational week	26.25 ± 2.19	25.96 ± 2.63	0,615
Maternal diabetes	10 (13,2)	3 (11,1)	1,0
Maternal hypertension	12 (15,8)	4 (14,8)	1,0
Maternal hypothyroidism	12 (15,8)	4 (14,8)	1,0
Preterm premature rupture of membrane	26 (34,2)	10 (38,5)	0,695
Antenatal steroid	40 (52,6)	16 (59,3)	0,553
Caesarean section	66 (86,8)	22 (81,5)	0,532
APGAR 1st min	5 (1-9)	2 (0-8)	0,206
APGAR 5th min	7,5 (3-10)	7 (1-9)	0,245
Respiratory distress sydrome	63 (82,9)	22 (81,5)	1,0
Early neonatal sepsis (culture positive)	28 (37,3)	8 (29,6)	0,473
Late neonatal sepsis (Culture Positive)	33 (43,4)	11 (44)	0,960
Hemodynamically significant patent ductus arteriosus before seizure	44 (57,9)	16 (59,3)	0,902
Caffeine dose at the time of seizure (mg/kg)	5 (5-8)	5(5-8)	0,850
*Electrolyte imbalance at the time of seizure**	17 (24,6)	5 (20)	0,639
Infection at the time of seizure	39 (52,7)	13 (48,1)	0,685
Postnatal hour of the first seizure	234 (16 – 1440)	168 (36 – 1920)	0,450
Electroencephalogram (Low ground rhythm)	11 (15,5)	3 (15,0)	1,0
Electroencephalogram (Epileptic activity)	32 (45,1)	10 (50)	0,696
Status epilepticus	9 (12,2)	0	-
Second-line medication	43 (56,6)	4 (14,8)	**0,001**
Cranial malformation	5 (6,6)	5 (18,5)	0,123
Intraventricular hemorrhage	40 (53,3)	19 (70,4)	0,124
Intraventricular hemorrhage (Stage 3 and 4)	12 (30)	10 (52,6)	0,093
Periventricular leukomalacia	12 (16,2)	4 (16,7)	1,0
Bronchopulmonary dysplasia (Moderate-Severe)	21 (29,6)	4 (16,7)	0,250
Retinopathy of prematurity (Requiring Treatment)	19 (25,7)	2 (8,3)	0,072
Necrotizing enterocolitis (Stage 2 and above)	11 (14,5)	5 (20)	0,535
Duration of hospital stay	84.89 ± 36.58	69.89 ± 38.35	0,084
*Presence of seizures after discharge***	4 (6)	1 (6)	0,830
*Motor-mental developmental delay***	37 (57,8)	6 (35,2)	0,098
*Medication maintenance period (Months)***	6 (0,13-120)	6 (0,1-60)	0,312
Mortality	12 (15,8)	9 (33,3)	0,052

Data are given as n (%), median (minimum -, maximum) or mean ± SD.
*: *Electrolyte imbalance was evaluated as hyponatremia, hypernatremia and hypocalcemia.*
**: *These data have been calculated for patients who survived and regularly attended follow-up appointments at the pediatric neurology department clinic.*

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INTRANASAL COLOSTRUM-DERIVED EXOSOMES AS A NEURORESTORATIVE TREATMENT FOR PERIVENTRICULAR LEUKOMALACIA IN RATS

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INTRODUCTION

The regenerative capacity of mesenchymal stem cell-derived exosomes is documented in neurology, especially for neonatal brain injuries. Colostrum is a reservoir of these exosomes, along with extracellular vesicles, microRNAs, and growth factors. This study explores the potential neurorestorative impacts of intranasally (i.n.) administered colostrum-derived exosomes in a rat model of periventricular leukomalacia (PVL).

MATERIAL AND METHODS

Exosomes were harvested from Sprague-Dawley lactating rat dams within the first five postpartum days. In the first phase, exosomes were labeled with the fluorescent dye PKH-67 and subsequently administered i.n. to five-day-old neonates (P5). At the third hour post-administration, the pups were sacrificed to observe the labeled exosomes within the brain tissue sections. In the second phase, a preliminary study was conducted to determine the optimal dose of lipopolysaccharide (LPS) to establish the PVL model, resulting in a 5 mg/kg intraperitoneal (i.p.) injection of LPS (E. coli, serotype 055:B5) on P5. The groups were as follows: control group (n = 10), which received only i.p. saline and i.n. saline; LPS group (n = 10), which was administered LPS (i.p.) and i.n. saline; and exosome group (n = 10), which received LPS followed by 10 mg/kg i.n. exosome treatment. Behavioral assessments and immunohistochemical analyses were conducted on days P6 and P11 to evaluate motor function and oligodendrocyte integrity, respectively.

RESULTS

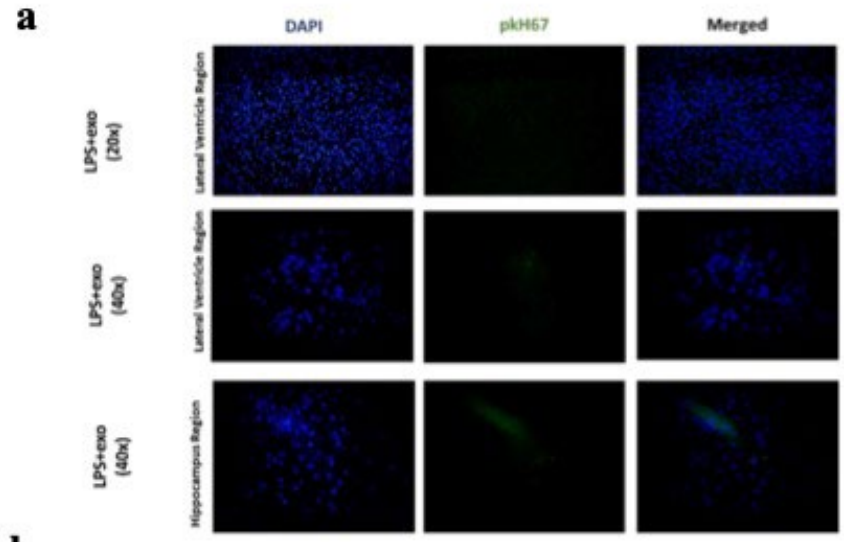
Colostrum-derived exosomes were successfully integrated into the neonatal rat brain, particularly concentrating around the hippocampus (Figure 1a). Behavioral analyses indicated that the exosome group's performance paralleled that of the control group and surpassed the LPS group. Immunohistochemical evaluation showed a preservation of oligodendrocytes in the exosome group as compared to the LPS group (Figures 1b, 1c).

CONCLUSIONS

This pioneering study investigates the role of colostrum-derived exosomes in treating neonatal brain injury, specifically PVL. Results indicate that these exosomes harbor neurorestorative potential against LPS-induced preterm white matter injury. While numerous preclinical studies have scrutinized pharmacological interventions in preterm brain injury models, the transition to clinical trial

phases remains elusive. Our findings suggest that with further validation, intranasal colostrum-derived exosomal therapy could emerge as a non-invasive, natural, and accessible clinical intervention for neonatal brain injuries.

There is no conflict of interest.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DAPI
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Merged
LPS+exo (20x)
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LPS+exo (40x)
Lateral Ventricle Region
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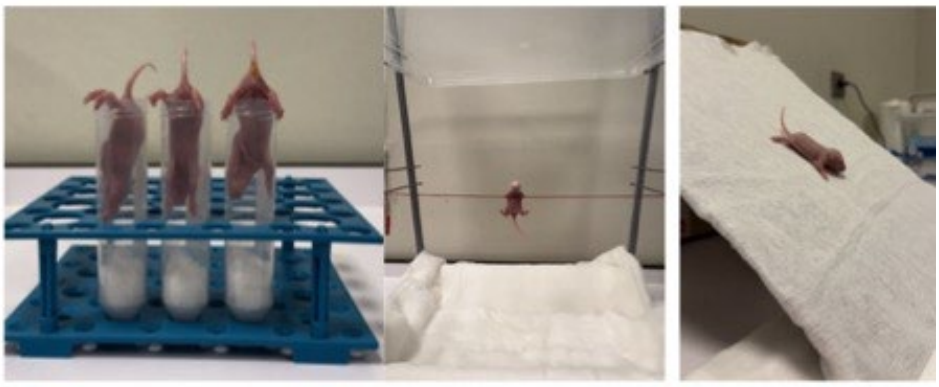
Hippocampus Region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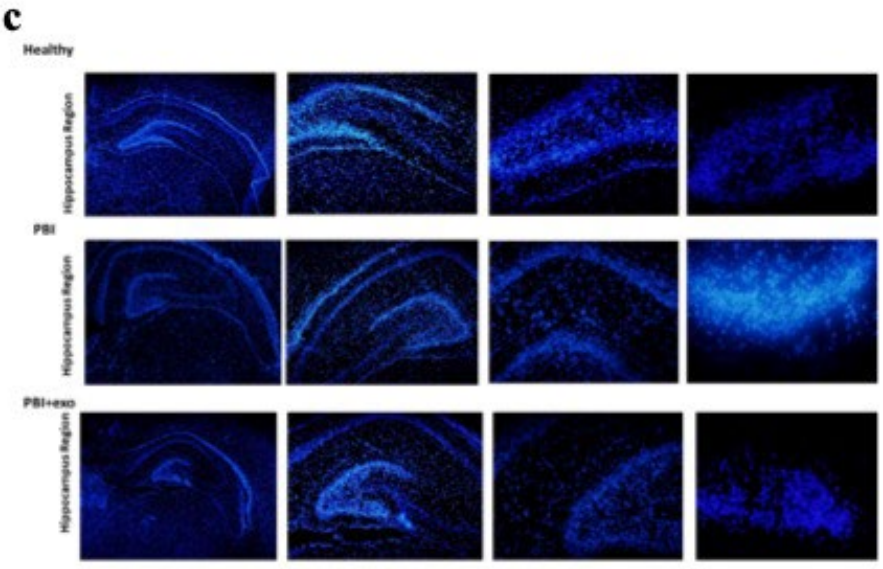
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Healthy
PBI
PBI+exo
Hippocampus Region
Hippocampus Region
Hippocampus Region

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Acoustic Brainstem Potentials in Congenital Cytomegalovirus Infection: University Medical Centre Ljubljana Experience

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INTRODUCTION
Normal hearing is key in the development of speech and normal global development in children. Congenital cytomegalovirus infection (cCMV), can lead to neurodevelopmental complications in children, including hearing loss. Although hearing loss is more frequently encountered in symptomatic patients and can be present at birth, it can also appear later in childhood and in initially asymptomatic individuals. In Slovenia, Otoacoustic Emissions (OAE) testing is used as a screening method for hearing loss in all newborns but can be normal in isolated acoustic nerve neuropathy. In such cases, Brainstem-Evoked Response Audiometry (BERA), is key for an early diagnosis and further monitoring.

PATIENTS AND METHODS
A retrospective analysis of the medical records of patients with confirmed cCMV, referred to the Neurophysiology laboratory of the University Medical Centre Ljubljana from 2002 to 2023 was performed. All patients were tested using the BERA method.

RESULTS
Fifty patients with cCMV (14 asymptomatic and 36 symptomatic) were referred to the neurophysiology laboratory during the study period and 94 BERA were performed in this group. Abnormal BERA results were recorded in 66 % of patients. The abnormalities were initially detected between three and six months of age. Hearing loss was present in 72 % of children with symptomatic cCMV and in 50 % of children with asymptomatic cCMV. Isolated hearing loss in asymptomatic cCMV infection with normal OAE at birth was detected in two patients. Both received antiviral treatment, resulting in improvement or stabilization of follow-up BERA.

CONCLUSIONS
Many cCMV patients will face hearing loss, more frequently symptomatic patients, which was also the case in our group of children. Hearing loss is more frequently a late manifestation of cCMV (a median delay of 33–44 months), but most hearing losses in previously unaffected patients in our group were discovered much earlier, between three and six months of age. BERA is superior to OAE and early and regular BERA follow-ups are mandatory to detect late-onset and progressive hearing loss in cCMV patients, offering the possibility of early audiology referral and intervention.

None declared

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THE MOST SEVERE FORM OF SMA IN A SMALL FOR GESTATIONAL AGE TERM INFANT WITH MULTIPLE FRACTURES OF THE EXTREMITIES

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INTRODUCTION

Werdnig-Hoffmann disease (SMA-type1) is the most common type of SMA which manifests during the prenatal period or within the first six months of life, affecting approximately one in every 10,000 live births globally. At the same time, there exists another form of spinal muscular atrophy, symptoms of which appear before birth as a decrease or complete absence of fetal movements in the last trimester of pregnancy. This rare and tremendously severe form is known as SMA type 0 or perinatal SMA. Infants with SMA type 0 or 1 usually have a low Apgar score and are often misdiagnosed with asphyxia at birth.

MATERIAL AND METHODS

A male infant born at full term but small for gestational age (37 weeks, 1800 g, 42 cm) via emergency cesarean section due to fetal distress After birth the boy required positive pressure ventilation, chest compressions, and epinephrine administration. The infant's Apgar scores at 1 and 5 minutes were 1 and 3, respectively. Upon admission to the Neonatal Intensive Care Unit (NICU), the infant presented with pale skin, severe central nervous system depression (coma), scattered rales over the lungs on mechanical ventilation, bradycardia episodes, multiple extremity bone fractures (humerus, radius, femur). Osteogenesis imperfecta was initially suspected. Therapeutic hypothermia was initiated because of severe birth asphyxia and symptoms of severe hypoxic-ischemic encephalopathy.

RESULTS

Imaging studies revealed multiple bone fractures, a ventricular septal defect on echocardiogram, and symmetrical periventricular hyperechogenicity on cranial ultrasound. Notably, no electrographic seizures were detected on amplitude-integrated electroencephalogram (aEEG). Newborn screening raised suspicion for spinal muscular atrophy (SMA), which was confirmed through molecular genetic testing (MLPA method), revealing complete deletion of SMN1 which is the main cause of SMA-1 with AR inheritance, deletion of exon 5 of NAIP, as well as deletion of one SMN2 allele which is related with severity of disease presentation.

CONCLUSION

Although severe asphyxia at birth is a fairly common diagnosis in full-term infants who require resuscitation after birth, have a low Apgar score and demonstrate severe neurological symptoms due to hypoxic-ischemic encephalopathy, other diseases, including SMA, may have similar clinical features, which requires careful differential diagnostic approach.

"None declared".

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PRELIMINARY RESULTS ON REDUCTION OF CEREBRAL NIRS (NEAR INFRA-RED SPECTROSCOPY) VARIABILITY AFTER EXOGENOUS SURFACTANT (ES) WITH DIFFERENT MODALITIES OF ADMINISTRATION IN A CONSECUTIVE GROUP OF PRETERM BABIES: A SINGLE CENTRE EXPERIENCE

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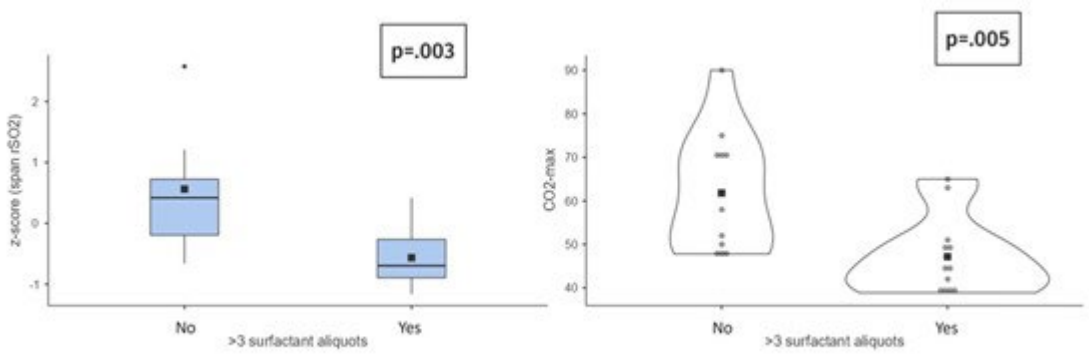
Introduction
Thirty years ago, the first attempt by Saliba to reduce negative effects (hypercarbia) by slowing the ES administration (1) while 19 years later we observed the first LISA attempt by Klebermass-Schrehof (2). Many studies, since that time, tried to minimize invasiveness of ES and subsequent cerebral blood flow perturbations studied by NIRS. We could not escape this medical challenge by looking for a less problematic modality of ES administration via delivering multiple aliquots of ES instead of a single one, as usually performed. The aim of the study was to test the hypothesis that a different way of administering ES in more aliquots could be a convincing way to undergo further studies.

Methods
Patients between 26+0 and 35+6 weeks of GA, requiring ES administration were enrolled (April 2023-February-2024). Differently fractioned doses were delivered according to an arbitrary standard dosage (0,3 ml per aliquot in babies < 29 wks; 0,6 ml in babies > 30 wks) and delivered while NIRS and transcutaneous CO2 (tCO2) monitoring was always guaranteed.

Results
Twenty four patients were enrolled, median GA 29 wks (IQR 4.5); BW 1223±560g. Fifty % of the cohort received less than 3 aliquots, the other 50% more than 3. Monitoring was started before procedure and continued 30' after the last ES aliquot administration. The variability of NIRS-SpO2 values was significantly higher in the first group (p=.007) with less aliquots administered, similarly to increased NIRS-rSO2 values (p=.003) and tCO2 maximal levels (p=.005-Table).

Conclusion
Our data obtained in the group with > 3 fractionated doses of ES seem to justify the preparation of a more robust study as the combination of reduced NIRS variability and reduced tCO2 maximum levels are consistent with a more stable cerebral blood flow during the problematic procedure of ES administration.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