Title: SafeBoosC III- MRI at term equivalent age.

Background

Infants born earlier than 28 weeks of gestational age are at higher risk of intracranial ischemic and hemorrhagic injuries, which often occur within the first 72 hours after birth[1]. During this period, several hemodynamic and respiratory events can occur and result in altered cerebral perfusion and oxygen supply and, finally, in brain injury[1].

The SafeBoosC phase II multicentre randomized clinical trial investigated the benefits and harms of monitoring cerebral oxygenation by near-infrared spectroscopy (NIRS) combined with an evidence-based treatment guideline during the first 72 hours of life vs. a control group with no NIRS monitoring and usual treatment[2]. This clinical trial demonstrated a significant reduction in the burden of cerebral hypoxia in the experimental group[2].

The overall objective of the SafeBoosC-III trial is to investigate the benefit and harms of treatment based on NIRS monitoring compared with usual treatment. The hypothesis is that treatment based on NIRS monitoring for extremely preterm infants during the first 72 hours of life will result in a reduction in severe brain injury or death at 36 weeks postmenstrual age (PMA) determined by cerebral ultrasound (US).

Two-dimensional cerebral ultrasound is easily performed at the bedside and shows a good correlation with brain magnetic resonance imaging (MRI) when assessing moderate and severe cerebral injury of extremely preterm infants[2]. At term age, however, MRI has been demonstrated to be more accurate than ultrasound to detect white matter (WM) injury and cerebellar haemorrage[3-4].

The evaluation of the impact of NIRS monitoring through brain MRI with a validated score[5] in a representative cohort, should confirm and strengthen SafeboosC III results and could serve as a pilot to determine clinically meaningful differences on brain MRI, and then, to know the Kidokoro WM injury Score distribution in this population to propose future studies.

Objectives

This secondary study aims to

1) Evaluate the impact of NIRS monitoring on the white matter evaluated through brain MRI validated score[5] at 40-44 weeks of PMA.
2) Evaluate the impact of NIRS monitoring on intraventricular and cerebellar hemorrhage evaluated through brain MRI at 40-44 weeks of PMA compared with cranial US until 36 weeks of PMA.

Hypothesis

Treatment based on NIRS monitoring for extremely preterm infants during the first 72 hours of life will decrease the mean white matter abnormality score at 40-44 weeks of postmenstrual age.

Methods.

Preterm infants <28 weeks of gestational age born at Hospital Clínic of Barcelona and Hospital Sant Joan de Déu undergo, as per protocol, a brain MRI at 40-44 weeks of PMA at the same facilities at Hospital Sant Joan de Déu.

Patients included on Safeboosc III with available brain MRI at term age will be included in this secondary study. *Figure 1* summarizes Hospital distribution of the patients.

Figure 1. Number of patients and brain MRI perfomed.

	Hospital Clinic of Barcelona	Hospital Sant Joan de Déu	Total
Total patients	59	32	91
Alive patients at 40-44 weeks of PMA	52 (88%)	24 (75%)	76 (83%)
Patients with brain MRI at 40-44 weeks of PMA	43 (82%)	18 (75%)	61 (80%)
NIRS monitored	18 (42%)	9 (50%)	27 (44%)
No NIRS monitored	25 (58%)	9 (50%)	34 (56%)

A validated MRI scoring system will be used to evaluate cerebral WM abnormalities with quantitative biometrics[5]. Besides the scoring items, the presence or absence of subependymal, intraventricular hemorrhage (classified based on Papile classification)[6], and cerebellar hemorrhage will be noted. Findings on brain MRI will be compared with US findings before 36 weeks of PMA or discharge home.

Qualitative and quantitative assessment of MRI will be performed by two independent pediatric neuroradiologists.

Cerebral WM abnormalities will be graded on a scale between zero and 4 for 6 variables[5]: 1) cystic degeneration, 2) focal signal abnormalities, 3) delayed myelination, 4) thinning of the corpus callosum, 5) dilated lateral ventricles, and 6) reduction of WM volume. Thinning of the corpus callosum will be assessed with measurements of callosal thickness at 3 positions (genu, midportion of the body, and splenium) on a midsagital section. Lateral ventricular dilation will be assessed by measurement of the lateral ventricular diameter on a coronal section at the level of the ventricular atrium. Reduction of WM volume will be determined by measurement of biparietal width on a coronal section. Because biparietal width increases with PMA on MRI, the measured value will be corrected with linear regression analysis according to the following equation: corrected biparietal width = measured biparietal width + the slope × (40 – postmenstrual age on MR imaging)[5].

Statistical analyses

Data will be analyzed with SPSS version 20.0 software (SPSS, Chicago, Illinois). Student t test or analysis of variance will be used when continuous parametric variables will be compared. Mann-Whitney U tests or Kruskal-Wallis tests will be used to compare continuous nonparametric variables. Chi-square tests will be used with categoric variables. Simple linear regression analysis will be used to obtain the slopes of the association between different measurements and postmenstrual age on MRI. Two-sided P values 0.05 will be used to indicate statistical significance.

Power calculation

An interquartile range between 1 and 2 points in the WM scale has been observed in similar studies[5], therefore considering the sample size we have power to detect a difference of 1.5 points in the WM MRI score between both groups, which could be considered clinically significant.

Power For Comparing Two Means

Input Data

Two-sided 95% Confidence Interval

	Group 1	Group 2	Difference*
Mean	3	4.5	-1.5
Sample size	27	34	
Standard deviation	2	2	
Variance	4	4	

Power = 82.89%
by the normal approximation method

* Mean difference= (Group 1 mean) - (Group 2 mean)

Ethics

The approval of the Ethics committees of both Hospitals will be requested after the steering committee will accept this study protocol. An additional paternal consent will not be required since the processing of the clinical data has been already signed within SafeboosC III consent.

3) Expected data of registration of the study protocol on clinicaltrials.gov

May 2022

4) Expected date of manuscript submission

December 2022

5) First author (investigator responsible for the study and publication)

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