



Extremely premature births during the peak of the COVID-19 pandemic: an international study of the active SafeBoosC III departments

Background

On the 11th of March 2020, COVID-19 was declared a pandemic by the World Health Organisation, which led to an almost worldwide lockdown (1). During the lockdown, reductions in preterm birth rates and very low birth weight infants have been reported in both Danish (2) and Irish (3) studies. Within the SafeBoosC-III investigator group, several neonatologists concurrently observed that the number of extremely low gestational age neonates (ELGAN) (gestational age below 28 weeks) admitted to their respective departments, had declined during the pandemic, while others observed no difference in the number of admitted ELGAN (oral communication). Furthermore, despite a 60% increase in the number of hospitals open for randomisation in the SafeBoosC-III trial from January to May, the randomisation rate has not increased as expected. We are therefore curious to evaluate if the number of admitted extremely preterm infants has decreased in the SafeBoosC-III departments during the global lockdown, and whether there is an association between the level of lockdown restrictions and change in the number of ELGAN admissions. We hope that this study will contribute further to the knowledge of the COVID-19 pandemics' effect on ELGAN birth as well as its effect on international randomised clinical trials.

Study design and methods

This is a retrospective, observational study based on the consortium of the SafeBoosC-III randomised clinical trial (4). The SafeBoosC-III trial investigates the benefit and harms of treatment guided by cerebral near-infrared spectroscopy monitoring compared with treatment and monitoring as usual in extremely preterm infants. All 79 neonatal intensive care units (NICU) that are active in the consortium will be invited to participate in this study. Primary investigators will be contacted and asked to provide the number of ELGAN admitted to their NICU within the most rigorous three months of the COVID-19 pandemic as well as the number of ELGAN admitted within the same period in 2019. The most rigorous three months of the COVID-19 pandemic will be a subjective definition by the local investigator, based on when the lockdown restrictions were strictest. Investigators will be asked to clarify how and where the information has been obtained from. Furthermore, investigators will be asked to classify the level of restrictions imposed upon the public, during the lockdown period, in a Likert scale format from 1-5. The scale used to assess this is based on the New Zealand COVID-19 alert levels (5). Additionally, investigators will be asked to categorise the impact of the COVID-19 lockdown on the everyday life of a pregnant woman.

Predefined regions based on the active SafeBoosC-III NICUs:

North America	Northern Europe	Eastern Europe	Southern Europe	Western Europe	Asia
USA	Denmark, Norway	Austria, Poland, Czech Republic, Ukraine, Turkey	Spain, Portugal, Italy, Greece	Germany, UK, Ireland, Switzerland, Belgium	India, China



Outcomes

The primary outcome will be the difference in the total number of ELGAN admissions in SafeBoosC-III departments during the peak three months of the COVID-19 pandemic in 2020 compared to the same three months period in 2019.

Secondary outcomes will be

- 1) The difference in the number of ELGAN admissions during the peak three months of the COVID-19 pandemic versus the same three months in 2019, within the following regions: North America, Northern Europe, Southern Europe, Western Europe, Eastern Europe, Asia.
- 2) Correlation between the level of lockdown restrictions and number of ELGAN admissions.

For the purpose of an exploratory analysis, we will ask investigators to rate the likelihood that restrictions outside or inside health institutions in their country/region, have led to non-admittance of ELGAN. Causes could be intrauterine death, or no transfer from place of birth

Statistical analysis

The number of ELGAN admissions during the three peak months in total, during the same months in 2019, within each region and within each level of lockdown restriction, will be reported as numbers. The primary outcome and the secondary outcome regarding the difference in the number of ELGAN admissions between years and regions will be analysed by using Fisher's Exact test for 1x2 tables. To analyse the correlation between the level of lockdown restrictions and the change in number of ELGAN admissions, we will use simple linear regression. The exploratory outcome investigating if lockdown restrictions could lead to non-admittance of ELGAN will not undergo statistical analysis but will be reported and discussed. For the primary outcome, an alfa level of 5% is chosen as a threshold for significance. To correct for multiple testing in the secondary outcomes, we have chosen an alfa level of 1%

Power analysis

In a previous funding application for the SafeBoosC-III trial, we estimated that the 93 departments taking part in the application, had a total of 3000 ELGAN admissions per year (4). Therefore, we expect participating departments on average to have had approximately 30 admissions in 2019, i.e. approximately seven admissions in a three months period. Therefore, if half of the NICUs (i.e. 40 departments) participate, we would expect a total of 280 EP infant admissions within the 40 departments in 2019. Thus, a 16.5% change in the primary outcome is needed to show a statistical significance at a 5% alfa level.

Publication and authorship

The study will be registered on clinicaltrials.gov. The results will be submitted to a peer-reviewed international journal while the manuscript will be placed in a preprint archive to disseminate the result without delay. One author per participating NICU can obtain co-authorship, by providing sufficient data as described in the data sheet document, as well as adhering to the Vancouver Criteria.



References

1. Hale, T., Webster, S., Petherick, A., Phillips, T., & Kira, B. (2020). Oxford covid-19 government response tracker. *Blavatnik School of Government*, 25.
2. Hedermann G, Hedley PL, Bækvad-Hansen M, et al. Arch Dis Child Fetal Neonatal Ed Epub ahead of print: [please include Day Month Year]. doi:10.1136/ archdischild-2020-319990
3. Philip RK, Purtill H, Reidy E, et al. Reduction in preterm births during the COVID-19 lockdown in Ireland: a natural experiment allowing analysis of data from the prior two decades.. medRxiv; 2020. DOI: 10.1101/2020.06.03.20121442.
4. Hansen ML, Pellicer A, Gluud C, et al. Cerebral near-infrared spectroscopy monitoring versus treatment as usual for extremely preterm infants: a protocol for the SafeBoosC randomised clinical phase III trial. *Trials*. 2019;20(1):811
5. <https://covid19.govt.nz/covid-19/alert-system/alert-system-overview/#covid-19-alert-system>