SUMMARY SOS BPD study

Supplemental oxygen strategies after the neonatal intensive care period in children with bronchopulmonary dysplasia (BPD)

Rationale: Every year in the Netherlands, 500 preterm born children develop bronchopulmonary dysplasia (BPD), a chronic lung disease with life-long sequelae. The main treatment of BPD is supplemental oxygen. However, no study has ever examined the optimal oxygen saturation (SpO_2) target in children with established BPD, while both too little and too much oxygen may lead to serious adverse events. International guidelines, based on expert opinion only, recommend a lower limit ranging between 93 and 95%, while limits of 90% are considered usual care in most Dutch neonatal units and regional hospitals. We hypothesize that a lower limit of 95% when compared to 90% leads to better lung growth assessed indirectly by body weight at 6 months corrected age.

Objective: The primary objective of this study is to investigate if targeting a higher SpO_2 (i.e. 95% lower limit) leads to superior growth of normal lung tissue (assessed indirectly by body weight) at 6 months corrected age as compared to targeting a lower SpO_2 (90% lower limit) in children with moderate-severe BPD from 36 weeks PMA and onwards.

Study design: Randomised controlled open multi-centre study with two arms: 1. Lower SpO_2 limit of 95%; 2. Lower SpO_2 limit of 90%. Follow up will be one year with three visits. SpO_2 curves will be audited from pulse oximeters and feedback will be given to the physicians and/or parents. They will be stimulated to actively wean the children from supplemental oxygen based on these curves and study group.

Study population: Children born < 32 weeks of gestational age with moderate or severe BPD, will be included between 36 and 38 weeks of PMA. BPD will be defined as oxygen need for ≥ 28 days from birth until 36 weeks of PMA. BPD severity will be assessed at 36 weeks PMA. Children who, at that time, need ≥ 30% supplemental oxygen or depend on nasal continuous positive airway pressure (nCPAP), high flow nasal cannula oxygen (HFNC) or mechanical ventilation are classified as having severe BPD. If children need >21% oxygen but < 30% they have moderate BPD. If needed, an oxygen reduction test will be performed to assess BPD severity. (3)

Intervention (if applicable): weaning of supplemental oxygen based on a lower SpO_2 limit of 95% as compared to 90% (usual care). Weekly saturation profiles will be gathered and

analysed. Based on the analysis, respiratory support can be adjusted (increased or decreased) so that the child will stay in the right oxygen saturation range.

Main study parameters/endpoints: The primary outcome is body weight at 6 months corrected age, as a surrogate for lung growth. Secondary outcomes are weight and height at 12 months corrected age, hospital re-admissions, parental quality of life, infant stress, length of hospital stay, duration of oxygen supplementation and unscheduled health care visits. Lung function and CT scores will be measured in a subgroup of patients. A cost-effectiveness analysis will be performed alongside this trial.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden and risks associated with participation in the study are limited. There are no extra visits to the hospital as the 2 visits follow the routine follow-up of patients born extremely preterm. At every visit weight, height and head circumference are measured, which is routine care. In a subgroup of patients lung function tests and/or a free breathing CT scan of the chest will be performed, only if these tests are routine care in the specific hospitals. The parents will be asked to fill in 2 questionnaires (CarerQOL and IBQ-R) at inclusion, 6 and 12 months. Parents will have the possibility to record data on respiratory complaints, admissions, and absence from work in an online monthly diary.
The risks of the study are negligible as the lower limit of 90% is considered usual care. Also, in a study in *younger* children from 32 weeks PMA onwards there was no difference in endpoints (growth, neurodevelopmental outcome) between a lower (91-94%) and a higher (95-98%) SpO_2 target. Our study includes children with an established diagnosis of BPD, from 36 weeks PMA onwards, which is the period that alveolarization starts, which implies that SpO_2 limits may be different in this group. Potential benefit of the study is that weaning of oxygen is performed in a controlled and well-monitored way with frequent feedback to treating physicians and/or parents. A disadvantage of the study may be that children in the high SpO_2 group will be longer on oxygen, whether in the hospital or at home. In the study by Askie et al length of hospital stay was not different for the high versus low SpO_2 group.