**Pilot Study: Does Sustained Lung Inflation at Birth Improve Cerebral Oxygen Saturation in Preterm Infants?**

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1. Abstract

Transition from fetus to newborn is a complex process with an ongoing discussion about the use of supplemental oxygen. It is unknown which oxygen concentration is appropriate. As the brain is the most vulnerable organ system of the infant, a direct way to assess its oxygenation would be potentially useful. Such a new approach is the measurement of regional cerebral oxygen saturation using nearinfrared spectroscopy.

Many preterm infants need positive pressure ventilation during the transition to air breathing at birth to assist lung aeration and the initiation of pulmonary gas ex-change. It is possible that an initial sustained inflation (SI) supports the transitional period of the lungs. Clinical studies have shown lower intubation rates when a SI is given. There are no data of cerebral side effects of SI.

The aim of the present study is to investigate in preterm infants with need of respiratory support, whether a SI immediately after birth improves cerebral oxygen saturation.

2. Background

2.1. Near Infrared Spectroscopy

Near-infrared-spectroscopy (NIRS) enables non-invasive measurement of oxygenation in regions of interest e.g. cerebral, renal and “peripheral muscle” tissue. In 1977 the principle was described by Jöbsis. NIRS is based on two fundamental facts: the relative transparency of biological tissue to near infrared light (wavelength 700-1000nm) and the presence of chromophores (colour bearing compounds) in the biological tissue, which have oxygenation-dependent absorption properties (e.g. haemoglobin and cytochrome oxidase) in the near infrared region. NIRS enables therefore the noninvasive continuous measurement (of changes in the concentration) of oxygenated haemoglobin (HbO2), deoxygenated haemoglobin (Hb) and cytochrome oxidase (CytOx).

Furthermore, spatially resolved spectroscopy, a new NIRS method, was recently introduced for evaluation of regional tissue oxygen saturation (rSO2). With this technology it is possible to measure regional tissue oxygen saturation in different organ systems (brain, kidney, liver, muscle, and others) or body regions (pre-, post-ductal peripheral tissue).

Regional tissue oxygen saturation depends on the local balance of oxygen delivery and oxygen consumption, and the regional arterial/venous volume ratio, reflecting oxygen saturation in veins (70-80%), capillaries (5%) and arteries (15-25%). The main component
of tissue oxygen saturation is venous blood, thus representing oxygen saturation after oxygen consumption by the tissue. Therefore, the values for regional oxygen saturation tend to be close to venous oxygen saturation, but do not equate venous saturation.

2.2 NIRS and changes in cerebral haemodynamics and oxygenation

Numerous studies investigated cerebral haemodynamics during different interventions: Effects of suctioning on cerebral haemodynamics during ventilation were studied and as expected there was a fall cerebral oxygenation. The effect of surfactant administration on cerebral blood volume (CBV) was studied. Whereas Hb and HbO2 changes seemed to be according to changes of arterial oxygen saturation, CBV showed inconsistent changes within different studies. Using NIRS, administration of aminophyllin and indomethacin showed significant effects on cerebral haemodynamics, whereas caffeine and ibuprofen had no or only small effects.

Further studies investigated the effects of different clinical situations and procedures such as a patent ductus arteriosus, blood pressure changes, cord clamping, and blood sampling from umbilical artery catheter on cerebral haemodynamics. Our group investigated changes of cerebral oxygenation during periodic breathing, and during episodes of apnoea in preterm infants. Furthermore, we used tilting manoeuvres to investigate the cerebral autoregulative capacity, showing that lower gestational age was associated with increased changes of CBV, and that preterm infants with periventricular leucencephalomalacia showed reduced cerebral autoregulative capacity. In these studies the NIRO 500 and 300 (Hamamtsu, Japan) were used.

2.3 Transition of the newborn and oxygen saturation

Transition from fetus to newborn is a complex physiological process. Within the recent years interest has grown in the use of pulsoximetry to monitor arterial oxygen saturation during this transitional period. All newborn infants have oxygen desaturation at birth. A newborn undergoing normal postnatal transition needs more than 5 minutes to attain an arterial oxygen saturation >80% and almost 10 minutes to reach 90%. Several studies have shown, that there are significant differences in the course of arterial oxygen saturation (SpO2) according to the mode of delivery. Newborn infants after elective CS showed lower SpO2 values during transition compared to infants after vaginal delivery.

There is an ongoing discussion about the use of supplemental oxygen during neonatal
resuscitation, because it is unknown which oxygen concentration is appropriate for preterm and term infants during resuscitation. As the brain is the most vulnerable organ system of the infant, a more direct way to assess its oxygenation in a simple non-invasive way would be potentially useful. A new approach to cerebral oxygenation is the measurement of regional oxygen saturation using NIRS. There are some reports of regional oxygen saturation of the brain on the first day of life \textsuperscript{xxii}, during the first weeks \textsuperscript{xxiii,xxiv,xxv,xxvi}, and during transition phase \textsuperscript{xxvii,xxviii}.

Our group published data on cerebral oxygen saturation within the first week of life \textsuperscript{xxix}, and for the first time in literature in a large group of newborn infants during transition\textsuperscript{xxx}. We have shown, that during transition of the newborn dynamics of changes in regional cerebral oxygen saturation (rSO$_2$brain) and pulsoximetric arterial oxygen saturation (SpO$_2$) were not paralleling each other. rSO$_2$brain did not show changes in periods were SpO$_2$ significantly changed. Therefore, measurement of both, arterial and regional oxygen saturation is necessary to estimate cerebral oxygen supply. In these studies the Invos™ Cerebral/Somatic Oximeter monitor (Covidien, USA) was used.

### 2.4 Sustained lung inflation

Many preterm infants need positive pressure ventilation (PPV) during the transition to air breathing at birth to assist lung aeration and the initiation of pulmonary gas ex-change. It is possible that an initial sustained inflation (SI) might overcome the long time constant of a liquid-filled lung and facilitate early gas exchange to reduce the need for intubation\textsuperscript{xxxi,xxxiv}. Clinical studies have shown lower intubation rates when a SI is given\textsuperscript{xxxi,xxiv}. However, this procedure is not commonly used because of the risk of overinflating and damaging the lung during the initial inflation\textsuperscript{xxv}. Despite this, the international guidelines on neonatal resuscitation state that an initial SI may be beneficial during stabilization at birth\textsuperscript{xxvi}.

In animal experiments with preterm rabbits it has ben shown, that duration of SI has to be between 10 and 20 seconds to fully aerate the lung and to establish an adequate functional residual capacity (FRC)\textsuperscript{xxvii}. Using this duration there were no signs of overinflation of the premature lung whatsoever. Furthermore it was shown, that SI plus subsequent application of positive endexspiratory pressure (PEEP) using a CPAP device promoted uniform lung aeration and created a much larger FRC at birth than ventilation without these techniques\textsuperscript{xxviii}. Very recently it has been shown that in preterm infants with respiratory distress syndrome, SI may decrease the need for mechanical ventilation without inducing evident adverse effects\textsuperscript{xxix}. Until now there is no literature, showing whether a SI after birth
3. Aims of the present study

The aim of the present study is to investigate in preterm infants with need of respiratory support, whether a SI immediately after birth influences cerebral oxygen saturation and cerebral blood volume. There are three specific aims.

3.1 Hypothesis I: SI and SpO2
According to physiology an increase in FRC with improvement of lung aeration may result in increase of SpO2, and thus a reduction of supplemental oxygen. The first hypothesis is, that use of SI increases SpO2 values, and reduces the need of supplemental oxygen.

3.2 Hypothesis II: SI and rSO2brain
According to physiology an increase of SpO2 may result in an increase of rSO2brain. The second hypothesis is, that the use of SI increases rSO2brain values.

3.3 Hypothesis III: SI and cerebral blood volume
SI has not shown any serious side effects in clinical trials untill now, but it may be associated with an significant change in CBV. Any positive pressure put on the thoracic wall may increase cerebral venous pressure, and may have influence on heart rate and cardiac output. Therefore, it remains unclear, whether the SI procedure impairs cerebral blood supply. It is unclear, whether there is reduction of cardiac output with reduction of CBV, or whether the increase on cerebral venous pressure results in increase of CBV. The third hypothesis is, that the use of SI significantly changes CBV.

4. Patients and Methods

4.1 Patients
Preterm neonates with a gestational age ≥28 and <34 weeks born at the Department of Obstetrics and Gynaecology, Medical University of Graz, who need respiratory support
during transition after birth (done by a neonatologist of the Department of Pediatrics, Medical University of Graz), will be enrolled into the study. Neonates with congenital malformations and neonates, who need primary intubation will be excluded.

4.2 Methods
4.2.1 Study design
Prospective randomised observational study.

4.2.2 Protocol
The medical history of any pathologic findings during pregnancy and birth will be collected. Gestational age, birth weight, circumference and diameter of arm and calf, gender, pH of umbilical artery and APGAR score will be documented in each neonate.

Resuscitation will be performed according the “European Consensus Guidelines” on the management of neonatal respiratory distress syndrome and the guidelines for neonatal resuscitation of the American Heart Association (of 2010). CPAP with mask will be performed with Neopuff Infant Resuscitator (Fisher&Paykel Healthcare, New Zealand). This T-piece ventilator is a pressure-limited mechanical device that supplies consistent peak inspiratory pressure (PIP) and PEEP, and is capable of delivering sustained inflation (SI). To avoid pressure leakage, a neonatal mask of appropriate size is used, which adequately covers both the mouth and nostrils of infants. To be sure about mask leakage the non-invasive respiratory-function monitoring is used.

4.2.3 Monitoring
The following non-invasive monitoring will be combined immediately after birth for the first 15 minutes of life:

1) Pulse oximetry and heart rate (IntelliVue MP50, Philips, Netherland)
2) Blood pressure measurement (IntelliVue MP50, Philips, Netherland)
3) Central temperature (IntelliVue MP50, Philips, Netherland)
4) NIRS (NIRO 200, Hamamatsu, Japan))
5) Video camera
6) Respiratory function monitor (Florian respirator monitors, Acutronic Medical Systems, Switzerland)
Data of the different devices will be stored in a polygraphic system (alpha-trace digitalMM, B.E.S.T. Medical Systems, Austria) for further analysis.

4.2.3.1 Pulse oximetry – arterial oxygen saturation and heart rate

For pulsoximetry the IntelliVue MP50 monitor (Philips, Netherland) will be used. The pulse oximetry sensor will be applied on the right palm or wrist immediately after birth for monitoring preductal arterial oxygen saturation and heart rate.

4.2.3.2 Blood pressure

For non-invasive blood pressure measurements the IntelliVue MP50 monitor (Philips, Netherland) will be used. The pneumatic cuff will be placed around the left upper arm and blood pressure measurements will be performed five and ten minutes after birth.

4.2.3.3 Central temperature

For noninvasive temperature measurements the IntelliVue MP50 monitor (Philips, Netherland) will be used. A rectal sensor will be placed for central temperature measurement.

4.2.3.4 NIRS

For NIRS measurements the NIRO 200 (Hamamatsu, Japan) will be used. This monitor uses a “continuous wave spatially resolved” technique for measurement of regional oxygen saturation (rSO2), this parameter is called tissue oxygenation index (TOI) within this device. Furthermore this monitor uses continuous wave technology to measure the following parameters: oxygenated haemoglobin (HbO2) and deoxygenated haemoglobin (Hb). The sum of these two is calculated and expressed as total haemoglobin (Hbtot). Changes of Hbtot represent changes in cerebral blood volume (CBV).

At the moment, the NIRO 200 is the only device, that is technically able to measure both, changes in regional cerebral oxygen saturation and changes in CBV, and is easy enough to use to be able to place a sensor immediately after birth, and to measure during the transition of the neonate. Very often the Invos™ Cerebral/Somatic Oximeter monitor (Covidien, USA) is used during transition, but this device will not give any information on changes in CBV. Immediately after birth a cerebral sensor will be placed on the left forehead.
4.2.3.5 Video camera

A video camera will record the term and preterm neonates during the whole measurement/transition time (first 15 minutes of life). *The camera is positioned in such a way, that no person can be identified (only hands can be seen). The recorded sequences allow identification of artefacts, and secure correct data analysis during sustained inflation.*

4.2.3.6. Respiratory function monitoring during CPAP or PPV with face mask

For respiratory function monitoring the Florian respirator monitor (Acutronic Medical Systems, Switzerland) will be used. It measures airway pressure and gas flow in and out of a face mask with a hot wire anemometer and its successful application during resuscitation has already been shown (57,58).

During CPAP or PPV the Florian respirator monitor displays continuously:

1. positive inspiratory pressure
2. positive end expiratory pressure
3. inspiratory and expiratory flow
4. inspiratory and expiratory tidal volume
5. leak between mask and face
6. respiratory rate
7. minute volume
8. spontaneous breathing

4.2.3 Randomisation

Preterm infants will be randomly assigned to one of two groups:

**Group A:** Standard resuscitation with CPAP (5cmH2O PEEP) and PPV (PIP 30cmH2O) with Neopuff Infant Resuscitator

**Group B:** Start with SI (PIP 30cmH2O) with duration of 15 sec, after that standard resuscitation with CPAP (5cmH2O PEEP) and PPV (PIP 30cmH2O) with Neopuff Infant Resuscitator. Only if heart rate continues to be below 100/min SI may be repeated twice.

*The randomization happens via internet using the “Randomizer”, a software program provided by the Institute for Medical Informatics, Statistics and Information, Medical University Graz.*

*There will only be descriptive statistical analysis.*
4.2.4 Standard resuscitation protocol

Ensure that the heart rate is >100bpm at minute 1.

If breathing is insufficient (none or insufficient breathing movements, retractions and nasal flaring) CPAP with mask will be applied with Neopuff Infant Resuscitator. CPAP is used with a PEEP of 5cm H2O, and intermittent positive pressure ventilation is used with a PIP of 30cmH2O (standard settings).

The goal of oxygen saturation should be an oxygen saturation value in the interquartile range of preductal saturations measured in healthy term babies following vaginal birth at sea level (minute 3: 70-75%, minute 5: 80-85%, minute 10: 85-95%)37. These targets may be achieved by initiating resuscitation with FiO2 of 0.3 and titrating the oxygen concentration to achieve an SpO2 in the target range as described above using pulse oximetry.

5. Research plan and time table

The project may start in Sept 2011 and is designed for a two year running time. Start with pilot study to ensure calculation of power (40 infants, 20 in each group).

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