The influence of cut-umbilical cord milking (C-UCM) on the cerebral oxygenation and perfusion of preterm and term infants

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1 Introduction

Fetal to neonatal transition is not only characterized by major changes in pulmonary perfusion, but hemodynamic changes as well. Both changes are strongly interrelated, and occur in a very short time period (first minutes of life).

The method of immediate umbilical cord clamping (within 15 seconds) after delivery of the newborn became routine 50-60 years ago. It was introduced as a package of care for reducing maternal postpartum haemorrhage. (1) Although umbilical cord clamping is a quick and simple intervention, the timing of umbilical cord clamping may have a large impact on the infant's health. (2)

During postnatal stabilisation of the newborn one of the essential aims is to establish lung aeration and increase pulmonary blood flow to improve oxygen delivery to the brain to meet the tissue demand. The concept of placental transfusion is the transfer of residual placental blood to the newborn resulting in increased haemoglobin levels and increased cardiac output and thus improved oxygen delivery. (3) In the last decade "delayed cord clamping" (DCC) was introduced to accomplish placental transfusion, especially in term infants. (4) Recently, different new concepts for promoting placental transfusion were developed including the concept of "physiological based cord clamping" (PBCC) (5). PBCC is defined as an approach, in which the first lung ventilation is facilitated, and the umbilical cord is clamped only after the establishment of pulmonary blood flow. Whereas in DCC the main intervention criterion is only the withholding of the clamping for a certain amount of time (2-4 minutes), in PBCC adequate pulmonary aeration is the criterion for clamping the umbilical cord. The debate on the optimal timing and type of umbilical cord clamping is still ongoing.

Besides DCC and PBCC, the alternative concept of "cord milking" was introduced(6) which includes "intact umbilical cord milking" (I-UCM) and "cut-umbilical cord milking" (C-UCM). I-UCM is based on grasping the unclamped umbilical cord and stripping the blood towards the neonate up to four times before clamping the cord. (3) In contrast, C-UCM is a procedure, in which the umbilical cord is clamped immediately after birth and cut with a cord length longer than 30 cm, and then it is manually milked once by the neonatologist simultaneously with the first breaths or with the initiation of respiratory support. (3,7) The blood volume administered to the preterm infant was 17.7 mL/kg/30cm. (8) Comparative prospective studies on the two

different approaches of cord milking (I-UCM and C-UCM) have not been published yet, and therefore it is unclear whether one of the approaches is superior compared to the other. However, C-UCM is supposed to be fast and easy to perform, especially during caesarean section or in situations in which urgent postnatal stabilisation interventions are needed. Therefore, the effect of placental transfusion promoted by C-UCM on cerebral oxygenation and perfusion is of special interest.

2 Background

2.1 Physiology of neonatal transition and the effects of umbilical cord clamping or milking

The fetal circulation is characterized by a high pulmonary vascular resistance and a low placental vascular resistance. Approximately 30-50% of fetal cardiac output perfuses the placenta, thus 30-50% of the venous return comes from the placenta. As most of the oxygenated blood coming from the placenta is preferentially shunted through the foramen ovale towards the left atrium, preload of the left ventricle is largely dependent on placental venous return in the fetus. At birth lung aeration results in a drop in pulmonary vascular resistance resulting in a simultaneous increase in pulmonary blood flow. The consecutive increase in pulmonary venous return gradually replaces the loss of placental venous return (following cord clamping). A delay in cord clamping (DCC or PBCC) or I-UCM may result in an increase in cardiac output, as the increase in pulmonary venous return is assisted by placental venous return for 2-3 minutes on the one hand, and the increase in neonatal blood volume due to placental transfusion on the other hand. Recent experimental studies in lambs have shown that immediate cord clamping (prior to lung aeration or lung ventilation) resulted in unstable hemodynamic parameters with an initial increase in carotid arterial flow and pressure, followed by a decrease in carotid arterial flow and pressure, accompanied with a significant increase in heart rate. (9) (Polglase et al 2015, =7neu) Instability of cerebral perfusion and oxygenation may be associated with brain damage in preterm infants.

The concept of C-UCM may substitute the adverse effects of immediate cord clamping by supplying additional placental blood to the infant, which is mostly performed during caesarean section or in the critically ill neonate.

2.2 Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) enables non-invasive measurement of tissue oxygenation in regions of interest e.g. cerebral, renal and peripheral muscle tissue. In 1977 the principle was described by Jöbsis. (10) NIRS is based on two fundamental facts: the relative transparency of biological tissue to near-infrared light (wavelength 700-1000 nm) 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. Therefore, NIRS enables the non-invasive continuous measurement (of changes in the concentration) of oxygenated haemoglobin (HbO2), deoxygenated haemoglobin (Hb) and cytochrome oxidase (CytOx).

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%). (11) 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. (11)

In the field of neonatology different NIRS devices are in clinical use, most of them are based on the method of "spatially resolved spectroscopy". This NIRS method was introduced for the evaluation of regional tissue oxygen saturation and is widely used for measurements on the cerebral tissue oxygenation (crSO2). (12) Moreover this technology enables measurements of changes in total haemoglobin which can be converted to changes in cerebral blood volume (ΔCBV). The disadvantage of this technique is that it is only possible to measure relative changes of these parameters.

Very recently, a new NIRS technology was introduced for clinical use. The tNIRS device of Hamamatsu (Japan) uses the method of the so called "time resolved spectroscopy". This technology is able to measure absolute values for total haemoglobin (Hb(tot)) and does enable the calculation of absolute CBV.

In animal experiments it has been shown, that immediate and delayed cord clamping influences cerebral oxygenation and perfusion measured non-invasively with NIRS. Human NIRS data in regard to different cord clamping procedures are not yet published at all. I-UCM has been introduced several years ago in preterm infants with need for respiratory support. It was shown, that this approach may improve short term and long term outcome of the preterm infants. (6) Furthermore, it was proven, that C-UCM was as effective as I-UCM in regard to the need of blood transfusions (4). Detailed analyses of the effects of such an approach on cerebral oxygenation and perfusion in preterm and term infants are still missing. Thus, further research on this topic is warranted.

2.3 Monitoring during immediate neonatal transition

Transition from fetus to extra-uterine life is a complex physiological process. Within the recent years interest has grown in the use of pulse oximetry to monitor arterial oxygen saturation (SpO2) and to guide medical interventions during the transitional period. (13-16) Immediately after birth, most of the newborn infants show oxygen desaturation with SpO2 values in the range of 40-70%. Newborn infants although undergoing normal postnatal transition frequently need more than 5 minutes to attain a SpO2 >80% and almost 10 minutes to reach 90%.

There is an ongoing discussion about the use of supplemental oxygen during neonatal stabilisation, since it is unknown which oxygen concentration may be appropriate for preterm and term infants. As the brain is the most vulnerable organ system of the infant, a more direct way to assess its oxygenation status in a simple non-invasive way would be potentially useful. A promising approach to assess cerebral oxygenation is the measurement of the regional tissue oxygen saturation by using NIRS.

Our research unit published data on cerebral oxygen saturation in newborn infants during immediate postnatal transition demonstrating a significant increase within the first 10 minutes after birth(17). Furthermore, we presented crSO2 data comparing vaginal delivery versus caesarean delivery. (18) Moreover, our group was the first to publish percentiles of cerebral regional oxygen saturation during the first 15 minutes after birth for the two most widely used NIRS devices (Medtronic INVOS 5100C(19)

and Hamamatsu NIRO 200NX(20)). Very recently, our group published data on the clinical use of these percentiles during neonatal transition in preterm infants with/without respiratory support. (21,22) Furthermore, we published data of the transitional behaviour of cerebral blood volume using NIRS in healthy term infants demonstrating a significant decrease of CBV during the first 15 minutes after birth. (23) Recently, we added CBV data of preterm and term infants with and without respiratory support, demonstrating differences in the postnatal course of CBV in those patients.

3 Aims of the present study

The aim of the study is to analyse whether C-UCM in preterm and term infants results in an improvement of cerebral oxygenation and perfusion during immediate neonatal transition measured with NIRS.

3.1 Hypotheses

Infants undergoing C-UCM after birth compared to infants without C-UCM show differences in cerebral oxygenation and perfusion in the first 15 min after birth.

3.1.1 Hypothesis I: C-UCM and CBV

In infants with C-UCM there is more CBV decrease immediately after birth, compared to infants without C-UCM, due to improved cerebral oxygen delivery.

3.1.2 Hypothesis II: C-UCM and crSO2

Infants with C-UCM have higher crSO2 values during immediate neonatal transition, compared to infants without C-UCM, again due to improved cerebral oxygen delivery.

3.1.3 Hypothesis III: C-UCM and stroke volume

In infants with C-UCM the stroke volume (SV) at 15 minutes after birth is higher, compared to infants without C-UCM.

3.1.4 Hypothesis IV: C-UCM and cardiac output

In infants with C-UCM the cardiac output (CO) at 15 minutes after birth is higher, compared to infants without C-UCM.

3.1.5 Hypothesis V: C-UCM and mean arterial blood pressure (MABP)

In infants with C-UCM the MABP at 5, 10 and 15 minutes after birth is higher, compared to infants without C-UCM.

4 Methods

4.1 Study population

4.1.1 Preterm infants

Neonates with a gestational age ≥28 - 37 weeks delivered by caesarean section at the Department of Obstetrics and Gynaecology, Medical University of Graz, will be enrolled into the study, provided written informed consent is obtained from parents prior to birth. Neonates with severe congenital malformations will be excluded.

4.1.2 Term Infants

Neonates with a gestational age ≥37 weeks delivered by caesarean section at the Department of Obstetrics and Gynaecology, Medical University of Graz, will be enrolled into the study, provided written informed consent is obtained from parents prior to birth. Neonates with severe congenital malformations will be excluded.

4.2 Study design

The present study is designed as a randomized controlled pilot trial. As there have not been prior human studies investigating C-UCM regarding the outcome measures cerebral oxygenation and perfusion, a randomized controlled pilot study is the appropriate first step to be able to calculate sample size for a bigger trial.

4.3 Sample Size

Sample size calculations were not performed, since there are no data from previous human studies available, and this pilot study needs to be conducted to generate data

for the sample size calculation of a consecutive main study. For this pilot study a sample size of 80 infants (20 subjects in the intervention group of preterm infants, 20 subjects in the intervention group of term infants, 20 subjects in each of the two control groups) is arbitrary designated.

4.4 Randomization

Based on a computer-generated randomization software (www.randomizer.at) the included neonates will be randomly assigned to the intervention group in which C-UCM will be performed or the control group without C-UCM. The randomization of the two different study populations (preterm/term infants) will be done separately. Blocked randomization with a block size of 8 will be used.

4.5 Procedure

The medical history focussing on any pathologic findings during pregnancy and delivery will be collected and stored anonymously.
After delivery of the neonate via caesarean section, in the intervention group the umbilical cord will be clamped within 30 seconds and cut long at least 30 cm by the obstetrician. The neonate is then placed under an overhead heater by the midwife. There, the umbilical cord must be untwisted and held in a vertical position. It is milked once by the neonatologist towards the baby at a speed of approximately 10 cm/s and then clamped 3 cm from the umbilicus by one member of the clinical team. In contrast, in the control group the umbilical cord is cut according to the standard procedure and no C-UCM is performed. The further treatment procedure is the same in both groups.
A NIRS transducer will be placed on the newborn's left forehead, and fixed with a modified neonatal CPAP cap or gauze bandage by a scientific staff member without disturbing routine medical care. Furthermore, a pulse oximeter sensor will be attached on the right wrist or palm to monitor preductal SpO2 and heart rate. Moreover 4 electrodes are fixed on the skin for the non-invasive cardiac output monitoring (NICOM) to evaluate SV and CO. All the measurements will be performed within the first 15 minutes after birth.

The pneumatic cuff for the oscillometric measurements of the arterial blood pressure will be placed around the left upper arm (or alternatively on the left lower leg) at 5, 10 and 15 minutes after birth. A capillary blood gas check 15 minutes after birth will be performed in all the patients; However infants in need for respiratory support during postnatal stabilisation receive this blood gas check routinely. Moreover, rectal temperature will be measured at 15 minutes after birth.
A stopwatch is started at delivery, the time points of umbilical cord clamping, C-UCM in the intervention group, establishment of NIRS measurement, establishment of SpO_2 measurement, and blood drawing for the gas check will be noted.

4.6 Materials

Immediately after birth initial medical care is performed in a 'Giraffe' incubator (GE Healthcare; United Kingdom) or on a resuscitation cot ('CosyCot', Fisher&Paykel Healthcare; New Zealand). If necessary, respiratory support is applied by using a 'Neopuff Infant T- Piece Resuscitator' (Perivent, Fisher& Paykel Healthcare; New Zealand) and a round face mask of appropriate size (LSR Silicon mask no. 0/0 or 0/1, Laerdal; Norway). NIRS measurements were carried out by using 't-NIRS' or 'NIRO 200-NX' tissue oxygenation monitor (Hamamatsu; Japan). The 'Aesculon Electrical Velocimetry monitoring system' (Osypka, Berlin, Germany) is used to assess CO and SV non-invasively. Vital signs (HR, SpO2, arterial blood pressure and rectal body temperature) were recorded by using an 'IntelliVue MP70 or MP30 Neonatal Monitor' (Philips; The Netherlands). For later analysis all parameters and the video recordings were stored using a multichannel system 'alpha-trace digital MM' (BEST Medical Systems; Austria). ***The Axis P1354 video camera (Axis Communications, Sweden) 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 the intervention.***

4.7 Primary and secondary outcome measures

The primary outcome parameters for this study are the changes in CBV within the first 15 minutes after birth.

Secondary outcome parameters include cTOI, SpO2, HR, SV, CO and MABP within the first 15 minutes after birth.

4.8 Statistical Analysis

The measurement will take place in the first 15 minutes after birth. Especially in the first three minutes missing values are very common. Therefore the analysis of continuous measured data will start at that first minute with <50% of newborns having missing values. To include all newborn infants with valid measurements after this time point a linear mixed models will be used to analyse the difference in CBV, cTOI, SpO2, HR, SV and CO between newborn infants with and without C-UCM. Categorical secondary outcome parameters (MABP) will be analysed using χ^2 or Fisher's exact Test. Patient's characteristics will be compared using t-Test or Mann Whitney U-Test for continuous variables and χ^2 or Fisher's exact Test for categorical variables.

5 Research plan and time table

The study may start in 2018. Recruitment will take one to two years.
The study is designed for an approximately three year running time.

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