BABYLUX

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Table of Contents

1. Executive Summary 4

2. Introduction 5

3. Clinical Protocol 6

4. Conclusions and Future Work 13

1. Executive Summary

The clinical partners have developed a protocol for verification of system performance in clinical care of newborn infants. Three groups of infants will be studied. Twenty term newborn infants immediately after delivery by caesarian section and again on the following day when stable, twenty preterm infants when their respirator is adjusted to normalise blood pCO2, and twenty unstable newborn infants during a 24 hours period. The purposes are to verify that the instrument produces expected changes in brain oxygenation and blood flow after birth, and when blood pCO2 changes, and that the variability of readings when changing sensor position and the signal loss due to movement and other disturbances during clinical care is of acceptable magnitude. Finally, users will report on user-friendliness as well as usefulness and trustworthiness of the data.

2. Introduction

This document includes the draft clinical protocol.

3. Clinical protocol

3.1. Participating centres

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2. Department of Clinical Sciences and Community Health, Università degli Studi di Milano FONDAZIONE IRCCS CA' GRANDA - OSPEDALE MAGGIORE POLICLINICO MILANO – Italy

3.2. Background

Over the last two decades, the percentage of preterm births in the Western hemisphere rose by ~20%. Preterm birth is associated with an increased risk of brain damage and neurodevelopmental deficit. Brain injury in preterm babies is a complex mixture of destructive events and developmental disturbances affecting the developing brain. The concept of gestationally determined regional vulnerability in the brain has been emphasized: the site and nature of the injury sustained being determined by a combination of the characteristics of the insult, the specific tissue and cell vulnerability and the gestation of the infant. The vulnerability of the white matter in the brain of premature babies is important. However, a more complex pan-brain developmental growth disruption is associated with preterm birth.

Different pathophysiological mechanisms are involved in injuring the developing brain, in particular infection-inflammation, pre- and/or postnatal malnutrition, and abnormalities in systemic and cerebral haemodynamics and oxygen supply.

The most vulnerable period regarding the latter is represented by the first hours and days after birth due to abnormal haemodynamic adaptation during the transitional circulation combined with the impact of respiratory distress syndrome. This leads to hypoperfusion, hypoxia/hyperoxia, ischemia and other issues. Disturbance of cerebral blood flow, i.e., hypoperfusion, is related to impaired cerebral autoregulation. Autoregulation is the ability to keep the organ blood flow constant despite fluctuations in perfusion pressure and it is accomplished by regulation of the arterial tone so that low perfusion pressure results in vasodilation and high pressure results in vasoconstriction. Cerebral autoregulation has limited capacity in critically ill premature babies and is thought to be particularly fragile in the immature brain. Impaired cerebral autoregulation leads to pressure passive flow which is a state where the blood flow follows the blood pressure: large fluctuations in flow seem to be involved in cerebral haemorrhages in premature infants due to rupture of the immature blood vessels. As tissue hypoxia as well as tissue hyperoxia cause brain injury, both should be avoided.

To that end, a continuous and non-invasive monitoring of cerebral perfusion and/or oxygenation has been searched for an end-organ monitoring with sufficient high time resolution to guide evidence-based treatment interventions is lacking. [Greisen G, 2011] Near infrared spectroscopy has the potential to become that monitor of the brain.

Near-infrared spectroscopy (NIRS) is a non-invasive technology that has been utilised to assess the adequacy of peripheral and cerebral oxygenation in the preterm infant. [Menke J, 2003] Near-infrared light penetrates deep into the tissue, and through spectroscopy, it is possible to monitor tissue oxygenation. NIRS uses the relative transparency of human tissue to light in the near-infrared region of the spectrum. The oxygen-dependent absorption of light by haemoglobin enables the calculation of relative changes in the oxygenated and deoxygenated haemoglobin. [Wolf M, 2009] The NIRS has been used in newborns since 1985 and it is particularly suitable for the neonatal population due to their thin scalp and skull. [Brazy JE, 1985] Quantification of oxygenation in a percentage from 0 to 100% has

been possible for 10 years and near-infrared spectroscopy commercial devices are currently being used in clinical trials as cerebral oximeter. [Hyttel-Sørensen S, 2013] This is most often done by spatially resolved spectroscopy. The assumption behind is that light propagates in a diffusional manner in a highly scattering media such as human tissue, and that the light attenuation by scattering is constant with light distances over 3 centimetres.
However, the usefulness of this approach depends on the assumption of stable oxygen consumption which depends both on the local tissue demand, perfusion (delivery) and oxygenation (supply). In order to estimate the oxygen consumption and the cerebral oxygen metabolism, a non-invasive, continuous, cot-side monitor of brain perfusion and oxygenation is needed and remains an unfilled niche in clinical care.
The BabyLux project aims to provide a precise, accurate, and robust device to continuously monitor cerebral oxygen metabolism and blood flow in critically ill newborn infants. This will be achieved by combining time resolved near-infrared spectroscopy (TRS) with newly developed diffuse correlation spectroscopy (DCS) in a single device. The innovative aspects of the project are related to the use of advanced solutions, based on state-of-the-art photonic components, which have already been tested in laboratory and clinical tests on adults.

3.2.1 Time Resolved Near-infrared spectroscopy (TRS) and Diffuse Correlation Spectroscopy (DCS)

The proposed solution will integrate two advanced photonic techniques, TRS and DCS. Both techniques rely on the use of an optical fibre probe (sensor) to illuminate with very low power near infrared light the scalp and to collect the diffusively reemitted optical signal that has propagated through the scalp and skull and therefore carries information on the deeper cortical region. The different absorption spectra of oxygenated and deoxygenated haemoglobin in the near infrared range allows for the noninvasive monitoring of the two species in the cortical tissue.
TRS and DCS prototypes are available and have been technically tested in laboratory settings and successfully validated during preclinical trial on adult volunteers and patients. [Torricelli A, 2011, Durduran T, 2010]

3.2.2 Measured TRS/DCS parameters

TRS measures the attenuation and the temporal broadening of relatively short light pulses (pulse duration ~100 ps) through a diffusive medium (e.g. a neonate's head). TRS has the ability to resolve path-lengths (or equivalently time-of-flights) of photons that have propagated through the tissues. This enables TRS to separate the absorption and scattering coefficients allowing for absolute measurements, and to utilize time-gating of path-lengths to emphasize signals from deeper tissues. This is particularly important for separating intra- and extra-cerebral signals for brain monitoring. [Torricelli A, 2014]
DCS relies on the fact that temporal correlation of light fields in turbid media also obeys a diffusion equation, albeit a slightly different one than is used for TRS. Thus DCS shares the light penetration advantages of TRS, but, since DCS explicitly measures red blood cell movement, it provides a direct measure of quantities such as cerebral blood flow (CBF). [Durduran T, 2010]
The specific combination of DCS and TRS allows for the assessment of cerebral oxygen metabolism and CBF in a complete (i.e. CBF and oxygenation are simultaneously and independently provided), accurate (i.e. based on absolute measurements of optical parameters) and robust (i.e. potentially less affected by artefacts related to superficial systemic activity or sensor/head movements) way.

3.3. Aim

Aim of this project is to perform clinical measurements using the BabyLux instrument in different clinical real-life settings to validate this new technology in terms of feasibility, reproducibility, and user friendliness in neonatal medicine, in order to provide a precise, accurate robust device to continuously monitor cerebral oxygen metabolism and blood flow in newborn infants.

3.4. Methods

The BabyLux integrated system will be validated in real-life settings by monitoring cerebral oxygenation and haemodynamics in healthy term neonates and critically ill preterm and term infants. Target tests, aimed to measuring main features related to both technical and physiological parameters, will be used.
Parental written informed consent will be asked.
The BabyLux system is tested in four different real-life settings to measure:

- (3.4.1) the rise in oxygenation and change in blood flow during the minutes after birth to specify the expected range of measurement;
- (3.4.2) the precision and reproducibility of measurements by reapplying the optodes several times on slightly different sites of the head in a relatively steady condition;
- (3.4.3) the cerebral vaso-reactivity to arterial carbon dioxide tension in mechanically ventilated newborns to monitor induced changes in cerebral blood flow;
- (3.4.4) the user friendliness and loss of signal in routine care situations (e.g. during 24-hour monitoring of neonates undergoing intensive care).

Infants with genetically defined syndromes or congenital malformations are excluded from the study.

3.4.1 Changes in cerebral oxygenation and haemodynamics after birth

Inclusion criteria:

- term newborns (with a gestational age > 37 weeks)
- delivered by an uncomplicated elective caesarean section

Exclusion criteria:

- Apgar score < 8
- need for respiratory support or supplementary oxygen during the transition

Immediately after birth the infants is wrapped in warm towels and the head and right hand are cleaned with towels to reduce vernix and amniotic fluid, which can influence sensor signal quality. The timer is started at the point of umbilical cord clamping. As soon as possible, after drying the head, the TRS/DCS sensor is positioned in the fronto-parietal region of the newborn's head and held in position by hand for 10 minutes from cord clamping. The pulse oximeter, to measure arterial oxygen saturation (SaO2) is positioned on the right arm or wrist (at the pre-ductal level), as soon as possible.
SaO2 and pulse are measured continuously with two Masimo SET pulse oximeter (Masimo Coorporation, CA, USA).

3.4.2 Precision and reproducibility of measurements

The reproducibility of measurements are evaluated by reapplying the BabyLux sensor several times on slightly different sites of the head in a relatively steady condition. Repeated measurements are carried out on the same infants enrolled in the 4.1 study, more than 24 hours after delivery.

The BabyLux sensor is positioned on the fronto-parietal region and then removed and replaced: six measurements of 30 seconds each with total sensor lift-off of 30 seconds between measurements are carried out.

3.4.3 The cerebral vaso-reactivity to arterial carbon dioxide

The cerebrovascular reactivity to changes in arterial carbon dioxide tension is tested in mechanically ventilated newborns.

Inclusion criteria:

- gestational age <37 weeks
- postnatal age at least 24 hours
- mechanically ventilation
- clinical stability
- normal brain ultrasound
- transcutaneous pCO2 monitoring (tcpCO2)

In case of hypercapnia (tcpCO2>7 kPa) or hypocania (tcpCO2<5 kPa) clinical changes in ventilatory settings are introduced according to routine clinical care in order to normalise pCO2. At least 20 min is allowed to assess the full effect of the change in ventilator setting. This may be repeated if necessary to normalise the tcpCO2.

3.4.4 Assessment of the user friendliness and loss of signal in routine care

The user friendliness and loss of signal are evaluated in routine care situations during 24-hour monitoring of neonates undergoing intensive care.

Inclusion criteria:

- postnatal age < 28 days
- clinical unstability
- ventilatory suppport by mechanical ventilation or nasalCPAP
- transcutaneous pCO2 monitoring

The BabyLux sensor is positioned on the fronto-parietal region and replaced every 4 to 6 hours to check for skin integrity.

The BabyLux system will be equipped with dedicated software developed by the BabyLux partners (Hemophotonics SL, Politecnico di Milano) to provide in real time the time course of the measured parameters: oxygen tissue saturation (StO2) and cerebral blood flow index (CBFi). Other data to indicate signal quality and information to assist the user manually to improve the signal if necessary is also available. The clinicians will be made aware that the data is experimental, but are free to consider them in clinical decisions if they choose to do so.

All operations of the system will be logged, as well as all manipulation of the sensor.

The user friendliness will be assessed by all users - physicians and nurses. On basis on their experience with the actual infant in the time period they have been involved, they will report on Likert scales from 'very bad' to 'very good' on the parameters 'operating the system', 'presentation of data', 'trustworthyness of StO2', 'trustworthyness of CBFi'

3.5. Data recording and management

Subjects are sequentially numbered. The list of subjects with their basic clinical data will be recorded in an electronic file.

During all measurements, NIRS data will be stored timelocked with other monitored

variables as relevant (arterial oxygen saturation, transcutaneous pCO2, mean arterial blood pressure, pulse rate).
Before analysis all data will be graphed and screening for artefacts by visual inspection. After removal of artefacts, the data will be locked.

3.6. Data analysis and statistical analysis

3.6.1 Sample size

60 neonates will be studied at the two sites.

- 20 for (4.1) and (4.2)
- 20 for (4.3)
- 20 for (4.4)

We will aim at the inclusion of approximately equal number of infants at each site for each of the groups.

3.6.2 Data analysis

- (4.1) The SpO2, StO2, oxygen extraction (OE: SpO2-StO2), fractional oxygen extraction (FTOE: SpO2-StO2)/SpO2), CBFi, and cerebral metabolic rate of oxygen index (CMRO2i: OE x CBFi) will be graphed versus time after cord clamping. It is expected that StO2 will rise by about 30%, and that CMRO2i and FTOE will remain relatively constant. The results will be compared to the literature.
- (3.4.2) Reproducibility (test-retest variability) will be determined by ANOVA.
- (3.4.3) Data containing 0.5 kPa change in tcpCO2 or more within 15 minutes after a change in ventilator settings will be analyses for CBFi-tcpCO2 reactivity. One minute of data just before the change and one minute of data 15 minutes later will be used. The expected reactivity is 30%/kPa.
- (3.4.4) Signal loss will be calculated per 24 hours. This will be compared to the results of the SafeBoosC-II. The system operations and sensor manipulations will be classified into suitable groups and tabulated. The mean Likerts scores will be calculated and the free text comments classified and typical comments used *verbatim* in the reporting process.

3.7. Safety

The BabyLux system is used non-invasively and, therefore, carries no significant risk for the patients involved. It is worth mentioning that DCS and TRS, like NIRS, are totally safe since they employ nonionizing radiation with typically a very low power. It has been estimated that the light intensity on the brain surface during NIRS can be safely estimated to be only a few per cent of the solar irradiation [Kiguchi M, 2007]. Moreover, both DCS and TRS based instruments have been tested for safety by the appropriate offices in several institutions. In particular a DCS based instrument is a non-significant risk (NSR) device as defined by Food and Drug Administration (FDA) and therefore does not require FDA approval for investigational use. The DCS based instrument has been approved for laser safety in both USA and Europe. TRS based instruments have been recently approved for studies on neonates by the Italian Ministry of Health [Document DGDFSC.VI/P//I 5 i m 2/2012/874, Ministero della Salute, 27/03/2013]. Similarly, the safety and feasibility of TRS measurements on neonates and preterm babies have been extensively demonstrated in the United Kingdom within the framework of the nEUROPt project (Noninvasive imaging of brain function and disease by pulsed near infrared light, EU FP7 Cooperation STREP - HEALTH-2008-201076).

The BabyLux system is a medical device not bearing CE marking and intended for clinical investigation. According to the existing procedures at national and European level, the BabyLux medical device will request the authorisation from the Italian Ministry of Health to conduct clinical investigation according to this clinical protocol.
Rare reversible local skin reactions, such as rashes and burns, have been observed underneath NIRS sensors in very preterm babies. These adverse events can be further minimised by frequently moving the placement the sensor.
Pulse oximetry and transcutaneous pCO2 monitoring are non-invasive technologies that are universally used and accepted for standard care of newborn infants.

3.8. Ethical considerations

The approval from the relevant ethics committees will be sought. Parental informed consent will be obtained. The measurements will be conducted in compliance with the guidelines of the Declaration of Helsinki in its latest form and the International Conference on Harmonisation good clinical practice guidelines (ICH GCP). Procedures will be established to prevent and/or minimise risk of complication for participants.

3.9. Financial issues

All financial issues will be covered by the BabyLux project (EUROPEAN COMMISSION, ICT Policy Support Programme, Competitiveness and Innovation Framework Programme, Grant agreement no: 620996).

3.10. Personal data

Child's personal medical data collected as part of the trial will be processed in accordance with the data protection legislation of the European Medicines Act. Independent persons or representatives of the regulatory authorities (e.g., regional council, federal superior authority and ethical committees) appointed to monitor clinical studies may have access to child's medical files.

3.11. Contact person

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3.12. References

- Brazy JE, Lewis DV, Mitnick MH, Jöbsis vander Vliet FF. Noninvasive monitoring of cerebral oxygenation in preterm infants: preliminary observations. Pediatrics. 1985 Feb.;75 (2):217-225.
- Durduran T, Choe R, Baker W, Yodh AG Diffuse optics for tissue monitoring and tomography. Rep Prog Phys, 2010, 73(7):076701–076744
- Greisen G, Leung T, Wolf M. Has the time come to use near-infrared spectroscopy as a routine clinical tool in preterm infants undergoing intensive care? Philos Trans A Math Phys Eng Sci. 2011 Nov 28; 369(1955):4440-51
- Hyttel-Sørensen S, Austin T, van Bel F, Benders M, Claris O, Dempsey EM, Fumagalli M, Gluud C, Hagmann C, Hellström-Westas L, Lemmers P, Naulaers G, van Oeveren W, Pellicer A, Pichler G, Roll C, Støy LS, Wolf M, Greisen G. Clinical use of cerebral oximetry in extremely preterm infants is feasible. Dan Med J. 2013 Jan;60(1):A4533
- Kiguchi, M., Ichikawa, N., Atsumori, H., Kawaguchi, F., Sato, H., Maki, A., Koizumi, H.,. Comparison of light intensity on the brain surface due to laser exposure during optical topography and solar irradiation. J. Biomed. Opt. 2007 Dec;12 (6), 062108.
- Menke J, Voss U, Möller G, Jorch G. Reproducibility of cerebral near infrared spectroscopy in neonates. Biol Neonate. 2003; 83(1):6␣11.
- Torricelli A, Contini D, Pifferi A, Caffini M, Re R, Zucchelli L, Spinelli L. Time domain functional NIRS imaging for human brain mapping, Neuroimage 2014 Jan; 85(1): 28-50
- Torricelli, A., Contini, D., Caffini, M., Zucchelli, L., Cubeddu, R., Spinelli, L., Molteni, E., Bianchi, A.M., Baselli, G., Cerutti, S., Visani, E., Gilioli, I., Rossi Sebastiano, D., Schiaffi, E., Panzica, F., Franceschetti, S. Assessment of cortical response during motor task in adults by a multimodality approach based on fNIRS–EEG, fMRI–EEG, and TMS. 2011 Proc. SPIE 8088, 808802.
- Wolf M, Greisen G. Advances in near-infrared spectroscopy to study the brain of the preterm and term neonate. Clin Perinatol. 2009 Dec. 1;36(4):807-34

4. Conclusions and future work

The verification of system performance as specified in this protocol is not expected to raise major problems. The recruitment of infants to the three subprojects is expected to be roughly equal in the NICUs of the two clinical partners.

Parental information sheets, consent forms will be added before submission for ethical approval late spring 2014. An investigator brochure will be developed in collaboration with the technical partners and the protocol will be modified into a clinical investigation plan as required for approval by the national authorities (device agencies) of Italy and Denmark.