A comparison between two NIRS oximeters (INVOS, OxyPrem) using measurement on the arm of adults and head of infants after caesarean section

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Abstract: Previously the NIRS oximeter OxyPrem was calibrated by comparison to the INVOS in a blood-lipid phantom. The aim of the present study was to test this calibration clinically. During vascular occlusions in 10 adults and after birth in 25 term infants the relationship was OxyPrem = 1.24 x INVOS - 23.6% and OxyPrem = 1.15 x INVOS - 16.2% on the adult arm and infant head, respectively. The precision during steady state was 4.0% (CI 3.4% to 4.6%) and 3.4% (CI 2.9% to 3.9%) on the arm, and 6.7% (CI 5.9% to 7.6%) and 4.7% (CI 3.5% to 5.9%) on the infant head for OxyPrem and INVOS, respectively. We conclude that the calibration on the blood-lipid phantom was unsuccessful in achieving agreement in clinical measurements.

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OCIS codes: (170.1470) Blood or tissue constituent monitoring; (170.6510) Spectroscopy, tissue diagnostics.

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1. Introduction

Cerebral oximetry by near infrared spectroscopy (NIRS) enables continuous, non-invasive monitoring of the oxygen balance of the brain. The regional tissue oxygenation, rStO2, is a volume-weighted estimate of the blood haemoglobin saturation in the blood pool of the tissue interrogated. rStO2 most closely reflects the haemoglobin saturation in the venous blood. Additionally, given relatively stable oxygen content in arterial blood and stable oxygen consumption of the brain, rStO2 can be used as a trend monitor of cerebral blood flow (CBF) [1].

While the technology has potential there is a lack of well-designed randomised clinical trials to test the clinical benefits and harms. SafeBoosC is a research project aiming to test cerebral oximetry during the first three days of life of the extremely preterm infants born before more than 12 weeks before term [2]. This project also includes the development of a prototype cerebral NIRS oximeter, OxyPrem, specifically dedicated to the preterm infant brain [3,4].

The normal ranges for the cerebral rStO2 in SafeBoosC were determined with the INVOS 5100c Adult SomaSensor (SAFB-SM)(Covidien, Boulder, CO, US) [5]. A key aspect in the planning has been to determine which devices to use in the trial, as different commercial NIRS devices may not be used interchangeably. Systematic differences in the estimates of...
rStO₂ are not only seen between devices, but also between different sensors from the same device [6,7].

Before launching SafeBoosC a series of studies on the adult forearm were carried out to test the agreement of several commercial devices with the INVOS [8,9]. Furthermore the OxyPrem was calibrated against the INVOS in a blood-lipid liquid phantom with scatter properties similar to the preterm head [10]. In brief the blood-lipid liquid was continuously pumped through an extracorporeal membrane oxygenator. The gas mixture to the oxygenator could be adjusted with O₂, N₂, and CO₂. As O₂ to the oxygenator was changed from 100% to 0% the haemoglobin saturation declined. The simultaneous measurements with INVOS and OxyPrem showed a linear relationship and suggested that a simple linear scaling of the OxyPrem rStO₂ values (INVOS-rStO₂ = OxyPrem-rStO₂ x 1.47 - 33.1) would result in comparable values.

The present study is both a clinical validation of that calibration procedure and a test of how agreement on the adult arm compares to agreement on the infant head with the overall purpose of finding a way to test and compare NIRS oximeters in the most time- and cost-effective way.

The hypothesis tested is that OxyPrem rStO₂ values are within 5 percentage points of the simultaneous INVOS rStO₂ on the newborn infant head and adult forearm irrespective of level of oxygenation.

2. Methods

This study was approved by the local Ethics Committee (Journal no. H-1-2012-094 and H-3-2011-153) and Danish Health and Medicines Authority (Journal no. LMST2012082484 and LMST2012015186) and conducted at the National University Hospital, Rigshospitalet, Denmark. Written informed consent was obtained from the participants before inclusion.

2.1 The NIRS oximeters

INVOS 5100c with the adult SomaSensor™ (SAFB-SM) uses two LED sources (730 and 810 nm) and two photodiode detectors at a distance of 3 and 4 cm, and “subtracts” the short distance signal from the longer distance in order to diminish the contribution of the skin and scalp.

OxyPrem is designed and manufactured by the Biomedical Optics Research Laboratory (BORL) of the Division of Neonatology at the University Hospital Zurich, Switzerland. It implements four light sources each consisting of three light emitting diodes with nominal wavelengths of 760 nm, 805 nm, and 870 nm, and two detectors (Fig. 1). The pair-wise source-detector separation is 1.5 and 2.5 cm. OxyPrem employs a self-calibrating principle using multiple light paths [11]. The symmetric source-detector geometry enables a calculation of light attenuation over distance that is less sensitive to differences in coupling factors between the tissue and sources and detectors as each detector and source is part of both a short and a long light path. For example, if a hair reduces the light reaching a detector this will affect a short and long light path equally thus not impacting the overall ratio of short paths to long paths light intensity.
2.2 The adult arm measurements

Recruitment of healthy volunteers was accomplished by an advertisement in a local university newspaper. Inclusion criteria included normal health and a skinfold thickness of less than 10 mm on the lower arm measured by the Harpden calliper. Exclusion criteria were local skin disease, hypertension, peripheral vascular disease, and pregnancy.

2.2.1 Deoxygenation after arterial cuff occlusion

All measurements were done with subjects placed in upright position with the lower arm at heart level. The sensors were placed on the upper anteromedial and upper anterolateral part of the forearm. The sensors were held in place with 3M Coban elastic wrap bandage.

All measurements were done simultaneously with the two instruments. After 20 seconds of measurement in resting steady state a cuff around the upper arm was inflated to more than 250 mmHg. The cuff was deflated six minutes after inflation. When rStO$_2$ had returned to resting steady state the sequence was repeated. After three of these vascular occlusion tests the sensor positions were switched and another three occlusions were carried out in a similar manner. The outline of each sensor was marked to ensure that the other sensor was applied approximately to the same spot when sensors changed position. The starting position of the sensors was chosen before the first inclusion using the function “sample” in R on the vector [1,1,1,1,2,2,2,2,2]. 1 and 2 are the possible starting positions of OxyPrem (Fig. 2).
2.2.2 Repeatability

10 measurements of 20 seconds each with each device were done on the same spot as outlined with a pen on the upper anteromedial part of the forearm. The sensors were lifted away from skin contact between each measurement. Only one instrument measured at a time. The subjects were asked to relax as much as possible throughout the experiment to minimize physiological changes.

2.3 The new-born infant head measurements

The measurements were done throughout the 10 minutes following cord clamping and on the second day of life. The parents to be were contacted the day before a planned, low risk caesarean section (CS) at term (gestational age 37 to 42 weeks).

2.3.1 Spontaneous oxygenation after birth

The measurements were done simultaneously with the two instruments. The NIRS sensors were placed transversely on the forehead symmetrically about the midline with at least six centimetres from the emitter of one sensor to the detector of the other. Two pulse oximeter sensors (Masimo SET IntelliVue Module, Masimo Corporation, Irvine, CA, US) were placed on the right and left hand, respectively. In all of the CSs the child was placed directly on the chest of the mother immediately after cord clamping.

2.3.2 Repeatability

On the second day of the infant’s life we did six measurements of 20 seconds each with total sensor lift-off intermittently, three on each side of the forehead. The measurements were done with one device at a time. All measurements were done with the infant at rest.

2.4 Data analysis

The data from the INVOS and the pulse oximeters were collected on a Phillips IntelliVue MP70 monitor (Phillips Medizinsysteme, Boeblingen GmbH, Boeblingen, Germany) and transferred real time to a laptop with ixTrend Express 2.0 (ixellence GmbH, Wildau, Germany). The OxyPrem data was transferred to a separate laptop. The clock on the laptops was synchronized prior to each recording session.

All post-processing data handling was done in Matlab (R2012b)(The MathWorks, Inc., MA, US). During the post-processing of the OxyPrem raw data a range of different data filters were tried including mean, median, Chebyshev Type II filter, moving mean, moving median, and combination of moving median and Chebyshev Type II filter. None proved better than the simple mean filter. The final OxyPrem output was 0.2 Hz. Afterwards the ixTrend was downsampled to 0.2 Hz while synchronized to the time points of the OxyPrem using the “synchronize” Matlab function with linear interpolation. The short period during sensor repositioning in the arm study was edited out manually by visual inspection of the time-series.
The time-series were additionally inspected for noise and missing values and if judged unsuitable for further analysis excluded from the analysis. The INVOS has cut-off values at 15% and 95%. Therefore time points where either INVOS or OxyPrem gave values below 16% or above 94% were also excluded from the analysis to avoid bias to the comparison between the two instruments.

2.5 Statistical analysis

The *a-priori* hypothesis was that the instruments give similar absolute values.

The NIRS data were paired. Sample sizes for the two parts of the study were calculated to have a power of 80% to detect a 5-percentage points difference between absolute values with a standard deviation of 5%.

The distribution of the data was checked visually and with the Shapiro-Wilk test and non-parametric analyses were applied in case of obvious deviations from the normal distribution.

A p-value below 0.05 was considered statistically significant.

All statistical tests were done in R (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/).

2.5.1 Response to deoxygenation and oxygenation

On the adult arm a one-minute segment starting approximately one minute after each cuff occlusion was chosen by visual inspection of the curves. This method was chosen to ensure stable signals from both devices for the analysis. Visual assessment was needed as the time from the beginning of the cuff inflation to a steadily, linearly declining oxygenation was variable. In the chosen time segments the rate of decline in rStO2 in %/minute was calculated.

The association between INVOS and OxyPrem was determined from a mixed effects model with INVOS as independent, OxyPrem as dependent, and occlusion as random effect.

On the infant head data from 2.5 to 4.5 minutes after cord clamping was used in a mixed effects model with INVOS rStO2 as independent, OxyPrem rStO2 as dependent, and subject as random factor.

The effect of population (adult arm/infant head) on the relationship between the OxyPrem and INVOS rStO2-values were analysed using a likelihood-ratio test.

2.5.2 Repeatability

The mean of each 20 seconds of measurement gave six rStO2 estimates on the infant head and ten on the adult arm. Repeatability for each instrument was determined by one-way ANOVA with subject as the factor. The within-subject standard deviation, $S_n$, was then estimated from the square root of the residual mean square. The 95% CI was $\pm 1.96 \times S_n/\{(2n(m - 1))^\frac{1}{2}\}$, where $n$ is number of subjects and $m$ the number of observations per subject. The repeatability coefficient was calculated as $1.96 \times 2^{\frac{1}{2}} \times S_n$ [12].

It has previously been shown in similar studies that repeatability and dynamic sensitivity is inversely related [8,9], thus to make the repeatability coefficients directly comparable the OxyPrem repeatability coefficient was divided by the fixed effects slope ($b_2$ in OxyPrem = $b_1 + b_2 \times$ INVOS) from the mixed effect model from the relevant population.

3. Results

10 (3 female/7 male) healthy adults with an age range of 21 to 34 years and a median skinfold of 3.2 mm (Inter quartile range (IQR) 0.9 mm) and 25 (15 female/10 male) infants with a median gestational age of 39 weeks and 0 days (range 37 + 1 to 41 + 1) were included. All infants had Apgar scores of 9 or 10 at 1 and 5 minutes. The mean birth weight was 3340 grams (standard deviation (SD) 486 grams).

Due to high levels of noise in the rStO2 signal of the OxyPrem in the operating room two infants were excluded from the infant head data set on spontaneous oxygenation after birth.
Furthermore three infants were excluded from the repeatability data set due to other technical issues.

3.1 Response to deoxygenation and oxygenation

3.1.1 Response to deoxygenation after arterial occlusion

The estimated mean rate of decline in rStO₂ after vascular occlusion was 16.8%/min (CI 14.7%/min to 18.9%/min) with INVOS and 21.9%/min (CI 18.3%/min to 25.4%/min) with OxyPrem. Figure 3 shows a typical time-series plot of the rStO₂ during six vascular occlusions.

INVOS and OxyPrem rStO₂ estimates differed on the arm with an overall mean slope $b_2$ of 1.24 (CI 1.15 to 1.34) and a mean intercept $b_1$ of $-23.6\%$ (CI $-29.4\%$ to $-17.7\%$) ($\text{OxyPrem} = b_1 + b_2 \times \text{INVOS}$) (Fig. 4).
3.1.2 Response to oxygenation after birth

The OxyPrem and INVOS rStO₂ estimates increased from 43.3% (CI 36.3% to 50.3%) and 53.4% (CI 45.6% to 61.1%) 3 minutes after cord clamping to 68.9% (CI 62.8% to 75.0%) and 76.6% (CI 71.8% to 81.4%) 8 minutes after cord clamping, respectively. The SpO₂ increased from 70.6% (CI 65.1% to 76.2%) to 87.3% (CI 82.9% to 91.7%). Figure 5 shows a typical time-series plot of the rStO₂ during the 10 minutes following umbilical cord clamping. Note the noisier OxyPrem signal.
Fig. 5. An example of the rStO₂ time series during the 10 minutes following umbilical cord clamping in a single subject. The solid line is INVOS and the dashed line is OxyPrem.

The INVOS and OxyPrem rStO₂ estimates were not significantly different on the infant head. The mean slope $b_2$ was 1.15 (CI 0.84 to 1.43) in the time segment from 2.5 to 4.5 minutes after cord clamping and the mean intercept $b_1$ was $-16.2\%$ (CI $-37.6\%$ to $5.4\%$) ($\text{OxyPrem} = b_1 + b_2 \times \text{INVOS}$) (Fig. 6).
Fig. 6. Scatter plot and linear fit of INVOS rStO$_2$ vs. OxyPrem rStO$_2$ values from 2.5 to 4.5 minutes after cord clamping. The points from each infant are joined.

3.2 Repeatability

3.2.1 The adult arm

The within-subject standard deviation, $S_w$, from the 10 repeated measurements on the arm was 4.0% (CI 3.4% to 4.6%) for OxyPrem and 3.4% (CI 2.9% to 3.9%) for INVOS corresponding to repeatability coefficients of 11.0% and 9.4%, respectively. The OxyPrem repeatability coefficient divided by the slope $b_2$ of 1.24 was 8.9%.

3.2.2 The infant head

$S_w$ of OxyPrem was 6.7% (CI 5.9% to 7.6%) and 4.7% (CI 3.5% to 5.9%) for INVOS. The repeatability coefficients were 18.6% and 13.0%, respectively. The INVOS-scaled OxyPrem repeatability coefficient divided by the slope $b_2$ of 1.15 was 16.2%.

3.3 Arm vs. infant head

The association between INVOS and OxyPrem values on the infant head was not significantly different from that on the arm ($\chi^2$ (d.f. 3), $p = 0.56$).
4. Discussion

4.1 Principal findings

The main finding of the present study is that the calibration of a prototype NIRS oximeter, OxyPrem, against the INVOS 5100c adult sensor on a blood-lipid phantom of the infant head did not result in agreement between the devices on the adult arm, whereas the disagreement on the infant head was statistically insignificant. The slopes of the association between the rStO2 estimates from the two devices, however, did not differ between the arm and the head. Lastly, the OxyPrem had better reproducibility on the arm compared to INVOS, but worse on the infant head.

4.2 Appraisal of method of comparison

The strength of the method is that it allows comparison of the rStO2 estimates of two NIRS instruments on two very different tissues in two different populations through changing oxygenation by applying 1) arterial occlusion on the adult arm and 2) measuring on the infant head in the minutes after birth. In combination with repeated measurement during physiological steady state on the resting arm and on the second day of the infants life, respectively, this allows comparison of the responsiveness to change in deoxygenation/oxygenation as well as the repeatability of the measurements, which we previously found inversely related [8,9].

The study has limitations. The circumstances surrounding a caesarean section are hard to standardize. The infants were dealt with differently and the time between birth and cord clamping varied. It could explain that some infants were quite well oxygenated already shortly after cord clamping. It resulted in a large variation in the within-subject oxygenation in the 2-minute period chosen for analysis in that part of the study. An unforeseen problem was the noise in the OxyPrem measurements in the operating theatre leading to exclusion of the data from two infants and the technical problems leading to exclusion of the data from three infants studied in the postnatal ward.

The statistical analysis to compare the response to oxygenation/deoxygenation was complicated by the noise in the OxyPrem signal on the infant head. The correlation estimate and the simple linear regression fit will be biased by noise in the independent variable, whereas a Bland-Altman plot [13] will be biased by difference in noise levels between the devices compared. Such difference was pronounced on the infant head. The bias will depend on the size of the difference in noise level, so the Bland-Altman plots were not comparable between arm and infant head as the difference in noise-level between the devices differed. The mixed effects model was done with INVOS as independent as the noise of the INVOS measurements was similar on head and arm. This way the linear fits were comparable between arm and head. The risk of a bias of the slope towards zero is not avoided, but since the slopes actually exceeded unity, the main conclusions are not affected.

It would strengthen a validation study like this to have blood samples for comparison. This is obviously not possible for the CS part, but it would be possible with the arm measurements. It is, however, uncertain how well a superficial venous sampling represents the muscle oxygenation in a state of no or low flow.

4.3 Repeatability of the OxyPrem

The auto-calibration principle of the OxyPrem should in theory improve the repeatability of measurements as the geometry makes it insensitive to superficial inhomogeneities [4] such as larger blood vessels, pigmentation, or hair. Furthermore, OxyPrem measures on two adjacent regions and taking the mean value should in itself improve repeatability by a factor $2^{1/2}$. We did not find the OxyPrem to be substantial better than the INVOS. First of all the wider light source-detector distance of the INVOS will probably to an extent level out the advantage of taking the mean of the estimates from two smaller adjacent regions. Another explanation...
could be that the poor repeatability of continuous wave NIRS is not so much caused by superficial heterogeneity, but inhomogeneities in deeper tissues. It has been shown that the arterial to venous volume ratio is changing both within and between in individuals [14,15]. A shift in this ratio changes the rStO2 estimate by NIRS.

Surprisingly, we found that the repeatability was quite different on the arm and infant head. On the infant head the INVOS was best, whereas the OxyPrem was better on the arm. This difference was probably caused by the noisy signal of OxyPrem on the head. An explanation could be that good light coupling is hard to achieve for all sources and detectors at all times, and that this could lead to intermittent light piping. Thus the hexagonal geometry could perhaps have the opposite effect than intended on a hard tissue surface as the forehead. Another possibility is the potential electrical interference from other electrical equipment nearby. The noise was most pronounced in the operating room. This suggest that electrical disturbance did contribute, but as the steady state measurements were done in the postnatal ward with no or very little other electrical equipment there must be other factors in play as well.

4.4 Comparison with previous work

Concerning the measurements on the arm the repeatability and dynamic response to the vascular occlusion test of the INVOS are in fine agreement with previous similar studies from our group [16,17].

It has been well established that the oxygenation increases after birth [18]. In the present study the increase in SpO2 from 70.6% at 3 minutes to 87.3% at 8 minutes after cord clamping is in line with what other groups have found [19–21]. It has also been shown that infants born by elective caesarean section tend to have lower saturations in the first minutes compared to infants born by vaginal delivery [22].

It has in several studies been shown that the cerebral tissue oxygenation increases during transition. Pichler et al. found that the cerebral rStO2 of term infants born by CS increased from 49.0% at 3 minutes (50th percentile) to 78.5% at 8 minutes with the INVOS neonatal sensor [23]. Almaazmi et al. used the small sensor of the FORE-SIGHT (Casmed, Branford, Conn., USA) and found in a similar population a median rStO2 of 42% at 2 minutes and 73 at 8 minutes after CS [24]. Urlesberger et al. found an increase from a mean 46% to 77% from 3 to 8 minutes (assessed from plot) after cord clamping after CS [25]. Our own group found an increase from 53.4% to 86.0% with INVOS neonatal sensor and 61.6% to 82.2% with FORE-SIGHT small sensor in a setup similar to the present study [26]. The main results of all these studies are similar. The cerebral rStO2 increases after birth. There are, however, differences in the estimated levels of oxygenation. One explanation could be that the start time is defined differently. Pichler et al. started the clock when the infant was 'fully delivered', Almaazmi et al. started the clock when the body had been delivered, whereas in Urlesberger et al. and our studies the clock was started at cord clamping, thus depending on the duration from delivery to cord clamping the cord clamping studies will likely show higher oxygenation at 3 minutes. Moreover different devices and sensors were used. It has previously been shown that both different devices and different types of sensor from same device have systematic differences in the rStO2 values and thus cannot be used interchangeably [6,27]. The present study is an example of how such differences between devices could lead to erroneous conclusions about the physiology if the instrument factor is not considered.

4.5 Clinical and scientific implications

The novel aspect of the present study is the clinical comparison of two continuous wave NIRS oximeters - a commercial and an academically developed prototype. It was a surprise that the results were not identical, and that the discrepancy was present for the adult forearm and the newborn head alike, since they had been calibrated to give identical results in a blood-lipid phantom. In that study the NIRS oximeters showed almost perfect simple linear
association in a homogenous blood-lipid phantom [10]. This gave way to simple calibration procedure of the OxyPrem of an offset and a scaling factor to aim for agreement between OxyPrem and INVOS in clinical use. Our results show that the calibration worked best on the infant head. As the phantom had scattering and absorption properties similar to the infant head, this was not surprising. However the high levels of noise in the OxyPrem signal during the measurements on the infants hinders any definite conclusions. There are several potential implications.

First calibration in the blood-lipid calibration may be of limited utility. There are, however, aspects of the phantom calibration that need further investigation. The impact of changes in scattering, i.e., the lipid concentration, and absorption, i.e., the haematocrit, on the association of the rStO\textsubscript{2} estimates of different devices needs further investigation. The variance of the linear association in the phantom needs to be determined. The calibration was done only on a single desaturation in a single phantom. In case of significant variation it is possible that a calibration using data from several desaturations would perform better. Furthermore we assumed that the phantom was homogeneous but regional differences in oxygenation in the phantom would be a problem. Finally, the OxyPrem uses source-detector distances 1.5 and 2.5 cm, while INVOS uses 3 and 4 cm. This difference is probably not important in a homogeneous medium as the phantom, but in the layered tissues of the arm and the head it could introduce systematic differences.

In regards to the SafeBoosC project the OxyPrem sensor design has to be evaluated further before the device would be eligible for use in the trial. The noise we experienced would not be compatible with clinical use. The problem remains that randomised trials with cerebral NIRS oximetry either have to use one device exclusively or find a way to test the comparability among devices and then perhaps adjust for any differences. It is reasonable to assume that all the commercial continuous wave NIRS devices estimate the same entity “cerebral oxygenation” - a venous weighted average of intravascular saturation, but as the agreement between devices and the repeatability within devices are poor, careful validation procedures must be used. Such procedure should include repeated measurements. The absolute rStO\textsubscript{2} threshold for intervention depends on good precision of a single rStO\textsubscript{2} estimate. Unfortunately too few of validation studies include estimation of the repeatability/precision, but focus on the accuracy.

5. Conclusion
Calibration of a prototype NIRS oximeter against the INVOS 5100c in a blood-lipid phantom did not result in good agreement on the adult arm during vascular occlusions or on the infant head in the ten minutes following cord clamping during elective caesarean section. The simple linear association of rStO\textsubscript{2} values of two devices was similar on arm and head.

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