Author's response to reviews

Title: Changes in cerebral oxygenation during early postnatal adaptation in newborns delivered by vacuum extraction measured by near-infrared spectroscopy

Authors:
- Tanja Karen (Tanja.Karen@uk-essen.de)
- Martin Wolf (Martin.Wolf@usz.ch)
- Rahel Nef (rahelnef@yahoo.com)
- Daniel Haensse (Daniel.Haensse@alumni.ethz.ch)
- Hans-Ulrich Bucher (buh@usz.ch)
- Gabriele Schulz (gs.schulz@gmx.de)
- Jean-Claude Fauchere (Jean-Claude.Fauchere@usz.ch)

Version: 3 Date: 26 September 2013

Author's response to reviews: see over
Dear Editor:

We thank you for reviewing our manuscript and for considering a revised version for publication in the Journal BMC Pediatrics. We resubmit our paper and after having addressed all the points raised by the editors and the reviewers in the point-by-point reply attached below. We have marked the changes to the manuscript using the “track changes” features and resubmitted a clean version and a version with the revisions marked.

We hope that this revision meets your and the reviewers’ expectations and that it can be accepted for publication in the present form. We are looking forward to your reply.

Yours sincerely

Tanja Karen

Jean-Claude Fauchère
Point by point reply:
Manuscript ID: MS: 4219624710286769

First revision: "Changes in cerebral oxygenation during early postnatal adaptation in newborns delivered by vacuum extraction measured by near-infrared spectroscopy"

The reviewers’ comments are in **bold** and our replies are in the regular font. Extracts from the text are in *italic* fonts.
We marked the changes to the manuscript using the “track changes” features and resubmitted a clean version and a version with the revisions marked.

**Reviewer #1 (Topun Austin)**

1. Reviewer’s comment:
**Figure 1d should read HR not HF**
Answer: Figure 1d shows now HR instead of HF.

2. Reviewer’s comment:
**Table 1 C-Section n= 15, n=19 in text: please clarify**
Answer: As written in the method and result sections the control group included 19 infants born after elective cesarean section. We have changed this number accordingly in Table 1: C-section n=19.

3. Reviewer’s comment:
**It would be helpful to expand on the consent process- was this obtained during labor/before labor?**
Answer: Due to the emergency nature of the vacuum delivery, we were given permission by the Ethics Committee to perform the first measurement immediately after birth, and to obtain a formal parental permission thereafter for the second measurement. Care was taken to have the father always present during the first measurement with a comprehensive explanation about his infant’s adaptation and the reason for the NIRS measurement. The measurement would not be performed in case a father would object. After these first 15 min of life the newborn was given to the mother time was given to the family to recover and for privacy. After some hours we went back to the family and explained why we did additionally the NIRS
measurement to our routinely neonatal care and then we asked for their consent and for the second measurement. None of the parents refused to participate in our study. Again the way how we performed our study and obtained the parental consent was well accepted by the parents as well as the whole team of midwives and obstetricians and the local ethics committee.

“The study design was approved by the hospital’s Ethic Committee. Due to the emergency situation leading to perform vacuum delivery due to fetal distress, oral consent was obtained by the present father for the first measurement and a formal written parental consent was obtained thereafter for the second measurement. All parents asked for permission agreed.”

4. Reviewer’s comment:

THI is an index of CBV; it is not widely reported in the literature, and it would be useful for the authors to comment on the reliability of this (and TOI) measurement. How does THI compare with the nTHI measurement obtained in newer NIRO instruments?

Answer: The NIRO 300’s most reliable parameter is the TOI, because it is a ratio and hence the absolute value of the scattering coefficient, which cannot be measured by the NIRO 300, and other factors reducing the reliability cancel out. By assuming a reasonable value of the scattering coefficient, the total haemoglobin concentration (THI) can be determined as an absolute value. Since this parameter requires an assumption, it is less reliable than the TOI. On the basis of measurements in single subjects, an error in the assumption will propagate directly to the THI value. But for a group of subjects in average as for any statistical mean, the error should average out and in particular, when a difference is found between two groups, this is a reliable result. For reasons unknown to us, Hamamatsu decided that in newer instruments the THI would no longer be displayed as an absolute value, but as a proportional change compared to the initial value. This means that the nTHI is initially set to 100% and all changes occurring overtime are presented in % of this initial value. It is important to note, that in this case a comparison between two groups has no meaning anymore. But since we applied the NIRO 300, the THI corresponds to an absolute value, where such a comparison is meaningful.

“TOI is the NIRO 300’s most reliable parameter, because it is a ratio and hence the absolute value of the scattering coefficient, which cannot be measured by the NIRO
and other factors reducing the reliability cancel out. By assuming a reasonable value of the scattering coefficient, the total haemoglobin concentration (THI) can be determined as an absolute value. Since this parameter requires an assumption, it is less reliable than the TOI. On the basis of measurements in single subjects, an error in the assumption will propagate directly to the THI value. But for a group of subjects in average as for any statistical mean, the error should average out and in particular, when a difference is found between two groups, this is a reliable result.”

5. Reviewer’s comment:
Details of haematocrit and timing of cord clamping between the two groups would be useful—could the difference in THI be explained by different haematocrits in the two groups?
Answer: In premature infants it has been shown that delayed cord clamping by 60 to 90 seconds improves cerebral oxygenation in the first 24 hours compared to conventionally cord clamping < 20 seconds (Baenziger O, Stolkin F, Keel M, von Siebenthal K, Fauchere JC, DasKundu S, Dietz V, Bucher HU, Wolf M: The influence of timing of cordclamping on postnatal cerebral oxygenation in preterm neonates: a randomized, controlled trial. Pediatrics 2007, 119(3):455-59.) In our study the timing of cord clamping between the two groups and as well as the hematocrit was not measured. The national recommendation with regard to cord clamping time after vacuum extraction in term infants who do not need resuscitation measures is 60 seconds, in this practice has been taken up in our perinatal center since then. We can therefore assume that there was no significant difference in the time of the cord clamping between both groups, and therefore the difference seen in THI cannot be explained by different haematocrits or due to different cord clamping times in the two groups. We did not change anything according to different haematocrit values or different cord clamping times in our manuscript.

Reviewer #2 (Thomas Alderlisten)
1. Reviewer’s comment:
Abstract: There seems to be a word mission in the final line of the background. Should this not be written as “…using near-infrared spectroscopy.”?
Answer: The last sentence of the background of the abstract has been corrected accordingly. “The aim was to study cerebral tissue oxygenation during postnatal adaptation in these infants using near-infrared spectroscopy.”

2. Reviewer’s comment:
Background: “For instance, arterial blood pressure can remain normal in a situation of impaired cardiac output due to compensatory vasoconstriction.” Although what stated here is essentially true, there is a lot of controversy on what is “normal” blood pressure. Consider rephrasing using something as reference range / above treatment threshold.
A rule of thumbs is a mean blood pressure equal to the gestational age (in weeks) for the first 24-48 hours. In clinical practice, the infant’s blood pressure is generally considered to be adequate as long as the urine output, arterial lactate and capillary refill are within normal limits.
Therefore we have rephrased the sentence accordingly.
“For instance, arterial blood pressure can remain normal in a situation of impaired cardiac output due to compensatory vasoconstriction and considering a mean arterial blood pressure equal to gestational age as a normal blood pressure within the first 24 – 48 of life.”

3. Reviewer’s comment:
Patients: Some clarification on patient numbers would be useful. Table 1 displays 2x n=15. Whereas the text reports 15 and 19, while actually these numbers should maybe 11 (movement artifacts) and 19?
Answer: As written in the method and result section the control group included 19 infants born after elective cesarean section. We have changed this number accordingly in Table 1: C-section n=19. For the vacuum group 15 patients were
enrolled, but four out of 15 NIRS measurements were omitted due to movement artifacts.

4. Reviewer’s comment:
Results:
a) Measurement at 12-24h was performed at a median age of 21 hours. Is 12-24 also the actual range? If not, please add range or IQR.
Answer: Yes, the range of the second measurement was between 12 and 24 hours (actual age), with median age of 21 hours.
b) 4 out of 15 measurements were omitted. Were these measurements omitted at all time points, or only at one of the four time points? If these neonates were excluded all timepoints, would it not be better to report this from start? (not mandatory, but a consideration).
Answer: 15 patients were enrolled in the vacuum group, and all the clinical data were compared to the 19 newborns born by elective cesarean section (Table 1). Four out of 15 NIRS measurements in the vacuum group were omitted due to movement artifacts at all time points. We did not change it in the manuscript.

5. Reviewer’s comment:
Discussion: a) I possible overlooked this, but isn’t the SaO2 a likely contributor to the observed difference in TOI both at 5 and 5-10 min.
Answer: We addressed the higher SaO2 levels as one contributor for higher TOI and THI in the vacuum group.
“We found higher SaO2 levels in the vacuum group during the first 5 minutes compared to the control group born by cesarean section, which can also explain higher TOI and THI in the first 10 minutes. This difference in SaO2 immediately after birth is in agreement with the published [2,4,5].”

b) Starting “Approximately 70-75% of this haemoglobin is in the venous...”
Although I agree with the facts stated here, references would be useful.
Answer: To address this comment, we have added references in the following paragraph:
It is known, that NIRS is particularly sensitive to small blood vessels and that the TOI represents the oxygen saturation of all the haemoglobin in these vessels.
Approximately 70-75% of this haemoglobin is in the venous, approximately 20-25% in the arterial and the rest in the capillary compartment (34-36).

c) “Although the infants of the vacuum group were born after fetal distress, this distress had only a short effect on cerebral hemodynamics lasting less than 24 hours when compared to healthy infants born after elective cesarean section.” I do not completely agree. Consider revising. The effect of TOI, SaO2 and HR is indeed temporarily. However, when you look at figure 1b, there is still an obvious difference in THI. Suggesting that there still might be an increased perfusion. Apparently it is not statistical significant, but only I just think…

Answer: There was still a trend for higher THI after 24 hours in the vacuum group, which might be a sign of increased perfusion, but this was not statistically significant. This may be explained by a high catecholamine release in the beginning after birth with initial vasoconstriiction followed by longer lasting dilatation of arterioles.

“Although the infants of the vacuum group were born after fetal distress, this distress had only a short effect on cerebral hemodynamics lasting less than 24 hours when compared to healthy infants born after elective cesarean section. There was still a trend for higher THI after 24 hours, but this observation was not statistically significant.”

d) Final section of discussion starting with “Since the light of NIRS penetrates the skin…” I understand what the authors are saying here. However, some revising could make things more clear. It is stated that THI and TOI are not influenced by superficial layers. I don't know if this is entirely true. With the beer lambert law there is obviously the problem that you do not know the contribution to attenuation caused by non-oxygen dependend light losses (tissue), I assume this is what the authors are reffering to. The diffusion theorem uses the fact that scatter becomes homogeneous at sufficiently large distances and determines the slope at multiple distances, which can be used to calculate an absolute value. So although this enables the calculation of an absolute value, isn’t it so that the a signal that is recorded arises from all tissue types underneath the probe? Thereby including the scalp (probably minimal contribution in neonates).

Answer: The major problem in NIRS measurements is the non-focused nature of the measurement, being an average of the tissues from source to detector; on the head these represent skin, scalp, skull, subarachnoid space, and grey and white brain matter. In the neonate, this type of measurement is a relatively smaller problem.
because the skin, scalp and skull are thin. In addition, the TOI and THI values are based on spatially resolved spectroscopy, which inherently removes the influence of superficial tissue, i.e. these signals are intracerebral. The NIRO 300 has three different distances. At all three distances, the light penetrates the superficial tissues, while at longer distances the light penetrates more brain tissue than at shorter ones. This means, that when we determine the light attenuation as a function of the distance, the superficial tissues act as constants, which may shift the curve up or down, but do not affect the slope. The latter is only affected by the brain. Since the TOI and THI are calculated from the slope, this means they are not influenced by superficial tissue.

Since the light of NIRS penetrates the skin and skull before it reaches the brain, one potential issue may be that the TOI and THI are influenced by these superficial tissues. In particular this may be a problem in case of a haematoma below the NIRS sensor. Therefore, we always placed the NIRS sensor on the right forehead, where there never was a haematoma. The NIRO 300 that we have employed as NIRS instrument has two modes of operation: 1) the approach based on the modified Lambert Beer law, which provides relative changes in the concentration of $O_2$Hb and HHb, which are known to be affected by superficial tissue. For this reason, these data have not been presented here. 2) The other approach is based on spatially resolved spectroscopy [23], which measures the decrease in intensity with the source detector distance and which was demonstrated by Franceschini [11] to remove the influence of superficial tissue. The TOI and THI values are calculated according to spatially resolved spectroscopy, and consequently reflect oxygenation and blood volume of the brain unaffected by superficial tissue.