The effect of the surgical ligation of the PDA on the cerebral tissue oxygenation - as measured by NIRS - in prematurely born infants

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REGULAR ARTICLE

Surgical closure of the patent ductus arteriosus and its effect on the cerebral tissue oxygenation

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Abstract

Aim: Surgical patent ductus arteriosus (PDA) ligation is considered after failure or contraindication of medical treatment. Till now ligation of the PDA has been associated with low morbidity and mortality although recently concerns have been raised about the possible association of ductal clipping and neurodevelopmental abnormalities later in life. By means of near-infrared spectroscopy (NIRS), we analysed the changes in the cerebral tissue oxygenation index (TOI) and fractional tissue oxygen extraction (FTOE) at the time of clipping as well as after clipping.

Method: Ten preterm infants with a symptomatic PDA who underwent surgical ligation were continuously monitored for heart rate (HR), mean arterial blood pressure (MABP), peripheral oxygen saturation (SaO_2) and TOI from 1 h before up to 1 h after clipping. FTOE and haemoglobin difference (HbD) were calculated. Changes in parameters at 5 min after ligation represent the effect of the clipping itself whereas changes up to 1 h-post-clipping represent the post-clipping effect.

Results: At the exact time of clipping, over the entire group, we found a significant increase in TOI of 2.9% ($p = 0.037$), in HbD of 12.5 μmol/l ($p = 0.047$) and in HR of 6.5 bpm ($p = 0.012$). FTOE significantly decreased by 0.02% ($p = 0.013$). One hour post-clipping, the cerebral and peripheral parameters were not significantly different from the control values before clipping.

Conclusion: The ductal clipping *in se* has no negative effect on the cerebral oxygenation.

INTRODUCTION

Abnormal persistence of the patent ductus arteriosus (PDA) is a clinical condition often associated with prematurity. A PDA with a left-to-right shunt negatively effects the pulmonary flow as well as the cerebral circulation and oxygenation (1) and may contribute to complications such as chronic lung disease (CLD) (2), intraventricular haemorrhage (IVH) (3) or periventricular leucomalacia (PVL) (4). Although several therapies like fluid restriction or pharmacotherapy may effectively reduce flow through the PDA (5), in 71% surgical ligation is needed after failure or contraindication of medication therapy (6). Till now it is considered a safe procedure with good clinical results and relatively low morbidity and mortality (7–9) although it remains associated with complications such as pneumothorax, bleeding, IVH or hypotension (7).

Several studies are performed to analyse the cerebral haemodynamics with ductal closure, not only during medication therapy (5,10–12) but also with ductal ligation (13–15). Recently, high concerns have been raised about the use of surgical ligation in the neonatal period: Kabra et al. found an increased incidence of neurodevelopmental abnormalities among infants treated with ligation (7). In contrast, Chorne et al. found no relationship between ductus ligation and subsequent neurodevelopmental outcome (16). This discrepancy holds because nowadays little is known about the impact of the surgical ligation itself on the cerebral perfusion and oxygenation.

Near-infrared spectroscopy (NIRS) and spatially resolved spectroscopy (SRS) allow the continuous and non-invasive measurement of the cerebral haemodynamics. NIRS measures changes in cerebral oxygenated (ΔHbO_2) and deoxygenated (ΔHbR) haemoglobin from which changes in the cerebral HbD can be calculated ($\Delta HbD = \Delta HbO_2 - \Delta HbR$) as a reflection of changes in the cerebral blood flow (ΔCBF). With SRS the cerebral tissue oxygenation index (TOI) can be measured and the fractional tissue oxygen extraction (FTOE) can be calculated as $(SaO_2 - TOI)/SaO_2$. These absolute values represent the cerebral oxygenation.

Zaramella et al. first used NIRS in combination with Doppler scanning to study the cerebral haemodynamics after clipping. Their intermittent data showed a decrease in TOI with no change in cerebral blood volume (CBV) (17). Huening et al. continuously recorded the cerebral parameters at the exact moment of clipping and found an abrupt but short-lasting increase in CBV with no change in the cerebral oxygenation (18). In this study, we used NIRS for the continuous monitoring of cerebral oxygenation to analyse the changes in TOI as well as FTOE, at the exact moment of clipping as well as up to 1 h post-clipping.

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PATIENTS AND METHODS

Patient population

Between June 2005 and November 2006, we included 10 preterm infants admitted to the Neonatal Intensive Care Unit of the University Hospital at Leuven, suffering from a PDA and in need of surgical ligation after failure of ibuprofen and/or indomethacin therapy.

Patients with a gestational age <32 weeks and weight <2000 g at birth were included. Infants with congenital malformations or cerebral complications were excluded.

Informed parental consent was required for participation in the study. The Medical Ethical Committee of the Universital Hospital approved the study.

Diagnosis of PDA

The diagnosis of a haemodynamic significant PDA was confirmed by echocardiographic examination. Severe PDA was marked by aortic back-flow as well as a left atrium-to-root ratio greater than 1.5. Clinical criteria for surgical ligation included deterioration of the respiratory distress syndrome and mechanical ventilation dependence at the time of surgery with increasing oxygen dependence and hypercapnia (17).

Monitoring of the cerebral haemodynamics

We used the NIRO 300 (NIRO 300, Hamamatsu®, Hamamatsu City, Japan) to measure the cerebral haemodynamics. This device uses NIRS to measure changes in oxygenated haemoglobin (ΔHbO_2), reduced haemoglobin (ΔHbR) and total haemoglobin (ΔHbT) of the brain. Near infrared light at four different wavelengths, i.e. 775, 810, 850 and 910 nm, is sent into tissue to calculate the proportional concentration of the two chromophores (HbR and HbO_2).

With SRS the TOI of the brain can be measured. Near infrared light is sent into tissue and becomes attenuated due to scatter loss and absorption loss. If the distance between the light source and the sensor is large enough (more than 3 cm), the isotropy of the scatter distribution becomes so homogeneous that the scatter loss gets the same at the three sensors. TOI can be calculated according to the diffusion equation as follows:

$$\frac{\text{k Hb O}_2}{\text{k Hb O}_2 + \text{k HbR}} = \text{TOI (\%)},$$

where k is the constant scattering distribution.

Because with SRS absolute values are provided, this technique is less sensitive for movement artefacts and continuous measurements are possible.

To investigate the balance between oxygen delivery and consumption, we calculated the FTOE, which reflects FOE (19), and which can be derived from SaO_2 and TOI:

$$\frac{SaO_2 - TOI}{SaO_2} = FTOE$$

The NIRO 300 optodes were placed at the right frontoparietal side of the infant with a 4 cm interoptode distance and a differential pathlength factor of 1.39. The data were recorded in an analogue way with a sampling frequency of 100 Hz by the data acquisition system Codas (Dataq Instruments®, USA).

The Ethics Commission of the University Hospitals Leuven approved the use of NIRS.

Ligation of the PDA

Ductal clipping was performed according to the standard procedure. Each infant was given 10 μg/kg fentanyl intravenously together with 0.1 μg/kg Pancuronium (Pavulon®) 30 min before the procedure started. Afterwards, Fentanyl was given continuously at 3 μg/kg/h. All the infants were mechanically ventilated. FiO_2 was given according to the peripheral saturation.

Study design

Physiologic as well as cerebral parameters were continuously recorded before, during and after the ductal clipping: heart rate (HR), mean arterial blood pressure (MABP) and arterial oxygen saturation ($SaO_{2)}$ (Pulse Oximeter, Novametrix,®) were recorded simultaneously by the Codas system (Dataq Instruments®, USA). With the NIRO-300 HbO_2, HbR, HbT and TOI were continuously measured.

Measurements

Figure 1 illustrates the 2 phases of the study. Phase 1a (pre-operative phase) is a stable recording of 45 minutes, before the start of the manipulation. It represents the control values. Phase 2 (pre-operative phase) consists of phase 2a, which is a recording during 5 minutes immediately before the PDA clipping, and of phase 2b, which is a recording during 5 minutes immediately after the PDA clipping. Phase 1b (post-operative phase) is a stable recording during 45 min after the clipping and manipulation.

Data analysis

Changes in HbD (μmol/l) were calculated as $\Delta HbO_2 - \Delta$HbR. FTOE was derived from the formula (SaO_2 − TOI)/SaO_2. Changes in CBV (ml/100 g) were calculated as $\Delta CBV = \Delta[HbT] \times 0.89/[Hb]$, where [Hb] is the large vessel Hb concentration (g/dl) and [HbT] is expressed in μmol/l (20). Data (ΔHbD, HbT, ΔCBV, TOI, FTOE, MABP, SaO_2 and HR) are summarized as median values over every epoch of 5 min during phases 1a and 1b and over every epoch of 1 min during phases 2a and 2b.

Statistical analysis

Normality was checked with the Kolmogorov–Smirnov test.

The paired Wilcoxon test was used to compare the physiologic and cerebral parameters before and after the ductal closure, for each infant individually as well as over the whole group. A p-value of < 0.05 was considered significant. For statistical analysis, Medcalc®v9.2.0.2 and STATISTICA® (StatSoft, Inc. (2002), *STATISTICA* for Windows Tulsa) were used.

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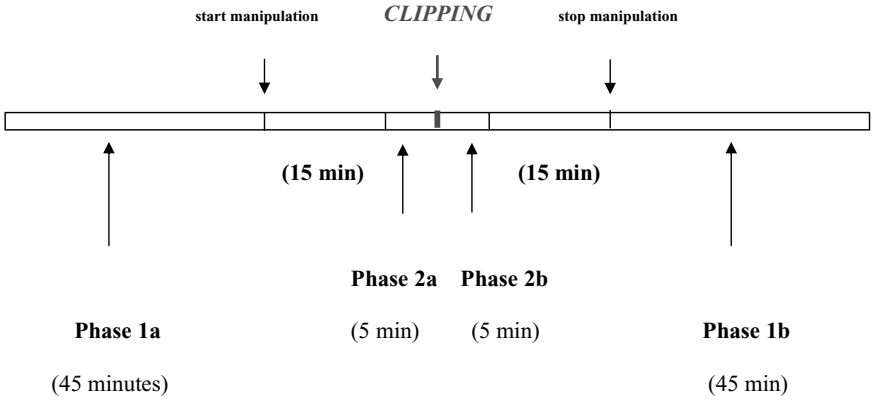


Figure 1 The 2 phases of the study.

RESULTS

Clinical characteristics

Ten preterm infants were studied. The mean postmenstrual age (PMA) was 27 weeks (24–32; SD: 2.64), the mean birth weight (BW) was 987.5 grams (555–1855; SD: 391) and the mean postnatal age (PNA) at the time of clipping was 33 days (6–88; SD: 30.9). All infants were mechanically ventilated during ligation (SIMV).

Five neonates had IVH at the moment of clipping. One infant died 4 days after the clipping due to a cardiorespiratory collapse, caused by sepsis. In all patients the ligation of the ductus was successful.

Cerebral parameters

Effect of the clipping itself: comparison of phases 2a and 2b

In the entire group, at the exact moment of clipping, TOI increased with 2.9% ($p = 0.037$), HbD with 12.5 μmol/l ($p = 0.047$) and HR with 6.5 bpm ($p = 0.012$). FTOE significantly decreased with 0.02% ($p = 0.013$). The remaining cerebral and peripheral parameters remained stable (Fig. S1, Table S1 in Supporting Information online).

Effect at 1 h post-clipping: comparison of phases 1a and 1b

From 20 up to 65 min after clipping, neither the physiological parameters (SaO_2, MABP, HR) nor the cerebral parameters (TOI, ΔHbD, HbT, ΔCBV, FTOE) were significantly different from the control values before the clipping (Table S2 in Supporting Information online).

DISCUSSION

A PDA is common in neonatal life and may disturb cerebral and peripheral circulation. As a treatment intravenous indomethacin and ibuprofen are frequently used. However concerns are raised regarding the safety of indomethacin when given over a short period as it causes a marked decline in CBF, CBV and oxygen delivery and thus reduces cerebral intracellular oxygenation (21,22). In contrast, ibuprofen has shown not to have a negative effect on the cerebral oxygenation (5,11,12). When medication therapy fails or is contraindicated, surgical ligation of the PDA is the treatment of choice (6). It is considered a safe procedure with good clinical results and relatively low morbidity and mortality (7–9), although it remains associated with complications such as pneumothorax, bleedings and IVH (7), and recently its impact on cerebral haemodynamics and neurodevelopmental outcome has been questioned. Kabra et al. found an increased incidence of neurodevelopmental abnormalities in addition to CLD and retinopathy of prematurity (ROP) among infants treated with ligation. However, because of their observational study design they could not determine if surgical ligation is a cause or just a marker for poor long-term outcome (23). In contrast, Chorne et al. found no relationship between ductal ligation and subsequent neurodevelopmental problems (16). These studies show that till nowadays information on the impact of clipping itself on the cerebral oxygenation is scarce and that continuous bedside monitoring of cerebral and physiological parameters can be helpful to minimize or even prevent intra- and post-operative complications.

NIRS provides continuous information on the cerebral circulation, tissue oxygenation and extraction. Zaramella et al. first used NIRS to assess the cerebral perfusion after surgical PDA ligation. They intermittently recorded the cerebral parameters at 35 min before and at 14 and 27 min after ductal closure and, unlike other studies (13,14), they found no increase in ΔCBV or diastolic blood pressure suggesting that the PDA before the clipping did not limit CBF. Moreover they found a decrease in TOI after ductal closure reflecting an increased oxygen extraction and consumption over the clip (17). Huening et al. recently performed continuous NIRS recordings from 2 min before up to 10 min post-clipping to assess cerebral changes. They found no change in MABP or TOI, although during the first 2 min after ductal closure they saw an abrupt increase in CBV with return to baseline within 5 min. This short increase in CBV suggests an abrupt stop of ductal steal and a subsequent increase in CBF with clipping, although not supported by an increase in HbD (18). We continuously monitored MABP, HR, SaO_2

together with NIRS-derived TOI as well as FTOE, at the exact time of clipping up to 1 h post-clipping. Just like Huening et al. (18) but in contrast to several studies (13,24,25), we did not find a change in MABP, neither at the exact moment of clipping, nor up to 1 h post-clipping, suggesting a stable cerebral circulation when PDA was present. HR increased with clipping, which may reflect reopening of the pulmonary vessels after decompression of the lungs, as suggested by many others studies (13,14,18,25,26).

In addition, with clipping we found a significant increase in TOI and a concomitant decrease in FTOE that may indicate an increase in oxygenated blood supply to the brain. These findings are supported by the rise in HbT and ΔCBV and the significant increase in ΔHbD, as a measure of CBF **(27)**. One hour post-clipping TOI, FTOE, ΔHbD and CBV were no longer different from baseline values indicating that the PDA before clipping had not limited cerebral circulation and that CBF during and after clipping was sufficient to ensure stable cerebral oxygenation. Moreover, this indicates that the effects of clipping on the cerebral haemodynamics are only acute and transient and unlikely to cause harm, as supported by the study of Huening et al. Although these observations stroke with the findings of Lemmers et al. who monitored infants with a PDA over a period of three days and found a lower cerebral oxygen saturation and a higher FTOE as compared to controls, suggesting a reduced oxygen delivery induced by ductal steal and a subsequent decrease of cerebral perfusion with a PDA (28). This discrepancy could be explained by limitations in our study design: we have recordings only up to 1 h post-clipping and we did not compare our TOI data with those of infants without a PDA. From the study of Lemmers et al., we would expect to see an increase in TOI not only at the exact moment of clipping but also afterwards. In contrast, in our study at 1 h post-clipping, TOI was no longer different from control values. It may be that at this time the neonate is not yet fully recovered from surgery whereas the cerebral effects of the clipping emerge only afterwards. To confirm this, recordings during a longer time after clipping are needed.

Although ductal ligation carries the risk of compromised cerebral perfusion in vulnerable premature infants, till now it has been considered a safe procedure with good clinical results and relatively low incidence of morbidity and mortality (7–9). This is supported by our study: we found no increased incidence of PVL, IVH or death with ductal ligation.

Our findings strongly recommend the use of surgical ligation as treatment of PDA since we found no changes in cerebral haemodynamics associated with clipping. Although Kabra et al. recently found a higher incidence of neurodevelopmental problems in infants treated with surgical ligation, they suggested that, since drugs can affect the cerebral perfusion and oxygenation and thereby cause cerebral damage, exposure to anaesthetic drugs during surgery may explain this association between surgery and subsequent neurosensory impairment (23). From literature, however, we know that fentanyl has no effect on cardiac output, HR or MABP (29) and that it causes no modification of general or cerebral haemodynamics (30). In our study, all infants were treated with fentanyl and up to 1 h after clipping no adverse effects on cerebral oxygenation were found.

From our findings we conclude that the surgical ligation of the ductus itself has no negative effect on the cerebral haemodynamics in prematurely born infants and that neurological abnormalities that have been reported after ductal clipping have to be explained by other factors than the surgical ligation itself.

Moreover, this study encourages the use of NIRS for the continuous, non-invasive measurement of the cerebral oxygenation, expressed as TOI and FTOE, in the neonatal population, even during surgery.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 Changes in physiological and cerebral parameters at the exact moment of clipping. Significance ($p < 0.05$) is indicated as S. Over the entire group, significant changes from baseline were seen in HR (+6.5 bpm), TOI (+2.9%), HbD (+12.5 μmol/l) (A) and FTOE (− 0.02%) (B).
Table S1 Comparison of phases 2a (5 min before the clipping) and 2b (5 min after the clipping)
Table S2 Comparison of phases 1a (stable 45-min period up to 20 min before clipping) and 1b (stable 45-min period, from 20 min after clipping)

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