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Manuscript ID: IJN-2102-2040

Manuscript Title: **Hemodynamic Significant Patent Ductus Arteriosus Effect on Tissue Oxygenation in Preterm Infant: A Study Using Near Infrared Spectroscopy**

Authors: Sunny Mariana Samosir,Martono Tri Utomo,Mahrus Abdul Rahman,Agus Harianto,Risa Etika,Dina Angelika,Kartika Darma Handayani,Mahendra Tri Arif Sampurna

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Manuscript Needs Major Revision (#IJN-2102-2040 (R2))

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Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

For each variable of interest, give sources of data and details of methods of assessment

Describe any efforts to address potential sources of bias

Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

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Authors: Sunny Mariana Samosir,Martono Tri Utomo,Mahrus Abdul Rahman,Agus Harianto,Risa Etika,Dina Angelika,Kartika Darma Handayani,Mahendra Tri Arif Sampurna

Date: 2021-02-16

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HEMODYNAMIC SIGNIFICANT PATENT DUCTUS ARTERIOSUS EFFECT ON TISSUE OXYGENATION IN PRETERM INFANT: A STUDY USING NEAR INFRARED SPECTROSCOPY

ABSTRACT

Background: Hemodynamic significant Patent Ductus Arterisous (hsPDA) is one of the main complications of preterm birth. However, its management still needs further development. Ductal stealing, resulting in pulmonary hyperperfusion and systemic hypoperfusion, potentially causes oxygenation disorders that lead to target organ disruptions (i.e. cerebral, abdominal, and renal). Hence, monitoring tissue oxygenation is essential to detect organ disorders. Previous studies revealed that near infrared spectroscopy (NIRS) showed a promising result as a non-invasive method to monitor tissue oxygenation.

Objective: The study aimed to analyze the tissue oxygen saturation (rSO_2) differences of premature babies with and without hsPDA.

Patients and Methods: A cross-sectional study was conducted on preterm infants aged 3-7 days with 24-$33^{6/7}$ weeks of gestation. hsPDA diagnosis was carried out by echocardiography; defined as >1.5mm diameter of ductus arteriosus and >1.4 left pulmonal artery and aorta (La/Ao) ratio. NIRS monitoring was carried out to measure tissue oxygen saturation of the cerebral (r_cSO_2), abdomen (r_aSO_2), and renal (r_rSO_2). The statistical analysis was undertaken using SPSS 21.0.

Results: There were 11 out of 52 infants categorized as hsPDA. Mean birth weight was 1213±293 gram; Mean gestational age was 30.72±2.01 weeks; and, Mean ductus diameter in hsPDA was 2.84±0.93 mm. There was no significant difference between the hsPDA and non-hsPDA groups in r_cSO_2 (75.27±9.14% vs 79.03±9.11%;p=0.238), r_aSO_2 (65.60±11.07% vs 67.48±10.17%;p=0.594), and r_rSO_2 (76.41±14.98% vs 82.61±10.41%;p=0.218).

Conclusion: The existence of hsPDA doesn't affect the oxygenation in cerebral, abdominal, and renal tissue in preterm babies. The decision regarding optimal time for ductal closure should be reconsidered.

Keywords:

preterm infant, hemodynamic significant patent ductus arteriosus, near infrared spectroscopy

INTRODUCTION

Ductus arteriosus (DA) will normally shrink after birth in term infant and be functionally closed at the age of 72 hours. The ductal closure is delayed until 4 days of age in 10% of preterm babies born in 30-37 weeks, 80% of those born in 25-28 weeks, and 90% of those born less than 24 weeks of gestational age[1,2]. The persistent DA can cause hemodynamic significant Patent Ductus Arteriosus (hsPDA) where the systemic shunt to the pulmonary vessels results in pulmonary hyperperfusion and systemic hypoperfusion[3]. Therefore, understanding tissue perfusion and oxygenation is important as a consideration for the administration of ductal closure therapy in premature infants to avoid further morbidity and mortality[4–6]. The ductal shunting from systemic to pulmonary blood flow has an impact on the cerebral, abdominal, and renal circulation[7]. Uncorrected hsPDA can cause intra ventricular hemorrhage, necrotizing enterocolitis (NEC), and renal insufficiency[6]. The long-term impact of decreased cerebral oxygenation in infants less than a month includes brain damage and development disorders[8].

Clinical assessment and echocardiography become reliable methods in diagnosing hsPDA. Near Infrared Spectroscopy (NIRS) has been validated as a non-invasive tool to measure tissue oxygen saturation (rSO_2) that can detect early changes in organ perfusion and oxygenation, thus, it can help identify and monitor the hsPDA therapy[9]. A study by van der Laan showed that cerebral and renal oxygenation are not affected by hsPDA.[6] Lemmers et al., and Cohen et al., proved the negative effects of hsPDA on cerebral oxygenation in premature infants[8,10]. There have been many studies on regional perfusion and oxygenation in premature infants with NIRS.[8–10] However, to the best of the researcher's knowledge, there have not been enough studies on regional oxygenation differences especially in preterm infants in our country, Indonesia, using NIRS.

The present study aimed to study regional tissue oxygenation differences in preterm infants with hemodynamic significant and non-hemodynamic significant Patent Ductus Arteriosus using NIRS in the early days of life of preterm babies.

PATIENTS AND METHODS

Patients

This cross-sectional study used 52 out of 191 preterm infants treated in the NICU during study times. The samples were determined using consecutive sampling technique. All preterm babies (with gestational age of 24-33 weeks) were born between November 2019 and May 2020 at the tertiary level neonatal intensive care unit of Dr.Soetomo General Hospital whose oxygen support devices (i.e. high flow nasal canula, continuous positive airway pressure, invasive and non-invasive ventilator) were eligible for inclusion. Patients with multiple congenital anomaly, ductal dependent cyanotic heart defect, early onset of septicemia, and incomplete consent from parents were excluded. Demographic and clinical data were collected from medical records. The sample size is calculated using a formula for continuous data with the aim of hypothesizing two or more group. The ratio between the hsPDA and non hsPDA group was based on the previous study.[11]

Echocardiography

Echocardiography screening was performed between 3rd and 7th postnatal day by pediatric cardiology consultant using Sonoscape Portable Digital Color Doppler Ultrasound System Model S9 (SonoScape, Shenzhen). Echocardiography was performed by one pediatric cardiology consultant to minimize performance variability. The samples were categorized into two groups: hsPDA and non hsPDA. The hsPDA was considered existing if there were a ductus arteriosus with diameter > 1.5 mm on constriction phase, pulmonal perfusion seen in the left pulmonal artery diameter and aorta diameter ratio (LA/Ao) was > 1.4, and left to right shunt were present. While DA that was already closed and did not fulfill the requirement for hsPDA was considered non-hsPDA.

NIRS Measurements

INVOS 5100C near infrared spectrometer and neonatal sensors (Covidien, USA) were used to monitor the tissue oxygen saturation on the day of echocardiography was performed. Multisite sensors were placed on the frontoparietal side of the infant's head to evaluate the cerebral tissue oxygen saturation (r_cSO_2), on the inferior side of umbilicus to evaluate the abdominal tissue oxygen saturation (r_aSO_2), and on the lateral posterior flank to evaluate the renal oxygen saturation (r_rSO_2). The evaluation was performed by different examiners without knowing the echocardiography result. The oxygen saturation changes were observed in 15 minutes continuously. Every 15 seconds, the machine records tissue oxygen saturation data. Mean regional rSO2 were used for further analysis. A pulse oxymeter was also put on the baby's right

Commented [i-[1]: Setting and location: 3rd level NICU in Dr Soetomo General Hospital

Period of recruitment = Nov 2019-May 2020

Commented [i-[2]: eligibility criteria, sources, and participant selection methods

Commented [i-[3]: the study size calculation

Commented [i-[4]: Period of sample recruitment and time framing for data collection. Echocardiography data collection

Commented [i-[5]: exposure: babies with and without hsPDA

Commented [i-[6]: effort to minimize bias

Commented [i-[7]: NIRS data collection hand to evaluate the peripheral oxygen saturation (spO_2) for further calculation of fractional tissue oxygen extraction (FTOE) on each location using the following formula: FTOE = (spO_2 – rSO_2)/spO_2. A 15-minute measurement was simultaneously observed and the mean values were obtained.

Statistical Analysis

Differences in clinical characteristics of the two sample groups of hsPDA and non hsPDA were analyzed using Chi square test, Fisher exact test, and exact probability test. Statistical analyses for each regional oxygen saturation and fractional tissue oxygen extraction between both groups were performed using independent t-test and Mann Whitney test. IBM SPSS 21.0 was used for all statistical analyses with significant value (p) at < .05.

Ethics

The ethical clearance was issued by the Ethical Committee of Dr. Soetomo General Hospital (No.1766/105/XI/2019).

RESULTS

Our study shows that three babies had multiple congenital anomalies, four babies had early onset of septicemia, and the others were excluded due to incomplete data and consent. Eleven infants classified as hsPDA group based on echocardiography. There were 25 (48%) and 27 (52%) preterm male and female babies, respectively. Majority of the subjects was in 28-<32 weeks of gestational age (55.8%) with mean gestational age was 30.72±2 weeks for hsPDA and 30.78±2 weeks for non hsPDA. Mean birth weight for hsPDA and non hsPDA were 1213±293 and 1272±306 grams, respectively.

Table 1 shows the neonatal characteristics for both groups. There was no significant difference in all variables. Therefore, the samples considered as homogenous.

This study obtained that the smallest DA's diameter was 1.5 mm and the largest one was 4.8 mm in the hsPDA group. From the eleven samples in hsPDA group, the duct diameter was obtained with an average of 2.84±0.93. The comparison between LA and Ao had an average score of 1.56±0.26. The ejection fraction of hsPDA and non hsPDA group were 71.55±5.72 and 73.94±9.4%, respectively.

Linear regression was used to evaluate comorbidities on samples, namely perinatal asphyxia, respiratory distress syndrome, and persistent pulmonary hypertension of the newborn as confounding factors of the regional oxygen saturation. All measurement was not significant. In accordance to Table 2, there were no significant differences in the tissue oxygen saturation ratio of cerebral (r_cSO_2), abdominal (r_aSO_2), or renal (r_rSO_2) areas between hsPDA babies and non hsPDA (p = .238, p = .598, and p = .218 respectively). Fractional oxygen extraction in cerebral (cFTOE), abdominal (aFTOE), and renal (rFTOE) areas between the hsPDA and non hsPDA groups also revealed non-significant difference (p = .473, p = .578, and p = .151, respectively).

Commented [i-[8]: outcome of this study (tissue oxygen saturation & fractional oxygen extraction in tissue)

DISCUSSION

The present study obtained the characteristics of the two groups that were not significantly different so that it can be compared. Previous study showed that the incidence of hsPDA increased with lower oxygen saturation[12]. The mean SpO2 in this study was around 97% with minimal setting of CPAP and mechanical ventilation. There were no significant differences in r_cSO_2 (p = .238) between the hsPDA and non hsPDA groups in the study. These findings are in line with previous observational cohort designs by van der Laan et al. in Netherland, in which oxygen saturation and oxygen extraction in cerebral and renal of 49 preterm infants with gestational age <32 weeks evaluated using NIRS were not affected by hsPDA.[6] The r_cSO_2 results in hsPDA group (69%) were lower than non hsPDA group (76%) and cFTOE in hsPDA group (0.22) were higher than non hsPDA group (0.33).

In contrast to the results of several previous research where a decrease in cerebral oxygenation was found in hsPDA, Lemmers et al. reported a lower r_cSO_2 in infants with hsPDA compared to the asymptomatic PDA group (62±9% and 72±10%, sequentially). The difference might be caused by several factors affecting the patient's hemodynamics. In Lemmers' study, the patients in hsPDA group mostly used ventilator, morphine as sedatives that caused peripheral vasodilation, and more inotropic than control. Dopamine administration could increase cardiac output that affected an elevating perfusion. In addition, in the previous study, the sampling period was earlier (in the first 72 hours) compared to the present study (3-7 postnatal days) which could affect the results of oxygenation measurement. It is agreed that the cerebral oxygen supply increases as the baby age. Tissue oxygen extraction (FTOE) was also significantly higher in premature infants with hsPDA than those with non hsPDA[13]. The relationship between oxygen transport (DO_2) and tissue oxygen consumption (VO_2) is fractional tissue oxygen extraction

($FTOE = VO_2/DO_2$). Negative correlation between r_cRSO_2 and cFTOE indicated that if there was a decrease in the brain oxygen supply in sick premature babies, there was an increase in cerebral oxygen extraction aimed to maintain oxygen availability in the brain[14].

A retrospective study by Chock et al. showed that a low r_cSO_2 value of < 66% was associated with the presence of hsPDA in preterm infants[9]. Although the oxygenation value in cerebral tissue of hsPDA infant was lower than non hsPDA, the average value was still higher compared to the < 40% cerebral oxygen saturation limit associated with the appearance of symptoms, such as ischemic lesions and neuron damage. The normal value of r_cSO_2 for preterm babies is 55-85%[15]. According to Dix et al., higher r_cSO_2 values in neonatal sensors compared to adult NIRS sensors might be caused by differences in NIRS signal reception process where neonatal NIRS sensor algorithmic adjusted to thinner neonatal calvarium so that the light is easier to enter[16].

Although the determination of "to treat or not to treat" is still a clinical question nowadays, Poon et al., reported an improvement in cFTOE after medical therapy and PDA ligation.[17] Observation using NIRS as an overview of PDA closure can help on evaluating the infants to reduce the burden of cerebral hypoxia. It is necessary to identify infants at high risk of long-term developmental disorders.

Although not statistically significant, r_aSO_2 was lower in premature infants with hsPDA than non hsPDA (65.60±11.07 and 67.48±10.17, respectively) with *p* of .594. Similarly, abdominal fractional oxygen extraction in infants with and without hsPDA were 0.33±0.11 and 0.3± 0.1, respectively (*p*= .578). The findings are similar to the results of a study by Petrova el al., where no significant difference was found between tissue oxygen saturation in cerebral, abdominal, and renal in preterm infants aged < 32 weeks of gestational age with PDA diameter of ≥ 3 compared to < 3 mm[18]. Similarly, Gorman et al. found no statistical difference in hsPDA infants who were given ibuprofen therapy and who were not.[19] It was reported that NIRS facilitated benefits in terms of showing a downward trend of 20% of the base value before clinical manifestation of NEC appeared. In our study, we found 3 preterm babies with hsPDA and 7 non-hsPDA who experienced NEC based on Bell stage criteria.

Different results were reported by Ledo et al., where infants with hsPDA had significantly lower abdominal tissue oxygen saturation during observational prospective studies of 72 premature infants.[20] Lower blood pressure and lower mesenteric oxygenation with increased extraction of oxygen by tissues were obtained. Continuous monitoring on abdominal oxygenation needs to be done in newborns where a transition of gastrointestinal tract from a relatively dormant organ to a main area of nutrient absorption requiring sufficient supply of oxygen. Unlike cerebral circulation that has an autoregulation protection mechanism, mesenteric circulation in the abdomen does not have the ability to auto-regulate. Therefore, it is at risk of gastrointestinal hypoxia. Ledo et al. stated that hsPDA babies had lower blood pressure with lower abdominal oxygenation. Abdominal FTOE also reported an increase in the first five days and stabilized on day six. The stability of the aFTOE on the 6^{th} day was along with the spontaneous closure of the DA. In the previous study, babies who got catecholamine were put in the exclusion group to minimize the confounding factors that affected oxygenation[20,21]. NIRS somatic sensors placed in the abdominal region were expected to detect oxygenation disturbances in abdomen. Abdominal oxygen saturation (r_aSO_2) depicts blood flow in the mesenteric artery as it is the main vascular supplier of the gastrointestinal tract[22].

In this study, there was no significant difference in r_rSO_2 value between hsPDA compared to non hsPDA(76.41±14.98 vs82.61±10.41) (p =.218). Normal value of r_rSO_2 in premature babies is 80%. New born average r_rSO_2 score is 40% that will increase in ten minutes to 80-90%, then decrease with improvements in renal blood flow and increase the utilization of oxygen in the kidneys[18]. In a cohort study of premature infants in the first week of life, it was found that r_rSO_2<66% was associated with the presence of hsPDA based on echocardiography criteria with a sensitivity of 81% and specificity of 77%. The difference could be due to the fact that the babies in the previous study who had r_rSO_2<66% were <1000grams of weight and used ventilators. Low $r_rSO_2$values can be caused by immature renal function or hemodynamic instability other than PDA[9]. Guzoglu et al. reported no significant difference in regional oxygen saturation of the kidneys with r_rSO2 value of 60% (ranged between 17-93%, p = .87) and rFTOE .37 (ranged between .06-.83, p = .87) in infants with hsPDA and control[6,22,23]. The r_rSO_2 value obtained in the present study is relatively higher than other studies. This can be caused due to NIRS renal measurements conducted on post natal days 3 to 7 when perfusion and utilization of oxygen in the kidneys were still in the transition process.

This study provides information of oxygen saturation in three region simultaneously in both groups. However, there are several limitations of this study. First, the NIRS measurement of tissue oxygen saturation is only performed in short period. Longitudinal study is needed to study the oxygen saturation trends. Second, tissue oxygen saturation assessment is based on NIRS only and not confirmed by other supporting examinations. And last, the small number of samples due to limitation of time.

CONCLUSION

The results of our study suggest that hsPDA does not affect the oxygenation in cerebral, abdominal, and renal in preterm infants during the examination. The decision regarding optimal time for ductal closure should be reconsidered. However, further large scale studies needs to be conducted to reassess the present findings.

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TABLES

Table 1. Subject characteristics

	hsPDA n (11)	non-hsPDA n (41)	Total n (52)	P
Sex				1.000*
Male	5 (9.6)	20 (38.5)	25 (48.1)	
Female	6 (11.5)	21 (40.4)	27 (51.9)	
Gestational age				1.000**
Extremely Preterm (<28 weeks)	1 (1.9)	3 (5.8)	4 (7.7)	
Very Preterm (28 - <32 weeks)	6 (11.5)	23 (44.3)	29 (55.8)	
Moderate Late Preterm (32 - <37 weeks)	4 (7.7)	15 (28.8)	19 (36.5)	
Birth weight				0.902**
ELBW (<1000 g)	2 (3.9)	6 (11.5)	8 (15.4)	
VLBW (<1500 g)	7 (13.5)	24 (46.1)	31 (59.6)	
LBW (<2500 g)	2 (3.9)	11 (21.1)	13 (25)	
Singleton/multiple birth				0.322
Singleton	11 (21.1)	35 (67.4)	46 (78.5)	
Multiple birth	0 (0.0)	6 (11.5)	6 (11.5)	
Respiratory support				0.474**
High flow nasal canule	1 (1.9)	1 (1.9)	2 (3.8)	
CPAP	7 (13.5)	33 (63.5)	40 (77)	
Non invasive ventilator	1 (1.9)	1 (1.9)	2 (3.8)	
Invasive ventilator	2 (3.9)	6 (11.5)	8 (15.4)	
HR (x/minute), *mean*± SD	165±14,4	148±10,5		
SpO_2 (%), *mean*± SD	97.1±2,7	97.0±1,9		
Hb, *mean* ± SD	15.73±3.46	15.37±2.58		0.702
Inotropes				0.101
No	8 (15.4)	38 (73.1)	46 (88.5)	
Yes	3 (5.7)	3 (5.7)	6 (11.5)	
Age during recruitment				
3 day	3 (5.7)	21 (40.5)	24 (46.2)	0.118

4 day	6 (11.5)	10 (19.3)	16 (30.8)	
5 day	1 (1.9)	5 (9.6)	6 (11.5)	
6 day	1 (1.9)	4 (7.7)	5 (9.6)	
7 day	0 (0.0)	1 (1.9)	1 (1.9)	
Infant's comorbidity				0.086
Respiratory distress synd.	6 (11.5)	12 (23.1)	18 (34.6)	
Perinatal Asphyxia	2 (3.8)	11 (21.1)	13 (24.9)	
PPHN	3 (5.7)	3 (5.7)	6 (11.4)	
Hyperbilirubinemia	4 (7.7)	6 (11.5)	10 (19.2)	
Others	1 (1.9)	9 (17.3)	10 (19.2)	
APGAR score in 5 minutes				0.886[*]
≤5	6 (11.5)	19 (36.5)	25 (48)	
>5	5 (9.6)	22 (42.4)	27 (52)	
Mode of delivery				0.094[**]
SC with general anesthesia	6 (11.5)	7 (13.5)	13 (25)	
SC with regional anesthesia	3 (5.7)	19 (36.5)	22 (42.2)	
Spontaneous birth	2 (3.8)	14 (27.0)	16 (30.7)	
Assisted vaginal birth	0 (0.0)	1 (1.9)	1 (1.9)	
Amniotic fluid				0.134[**]
Clear	10 (19.3)	38 (73.1)	(92.4)	
Turbid	1 (1.9)	0 (0.0)	(1.9)	
Meconium	0 (0.0)	3 (5.7)	(5.7)	
Mother's comorbidy				0.357[**]
Healthy	1 (1.9)	2 (3.8)	3 (5.7)	
Hypertension	6 (11.5)	11 (21.1)	17 (32.7)	
Obesity	0 (0.0)	2 (3.8)	2 (3.8)	
Antenatal bleeding	1 (1.9)	1 (1.9)	2 (3.8)	
Combination of 2	1 (1.9)	14 (26.9)	15 (28.8)	
Combination of 3	2 (3.8)	9 (17.3)	11 (21.1)	
Others	0 (0.0)	2 (3.8)	2 (3.8)	
Antenatal corticosteroid				1.000
No	7 (13.5)	27 (52)	34 (65.5)	
Yes	4 (7.7)	14 (26.8)	18 (34.5)	

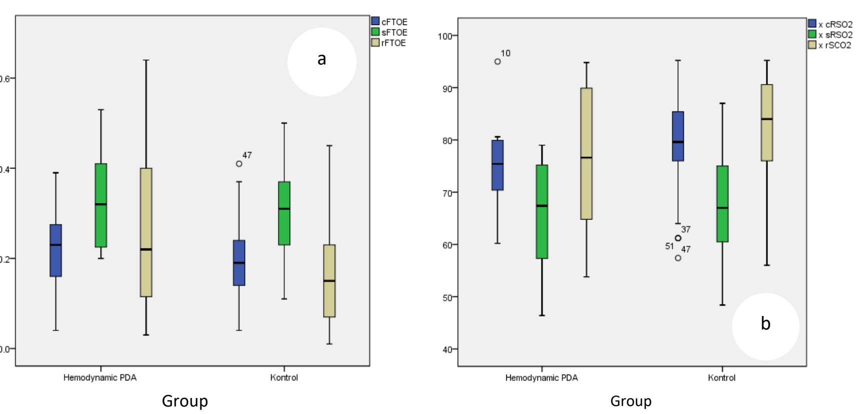
Table 2 Comparison of Regional Oxygen Saturation & Fractional Oxygen Extraction of hsPDA and non hsPDA

	hsPDA		Non hs-PDA		p
	(n)	(mean±SD)	(n)	(mean±SD)	
r_cSO_2	11	75.27±9.14	41	79.03±9.11	0.238
r_aSO_2	11	65.60±11.07	41	67.48±10.17	0.594
r_cSO_2	11	76.41±14.98	41	82.61±10.41	0.218
cFTOE	11	0.22±0.09	41	0.19±0.08	0.473
aFTOE	11	0.33±0.11	41	0.30±0.10	0.578
rFTOE	11	0.26±0.19	41	0.16±0.12	0.151

FIGURES

Figure 1a. Box plot diagram of regional FTOE values on hsPDA and non hsPDA group

Figure 1b.Box plot diagram of regional rSO_2 values on hsPDA and non hsPDA group



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Manuscript ID: IJN-2102-2040 (R3)

Manuscript Title: **Hemodynamic Significant Patent Ductus Arteriosus Effect on Tissue Oxygenation in Preterm Infant: A Study Using Near Infrared Spectroscopy**

Authors: Martono Tri Utomo,Risa Etika,Mahrus Abdul Rahman,Mahendra Tri Arif Sampurna,Sunny Mariana Samosir

Date: 2021-02-16

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HEMODYNAMIC SIGNIFICANT PATENT DUCTUS ARTERIOSUS EFFECT ON TISSUE OXYGENATION IN PRETERM INFANT: A STUDY USING NEAR INFRARED SPECTROSCOPY

ABSTRACT

Background: Hemodynamic significant Patent Ductus Arterisous (hsPDA) is one of the main complications of preterm birth. However, its management still needs further development. Ductal stealing, resulting in pulmonary hyperperfusion and systemic hypoperfusion, potentially causes oxygenation disorders that lead to target organ disruptions (i.e. cerebral, abdominal, and renal). Hence, monitoring tissue oxygenation is essential to detect organ disorders. Previous studies revealed that near infrared spectroscopy (NIRS) showed a promising result as a non-invasive method to monitor tissue oxygenation.

Objective: The study aimed to analyze the tissue oxygen saturation (rSO_2) differences of premature babies with and without hsPDA.

Patients and Methods: A cross-sectional study was conducted on preterm infants aged 3-7 days with $24\text{-}33^{6/7}$ weeks of gestation. hsPDA diagnosis was carried out by echocardiography; defined as >1.5mm diameter of ductus arteriosus and >1.4 left pulmonal artery and aorta (La/Ao) ratio. NIRS monitoring was carried out to measure tissue oxygen saturation of the cerebral (r_cSO_2), abdomen (r_aSO_2), and renal (r_rSO_2). The statistical analysis was undertaken using SPSS 21.0.

Results: There were 11 out of 52 infants categorized as hsPDA. Mean birth weight was 1213±293 gram; Mean gestational age was 30.72±2.01 weeks; and, Mean ductus diameter in hsPDA was 2.84±0.93 mm. There was no significant difference between the hsPDA and non-hsPDA groups in r_cSO_2 (75.27±9.14% vs 79.03±9.11%;p=0.238), r_aSO_2 (65.60±11.07% vs 67.48±10.17%;p=0.594), and r_rSO_2 (76.41±14.98% vs 82.61±10.41%;p=0.218).

Conclusion: The existence of hsPDA doesn't affect the oxygenation in cerebral, abdominal, and renal tissue in preterm babies. The decision regarding optimal time for ductal closure should be reconsidered.

Keywords:

preterm infant, hemodynamic significant patent ductus arteriosus, near infrared spectroscopy

INTRODUCTION

Ductus arteriosus (DA) will normally shrink after birth in term infant and be functionally closed at the age of 72 hours. The ductal closure is delayed until 4 days of age in 10% of preterm babies born in 30-37 weeks, 80% of those born in 25-28 weeks, and 90% of those born less than 24 weeks of gestational age[1,2]. The persistent DA can cause hemodynamic significant Patent Ductus Arteriosus (hsPDA) where the systemic shunt to the pulmonary vessels results in pulmonary hyperperfusion and systemic hypoperfusion[3]. Therefore, understanding tissue perfusion and oxygenation is important as a consideration for the administration of ductal closure therapy in premature infants to avoid further morbidity and mortality[4–6]. The ductal shunting from systemic to pulmonary blood flow has an impact on the cerebral, abdominal, and renal circulation[7]. Uncorrected hsPDA can cause intra ventricular hemorrhage, necrotizing enterocolitis (NEC), and renal insufficiency[6]. The long-term impact of decreased cerebral oxygenation in infants less than a month includes brain damage and development disorders[8].

Clinical assessment and echocardiography become reliable methods in diagnosing hsPDA. Near Infrared Spectroscopy (NIRS) has been validated as a non-invasive tool to measure tissue oxygen saturation (rSO_2) that can detect early changes in organ perfusion and oxygenation, thus, it can help identify and monitor the hsPDA therapy[9]. A study by van der Laan showed that cerebral and renal oxygenation are not affected by hsPDA.[6] Lemmers et al., and Cohen et al., proved the negative effects of hsPDA on cerebral oxygenation in premature infants[8,10]. There have been many studies on regional perfusion and oxygenation in premature infants with NIRS.[8–10] However, to the best of the researcher's knowledge, there have not been enough studies on regional oxygenation differences especially in preterm infants in our country, Indonesia, using NIRS.

The present study aimed to study regional tissue oxygenation differences in preterm infants with hemodynamic significant and non-hemodynamic significant Patent Ductus Arteriosus using NIRS in the early days of life of preterm babies.

PATIENTS AND METHODS

Patients

This cross-sectional study used 52 out of 191 preterm infants treated in the NICU during study times. The samples were determined using consecutive sampling technique. All preterm babies (with gestational age of 24-33 weeks) were born between November 2019 and May 2020 at the tertiary level neonatal intensive care unit of Dr.Soetomo General Hospital whose oxygen support devices (i.e. high flow nasal canula, continuous positive airway pressure, invasive and non-invasive ventilator) were eligible for inclusion. Patients with multiple congenital anomaly, ductal dependent cyanotic heart defect, early onset of septicemia, and incomplete consent from parents were excluded. Demographic and clinical data were collected from medical records. The sample size is calculated using a formula for continuous data with the aim of hypothesizing two or more group. The ratio between the hsPDA and non hsPDA group was based on the previous study.[11]

Commented [i-[1]: these sentences were moved from the result section.

Echocardiography

Echocardiography screening was performed between 3rd and 7th postnatal day by pediatric cardiology consultant using Sonoscape Portable Digital Color Doppler Ultrasound System Model S9 (SonoScape, Shenzhen). Echocardiography was performed by one pediatric cardiology consultant to minimize performance variability. The samples were categorized into two groups: hsPDA and non hsPDA. The hsPDA was considered existing if there were a ductus arteriosus with diameter > 1.5 mm on constriction phase, pulmonal perfusion seen in the left pulmonal artery diameter and aorta diameter ratio (LA/Ao) was > 1.4, and left to right shunt were present. While DA that was already closed and did not fulfill the requirement for hsPDA was considered non-hsPDA.

NIRS Measurements

INVOS 5100C near infrared spectrometer and neonatal sensors (Covidien, USA) were used to monitor the tissue oxygen saturation on the day of echocardiography was performed. Multisite sensors were placed on the frontoparietal side of the infant's head to evaluate the cerebral tissue oxygen saturation (r_cSO_2), on the inferior side of umbilicus to evaluate the abdominal tissue oxygen saturation (r_aSO_2), and on the lateral posterior flank to evaluate the renal oxygen saturation (r_rSO_2). The evaluation was performed by different examiners without knowing the echocardiography result. The oxygen saturation changes were observed in 15 minutes continuously. Every 15 seconds, the machine records tissue oxygen saturation data. Mean regional rSO2 were used for further analysis. A pulse oxymeter was also put on the baby's right hand to evaluate the peripheral oxygen saturation (spO_2) for further calculation of fractional tissue oxygen extraction (FTOE) on each location using the following formula: FTOE = (spO_2 – rSO_2)/spO_2. A 15-minute measurement was simultaneously observed and the mean values were obtained.

Statistical Analysis

Differences in clinical characteristics of the two sample groups of hsPDA and non hsPDA were analyzed using Chi square test, Fisher exact test, and exact probability test. Statistical analyses for each regional oxygen saturation and fractional tissue oxygen extraction between both groups were performed using independent t-test and Mann Whitney test. Analysis using logistic regression also performed which show no significant relationship between hsPDA and non hsPDA group. IBM SPSS 21.0 was used for all statistical analyses with significant value (*p*) at < .05.

Commented [i-[2]: add on

Ethics

The ethical clearance was issued by the Ethical Committee of Dr. Soetomo General Hospital (No.1766/105/XI/2019).

RESULTS

In this study, three babies had multiple congenital anomalies, four babies had early onset of septicemia, and the others were excluded due to incomplete data and consent. Eleven infants classified as hsPDA group based on echocardiography. There were 25 (48%) and 27 (52%) preterm male and female babies, respectively. Majority of the subjects was in 28-<32 weeks of gestational age (55.8%) with mean gestational age was 30.72±2 weeks for hsPDA and 30.78±2 weeks for non hsPDA. Mean birth weight for hsPDA and non hsPDA were 1213±293 and 1272±306 grams, respectively.

Table 1 depicts the neonatal characteristics for both groups. There was no significant difference in all variables. Therefore, the samples considered as homogenous.

This study obtained that the smallest DA's diameter was 1.5 mm and the largest one was 4.8 mm in the hsPDA group. From the eleven samples in hsPDA group, the duct diameter was obtained with an average of 2.84±0.93. The comparison between LA and Ao had an average score of 1.56±0.26. The ejection fraction of hsPDA and non hsPDA group were 71.55±5.72 and 73.94±9.4%, respectively.

Linear regression was used to evaluate comorbidities on samples, namely perinatal asphyxia, respiratory distress syndrome, and persistent pulmonary hypertension of the newborn as confounding factors of the regional oxygen saturation. All measurement was not significant. In accordance to Table 2, there were no significant differences in the tissue oxygen saturation ratio of cerebral (r_cSO_2), abdominal (r_aSO_2), or renal (r_rSO_2) areas between hsPDA and non hsPDA groups (p = .238, p = .598, and p = .218 respectively). Fractional oxygen extraction in cerebral (cFTOE), abdominal (aFTOE), and renal (rFTOE) areas between the hsPDA and non hsPDA groups also revealed non-significant difference (p = .473, p = .578, and p = .151, respectively).

DISCUSSION

The present study obtained the characteristics of the two groups that were not significantly different so that it can be compared. Previous study showed that the incidence of hsPDA increased with lower oxygen saturation[12]. The mean SpO2 in this study was around 97% with minimal setting of CPAP and mechanical ventilation. There were no significant differences in r_cSO_2 (p = .238) between the hsPDA and non hsPDA groups in the study. These findings are in line with previous observational cohort designs by van der Laan et al. in Netherland, in which oxygen saturation and oxygen extraction in cerebral and renal of 49 preterm infants with gestational age <32 weeks evaluated using NIRS were not affected by hsPDA.[6] The r_cSO_2 results in hsPDA group (69%) were lower than non hsPDA group (76%) and cFTOE in hsPDA group (0.22) were higher than non hsPDA group (0.33).

In contrast to the results of several previous research where a decrease in cerebral oxygenation was found in hsPDA, Lemmers et al. reported a lower r_cSO_2 in infants with hsPDA compared to the asymptomatic PDA group (62±9% and 72±10%, sequentially). The difference might be caused by several factors affecting the patient's hemodynamics. In Lemmers' study, the patients in hsPDA group mostly used ventilator, morphine as sedatives that caused peripheral vasodilation, and more inotropic than control. Dopamine administration could increase cardiac output that affected an elevating perfusion. In addition, in the previous study, the sampling period was earlier (in the first 72 hours) compared to the present study (3-7 postnatal days) which could affect the results of oxygenation measurement. It is agreed that the cerebral oxygen supply increases as the baby age. Tissue oxygen extraction (FTOE) was also significantly higher in premature infants with hsPDA than those with non hsPDA[13]. The relationship between oxygen transport (DO_2) and tissue oxygen consumption (VO_2) is fractional tissue oxygen extraction ($FTOE=VO_2/DO_2$). Negative correlation between r_cRSO_2 and cFTOE indicated that if there was a decrease in the brain oxygen supply in sick premature babies, there was an increase in cerebral oxygen extraction aimed to maintain oxygen availability in the brain[14].

A retrospective study by Chock et al. showed that a low r_cSO_2 value of < 66% was associated with the presence of hsPDA in preterm infants[9]. Although the oxygenation value in cerebral tissue of hsPDA infant was lower than non hsPDA, the average value was still higher compared to the < 40% cerebral oxygen saturation limit associated with the appearance of symptoms, such as ischemic lesions and neuron damage. The normal value of r_cSO_2 for preterm babies is 55-85%[15]. According to Dix et al., higher r_cSO_2 values in neonatal sensors compared to adult NIRS sensors might be caused by differences in NIRS signal reception process where neonatal NIRS sensor algorithmic adjusted to thinner neonatal calvarium so that the light is easier to enter[16].

Although the determination of "to treat or not to treat" is still a clinical question nowadays, Poon et al., reported an improvement in cFTOE after medical therapy and PDA ligation.[17] Observation using NIRS as an overview of PDA closure can help on evaluating the infants to reduce the burden of cerebral hypoxia. It is necessary to identify infants at high risk of long-term developmental disorders.

Although not statistically significant, r_aSO_2 was lower in premature infants with hsPDA than non hsPDA (65.60±11.07 and 67.48±10.17, respectively) with p of .594. Similarly, abdominal fractional oxygen extraction in infants with and without hsPDA were 0.33±0.11 and 0.3± 0.1, respectively (p= .578). The findings are similar to the results of a study by Petrova el al., where no significant difference was found between tissue oxygen saturation in cerebral, abdominal, and renal in preterm infants aged < 32 weeks of gestational age with PDA diameter of ≥ 3 compared to < 3 mm[18]. Similarly, Gorman et al. found no statistical difference in hsPDA infants who were given ibuprofen therapy and who were not.[19] It was reported that NIRS facilitated benefits in terms of showing a downward trend of 20% of the base value before clinical manifestation of NEC appeared. In our study, we found 3 preterm babies with hsPDA and 7 non-hsPDA who experienced NEC based on Bell stage criteria.

Different results were reported by Ledo et al., where infants with hsPDA had significantly lower abdominal tissue oxygen saturation during observational prospective studies of 72 premature infants.[20] Lower blood pressure and lower mesenteric oxygenation with increased extraction of oxygen by tissues were obtained. Continuous monitoring on abdominal oxygenation needs to be done in newborns where a transition of gastrointestinal tract from a relatively dormant organ to a main area of nutrient absorption requiring sufficient supply of oxygen. Unlike cerebral circulation that has an autoregulation protection mechanism, mesenteric circulation in the abdomen does not have the ability to auto-regulate. Therefore, it is at risk of gastrointestinal hypoxia. Ledo et al. stated that hsPDA babies had lower blood pressure with lower abdominal oxygenation. Abdominal FTOE also reported an increase in the first five days and stabilized on day six. The stability of the aFTOE on the 6th day was along with the spontaneous closure of the DA. In the previous study, babies who got catecholamine were put in the exclusion group to minimize the confounding factors that affected oxygenation[20,21]. NIRS somatic sensors placed in the abdominal region were expected to detect oxygenation disturbances in abdomen. Abdominal oxygen saturation (r_aSO_2) depicts blood flow in the mesenteric artery as it is the main vascular supplier of the gastrointestinal tract[22].

In this study, there was no significant difference in r_rSO_2 value between hsPDA compared to non hsPDA(76.41±14.98 vs82.61±10.41) (p =.218). Normal value of r_rSO_2 in premature babies is 80%. New born average r_rSO_2 score is 40% that will increase in ten minutes to 80-90%, then decrease with improvements in renal blood flow and increase the utilization of oxygen in the kidneys[18]. In a cohort study of premature infants in the first week of life, it was found that r_rSO_2<66% was associated with the presence of hsPDA based on echocardiography criteria with a sensitivity of 81% and specificity of 77%. The difference could be due to the fact that the babies in the previous study who had r_rSO_2<66% were <1000grams of weight and used ventilators. Low $r_rSO_2$values can be caused by immature renal function or hemodynamic instability other than PDA[9]. Guzoglu et al. reported no significant difference in regional oxygen saturation of the kidneys with r_rSO2 value of 60% (ranged between 17-93%, p = .87) and rFTOE .37 (ranged between .06-.83, p = .87) in infants with hsPDA and control[6,22,23]. The r_rSO_2 value obtained in the present study is relatively higher than other studies. This can be caused due to NIRS renal measurements conducted on post natal days 3 to 7 when perfusion and utilization of oxygen in the kidneys were still in the transition process.

This study provides information of oxygen saturation in three region simultaneously in both groups. However, there are several limitations of this study. First, the NIRS measurement of tissue oxygen saturation is only performed in short period. Longitudinal study is needed to study the oxygen saturation trends. Second, tissue oxygen saturation assessment is based on NIRS only and not confirmed by other supporting examinations. And last, the small number of samples due to limitation of time.

CONCLUSION

The results of our study suggest that hsPDA does not affect the oxygenation in cerebral, abdominal, and renal in preterm infants during the examination. The decision regarding optimal time for ductal closure should be reconsidered. However, further large scale studies needs to be conducted to reassess the present findings.

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TABLES

Table 1. Subject characteristic

	hsPDA n (11)	**non-hsPDA n (41)**	**Total n (52)**	**P**
Sex				1.000*
Male	5 (9.6)	20 (38.5)	25 (48.1)	
Female	6 (11.5)	21 (40.4)	27 (51.9)	
Gestational age				1.000**
Extremely Preterm (<28 weeks)	1 (1.9)	3 (5.8)	4 (7.7)	
Very Preterm (28 - <32 weeks)	6 (11.5)	23 (44.3)	29 (55.8)	
Moderate Late Preterm (32 - <37 weeks)	4 (7.7)	15 (28.8)	19 (36.5)	
Birth weight				0.902**
ELBW (<1000 g)	2 (3.9)	6 (11.5)	8 (15.4)	
VLBW (<1500 g)	7 (13.5)	24 (46.1)	31 (59.6)	
LBW (<2500 g)	2 (3.9)	11 (21.1)	13 (25)	
Singleton/multiple birth				0.322
Singleton	11 (21.1)	35 (67.4)	46 (78.5)	
Multiple birth	0 (0.0)	6 (11.5)	6 (11.5)	
Respiratory support				0.474**
High flow nasal canule	1 (1.9)	1 (1.9)	2 (3.8)	
CPAP	7 (13.5)	33 (63.5)	40 (77)	
Non invasive ventilator	1 (1.9)	1 (1.9)	2 (3.8)	
Invasive ventilator	2 (3.9)	6 (11.5)	8 (15.4)	
HR (x/minute), *mean*± SD	165±14,4	148±10,5		
SpO_2 (%), *mean*± SD	97.1±2,7	97.0±1,9		
Hb, *mean* ± SD	15.73±3.46	15.37±2.58		0.702
Inotropes				0.101
No	8 (15.4)	38 (73.1)	46 (88.5)	
Yes	3 (5.7)	3 (5.7)	6 (11.5)	
Age during recruitment				
3 day	3 (5.7)	21 (40.5)	24 (46.2)	0.118

4 day	6 (11.5)	10 (19.3)	16 (30.8)	
5 day	1 (1.9)	5 (9.6)	6 (11.5)	
6 day	1 (1.9)	4 (7.7)	5 (9.6)	
7 day	0 (0.0)	1 (1.9)	1 (1.9)	
Infant's comorbidity				0.086
Respiratory distress synd.	6 (11.5)	12 (23.1)	18 (34.6)	
Perinatal Asphyxia	2 (3.8)	11 (21.1)	13 (24.9)	
PPHN	3 (5.7)	3 (5.7)	6 (11.4)	
Hyperbilirubinemia	4 (7.7)	6 (11.5)	10 (19.2)	
Others	1 (1.9)	9 (17.3)	10 (19.2)	
APGAR score in 5 minutes				0.886*
≤5	6 (11.5)	19 (36.5)	25 (48)	
>5	5 (9.6)	22 (42.4)	27 (52)	
Mode of delivery				0.094**
SC with general anesthesia	6 (11.5)	7 (13.5)	13 (25)	
SC with regional anesthesia	3 (5.7)	19 (36.5)	22 (42.2)	
Spontaneous birth	2 (3.8)	14 (27.0)	16 (30.7)	
Assisted vaginal birth	0 (0.0)	1 (1.9)	1 (1.9)	
Amniotic fluid				0.134**
Clear	10 (19.3)	38 (73.1)	(92.4)	
Turbid	1 (1.9)	0 (0.0)	(1.9)	
Meconium	0 (0.0)	3 (5.7)	(5.7)	
Mother's comorbidy				0.357**
Healthy	1 (1.9)	2 (3.8)	3 (5.7)	
Hypertension	6 (11.5)	11 (21.1)	17 (32.7)	
Obesity	0 (0.0)	2 (3.8)	2 (3.8)	
Antenatal bleeding	1 (1.9)	1 (1.9)	2 (3.8)	
Combination of 2	1 (1.9)	14 (26.9)	15 (28.8)	
Combination of 3	2 (3.8)	9 (17.3)	11 (21.1)	
Others	0 (0.0)	2 (3.8)	2 (3.8)	
Antenatal corticosteroid				1.000
No	7 (13.5)	27 (52)	34 (65.5)	
Yes	4 (7.7)	14 (26.8)	18 (34.5)	

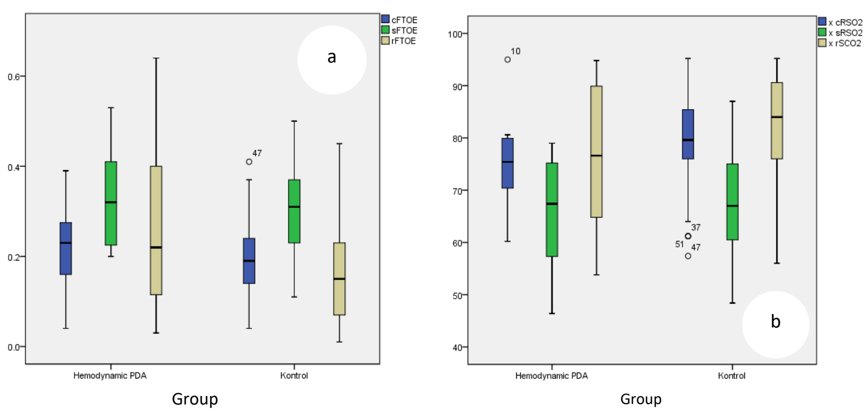
Table 2 Comparison of Regional Oxygen Saturation & Fractional Oxygen Extraction of hsPDA and non hsPDA

	hsPDA		Non hs-PDA		p
	(n)	(mean±SD)	(n)	(mean±SD)	
r_cSO_2	11	75.27±9.14	41	79.03±9.11	0.238
r_aSO_2	11	65.60±11.07	41	67.48±10.17	0.594
r_cSO_2	11	76.41±14.98	41	82.61±10.41	0.218
cFTOE	11	0.22±0.09	41	0.19±0.08	0.473
aFTOE	11	0.33±0.11	41	0.30±0.10	0.578
rFTOE	11	0.26±0.19	41	0.16±0.12	0.151

FIGURES

Figure 1a. Box plot diagram of regional FTOE values on hsPDA and non hsPDA group

Figure 1b.Box plot diagram of regional rSO_2 values on hsPDA and non hsPDA group



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Authors: Sunny Mariana Samosir,Martono Tri Utomo,Mahrus Abdul Rahman,Agus Harianto,Risa Etika,Dina Angelika,Kartika Darma Handayani,Mahendra Tri Arif Sampurna

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HEMODYNAMIC SIGNIFICANT PATENT DUCTUS ARTERIOSUS EFFECT ON TISSUE OXYGENATION IN PRETERM INFANT: A STUDY USING NEAR INFRARED SPECTROSCOPY

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ABSTRACT

Background: Hemodynamic significant Patent Ductus Arterisous (hsPDA) is one of the main complications of preterm birth. However, its management still needs further development. Ductal stealing, resulting in pulmonary hyperperfusion and systemic hypoperfusion, potentially causes oxygenation disorders that lead to target organ disruptions (i.e. cerebral, abdominal, and renal). Hence, monitoring tissue oxygenation is essential to detect organ disorders. Previous studies revealed that near infrared spectroscopy (NIRS) showed a promising result as a non-invasive method to monitor tissue oxygenation.

Objective: The study aimed to analyze the tissue oxygen saturation (rSO_2) differences of premature babies with and without hsPDA.

Patients and Methods: A cross-sectional study was conducted on preterm infants aged 3-7 days with 24-$33^{6/7}$ weeks of gestation. hsPDA diagnosis was carried out by echocardiography; defined as >1.5mm diameter of ductus arteriosus and >1.4 left pulmonal artery and aorta (La/Ao) ratio. NIRS monitoring was carried out to measure tissue oxygen saturation of the cerebral (r_cSO_2), abdomen (r_aSO_2), and renal (r_rSO_2). The statistical analysis was undertaken using SPSS 21.0.

Results: There were 11 out of 52 infants categorized as hsPDA. Mean birth weight was 1213±293 gram; Mean gestational age was 30.72±2.01 weeks; and, Mean ductus diameter in hsPDA was 2.84±0.93 mm. There was no significant difference between the hsPDA and non-hsPDA groups in r_cSO_2 (75.27±9.14% vs 79.03±9.11%;p=0.238), r_aSO_2 (65.60±11.07% vs 67.48±10.17%;p=0.594), and r_rSO_2 (76.41±14.98% vs 82.61±10.41%;p=0.218).

Conclusion: The existence of hsPDA doesn't affect the oxygenation in cerebral, abdominal, and renal tissue in preterm babies. The decision regarding optimal time for ductal closure should be reconsidered.

Keywords:

preterm infant, hemodynamic significant patent ductus arteriosus, near infrared spectroscopy

INTRODUCTION

Ductus arteriosus (DA) will normally shrink after birth in term infant and be functionally closed at the age of 72 hours. The ductal closure is delayed until 4 days of age in 10% of preterm babies born in 30-37 weeks, 80% of those born in 25-28 weeks, and 90% of those born less than 24 weeks of gestational age[1,2]. The persistent DA can cause hemodynamic significant Patent Ductus Arteriosus (hsPDA) where the systemic shunt to the pulmonary vessels results in pulmonary hyperperfusion and systemic hypoperfusion[3]. Therefore, understanding tissue perfusion and oxygenation is important as a consideration for the administration of ductal closure therapy in premature infants to avoid further morbidity and mortality[4–6]. The ductal shunting from systemic to pulmonary blood flow has an impact on the cerebral, abdominal, and renal circulation[7]. Uncorrected hsPDA can cause intra ventricular hemorrhage, necrotizing enterocolitis (NEC), and renal insufficiency[6]. The long-term impact of decreased cerebral oxygenation in infants less than a month includes brain damage and development disorders[8].

Clinical assessment and echocardiography become reliable methods in diagnosing hsPDA. Near Infrared Spectroscopy (NIRS) has been validated as a non-invasive tool to measure tissue oxygen saturation (rSO_2) that can detect early changes in organ perfusion and oxygenation, thus, it can help identify and monitor the hsPDA therapy[9]. A study by van der Laan showed that cerebral and renal oxygenation are not affected by hsPDA.[6] Lemmers et al., and Cohen et al., proved the negative effects of hsPDA on cerebral oxygenation in premature infants[8,10]. There have been many studies on regional perfusion and oxygenation in premature infants with NIRS.[8–10] However, to the best of the researcher's knowledge, there have not been enough studies on regional oxygenation differences especially in preterm infants in our country, Indonesia, using NIRS.

The present study aimed to study regional tissue oxygenation differences in preterm infants with hemodynamic significant and non-hemodynamic significant Patent Ductus Arteriosus using NIRS in the early days of life of preterm babies.

PATIENTS AND METHODS

Patients

This cross-sectional study used 52 out of 191 preterm infants treated in the NICU during study times. The samples were determined using consecutive sampling technique. All preterm babies (with gestational age of 24-33 weeks) were born between November 2019 and May 2020 at the tertiary level neonatal intensive care unit of Dr.Soetomo General Hospital whose oxygen support devices (i.e. high flow nasal canula, continuous positive airway pressure, invasive and non-invasive ventilator) were eligible for inclusion. Patients with multiple congenital anomaly, ductal dependent cyanotic heart defect, early onset of septicemia, and incomplete consent from parents were excluded. Demographic and clinical data were collected from medical records. The sample size is calculated using a formula for continuous data with the aim of hypothesizing two or more group. The ratio between the hsPDA and non hsPDA group was based on the previous study.[11]

Commented [i-[1]: these sentences were moved from the result section.

Echocardiography

Echocardiography screening was performed between 3rd and 7th postnatal day by pediatric cardiology consultant using Sonoscape Portable Digital Color Doppler Ultrasound System Model S9 (SonoScape, Shenzhen). Echocardiography was performed by one pediatric cardiology consultant to minimize performance variability. The samples were categorized into two groups: hsPDA and non hsPDA. The hsPDA was considered existing if there were a ductus arteriosus with diameter > 1.5 mm on constriction phase, pulmonal perfusion seen in the left pulmonal artery diameter and aorta diameter ratio (LA/Ao) was > 1.4, and left to right shunt were present.

While DA that was already closed and did not fulfill the requirement for hsPDA was considered non-hsPDA.

NIRS Measurements

INVOS 5100C near infrared spectrometer and neonatal sensors (Covidien, USA) were used to monitor the tissue oxygen saturation on the day of echocardiography was performed. Multisite sensors were placed on the frontoparietal side of the infant's head to evaluate the cerebral tissue oxygen saturation (r_cSO_2), on the inferior side of umbilicus to evaluate the abdominal tissue oxygen saturation (r_aSO_2), and on the lateral posterior flank to evaluate the renal oxygen saturation (r_rSO_2). The evaluation was performed by different examiners without knowing the echocardiography result. The oxygen saturation changes were observed in 15 minutes continuously. Every 15 seconds, the machine records tissue oxygen saturation data. Mean regional rSO2 were used for further analysis. A pulse oxymeter was also put on the baby's right hand to evaluate the peripheral oxygen saturation (spO_2) for further calculation of fractional tissue oxygen extraction (FTOE) on each location using the following formula: FTOE = (spO_2 – rSO_2)/spO_2. A 15-minute measurement was simultaneously observed and the mean values were obtained.

Statistical Analysis

Differences in clinical characteristics of the two sample groups of hsPDA and non hsPDA were analyzed using Chi square test, Fisher exact test, and exact probability test. Statistical analyses for each regional oxygen saturation and fractional tissue oxygen extraction between both grous were performed using independent t-test and Mann Whitney test. IBM SPSS 21.0 was used for all statistical analyses with significant value (p) at < .05.

Ethics

The ethical clearance was issued by the Ethical Committee of Dr. Soetomo General Hospital (No.1766/105/XI/2019).

RESULTS

In this study, three babies had multiple congenital anomalies, four babies had early onset of septicemia, and the others were excluded due to incomplete data and consent. Eleven infants classified as hsPDA group based on echocardiography. There were 25 (48%) and 27 (52%) preterm male and female babies, respectively. Majority of the subjects was in 28-<32 weeks of gestational age (55.8%) with mean gestational age was 30.72±2 weeks for hsPDA and 30.78±2 weeks for non hsPDA. Mean birth weight for hsPDA and non hsPDA were 1213±293 and 1272±306 grams, respectively.

Table 1 depicts the neonatal characteristics for both groups. There was no significant difference in all variables. Therefore, the samples considered as homogenous.

This study obtained that the smallest DA's diameter was 1.5 mm and the largest one was 4.8 mm in the hsPDA group. From the eleven samples in hsPDA group, the duct diameter was obtained with an average of 2.84±0.93. The comparison between LA and Ao had an average score of 1.56±0.26. The ejection fraction of hsPDA and non hsPDA group were 71.55±5.72 and 73.94±9.4%, respectively.

Linear regression was used to evaluate comorbidities on samples, namely perinatal asphyxia, respiratory distress syndrome, and persistent pulmonary hypertension of the newborn as confounding factors of the regional oxygen saturation. All measurement was not significant. In accordance to Table 2, there were no significant differences in the tissue oxygen saturation ratio of cerebral (r_cSO_2), abdominal (r_aSO_2), or renal (r_rSO_2) areas between hsPDA and non hsPDA groups (p = .238, p = .598, and p = .218 respectively). Fractional oxygen extraction in cerebral (cFTOE), abdominal (aFTOE), and renal (rFTOE) areas between the hsPDA and non hsPDA groups also revealed non-significant difference (p = .473, p = .578, and p = .151, respectively).

DISCUSSION

The present study obtained the characteristics of the two groups that were not significantly different so that it can be compared. Previous study showed that the incidence of hsPDA increased with lower oxygen saturation[12]. The mean SpO2 in this study was around 97% with minimal setting of CPAP and mechanical ventilation. There were no significant differences in r_cSO_2 (p = .238) between the hsPDA and non hsPDA groups in the study. These findings are in line with previous observational cohort designs by van der Laan et al. in Netherland, in which oxygen saturation and oxygen extraction in cerebral and renal of 49 preterm infants with gestational age <32 weeks evaluated using NIRS were not affected by hsPDA.[6] The r_cSO_2 results in hsPDA group (69%) were lower than non hsPDA group (76%) and cFTOE in hsPDA group (0.22) were higher than non hsPDA group (0.33).

In contrast to the results of several previous research where a decrease in cerebral oxygenation was found in hsPDA, Lemmers et al. reported a lower r_cSO_2 in infants with hsPDA compared to the asymptomatic PDA group (62±9% and 72±10%, sequentially). The difference might be caused by several factors affecting the patient's hemodynamics. In Lemmers' study, the patients in hsPDA group mostly used ventilator, morphine as sedatives that caused peripheral vasodilation, and more inotropic than control. Dopamine administration could increase cardiac output that affected an elevating perfusion. In addition, in the previous study, the sampling period was earlier (in the first 72 hours) compared to the present study (3-7 postnatal days) which could affect the results of oxygenation measurement. It is agreed that the cerebral oxygen supply increases as the baby age. Tissue oxygen extraction (FTOE) was also significantly higher in premature infants with hsPDA than those with non hsPDA[13]. The relationship between oxygen transport (DO_2) and tissue oxygen consumption (VO_2) is fractional tissue oxygen extraction ($FTOE=VO_2/DO_2$). Negative correlation between r_cRSO_2 and cFTOE indicated that if there was a decrease in the brain oxygen supply in sick premature babies, there was an increase in cerebral oxygen extraction aimed to maintain oxygen availability in the brain[14].

A retrospective study by Chock et al. showed that a low r_cSO_2 value of < 66% was associated with the presence of hsPDA in preterm infants[9]. Although the oxygenation value in cerebral tissue of hsPDA infant was lower than non hsPDA, the average value was still higher compared to the < 40% cerebral oxygen saturation limit associated with the appearance of symptoms, such as ischemic lesions and neuron damage. The normal value of r_cSO_2 for preterm babies is 55-85%[15]. According to Dix et al., higher r_cSO_2 values in neonatal sensors compared to adult NIRS sensors might be caused by differences in NIRS signal reception process where neonatal NIRS sensor algorithmic adjusted to thinner neonatal calvarium so that the light is easier to enter[16].

Although the determination of "to treat or not to treat" is still a clinical question nowadays, Poon et al., reported an improvement in cFTOE after medical therapy and PDA ligation.[17] Observation using NIRS as an overview of PDA closure can help on evaluating the infants to reduce the burden of cerebral hypoxia. It is necessary to identify infants at high risk of long-term developmental disorders.

Although not statistically significant, r_aSO_2 was lower in premature infants with hsPDA than non hsPDA (65.60±11.07 and 67.48±10.17, respectively) with p of .594. Similarly, abdominal fractional oxygen extraction in infants with and without hsPDA were 0.33±0.11 and 0.3± 0.1, respectively (p= .578). The findings are similar to the results of a study by Petrova el al., where no significant difference was found between tissue oxygen saturation in cerebral, abdominal, and renal in preterm infants aged < 32 weeks of gestational age with PDA diameter of ≥ 3 compared to < 3 mm[18]. Similarly, Gorman et al. found no statistical difference in hsPDA infants who were given ibuprofen therapy and who were not.[19] It was reported that NIRS facilitated benefits in terms of showing a downward trend of 20% of the base value before clinical manifestation of NEC appeared. In our study, we found 3 preterm babies with hsPDA and 7 non-hsPDA who experienced NEC based on Bell stage criteria.

Different results were reported by Ledo et al., where infants with hsPDA had significantly lower abdominal tissue oxygen saturation during observational prospective studies of 72 premature infants.[20] Lower blood pressure and lower mesenteric oxygenation with increased extraction of oxygen by tissues were obtained. Continuous monitoring on abdominal oxygenation needs to be done in newborns where a transition of gastrointestinal tract from a relatively dormant organ to a main area of nutrient absorption requiring sufficient supply of oxygen. Unlike cerebral circulation that has an autoregulation protection mechanism, mesenteric circulation in the abdomen does not have the ability to auto-regulate. Therefore, it is at risk of gastrointestinal hypoxia. Ledo et al. stated that hsPDA babies had lower blood pressure with lower abdominal oxygenation. Abdominal FTOE also reported an increase in the first five days and stabilized on day six. The stability of the aFTOE on the 6^{th} day was along with the spontaneous closure of the DA. In the previous study, babies who got catecholamine were put in the exclusion group to minimize the confounding factors that affected oxygenation[20,21]. NIRS somatic sensors placed in the abdominal region were expected to detect oxygenation disturbances in abdomen. Abdominal oxygen saturation (r_aSO_2) depicts blood flow in the mesenteric artery as it is the main vascular supplier of the gastrointestinal tract[22].

In this study, there was no significant difference in r_rSO_2 value between hsPDA compared to non hsPDA(76.41±14.98 vs82.61±10.41) (p =.218). Normal value of r_rSO_2 in premature babies is 80%. New born average r_rSO_2 score is 40% that will increase in ten minutes to 80-90%, then decrease with improvements in renal blood flow and increase the utilization of oxygen in the kidneys[18]. In a cohort study of premature infants in the first week of life, it was found that r_rSO_2<66% was associated with the presence of hsPDA based on echocardiography criteria with a sensitivity of 81% and specificity of 77%. The difference could be due to the fact that the babies in the previous study who had r_rSO_2<66% were <1000grams of weight and used ventilators. Low $r_rSO_2$values can be caused by immature renal function or hemodynamic instability other than PDA[9]. Guzoglu et al. reported no significant difference in regional oxygen saturation of the kidneys with r_rSO2 value of 60% (ranged between 17-93%, p = .87) and rFTOE .37 (ranged between .06-.83, p = .87) in infants with hsPDA and control[6,22,23]. The r_rSO_2 value obtained in the present study is relatively higher than other studies. This can be caused due to NIRS renal measurements conducted on post natal days 3 to 7 when perfusion and utilization of oxygen in the kidneys were still in the transition process.

This study provides information of oxygen saturation in three region simultaneously in both groups. However, there are several limitations of this study. First, the NIRS measurement of tissue oxygen saturation is only performed in short period. Longitudinal study is needed to study the oxygen saturation trends. Second, tissue oxygen saturation assessment is based on NIRS only and not confirmed by other supporting examinations. And last, the small number of samples due to limitation of time.

CONCLUSION

The results of our study suggest that hsPDA does not affect the oxygenation in cerebral, abdominal, and renal in preterm infants during the examination. The decision regarding optimal time for ductal closure should be reconsidered. However, further large scale studies needs to be conducted to reassess the present findings.

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TABLES

Table 1. Subject characteristic

	hsPDA n (11)	**non-hsPDA n (41)**	**Total n (52)**	**P**
Sex				1.000[*]
Male	5 (9.6)	20 (38.5)	25 (48.1)	
Female	6 (11.5)	21 (40.4)	27 (51.9)	
Gestational age				1.000[**]
Extremely Preterm (<28 weeks)	1 (1.9)	3 (5.8)	4 (7.7)	
Very Preterm (28 - <32 weeks)	6 (11.5)	23 (44.3)	29 (55.8)	
Moderate Late Preterm (32 - <37 weeks)	4 (7.7)	15 (28.8)	19 (36.5)	
Birth weight				0.902[**]
ELBW (<1000 g)	2 (3.9)	6 (11.5)	8 (15.4)	
VLBW (<1500 g)	7 (13.5)	24 (46.1)	31 (59.6)	
LBW (<2500 g)	2 (3.9)	11 (21.1)	13 (25)	
Singleton/multiple birth				0.322
Singleton	11 (21.1)	35 (67.4)	46 (78.5)	
Multiple birth	0 (0.0)	6 (11.5)	6 (11.5)	
Respiratory support				0.474[**]
High flow nasal canule	1 (1.9)	1 (1.9)	2 (3.8)	
CPAP	7 (13.5)	33 (63.5)	40 (77)	
Non invasive ventilator	1 (1.9)	1 (1.9)	2 (3.8)	
Invasive ventilator	2 (3.9)	6 (11.5)	8 (15.4)	
HR (x/minute), *mean*± SD	165±14,4	148±10,5		
SpO_2 (%), *mean*± SD	97.1±2,7	97.0±1,9		
Hb, *mean* ± SD	15.73±3.46	15.37±2.58		0.702
Inotropes				0.101
No	8 (15.4)	38 (73.1)	46 (88.5)	
Yes	3 (5.7)	3 (5.7)	6 (11.5)	
Age during recruitment				
3 day	3 (5.7)	21 (40.5)	24 (46.2)	0.118

4 day	6 (11.5)	10 (19.3)	16 (30.8)	
5 day	1 (1.9)	5 (9.6)	6 (11.5)	
6 day	1 (1.9)	4 (7.7)	5 (9.6)	
7 day	0 (0.0)	1 (1.9)	1 (1.9)	
Infant's comorbidity				0.086
Respiratory distress synd.	6 (11.5)	12 (23.1)	18 (34.6)	
Perinatal Asphyxia	2 (3.8)	11 (21.1)	13 (24.9)	
PPHN	3 (5.7)	3 (5.7)	6 (11.4)	
Hyperbilirubinemia	4 (7.7)	6 (11.5)	10 (19.2)	
Others	1 (1.9)	9 (17.3)	10 (19.2)	
APGAR score in 5 minutes				0.886*
≤5	6 (11.5)	19 (36.5)	25 (48)	
>5	5 (9.6)	22 (42.4)	27 (52)	
Mode of delivery				0.094**
SC with general anesthesia	6 (11.5)	7 (13.5)	13 (25)	
SC with regional anesthesia	3 (5.7)	19 (36.5)	22 (42.2)	
Spontaneous birth	2 (3.8)	14 (27.0)	16 (30.7)	
Assisted vaginal birth	0 (0.0)	1 (1.9)	1 (1.9)	
Amniotic fluid				0.134**
Clear	10 (19.3)	38 (73.1)	(92.4)	
Turbid	1 (1.9)	0 (0.0)	(1.9)	
Meconium	0 (0.0)	3 (5.7)	(5.7)	
Mother's comorbidy				0.357**
Healthy	1 (1.9)	2 (3.8)	3 (5.7)	
Hypertension	6 (11.5)	11 (21.1)	17 (32.7)	
Obesity	0 (0.0)	2 (3.8)	2 (3.8)	
Antenatal bleeding	1 (1.9)	1 (1.9)	2 (3.8)	
Combination of 2	1 (1.9)	14 (26.9)	15 (28.8)	
Combination of 3	2 (3.8)	9 (17.3)	11 (21.1)	
Others	0 (0.0)	2 (3.8)	2 (3.8)	
Antenatal corticosteroid				1.000
No	7 (13.5)	27 (52)	34 (65.5)	
Yes	4 (7.7)	14 (26.8)	18 (34.5)	

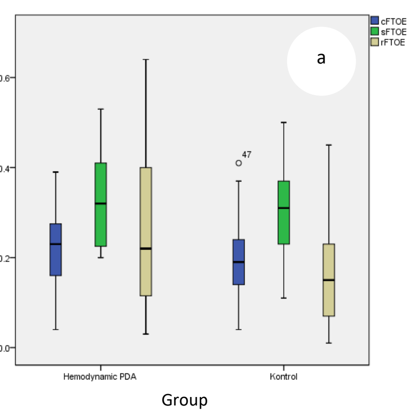
Table 2 Comparison of Regional Oxygen Saturation & Fractional Oxygen Extraction of hsPDA and non hsPDA

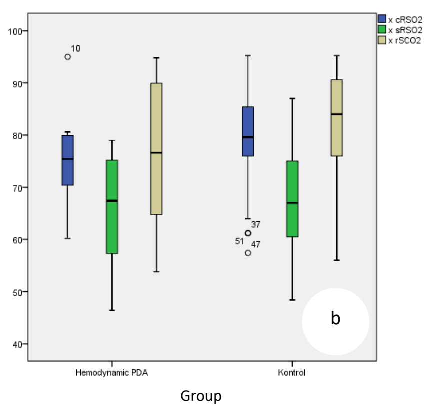
	hsPDA		Non hs-PDA		p
	(n)	(mean±SD)	(n)	(mean±SD)	
r_cSO_2	11	75.27±9.14	41	79.03±9.11	0.238
r_aSO_2	11	65.60±11.07	41	67.48±10.17	0.594
r_cSO_2	11	76.41±14.98	41	82.61±10.41	0.218
cFTOE	11	0.22±0.09	41	0.19±0.08	0.473
aFTOE	11	0.33±0.11	41	0.30±0.10	0.578
rFTOE	11	0.26±0.19	41	0.16±0.12	0.151

FIGURES

Figure 1a. Box plot diagram of regional FTOE values on hsPDA and non hsPDA group

Figure 1b.Box plot diagram of regional rSO_2 values on hsPDA and non hsPDA group





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Manuscript Needs Major Revision (#IJN-2102-2040 (R4))

2 messages

Iranian Journal of Neonatology IJN <ijn@mums.ac.ir> Mon, Nov 1, 2021 at 12:37 PM
To: mrmartono73@gmail.com

Manuscript ID: IJN-2102-2040 (R3)

Manuscript Title: **Hemodynamic Significant Patent Ductus Arteriosus Effect on Tissue Oxygenation in Preterm Infant: A Study Using Near Infrared Spectroscopy**

Authors: Martono Tri Utomo,Risa Etika,Mahrus Abdul Rahman,Mahendra Tri Arif Sampurna,Sunny Mariana Samosir

Dear **Mr. Martono Tri Utomo**

Your manuscript has obtained major revisions. In this case we normally treat it as unacceptable for publication. However, as numerous editorial errors have pointed out by the reviewers, the **Iranian Journal of Neonatology IJN** editor believes that the manuscript could be rectified and prepare for possible publication.

Please let us know your views in this regard and in the case of positive response, reply us within 7 days time.

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Reviewers Recommendation:

Reviewer 1:

Reviewer Comment For Author:

Dear author, please check the following:
- The authors stated, " This cross-sectional study used 52 out of 191 preterm infants treated in the NICU during study times. The samples were determined using consecutive sampling technique". These sentences should be moved to the patient section.
- The authors stated, “The study aimed to analyze the tissue oxygen saturation (rSO2) differences of premature babies with and without hsPDA”. To this end, the logistic regression could be suitable. Therefore, add the odds ratio in the results section.
- In Figure 1, concerning the outliers, the analysis is re-examined.

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Acknowledgement of Revision (#IJN-2102-2040 (R4))

1 message

Iranian Journal of Neonatology IJN <ijn@mums.ac.ir> Sun, Nov 7, 2021 at 9:35 PM
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Authors: Martono Tri Utomo,Risa Etika,Mahrus Abdul Rahman,Mahendra Tri Arif Sampurna,Sunny Mariana Samosir

Date: 2021-02-16

Dear **Mr. Martono Tri Utomo**

Thank you for submitting the revised file of your manuscript to the **Iranian Journal of Neonatology IJN**

The Editorial Office will proceed on your manuscript and inform you in the earliest time.

If there is anything else, please do not hesitate to contact us.

Truly yours,

Executive Managing Director of **Iranian Journal of Neonatology IJN**

Gmail **Martono Utomo <mrmartono73@gmail.com>**

Acceptance of Manuscript (#IJN-2102-2040 (R4))

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Manuscript Title: **Hemodynamic Significant Patent Ductus Arteriosus Effect on Tissue Oxygenation in Preterm Infant: A Study Using Near Infrared Spectroscopy**

Authors: Martono Tri Utomo,Risa Etika,Mahrus Abdul Rahman,Mahendra Tri Arif Sampurna,Sunny Mariana Samosir

Dear **Mr. Martono Tri Utomo**

This is to confirm that after technical and in-house evaluation, the above mentioned manuscript has been finalized and accepted for publication in the journal.

A copy of the Journal issue with 5 reprints will be sent to the corresponding author after publication.

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