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AUTOREFERÁT DISERTAČNÍ PRÁCE

The importance of tissue oxygenation changes in monochorionic twins for predicting severe neonatal morbidity

Význam změn tkáňové oxygenace u monochoriálních dvojčat v predikci závažné neonatální morbidity

MUDr. Peter Korček

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Školitel: prof. MUDr. Zbyněk Straňák, PhD, MBA

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Školitel: prof. MUDr. Zbyněk Straňák, PhD, MBA

Abstrakt

Přestože došlo ke zlepšení perinatální péče v posledních desetiletích, jsou vícečetná těhotenství asociovaná se zvýšeným rizikem komplikací, jako např. předčasný porod, fetální růstová restrikce (fetal growth restriction - FGR) a transfuzní syndrom (twin-twin transfusion syndrome - TTTS). Intrauterinní cirkulační nestabilita a nezralá mozková vaskulatura významně přispívají k riziku vážného perinatálního poškození a zhoršeného neurologického vývoje dětí z vícečetných gravidit. Měření cerebrální oxygenace ($crSO_2$) pomocí metody Near-Infrared Specotroscopy (NIRS) se používá stále častěji u rizikových novorozenců. I přes rozšířenost metody však existují omezená data s ohledem na nezralá dvojčata a jejich cerebrální tkáňovou perfuzi.

Cílem práce bylo analyzovat $crSO_2$ pomocí metody NIRS u nezralých monochoriálních a bichoriálních dvojčat v prvních 72 hodinách života a objasnit korelaci mezi fetálními komplikacemi a postnatálním vývojem $crSO_2$. Na základě dominantních fetálních komplikací jsme rozdělili studijní populaci na 4 skupiny: donoři (1) a recipienti (2) z monochoriální gravidity s TTTS, novorozenci s FGR (3) a novorozenci bez významné fetální komplikace (4). Použitím analýzy smíšeného modelu jsme zjistili signifikantní rozdíly v $crSO_2$ mezi jednotlivými skupinami. Ve skupině recipientů byly zaznamenány nejnižší hodnoty $crSO_2$ v průběhu zkoumaného období, naproti tomu donoři a novorozenci s růstovou restrikcí měli hodnoty $crSO_2$ nejvyšší.

Nebyly však nalezeny statisticky významné rozdíly v mortalitě a morbiditě mezi sledovanými skupinami.

V předložené práci demonstrujeme signifikantní korelaci mezi postnatální cerebrální oxygenací a fetálními komplikacemi u nezralých dětí z monochoriálních a bichoriálních gravidit. Prezentované výsledky objasňují u těchto novorozenců alterovanou cerebrální hemodynamiku, která reflektuje vznik a vývoj specifických fetálních komplikací. Změny v cerebrální oxygenaci mohou u dětí z mnohočetných gravidit přispívat ke zhoršenému neuropsychickému vývoji.

Abstract

Despite improvements in perinatal outcome in recent decades, multiple pregnancies are associated with increased risk of complications including preterm birth, fetal growth restriction (FGR) and twin-twin transfusion syndrome (TTTS). Fetal circulatory disturbances and immature cerebral vasculature increase the risk for serious perinatal injury and adverse neurodevelopmental outcome in multiple births. Cerebral oxygenation ($crSO_2$) monitoring using near-infrared spectroscopy (NIRS) is increasingly used in high-risk infants. However, limited data are available in twin preterm infants with respect to cerebral tissue perfusion.

The aim of this project was to measure $crSO_2$ using NIRS in preterm monochorionic and dichorionic twins during the first 72 hours of life and find out correlation between underlying fetal conditions and $crSO_2$ development. We divided the study population into 4 subgroups based on major fetal pathology: donor (1) and recipient (2) monochorionic twins (with TTTS), selective FGR infants (3) and twins without fetal compromise (4). We observed significant variation in $crSO_2$ among the subgroups using mixed model analysis. The recipient twins exhibited the lowest $crSO_2$ throughout the study period, whereas the FGR and donor twins presented with the highest values. Nevertheless, we found no statistically significant differences in neonatal mortality and morbidity among subgroups.

In conclusion, we were able to reveal significant correlation between $crSO_2$ values postnatally and underlying fetal pathology in monochorionic and dichorionic preterm twins. The presented $crSO_2$ patterns in these infants provide some insight into altered cerebral hemodynamics that stems from the fetal complications. The cerebral tissue oxygenation changes may contribute to adverse neurodevelopmental outcome in multiple births.

1. Introduction

The proportion of multiple pregnancies out of all pregnancies is expanding. The rise can be explained by the increasing maternal age at childbirth as well as the use of assisted reproduction.[1] Multiple pregnancies carry higher risks of stillbirth and adverse fetal outcomes.[2,3] When compared with singletons, newborns from multiple pregnancies have substantially higher rates of preterm birth, perinatal morbidity and mortality and adverse long-term neurodevelopmental outcome.[1-3]

Twins are by far the most common form of multiple births. Importantly, Czech Republic has had one of the highest multiple and twinning rates among European countries.[1] Twins can exist in the uterus in a number of ways: dichorionic-diamniotic (DCDA), monochorionic-diamniotic (MCDA) and rarely monochorionic-monoamniotic twins.[2,3] These multiple pregnancies are associated with increased risk of complications including preterm birth, fetal growth restriction (FGR), twin–twin transfusion syndrome (TTTS) and congenital abnormalities.[2,3]

Monochorionic twin pregnancies can suffer from TTTS, specific complication due to pathological anastomoses in the shared placenta leading to unbalanced blood flow through arterio-venous anastomoses between twins.[3,4] This condition causes hypervolemia, higher afterload through increased vascular resistance, hypertrophic cardiomyopathy and finally cardiac failure in the recipient twin.[5,6] In contrast, the donor twin is hypovolemic, has low cardiac output (CO),

tissue hypoperfusion and activated renin-angiotensin-aldosterone axis. TTTS occurs at a frequency of 10–15 % in MCDA twin pregnancies, and the majority of these cases are diagnosed during the second trimester.[5,6]

Alternatively, selective FGR (occurring in 12-25%) can occur in either monochorionic or dichorionic twin pregnancies and represents uneven placental distribution between twins.[5,6] Placental insufficiency can lead to "brain-sparing" effect - cardiovascular adaptation of the fetus to maintain adequate cerebral perfusion.[7]

Neurodevelopmental outcome remains the most challenging issue in multiple births.[8,9] Fetal circulatory disturbances and immature vasculature (particularly in the germinal matrix and periventricular white matter) increase the risk for perinatal brain injury and adverse neurodevelopmental outcome.[10,11] Multiple risk factors can further aggravate the cerebral perfusion and brain development – myocardial dysfunction, decreased CO, systemic hypotension and cerebral blood flow (CBF) fluctuations.[12]

Accurate measurement of circulatory dysfunction, including cerebral tissue oxygenation (crSO2) is useful in early postnatal period.[13] Near-infrared spectroscopy (NIRS) becomes commonly used in critically ill infants and offers non-invasive monitoring of organ perfusion.[13] However, limited data are available in twin preterm infants with respect to cerebral tissue perfusion.

2. Project Goals

The project goal was to find out possible correlation between cerebral oxygenation and fetal development and hemodynamic complications in preterm monochorionic and dichorionic twins.

3. Hypotheses

A. There are no differences in regional cerebral oxygenation between monochorionic and dichorionic twins.

B. There is no discordance in regional cerebral oxygenation among individual twins.

C. The changes in regional cerebral oxygenation can predict adverse outcome (intra/periventricular hemorrhage, periventricular leukomalacia, neurodevelopmental impairment, cerebral palsy).

4. Materials and Methods

4.1. Subjects

The institutional Ethical Committee of Institute for the Care of Mother and Child approved the study under the guidelines of the Helsinki Declaration (reference SOP 15/05/2008). Written informed consent was obtained from parents of all infants enrolled in the study. Preterm infants from multiple pregnancies < 32 weeks of gestation were enrolled and followed-up in this prospective, observational study.

Patients with serious contributing morbidities were excluded: prenatally diagnosed congenital malformations and chromosomal abnormalities, prenatally acquired brain lesion, birth below limit of viability (gestational age < 24+0), need of chest compression at the delivery room and significant skin lesion contraindicating the use of NIRS sensor. The patient enrollment took place between October 2016 and January 2018 at the Institute for the Care of Mother and Child, Prague.

4.2. Cerebral Oxygenation

Cerebral regional oxygenation was measured with a NIRS monitor (INVOS 5100C, Medtronic, Dublin, Ireland) with sample rate of 1 Hz. Measurements started within 1 hour from birth and lasted up to 72 hours of age. A transducer (INVOS Cerebral Oximetry Infant-

Neonatal sensor, Medtronic, Dublin, Ireland) was placed on the frontoparietal side of infant's head.

The method takes advantage of near-infrared spectral absorption by deoxygenated and oxygenated hemoglobin. Using Beer-Lambert law and machine-specific detection algorithms, oxyHb and dHb can be calculated into percentage oxygenation (oxyHb / [oxyHb + dHb]) with range 0-100%. NIRS represents mainly venous oxygen saturation as 70-80 % of cerebral blood is venous blood.[13]

Artifacts in $crSO_2$ were removed manually before results were analyzed. Artifacts were defined as: changes in $crSO_2$ that could not be physiologically explained (e.g. a 30% step change between 2 subsequent data points) or changes that were accompanied by severe distortion in the other parameters suggesting infant movement or handling. Thereafter, $crSO_2$ was averaged for every 1-hour period. No action was taken based on recorded values.

4.3. Definition of Morbidities

Twin-Twin Transfusion Syndrome was defined using the following criteria: a single placenta, same sex, and significant amniotic fluid volume discordance between the two fetuses - with a deep vertical pocket of ≥ 8 cm in the sac of the recipient twin and ≤ 2 cm in the sac of the donor twin. Fetal therapy (selective laser coagulation of placental vessels) was performed accordingly.[14]

Fetal Growth Restriction was diagnosed prenatally by obstetricians using 2D and Doppler measurement of the fetus (abdominal circumference, estimated fetal weight, end-diastolic flow patterns in the umbilical and uterine artery).[15]

Fetal growth restriction was confirmed postnatally using Fenton growth charts.[16] Other neonatal outcomes (respiratory distress syndrome, patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis and periventricular leukomalacia) were followed up according to the Vermont Oxford definition.[17]

Blood counts were measured with a Coulter Micro Dif II (Coulter Electronics Ltd., Fullerton, US) in all patients up to 2 hours after admission. Transfusion was indicated according to hemoglobin level (< 120 g/L) and clinical judgment.

4.4. Statistical Analysis

The study group was divided into 4 subgroups based on major fetal pathology: donor (1) and recipient (2) monochorionic twins, FGR infants (3) and newborns without any known fetal pathology (4). Statistical analysis reflected subjects' specificity (twins) using linear mixed model for scale variables and generalized linear model for categorical variables. Patterns of $crSO_2$ were evaluated using mixed model analysis with random effect (pair) and repeated measurement based on covariance structure.

Cerebral oxygenation graph was modelled using estimated marginal mean and standard error. Clinical variables are reported using descriptive statistical methods. All reported *p*-values are two-sided and $p < 0.05$ was considered statistically significant. The analysis was performed with Statistical Package for Social Sciences (SPSS 26.0; SPSS Institute, Chicago, IL, USA).

5. Results

5.1. Neonatal Outcome

Overall, 62 preterm newborns were included. We used linear mixed model with random effect (pair) for analyzing scale variables among the subgroups. We found significant difference in birth weight among the 4 subgroups ($p < 0.001$). No significant differences were found in other scale variables, including admission hemoglobin and hematocrit ($p = 0.501$ and $p = 0.476$, respectively).

For the analysis of categorical variables among the 4 subgroups, we used generalized linear model with random effect (pair). The incidence of severe neonatal morbidities was low among subgroups and did not allow to detect any statistical differences even when we analyzed composite morbidity (hypotension, necrotizing enterocolitis, severe intraventricular hemorrhage (grade 3 and 4) and periventricular leukomalacia; $p = 0.089$). No statistically significant differences were noticed in neonatal mortality. In addition, no significant differences were found in red blood cell transfusion (RBCT) in the first 72 hours or fetal therapy among the subgroups ($p = 0.337$ and $p = 1.0$, respectively).

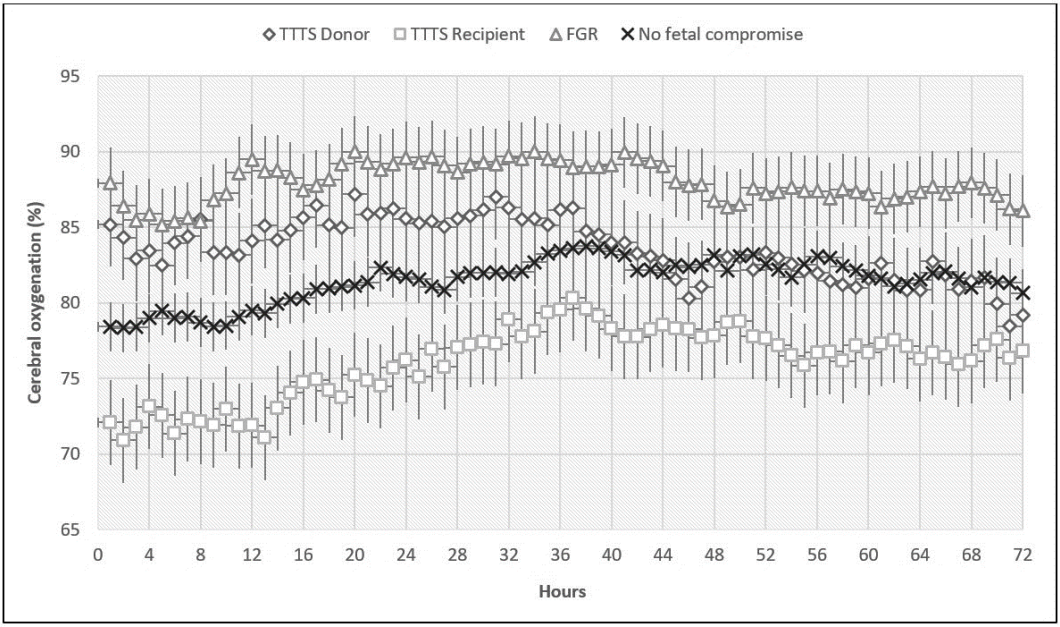
5.2. Cerebral Oxygenation

A total of 4464 1-hour $crSO_2$ averages were used for analysis. The recipient twins exhibited the lowest $crSO_2$ (expressed as mean ± SE) throughout the study period (76±0.3%), whereas the FGR and donor twins presented with the highest values (86±0.3% and 83±0.4% respectively). Newborns without any observed fetal complication (TTTS or FGR) presented with $crSO_2$ of 81±0.2%. Graphical overview of $crSO_2$ development among the subgroups (using estimated marginal mean and standard error) is shown in **Figure 1**.

We observed significant variances in $crSO_2$ over time among the subgroups using mixed model analysis with random effect (pair) and repeated measurement based on covariance structure (type III tests of fixed effects: $p < 0.001$). Using estimates of fixed effects, significant differences were found between the subgroup with no fetal compromise (reference subgroup) and FGR and recipient infants ($p < 0.001$ and $p = 0.038$, respectively). When analyzing the reference subgroup and donor twins only, the difference was not significant ($p = 0.356$). Moreover, the $crSO_2$ values for donor twins were comparable with the reference subgroup after 36 hours.

When Hb was added to the mixed model, the analysis revealed significant correlation between Hb and $crSO_2$ (type III tests of fixed effects: $p < 0.001$). Using mixed model test, there was no significant correlation between RBCT and $crSO_2$ ($p = 0.284$).

Figure 1. Postnatal cerebral oxygenation patterns based on underlying fetal pathology. TTTS = twin-twin transfusion syndrome; FGR = fetal growth restriction.



6. Discussion

6.1. Recipient Twins

We observed the lowest $crSO_2$ in recipient twins throughout the study period. The main contributing factor might be substantial hypertrophic cardiomyopathy causing reduction in myocardial compliance and leading to outflow obstruction and poorer CO.[18,19] These changes can decrease cerebral blood flow and oxygenation.[20] Cerebral vasoconstriction and ischemia mediated through endothelin ET_A receptors are also involved.[21] Targeted neonatal echocardiography (TNE) confirmed hypertrophic cardiomyopathy in all our enrolled recipients. Furthermore, polycythemia (leading to higher blood viscosity) can reduce cerebral blood flow and $crSO_2$.[6] Recipient twins displayed the highest Hb values at birth among the subgroups and this relative polycythemia-hyperviscosity significantly correlated with lower $crSO_2$ within the subgroup.

6.2. Donor Twins

In contrast, the mean $crSO_2$ in donor twins was significantly higher. Donor twins suffer from absolute hypovolemia which results in the redistribution of blood flow.[6,19] Renal hypoperfusion activates the renin-angiotensin system that causes increased vascular resistance with smooth muscle hypertrophy.[6,18] These changes can lead to secondary placental dysfunction and fetal growth restriction.[22] Due to pathological anastomoses, donor twins commonly develop anemia

that can augment the established hyperdynamic circulation.[23] As a consequence, cerebral blood flow increases to maintain adequate tissue oxygenation.

6.3. Fetal Growth Restriction

Although FGR infants exhibited high $crSO_2$ values similar to donor twins, we hypothesize different pathophysiological mechanisms in this subgroup. Primary placental insufficiency and subsequent chronic fetal hypoxia induce adaptive CO redistribution to favour essential organs, including the brain - the "brain sparing" effect.[24] Furthermore, animal models showed an increase in cerebral capillaries size as a reaction to hypoxic environment.[25,26] Cohen et al demonstrated the effect persistence during postnatal adaptation which could explain higher cerebral blood flow and $crSO_2$.[27] Furthermore, severe hypoglycemia is commonly observed in these infants, and this can also cause a significant increase in the cerebral blood flow.[28,29]

6.4. No Fetal Compromise

In the subgroup of newborns without fetal compromise, $crSO_2$ gradually improved over the first 36 hours and then stabilized thereafter. This is in accordance with available literature as relatively large study on preterm infants < 32 weeks showed that average $crSO_2$ at admission was 65%, peaked at around 36 hours of age and then

slowly declined in the first 72 hours.[30] Another study presented $crSO_2$ values from 439 infants < 32 weeks' gestation in the first three days of life and the resulting $crSO_2$ range was 55–85%.[31] There is a number of reasons for this pattern. During the first days of life, preterm infants demonstrate generally low baseline cerebral blood flow and higher oxygen consumption with increased oxygen extraction in preterm infants.[32,33] In addition, myocardial dysfunction with decreased CO and systemic hypoperfusion can contribute to lower $crSO_2$ during this period. As myocardial performance improves (ventricular stroke volume and CO increase), $crSO_2$ gradually increases and stabilizes.[33]

6.5. Study Limitations

Despite varied $crSO_2$ patterns, we did not find significant difference in morbidity or mortality among the subgroups. This could be explained by relatively low number of infants within the subgroups. Furthermore, $crSO_2$ did not reach critical levels even in the recipient twins who presented with the lowest values. In one study of preterm infants < 30 weeks' gestation, increased mortality was observed if $crSO_2$ dropped below 40%.[34]

Animal studies revealed that $crSO_2$ of 55% represents a safety level or cerebral oxygenation, in which brain maintains physiologic metabolism and only it took 30 minutes of $crSO_2$ < 35% to initiate subcellular damage and several hours to cause neuronal apoptosis.[35,36]

7. Conclusions

Postnatal cerebral oxygenation among monochorionic and dichorionic preterm twins correlates significantly with the underlying fetal pathology. The presented $crSO_2$ patterns could provide some insight into altered cerebral hemodynamics that stems from the underlying fetal pathology. Early detection of altered cerebral tissue oxygenation may decrease the risk of cerebral impairment and adverse neurodevelopmental outcome in this population.

A. We observed significant differences in regional cerebral oxygenation between monochorionic and dichorionic twins.

B. We revealed statistically significant discordance in regional cerebral oxygenation among individual twins.

C. Despite varied $crSO_2$ patterns, we did not find significant difference in morbidity (intra/periventricular hemorrhage, periventricular leukomalacia) or mortality among the subgroups. This could be explained by a small overall number of patients, as well as relatively low number of infants within the subgroups. Furthermore, $crSO_2$ did not reach critical levels even in the recipient twins who presented with the lowest values.

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9. List of Abbreviations

CBF	cerebral blood flow
CO	cardiac output
$crSO_2$	cerebral tissue oxygenation
DCDA	dichorionic diamniotic
FGR	fetal growth restriction
MCDA	monochorionic diamniotic
NIRS	near-infrared spectroscopy
RBCT	red blood cell transfusion
TNE	targeted neonatal echocardiography
TTTS	twin-twin transfusion syndrome

10. Author Publications

A. **Korček P**, Širc J, Straňák Z. Cerebral oxygenation reflects fetal development in preterm monochorionic and dichorionic twins. Early Human Development 2020; 144: 105025. *[First Author; Impact Factor 2.2]*

B. **Korček P**, Straňák Z, Širc J, Naulaers G. The role of near-infrared spectroscopy monitoring in preterm infants, Journal of Perinatology (Nature America) 2017; 37: 1070-1077. *[First Author; Impact Factor 2.1]*

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D. Straňák Z, **Korček P**, Hympánová L, Kynčl M, Krofta L. Prenatally acquired multiple limb ischemia in a very low birth weight monochorionic twin. Fetal Diagnosis and Therapy 2017; 41: 237-238. *[Corresponding Author; Impact Factor 2.0]*

E. **Korček P**, Straňák Z. Fetal distress and circulatory disturbance in monochorionic twins: possible risk factors for sialadenitis? International Journal of Pediatric Otorhinolaryngology 2015; 79: 2476-2478. *[First Author; Impact Factor 1.2]*

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H. **Korček P**, Straňák Z, Čunát V. Congenital Lactobacillus Blood Stream Infection in Extremely Preterm Twins. Indian J Pediatr 2016; 83: 1027. *[First Author; Impact Factor 1.1]*