

# The role of oxidative stress in pathogenesis of neonatal sepsis in preterm infants

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## ABSTRACT

Literature data confirm the important role of free radicals of nitrogen and oxygen in mechanisms of cells' and tissues' disorders at neonatal sepsis. Derangements of intracellular oxidation-reduction balance disorder functioning of cells and thereby result in homeostatic alterations and development of oxidative stress in organism. In previous works have been shown that intensity of oxidative stress at neonatal sepsis is especially high in preterm infants. The aim of our work was investigation of changes of oxidative metabolism indices in preterm infants after course of antisepsis therapy. As the results of investigation have shown, carried out antioxidant and detoxifying therapy does not provide significant decrease in intensity of free radical oxidation processes. These circumstances interfere with improvements of neonates' clinical state.

**KEYWORDS:** *free radicals, preterm infants, sepsis, nitric oxide, oxidative stress, antioxidants*

Neonatal sepsis is one of the topical problems in modern medicine, which is related with increasing amount of infants with sepsis and high mortality rate. It is remarkable that sepsis is detected 3-10 times more in infants predominantly with less gestation age. Mortality rate in preterm infants is higher than in term neonates respectively.

In preterm infants the sepsis course peculiarities and severity of its outcome are determined by underdeveloped protective-compensatory reactions.

According to the literature data, in case of sepsis oxygen and nitrogen free radicals play important role in the mechanisms of tissue injury. Intracellular oxidation-reduction balance disorders determine malfunctioning of cells, which is the reason of disordered homeostasis and oxidative stress. Has been shown (Sanodze N., 2005) that intensity of oxidative stress at neonatal sepsis is especially high in preterm infants.

The aim of present work was investigation of oxidative metabolism and content of nitric oxide in preterm infants after course of antisepsis therapy.

## MATERIAL AND METHODS

A total of 20 preterm infants (9 girls, 11 boys) with sepsis have been investigated. They underwent treatment course in pediatric clinic at Tbilisi State Medical University in 2004-2005 years. Practically healthy 10 neonates consisted the control group.

For investigation of mechanisms of oxidative disorders in organism, antioxidants ( $\text{Fe}^{3+}$ -transferin, ceruloplasmin) and pro-oxidants ( $\text{Mn}^{2+}$ , superoxidradicals ( $\text{O}_2^-$ ) and lipoperoxides - LOO.) systems' activity and free NO and its metabolites, NO complexes with haem iron (HbNO) concentration have been studied with the use of electronic paramagnetic resonance (EPR) method (radio-spectrometer P9-1307 [Russia]). Blood for EPR study was placed in polyethylene tubes and kept in liquid nitrogen ( $-196^\circ\text{C}$ ).

Free NO in blood was defined using the spin-trap – N-diethyldithiocarbamate (DETC) (Sigma) with the dose of 50 mg/ml (Mikoyan V.D., et al., 1995). EPR specters of  $\text{NO-Fe}^{2+}$ - $(\text{DETC})_2$  complexes were defined at the temperature of liquid nitrogen and 20 mvt microwave (Galagan M.E. et al., 1997). Superoxidradicals were defined using the spin-trap - 5-methyl-1-pirolin-IV-oxid (DMPO) (Sigma).

Duration of incubation of blood and DMPO (with the dose of 50 mM/1 ml blood [Xia Y., Zweer J.L., 1997]) was 3 minute at indoor temperature.

Peroxidradicals were defined with the use of spin-trap -  $\alpha$ -phenyl-buthinitron (PBN) (Sigma).

Duration of incubation of blood and PBN (with the dose of 40 mM/1 ml blood [Tabatabaie T., et al., 1997]) was 3 minute at indoor temperature.

$\text{O}_2^-$  and LOO. EPR specters were studied at indoor temperature and 20 mvt microwave (Kramer H.J., et al., 1994, Tabatabaie T., et al., 1997, Xia Y., Zweer J.L. (1997).

## RESULTS AND DISCUSSION

Changes of blood paramagnetic centers before and after treatment in preterm infants with sepsis are presented in Tab.1.

As it has shown, preterm infants reveal intense EPR signals of superoxidradicals and lipoperoxides. Intensity of oxidized EPR signal exceeds control data by 30%, while  $\text{Fe}^{3+}$ -transferrin content is decreased by 33%.

Received data points on intensification of free radical processes in preterm infants with sepsis.

Free NO content in blood of preterm infants with sepsis is not far from the control data however, EPR signal of HbNO-complexes is intensified indicating exaggerated production of NO and developed hypoxia.

Presence of  $\text{Mn}^{2+}$  ions, in cooperation with increased production of lipoperoxides, indicates membrane structure disorder.

After treatment of preterm infants suffering from sepsis, content of superoxide radicals were not changed. Intensity of oxidized ceruloplasmin and  $\text{Fe}^{3+}$ -transferrin EPR signals remain intact as well that points on increased intensity of free radical oxidation.

Decrease in lipoperoxide and  $\text{Mn}^{2+}$  ions content probably is the result of treatment with detoxifying remedies. On the background of anti-hypoxic therapy intensity of hypoxia is reduced that contributes to restoration of oxygen carrying capacity of hemoglobin. Due to the aforesaid, excessively produced NO releases from HbNO complexes and accumulates in blood that is probably of compensatory nature. Though, in the presence of oxidative stress, NO transformation into peroxynitrite is expected.

Thus, it could be concluded that in preterm infants with sepsis oxidative stress display. Antihypoxic and detoxifying therapy is unable to reduce significantly free

radical oxidation processes and improve clinical state of neonates.

	NO	O <sub>2</sub> <sup>-</sup>	LOO <sup>·</sup>	Fe <sup>3+</sup> -tr	cp	HbNO	Mn <sup>2+</sup>
Control	16,8±1,0	-	-	30,0±2,5	15,0±2,0	-	-
Sepsis - <b>before treatment</b>	14,3±2,0	8,1±0,9	15,8±1,9	20,6±2,0	19,7±0,9	5,6±1,2	2,4±0,7
Sepsis - <b>after treatment</b>	23,0±1,5	9,9±0,8	7,0±0,9	21,7±2,0	20,0±1,6	-	1,0±0,5

**Tab.1** Clinical description of patients.

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## Роль окислительного стресса в патогенезе неонатального сепсиса у недоношенных новорожденных

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### РЕЗЮМЕ

Данные литературы свидетельствуют о важной роли свободных радикалов азота и кислорода в механизмах повреждения клеток и тканей при неонатальном сепсисе. Нарушение внутриклеточного окислительно-восстановительного баланса вызывает нарушение функционирования клеток, тем самым, способствуя изменению гомеостаза и развитию окислительного стресса в организме. Ранее нами было показано, что интенсивность окислительного стресса при неонатальном сепсисе особенно высока у недоношенных новорожденных. Целью исследования являлось изучение динамики окислительного метаболизма у недоношенных новорожденных после проведения курса антисептической терапии. Установлено, что антиоксидантная и противоиотоксикационная терапия не обеспечивает значительного снижения интенсивности процессов свободнорадикального окисления, препятствуя улучшению клинического состояния новорожденных.

**Ключевые слова:** свободные радикалы, недоношенные новорожденные, сепсис, оксид азота, окислительный стресс, антиоксиданты