International Journal of Immunopathology & Pharmacology

Original article

International Journal of Immunopathology and Pharmacology
2016, Vol. 29(1) 23–29

DOI: 10.1177/0394632015607952
iji.sagepub.com
SAGE

Visfatin: New marker of oxidative stress in preterm newborns

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Abstract

Background: Oxidative stress is involved in several neonatal conditions characterized by an upregulation in the production of oxidative or nitrative free radicals and a concomitant decrease in the availability of antioxidant species. Oxygen, which is obviously vital to survival, can be highly damaging to neonatal tissue which is known to be poorly equipped to neutralize toxic derivatives. Thus, exposure of the newborn infant to high oxygen concentrations during resuscitation at birth increases oxidative damage. Visfatin is an adipocytokine involved in oxidative stress and an important mediator of inflammation that induces dose-dependent production of both pro-inflammatory and anti-inflammatory cytokines. To our knowledge, the diagnostic value of visfatin as a marker of oxidative stress in preterm newborns has not been investigated.

Objective: The aim of this study was to evaluate visfatin levels in preterm neonates resuscitated with different concentrations of oxygen in the delivery room.

Patients: Fifty-two preterm newborns with gestational age less than 32 weeks, resuscitated randomly with different oxygen concentrations (40%, 60%, or 100%) were enrolled at the University Hospital of Messina, over a 12-month period to evaluate serum visfatin levels at T0 (within 1 h after birth), T24 h, T72 h, and T168 h of life.

Results: At T72 h and T168 h, higher serum visfatin values in the high-oxygen group compared to the low- and mild-oxygen subjects ($P = 0.002$ and $P < 0.001$, respectively) were noted.

Conclusion: The results of this study suggest that visfatin could be a new marker of oxidative stress in preterm newborns.

Keywords

NAMPT/visfatin, oxidative stress, oxygen, preterm newborns, resuscitation

Date received: 12 May 2015; accepted: 1 September 2015

Introduction

Preterm newborns are challenged by excessive oxidative injury, resulting from several perinatal stimuli, such as intrauterine infections, resuscitation in delivery room, mechanical ventilation, and postnatal complications, in the presence of immature antioxidant capacities.

Free radicals (FRs) are molecular species with an unpaired electron in the outer shell which renders them highly reactive and unstable.[1] FRs containing oxygen may be termed a reactive oxygen species (ROS). The accumulation of reactive FRs, beyond the capacity of the endogenous antioxidant defence system to scavenge them, results in damage to DNA, proteins, and lipids that compromises

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cell function, leading to cell death via apoptosis or necrosis.[2]

Oxidative stress (OS) is implicated in the pathogenesis of several pathologic conditions of the preterm newborn, commonly referred to as "oxygen radical diseases of neonatology" to underline the crucial role of OS in this wide range of neonatal morbidities.[3]

In recent years, visfatin, an ubiquitous adipokine secreted from visceral fat, has been described as a potent marker of inflammation and dysfunction. Visfatin is also known as nicotinamide phosphoribosyltransferase (NAMPT) and is the rate-limiting enzyme in the salvage pathway of nicotinamide adenine dinucleotide (NAD+) biosynthesis in mammals. NAD+ is a ubiquitous coenzyme involved in redox reactions, carrying electrons from one reaction to another. NAD+ is an oxidizing agent: it accepts electrons from other molecules and becomes NADH, the reduced form of NAD+. These electron transfer reactions are the main function of NAD+. An increased regeneration of NAD+ is required in conditions of OS; therefore NAMPT/visfatin, as a regulator of NAD+ metabolism, might hold a key position in the control of fundamental cellular processes.[4]

Primarily, serum visfatin levels have been found to be increased in obesity and in other disorders related to insulin resistance and inflammation, such as type 2 diabetes, polycystic ovary syndrome, and inflammatory bowel disease.[5] Furthermore, it has been reported that this adipokin is upregulated by infection, hypoxia, and pro-inflammatory cytokines and may, in turn, upregulate the inflammatory cascade.[6,7] Lately, visfatin has been associated with OS.[7] However, the pathophysiological role of visfatin in humans remains largely unknown.

Few studies investigated the role of visfatin in neonates. It has been reported that visfatin concentration in newborns is not correlated with sex but with birth weight,[8] although high concentrations of visfatin have been found in infants with intrauterine growth restriction (IUGR) compared to those of normal weight, probably due to major visceral adiposity or to an altered fetal development of adiposity in IUGRs.[9] In particular, research focused on visfatin in fetal growth related to maternal conditions, such as gestational diabetes and preeclampsia.[10–13] It is also well known that maternal smoking can influence the cord serum visfatin levels[14] and that visfatin is also elevated in the amniotic fluid of women with microbial invasion of the amniotic cavity and histological chorioamnionitis[15] and in neonates with sepsis.[16] To our knowledge, visfatin levels in preterm newborns have been examined only in relation to insulin resistance[17] and no studies have investigated the correlation between visfatin and OS in preterm newborns.

The aim of this prospective study was to evaluate serum visfatin levels in preterm newborns resuscitated at birth with different oxygen concentrations (40%, 60%, or 100%), and to investigate the potential utility of this peptide as a novel marker of OS in neonatal diseases.

Materials and methods

Subjects

Sixty preterm newborns with gestational age less than 32 weeks who required cardiopulmonary resuscitation in the delivery room were enrolled at the University Hospital of Messina, Italy, over a 12-month period, and divided into groups of 20 according to three oxygen concentrations for delivery room resuscitation.

The study was conducted in accordance with the principles of the Declaration of Helsinki. Pregnant women admitted for preterm labor were informed about the aims of the research and fully informed about the study protocol. Participation in this study was voluntary. Only maternally uncomplicated pregnancies (no gestational diabetes, no pre-eclampsia, no smoking habits, no IUGR) were considered. Parents provided written informed consent.

Methods

As called into the delivery room, the medical team of the Neonatal Intensive care Unit (NICU) randomly assigned each newborn to three different oxygen concentrations during neonatal resuscitation: 40%, 60%, or 100%. Allocation to treatment groups was undertaken by an independent researcher using a permuted block design. A fixed block size of 10 was used to ensure that equal numbers of participants were randomized into the three groups (ratio 1:1:1). Randomization details were provided in an opaque sealed envelope containing the allocation. Neonatal resuscitation in the delivery room was performed according to 2010 American Heart Association Guidelines.[18] For neonates resuscitated

Table 1. Characteristics of infants of each oxygen concentration group.

Oxygen concentration	40%	60%	100%	*P* value
Neonates (n)	(17)	(17)	(18)	
GA	30.2 ± 2.8	29.3 ± 2.6	28.2 ± 2.7	0.288
BW	1478 ± 409	1278 ± 568	1318 ± 518	0.249
Duration of MV	33.5 ± 15.1	35.6 ± 13.5	34.8 ± 11.4	0.903
Maximum value of O_2	40.5 ± 9.2	39.8 ± 8.3	42.1 ± 9.4	0.706

Data are expressed as mean ± standard deviation.
*P value less than 0.05 was considered significant.
BW, birth weight (g); GA, gestational age (weeks); MV, mechanical ventilation (h); O_2, oxygen concentration (%).

with oxygen concentration of 40% and 60%, if heart rate (HR) did not improve (HR <100 beats per minute) within 60 s, oxygen was switched to oxygen 100%.

Immediately after birth, preterm neonates were admitted in NICU. Umbilical artery and vein catheterization was promptly performed and blood samples for serum visfatin analysis were collected at T0 (within 1 h after birth), T24 h, T72 h, and T168 h of life. Blood samples were immediately centrifuged and serum kept frozen at −20°C until analysis.

Visfatin was assessed with enzyme-linked immunosorbent assay (ELISA) kits from Phoenix Pharmaceutical (Belmont, CA, USA) according to the manufacturer's protocol; intra- and interassay CVs were less than 6%. To exclude sepsis, at the same time, samples were collected for full blood count, reactive protein C (CRP), and blood culture. Newborns with CRP >1 mg per 100 mL and positive blood culture were excluded from the study, to avoid the influence of sepsis on serum visfatin levels.[16]

Birth body weight, gestational age, hours of mechanical ventilation (if required) in the first week of life, and maximum concentration of oxygen administered were recorded.

Statistical analysis

Statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Significance level was set at $P < 0.05$. Kolmogorov-Smirnov test was used to test normality of distribution. Parametric tests (ANOVA, t-test) were performed in case of normal distribution. Non-parametric tests were also employed to analyze data for which an underlying distribution is not assumed. The variation of serum visfatin values at different time points on each subject was analyzed by Friedman test. Correlation between serum visfatin levels and birth weight and gestational age was investigated through Spearman's correlation coefficient.

Results

Twenty preterm newborns were enrolled for each oxygen group. Only 52 subjects completed the study. Eight neonates developed sepsis (2, 3, and 3, respectively, in the groups resuscitated with oxygen concentrations of 40%, 60%, and 100%, respectively), and were excluded. Five of them died. During resuscitation in the delivery room only one newborn started resuscitation with oxygen 40% and was then switched to pure oxygen group. Characteristics of the infants of each oxygen concentration group are summarized in Table 1.

Serum visfatin levels at T0, T24 h, T72 h, and T168 h of life are reported in Table 2. At T72 h and T168 h, significantly higher serum visfatin values were noted in high-oxygen group compared to low- and mild-oxygen subjects ($P = 0.002$ and $P < 0.001$, respectively). Additionally, Friedman test showed a significant increase in visfatin levels from T0 to T168 h in 100% oxygen group ($P < 0.001$).

Discussion

OS is a common mechanism of cellular injury involved in pathological condition such as ischemia-reperfusion, hypoxia-hyperoxia, and infection, which alters cellular metabolism and redox status with production of FRs.[19] Overproduction of FR species exceeds the antioxidant capacity of newborns, especially in preterms.[20] This susceptibility to oxidative damage promotes an increased risk of FR-related disease. The contribution of OS to the pathogenesis and progression of neonatal diseases

Table 2. Serum visfatin levels at T0, T24 h, T72 h, and T168 h of life. *P* value with Friedman test showed a significant increase in visfatin levels from T0 to T168 h in the 100% oxygen group.

Oxygen concentration	40%	60%	100%	*P* value
T0	5.7 ± 2.7	7.7 ± 2.1	6.7 ± 2.1	0.314
T24 h	5.0 ± 2.2	6.6 ± 3.5	7.5 ± 1.9	0.135
T72 h	5.4 ± 1,3	7.0 ± 2.3	9.9 ± 2.1	0.002*
T168 h	5.1 ± 1.1	7.9 ± 2.5	11.8 ± 1.2	<0.001*
P value paired Friedman test	0.815	0.572	<0.001*	

Data are expressed as mean ± standard deviation.
**P* value less than 0.05 was considered significant.

is only partially understood,[21] and OS is considered to play a crucial role in a wide range of neonatal morbidities, including hypoxic-ischaemic encephalopathy (HIE),[22] intraventricular hemorrhage (IVH),[23] periventricular leukomalacia,[24] bronchopulmonary dysplasia (BPD),[25] retinopathy of prematurity (ROP),[26] and necrotizing enterocolitis (NEC).[27,28] Furthermore, it became clear that free FRs are involved in influencing the ductus arteriosus and pulmonary circulation[29,30] and that antioxidants could have a role in the treatment of these disorders.[31]

Although the resuscitation of newborn infants was traditionally performed with pure oxygen,[32,33] it is recognized worldwide that OS is elevated when resuscitation is performed with 100% oxygen.[34] The American Heart Association guidelines focused on the optimal management of oxygen during neonatal resuscitation, emphasizing that both insufficient and excessive oxygenation can be harmful to the newborn infant.[18]

An interesting predictive role of OS biomarkers for early identification of newborns at high risk of OS has been reported.[19]

Recent studies have investigated the critical role of adipose-derived factors, also known as adipokines, in several inflammatory pathways. Visfatin (Pre-B-cell colony-enhancing factor 1 homolog/Nampt) is a recently discovered adipokine with pleiotropic functions. In adults, anthropometric variables such as weight and body mass index (BMI) seem to correlate with serum visfatin levels.[16,35] Literature data are still controversial in pediatric populations, especially in term and preterm newborns. Serum visfatin concentrations seems significantly related to birth weight,[8] although visfatin levels appear to be influenced by other maternal[36] and neonatal factors including IUGR,[9] smoking mothers[14] and sepsis.[16] To our knowledge no data are available on the correlation between visfatin levels and OS potentially related to high oxygen concentration administered during resuscitation at birth. In this study, we evaluated serum visfatin concentrations at T0, T24 h, T72 h, and T168 h of life in 52 preterm newborns less than 32 weeks of gestation who received different oxygen supplementation in the delivery room. First, in comparison to López-Bermejo[14] and Malamitsi-Puchner[37] that, respectively, reported mean visfatin values of 29.1 ng/mL and 19.35 ng/mL in AGA term infants, we found that our preterm infants had lower serum visfatin levels and our results are in accordance with previously published data.[16,17,38] Furthermore, serum visfatin values were inversely correlated to birth weight and gestational age, though these data were not statistically significant.

Second, at T72 h and T168 h, higher serum visfatin values were noted in infants resuscitated with 100% oxygen compared with those who received 40% or 60% oxygen at birth, with no significant difference in the maximum oxygen concentration or hours of mechanical ventilation required during the first week of life. These findings confirm that OS is higher when resuscitation is performed with higher oxygen supplementation compared to low- and mild-oxygen groups, and suggest that elevated levels of visfatin could be related to an increased risk for oxidative injury.

A previous study from López-Bermejo et al.[14] demonstrated that visfatin levels were higher in the cord serum of term infants from mothers who were smokers. As maternal smoking is associated with an increased load of OS to the fetus, the elevation of visfatin levels could aim to counteract the negative effects smoker oxidative compounds on the developing organism, just like the increased visfatin

levels that we observed in neonates resuscitated with 100% oxygen could aim to counteract the effects of ROS.

Supporting these results, it has recently been demonstrated that the mechanism nicotinamide phosphoribosyltransferase (NAMPT)-mediated NAD+ biosynthesis/visfatin, through the formation of oxidase-dependent oxygen of FRs, may involve regulation of expression of genes related to OS and inflammatory response.[39] Although the underlying molecular mechanisms remain unknown, it is suggested that NAMPT/visfatin can function as a cytokine (GM-CSF, IL-2, IL-1β, IL-6, and IL-13)[40] which is upregulated in a variety of acute and chronic inflammatory neonatal diseases.[41,42] We postulate that the higher visfatin concentration found in neonates more exposed to OS could be due to the increased demand of NAD+. As is known, NAMPT/visfatin is the rate-limiting enzyme in the salvage pathway of NAD+.

In light of these data, we hypothesized that the use of visfatin as a marker of OS can be useful in early identification of newborns at higher risk of tissue damage, and help predict subjects that could benefit more from antioxidant treatments. Further studies are needed to better investigate the biochemical pathways of NAMP/visfatin in OS of newborns, to evaluate if elevated visfatin levels could have a prognostic value in high-risk preterm neonates and if these peptide serum concentrations change in response to antioxidant therapies, predicting their potential utility.

However, the pathophysiology of visfatin at molecular and cellular levels are still far from being fully understood. Certainly, more detailed, in-depth *in vivo* and *in vitro* studies are needed to elucidate molecular and cellular mechanisms underpinning the role of visfatin in associated FR-related neonatal diseases.

Acknowledgements

The authors are grateful to the patients and their families for their support for our article, and to our colleagues of the Department of Pharmacy for the assessment of serum visfatin values.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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