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Commentary

Seeking biomarkers that predict neurodevelopmental impairment in preterm infants

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Commentary

Licht! Mehr Licht!

Johann Wolfgang von Goethe (1749-1832)

The International Network for Evaluating Outcomes of Neonates (iNeo) recently published the survival rate to discharge of a cohort of extremely preterm infants in high-income countries. The mean survival rate to discharge from a total of 88,327 preterm infants was 87% with a range of 78% to 93% [1]. Of note, around 50% of survivors, would develop neurodevelopmental impairment (NDI) [2]. The principal mechanisms for short-and-long-term brain damage are hypoxia, inflammation, oxidative and nitrosative stress, and programmed cell death. These pathogenic mechanisms are frequently triggered *in utero* but prolong their deleterious effects during postnatal life [2]. Thus, identifying reliable biomarkers capable of early predicting NDI would not only be of inestimable help to clinicians it also would open the gate for exploring new drugs or interventions to ameliorate the somber prognosis of these vulnerable patients.

Erythropoietin (Epo), a glycoprotein hormone, is produced in response to low arterial partial pressure of oxygen perfusing oxygen-sensitive renal peritubular fibroblasts. Epo gene expression is triggered by the hypoxia-inducible transcription factors (HIF) when binding to the hypoxia responsive element after translocating into the cell nucleus. Of note, under hypoxic conditions HIFs trigger the expression of more than 70 genes involved in angiogenesis and oxygen supply, proliferation, anti-apoptosis, anti-inflammatory and redox homeostasis thus conferring Epo relevant tissue protective properties [3]. In the Preterm Erythropoietin (Epo) Neuroprotection (PENUT) trial, Juul et al. [4], based on preclinical models of neonatal brain injury, randomized extremely preterm infants to become treated with Epo to elicit neuroprotective effects. However, Epo-treated infants didn't show improvement in the combined primary outcomes of severe NDI or death at 2 years of age as compared with the non-treated controls. In a subsequent study of the PENUT trial published in this article of *EBioMedicine*[5], baseline Epo analyzed 24 hours after birth and Tau concentrations at 7 and 14 days were both associated with a significantly increased risk of death or severe disability (BSID-III Motor and Cognitive Subscales < 70 or severe cerebral palsy).

The results of the PENUT trial have been clinically disappointing especially because it was preceded by robust experimental results [6] and a meta-analysis that showed a reduction in the Mental Developmental Index score <70 at 18-22 months of postmenstrual age although it didn't show efficacy with respect to sensorimotor evaluation [7]. The etiology of NDI in preterm infants is multifaceted and often the consequence of *in utero* experienced aggressions from diverse etiology such as hypoxia, infections, or hypertension among others. Thus, despite the potential benefits of Epo treatment concomitant pathogenetic agents or activated pathways may decrease its effectiveness. The relevance of the findings of Wood et al. [5], reside in having for the first-time assessed reliable biomarkers capable of predicting severe NDI at two years of age. Although magnetic resonance imaging is highly reliable for assessing brain damage and predicting outcome, clinical instability in the first days after birth often hinder its applicability in extremely preterm infants [6]. In this scenario, the association between baseline Epo and Tau plasma levels reflecting tissue hypoxia and inflammation and severe NDI at two years is a remarkable finding. Both these markers provide clinicians with predictive tools to promptly identify preterm infants at risk of developing NDI later in infancy. However, baseline endogenous Epo determinations reflecting tissue hypoxia were performed within 24 hours after birth [5]. Preterm infants frequently need supplemental oxygen immediately after birth in the delivery room and even thereafter when developing respiratory insufficiency [8]. Oxygen supply and hypoxia/hyperoxia may influence endogenous Epo production, trigger free radical formation, and enhance inflammation thus provoking changes in plasma biomarkers' levels. Performing the first baseline endogenous Epo analysis in cord blood instead could

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perhaps reduce the interference of postnatal interventions in the analytical results and allow to better differentiate between intrauterine and extrauterine hypoxia. Moreover, in the study by Wood et al. [5], no markers of oxidative stress were determined. Lipid peroxidation byproducts such as neuroprostanes and neurofurans, and di-homo-isoprostanes and di-homo-isofurans reflect free radical damage to docosahexanoic acid and adrenic acid present in cell membranes and cerebral white matter, respectively [9]. Hence, concomitant determinations of these biomarkers could add valuable diagnostic and prognostic information.

Notwithstanding, the predictive value of baseline plasma levels of Epo in the first 24 hours after birth to identify poor neurological outcome in preterm infants constitute an important advance in Neonatology. Hence, Epo plasma levels are available in most clinical laboratories and adequately interpreted can contribute to early identification of at-risk patients and facilitate clinical decision taking and parental information. Further studies should investigate if performing the baseline determinations of Epo in cord blood and/or adding specific brain biomarkers of oxidative stress enhance the predictability of NDI in preterm infants.

Contributors

All authors read and agreed to submit the final manuscript.

Declaration of Competing Interest

Authors declare not having conflicts of interest or disclosures in relation to the present manuscript.

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References

[1] Helenius K, Sjörs G, Shah PS, et al. Survival in very preterm infants: an international comparison of 10 national neonatal networks. Pediatrics 2017;140:e20171264.
[2] Ophelders DRMG, Gussenhoven R, Klein L, et al. Preterm brain injury, antenatal triggers, and therapeutics: timing is key. Cells 2020;9:1871.
[3] Dengler VL, Galbraith M, Espinosa JM. Transcriptional regulation by hypoxia inducible factors. Crit Rev Biochem Mol Biol 2014;49:1–15.
[4] Juul SE, Comstock BA, Wadhawan R, et al. A randomized trial of erythropoietin for neuroprotection in preterm infants. New Engl J Med 2020;383:233–43.
[5] Wood T, Parikh P, Comstock BA, et al. Early biomarkers of hypoxia and inflammation and two-year neurodevelopmental outcomes in the preterm erythropoietin neuroprotection (PENUT) trial. EBioMedicine 2021;72:103605.
[6] Teramo KA, Klemetti MM, Widness JA. Robust increases in erythropoietin production by the hypoxic fetus is a response to protect the brain and other vital organs. Pediatr Res 2018;84:807–12.
[7] Merchant N, Azzopardi E. Early predictors of outcome in infants treated with hypothermia for hypoxic-ischemic encephalopathy. Dev Med Child Neurol 2015;57 (Suppl_3):8–16.
[8] Vento M, Saugstad OD. Targeting oxygen in term and preterm infants starting at birth. Clin Perinatol 2019;46:459–73.
[9] Cascant-Vilaplana MM, Sánchez-Illana A, Piñeiro-Ramos JD, et al. Do levels of lipid peroxidation biomarkers reflect the degree of brain injury in newborns? Antioxid Redox Signal 2021 Aug 19 Online ahead of print. doi: 10.1089/ars.2021.0168.