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## Original Article

# Effects of vitamin B-6 supplementation on oxidative stress and inflammatory response in neonatal rats receiving hyperoxia therapy

Q6 Ming-Sheng Lee<sup>a</sup>, Tzu-Cheng Su<sup>b</sup>, Yi-Chia Huang<sup>c</sup>, Rei Cheng Yang<sup>d</sup>,  
Jun-Kai Kao<sup>e</sup>, Cheng-Han Lee<sup>f</sup>, Jui-Ju Tseng<sup>g</sup>, Chien-Sheng Hsu<sup>h</sup>,  
Q1 Chin-Lin Hsu<sup>c,i,\*</sup>

<sup>a</sup> Department of Pediatric Pulmonology and Critical Care, Changhua Christian Children Hospital, Taiwan

<sup>b</sup> Department of Pathology, Changhua Christian Hospital, Changhua, Taiwan

<sup>c</sup> Department of Nutrition, Chung Shan Medical University, Taichung, Taiwan

<sup>d</sup> Department of Pediatric Neurology, Changhua Christian Children Hospital, Taiwan

<sup>e</sup> Department of Pediatric Immunology, Changhua Christian Children Hospital, Taiwan

<sup>f</sup> Department of Neonatal Medicine, Changhua Christian Children Hospital, Taiwan

<sup>g</sup> Department of Pediatric Gastroenterology and Hepatology, Changhua Christian Children Hospital, Taiwan

<sup>h</sup> Frontier Molecular Medical Research Center in Children, Changhua Christian Children Hospital, Changhua County, Taiwan

<sup>i</sup> Department of Nutrition, Chung Shan Medical University Hospital, Taichung, Taiwan

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## ABSTRACT

Hyperoxia is often used in the treatment of neonates. However, protracted use of hyperoxia leads to significant morbidity. The purpose of this study was to evaluate the effects of vitamin B-6 supplementation on oxidative stress and inflammatory responses in neonatal rats undergoing hyperoxia therapy. The study consisted of 2 parts: a survival study and a vitamin B-6 efficacy study for 16 days. Neonatal rats were randomly divided into either the control group, B-6 group (subcutaneously injected with 90 mg/kg/d of pyridoxal 5'-phosphate [PLP]), O<sub>2</sub> group (treated with 85% oxygen), or O<sub>2</sub> + B-6 group (simultaneously treated with 85% oxygen and 90 mg/kg/d PLP). After the survival study was done, the vitamin B-6 efficacy study was performed with duplicate neonatal rats sacrificed on the 3rd, 6th, 9th, and 16th day. Serum inflammatory cytokines, tissue pathology, and malondialdehyde (MDA) levels were measured. In the survival study, the survival rate of neonatal rats in the control, B-6, O<sub>2</sub>, and O<sub>2</sub> + B-6 group on the 16th day were 100%, 100%, 25%, and 62.50%, respectively. The efficacy study showed lung polymorphonuclear granulocyte (PMN) and macrophage infiltration, increased liver hemopoiesis, and higher MDA levels in liver homogenates at days 3 through 16 in the O<sub>2</sub> group. Vitamin B-6 supplementation considerably increased serum inflammatory cytokines in either the 6th or 9th day and decreased liver MDA level before the 6th day. These results indicate that neonatal rats receiving hyperoxia treatment suffered divergent serum inflammatory responses and were in increased liver

\* Corresponding author. Department of Nutrition, Chung Shan Medical University, Taichung, Taiwan. Fax: +886 4 23248175.

E-mail address: [clhsu@csmu.edu.tw](mailto:clhsu@csmu.edu.tw) (C.-L. Hsu).

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oxidative stress. Vitamin B-6 supplementation seemed to improve survival rates, change systemic inflammatory response, and decrease liver oxidative stress while neonatal rats were under hyperoxia treatment.

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## 1. Introduction

Hyperoxia is often used in neonatal intensive care units for supportive care. Hyperoxia is defined as an excess of oxygen in tissues and organs (fraction of inspired oxygen > 60%), which can lead to the development of chronic lung disease [1,2], retinopathy, and brain injury in neonates [3,4]. A fetus develops in the uterus, which is a relatively hypoxic environment, and fetal antioxidant capabilities, such as the superoxide dismutase and glutathione antioxidant systems, are immature [5,6]. After birth, some neonates are exposed to hyperoxic conditions, which can increase levels of reactive oxygen species (ROS). This can in turn induce cellular damage through local activation of proinflammatory signaling and the recruitment of inflammatory cells into the vital organs, thereby resulting in uncontrolled tissue injury [7,8].

Accordingly, antioxidative therapy might prevent neonates from hyperoxia-induced complications. Many vitamins with antioxidative actions, such as vitamin A, C, and E, have been evaluated in neonates to prevent hyperoxia-induced injury, but the results have been inconclusive [9–11]. Vitamin B-6 (15–30 mg/kg/d) has been used as an effective agent in the treatment of pyridoxine-dependent seizure in neonates since 1954 [12,13]. In recent decades, vitamin B-6 has been shown to have a crucial role in antioxidant mechanism and inflammatory responses [14–18]. Vitamin B-6 is not only readily available in clinical settings but also a water-soluble vitamin, which might be safer than lipid soluble vitamins (e.g., vitamin A or E) as therapy for neonates.

Vitamin B-6 is a collective term for the metabolically and functionally related pyridoxine, pyridoxamine, and pyridoxal, as well as their phosphorylated forms, pyridoxine 5'-phosphate, pyridoxamine 5'-phosphate and pyridoxal 5'-phosphate (PLP). Pyridoxal 5'-phosphate is the physiologically active coenzyme form of vitamin B-6. Although the exact mechanism has not been fully ascertained, PLP may react with peroxy radicals and thereby scavenge free radicals and inhibit lipid peroxidation through its hydroxyl and amine group on the pyridine ring [14–16,19]. In addition, PLP acts as a coenzyme in the production of cytokines and other polypeptide mediators during inflammatory response [17]. Inadequate vitamin B-6, therefore, might directly decrease its antioxidant capacities or compromise inflammatory responses [20,21].

If neonates are under increased oxidative stress and inflammatory response during hyperoxia therapy [22,23], this could exhaust the use and metabolic turnover of plasma PLP and decrease tissue PLP reserves [24,25]. Therefore, it might be useful to determine whether vitamin B-6 supplementation would have a preventive effect in reducing oxidative stress or

inflammatory responses while neonates are receiving hyperoxia therapy. In this study, we imitated clinical conditions by using neonatal rats in a hyperoxic environment. We then evaluated whether vitamin B-6 supplementation had an effect on oxidative stress, inflammatory response, and survival in neonatal rats with hyperoxia therapy.

## 2. Methods

### 2.1. Animals and study design

The first part of this study was a survival study and the second part of this study was a vitamin B-6 efficacy study. In the survival study, four pregnant Wistar rats were obtained from BioLASCO Taiwan Co., Ltd. and were raised in the animal center of Changhua Christian Hospital for 1 week before delivery. Sufficient water and normal diet were freely provided to the maternal rats, which were kept in a 12:12-h light–dark cycle. After delivery within 12 h, neonatal rats were randomly divided into four groups: 1) control group, neonatal rats were treated with room air and daily normal saline injections (equivalent volume of PLP); 2) hyperoxia group (O<sub>2</sub> group), neonatal rats were housed in a chamber (air jacket multi-gas incubator, Astec Co., Ltd.) and treated with 85% O<sub>2</sub> and daily normal saline injections; 3) vitamin B-6 group (B-6 group), neonatal rats were subcutaneously injected with PLP (90 mg/kg/d); 4) hyperoxia combined with vitamin B-6 group (O<sub>2</sub> + B-6 group), neonatal rats simultaneously treated with 85% O<sub>2</sub> and daily subcutaneous PLP (90 mg/kg/d) injections. All neonatal rats were fed by maternal rats during the experimental period. Maternal rats were rotated daily between the O<sub>2</sub>-exposed rats and room air-exposed rats to avoid O<sub>2</sub> toxicity and to eliminate maternal effects among groups. Body weight and mortality of neonatal rats were monitored daily for 16 days.

The second part of this study was a vitamin B-6 efficacy study. In the first run of the efficacy study, we repeated the survival study design for 16 days, and neonatal rats of each group were sacrificed on the 16th day. Phenobarbital was injected intraperitoneally before the rats were sacrificed. In the second run of the efficacy study, another 6 pregnant Wistar rats were obtained and raised in the animal center of Changhua Christian Hospital for 1 week before delivery. Within 12 h after delivery, neonatal rats were randomly divided into 4 groups, as in the survival study. Four fertile maternal rats were selected and rotated daily between the oxygen and room air-exposed neonatal rats. On the 3rd, 6th, and 9th day, neonatal rats of each group were sacrificed. Neonatal rats with poor activity in each group were sacrificed in priority in order to keep the experimental numbers in each

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