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Neonates with sickle cell disease are vulnerable to blue light phototherapy-induced oxidative stress and proinflammatory cytokine elevations

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ABSTRACT

Sickle cell disease is a frequent genetic anomaly characterized by altered molecular structure of hemoglobin resulting into crescent-like deformation of the red blood corpuscles. Neonatal jaundice is a frequent co-morbidity in sickle cell disease. Phototherapy induces isomerization of bilirubin rendering it extractable through urine and hence it is used as a routine treatment of neonatal jaundice. An exposure to light phototherapy as a treatment of neonatal jaundice induces oxidative stress. It is hypothesized that such exposure of neonates with sickle cell disease to the blue light phototherapy as a treatment of neonatal jaundice induces severe oxidative stress and increases the levels of proinflammatory cytokines. This hypothesis is supported with two case studies of sickle cell disease suffering neonates who were exposed to blue light phototherapy to treat jaundice. In both these cases, exposure to phototherapy induced oxidative stress (increased lipid peroxidation and superoxide dismutase, slight change in activity of catalase and GSH) and elevated the levels of proinflammatory cytokine (TNFα, IL-1, and IL-6) in the sickle cell disease suffering neonates. These observations warrant further investigations to determine the consequences and clinical significance of the blue phototherapy-induced oxidative and proinflammatory stress in Sickle cell disease suffering neonates exposed to phototherapy as a treatment of jaundice.

Introduction

Sickle cell disease (SCD) is the most common inherited disease with the highest prevalence around the world. Over 300,000–400,000 children are born with SCD every year [1]. Approximately 90% of these births occur in the low to middle income countries including sub-Saharan Africa, Middle East counties, Indian subcontinent, Mediterranean and Caribbean regions [1–3]. It's an autosomal, recessive, single nucleotide mutation in the β-globin gene. In SCD, the hydrophilic glutamic acid residue at position 6 in the β-globin chain is replaced by hydrophobic valine residue which leads to conformational change in hemoglobin molecules [4]. The hemoglobin resulting from SCD related mutation is designated as HbS as opposed to the normal adult hemoglobin HbA. The HbS renders erythrocytes more fragile and distorts them to the 'sickle' like shapes and prone to hemolysis. During their passage through the blood capillaries, the sickled red blood corpuscles (RBCs) interact with the vascular endothelium leading to the increased vascular, inflammatory, and oxidative stress. The increased levels of proinflammatory cytokines, hypoperfusion of tissues, and ischemia–reperfusion injuries trigger the painful episodes associated with the SCD [4–6].

In SCD sufferers, the polymerization of deoxy-HbS is responsible for the sickling of RBCs. Deoxy-HbS polymerization occurs at the physiological venous oxygen saturation and its extent steeply increases as the oxygen saturation falls [7]. A variant of hemoglobin called foetal hemoglobin known as HbF inhibits the polymerization of deoxy-HbS. HbF is the main oxygen transport protein in the human fetus during the development in the uterus. The concentration of HbF falls along the first six months of life. The higher concentrations of HbF retard the process of polymerization of the deoxy-HbS and protect the RBCs from the resultant deformation [8]. Hence the SCD suffering neonates remain symptomless in the initial few months of life due to the presence high concentrations of HbF [9].

The outcomes of certain recent studies indicate that the protective effect of HbF does not prevent all the complications of the SCD.

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The SCD sufferers remain susceptible to the effects of polymerized HbS even in the presence of HbF [10,11]. The causes of death in the SCD newborns include septicemia, pneumonia/acute chest syndrome, gastroenteritis, and acute splenic sequestration [12]. Bonds, 2005 has also reported that foetal distress (13%), jaundice (25%), anaemia (10%), and respiratory distress syndrome (6%) are the most common complications evident in SCD suffering neonates [12]. These findings indicate that the SCD neonates may be prone to the adverse effects of the therapeutic interventions and there is a need to establish the safety of such interventions. Neonatal jaundice is the most frequent co-morbidity of SCD [13,14] and there are possibilities of SCD neonates are indiscriminately exposed to phototherapy as a preferred mode of treatment. It is available with different light sources and devices.

The wavelength of the blue light phototherapy (380–550 nm) is near-UV region and this is considered more effective as compared to green light or white light in reducing bilirubin by structural and functional isomerization [15]. Due to its higher efficacy blue light phototherapy is a preferred mode of treatment of neonatal jaundice. However, near-UV wavelength also inflicts certain untoward effects. It induces oxidative stress, immune disturbance, skin diseases and childhood asthma [16–19]. The SCD suffering neonates may prove to be sensitive to such adverse effects due to compromised antioxidant capacities and susceptibility to immune function alterations [20,21] (Fig. 1).

Hypothesis

Exposure of the neonates suffering from SCD to blue light phototherapy as a treatment of jaundice induces oxidative stress and rise in pro-inflammatory cytokines levels in their circulation.

Evaluation of the hypothesis

To substantiate the effects of phototherapy on the SCD newborns, we collected data from two cases of SCD suffering neonates who were prescribed phototherapy as a treatment of jaundice and were exposed to blue light phototherapy. The effects of the exposure to phototherapy on the plasma levels of proinflammatory cytokines TNF-α, IL-1, IL-6, and IL-8 were determined before and after the exposure. The intensity phototherapy-induced oxidative stress was estimated as activities of catalase and superoxide dismutase along with levels of reduced glutathione and Malondialdehyde before and after the exposure to phototherapy.

Selection of cases

The procedures involved in this study were approved in advance by the Institutional Human Ethical Committee of R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, India. The blood samples collected for routine laboratory investigations like bilirubin were used for the determination of cytokines and oxidative stress and no extra blood samples were obtained for the purpose data generation. Written informed consent was endorsed by the both the parents prior to the enrollment of the newborns for this investigation.

To trace the cases of SCD suffering infants, we followed the cases of expecting couples visiting for pregnancy related health checkups to the District Civil Hospital in a tribal district of Nandurbar. The detailed follow-up of the couple who were either SCD carriers or sufferers was maintained as potential parents of the SCD sufferers. The newborns from such couples were enrolled in the present investigation. During a six months follow-up, we came across 8 such cases where both the parents were either carriers or sufferers of SCD and the delivered babies were found to SCD sufferers. Out of these 8 newborns, two suffered from symptoms of icterus and were prescribed phototherapy.

Case 1

Both the parents were the carriers of SCD. The full term baby boy was born as the first child. The birth weight of the baby boy was 2.6 kg. After birth, the mother and the child were admitted for two days in the hospital. During the hospitalization, jaundice

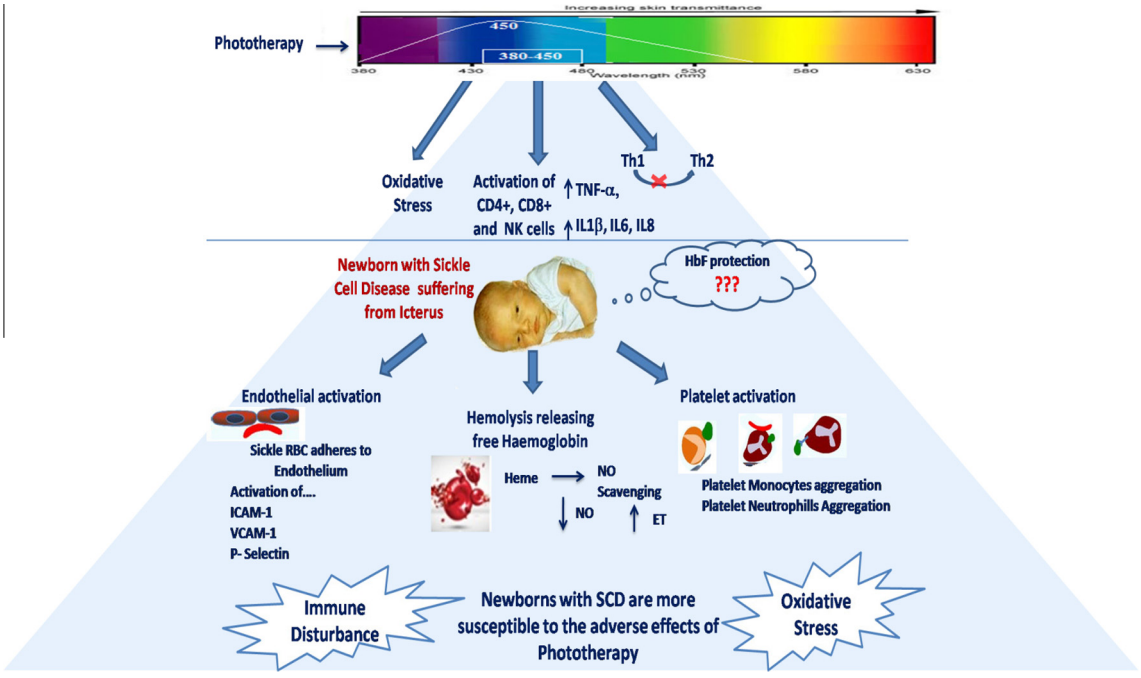

Fig. 1. Mechanism of blue light phototherapy induced oxidative stress and cytokine elevation.