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RESEARCH ARTICLE

Pediatric parenteral nutrition and hydroperoxide toxicity: Evaluation of the effectiveness of photoprotection medical devices

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Abstract

Exposure of parenteral nutrition (PN) to light induces hydroperoxide (HPO) formation whose toxicity, especially in pediatrics, is documented. In this context, we evaluated the efficacy of photoprotection medical devices used in our institution to protect PN from degradation after two different exposures to light. A mixed oil lipid emulsion (Smoflipid®) in standard or opaque syringes and a ternary PN mixture bags (Numetah®) with or without opaque overwrap were exposed for at least 420 min to a xenon lamp. Samples of Smoflipid® in standard or opaque syringes were also exposed for 24 h to conditions reproducing those of a neonatal intensive care unit. The use of opaque syringes for Smoflipid® administration or opaque overwraps for Numetah® administration reduced HPO formation by an average of 14% and 40%, respectively, compared to standard conditions after at least 420 min to a xenon lamp. When Smoflipid® samples were administered with standard or opaque syringes and exposed to a phototherapy lamp, the fold-change in the HPO concentration increased, respectively, by 6.3 or 5.4 at 24 h compared with syringes unexposed to phototherapy lamp. Although the observed differences were non-significant, it nonetheless appears prudent to use photoprotection of PN during administration, particularly in patients with immature or compromised antioxidant capacity.

KEYWORDS

lipid peroxidation, medical devices, parenteral nutrition, pediatric, photoprotection

INTRODUCTION

In neonatal intensive care, preterm newborns often require parenteral nutrition (PN) in the first weeks of life, in particular, when they are voluntarily exposed to natural or artificial light to prevent neonatal hyperbilirubinemia.[1] However, exposure of PN to light induces the formation of hydroperoxides (HPO) whose toxicity is already

Pierre Nizet and Nicolas Guillard contributed equally to this work.

documented.[2–5] In vivo, these HPO diffuse into the cells and form free radicals in the presence of metal ions that can react with molecular species (proteins, lipids, and DNA), leading to dysregulation of the inflammatory response, cell death, and tissue injury.[6–8] When patient's antioxidant systems are immature, the toxicity of these oxygen-rich HPO is high and can lead to various complications such as bronchopulmonary dysplasia, necrotizing enterocolitis, and retinopathy.[9] In addition, the appearance of these HPO in the mixtures clearly changes the quality of the administered PN.[10]

In September 2019, the French agency ANSM (Agence Nationale de Sécurité des Médicaments et des produits de santé) addressed a safety information to healthcare professionals and emphasized the obligation to protect PN bags that contain amino acids and/or lipids from light during their administration, especially, in newborns and children under 2 years of age.[11] However, no practical information has been provided regarding the administration modalities nor the technical characteristics of the photoprotection medical devices (MD) to be used in hospital.

Complete photoprotection of PN admixtures refers to implementing light-protective measures during the multiple steps of the PN process: (1) sterile compounding in the pharmacy, (2) transport and delivery to the patient care area, and (3) administration to the patient.[12] Several studies have evaluated the clinical impact of some photoprotection MD,[4,13–15] but to our knowledge, no recent study has evaluated the effectiveness of the MD in association with HPO concentration formed in PN. In this study, we focused on the photoprotective MD of parenteral nutrition during administration in connection with the ANSM information safety.

The objective of this study was to evaluate the concentration of HPO with and without use of photoprotection MD referenced in our institution (1) after deliberate light overexposure of PN, and (2) during a realistic scenario in a hospital context.

MATERIALS AND METHODS

Materials

Lipid emulsion (Smoflipid®, 200 mg/mL), a mixture of water and oil comprising four different types of lipids: soybean oil, olive oil, fish oil, and medium chain triglycerides, was purchased from Fresenius Kabi (Uppsala, Sweden). Ternary mixture (Numetah® G16%), indicated for use in newborns and children under 2 years of age and marketed as a tri-compartment bag and composed of a 50% dextrose monohydrate solution, a 12.5% lipid emulsion (80% olive oil and 20% soybean oil), and a 5.9% amino acid solution containing electrolytes, was purchased from Baxter (Deerfield, USA). Photoprotection MD tested were (1) 50-mL opaque syringes (ref. 300,869, Becton Dickinson, San Jose, USA) which are used to protect lipid emulsion, and (2) opaque overwraps (ref. 29,866, Bexen Medical, Hernani, Spain) which used to protect ternary mixture bags. According to the technical data of manufacturer, opaque syringes and opaque overwraps are capable of absorbing 90% of radiation between 290 and 450 nm. Fifty-milliliter standard syringes (ref 300,865) also purchased from Becton Dickinson were used as control MD.

Induction of lipid peroxidation after deliberate light overexposure of the mixed oil lipid emulsion and ternary mixture

Smoflipid® samples in standard and opaque syringes, as well as Numetah® G16% bags protected or not from light by overwraps, were exposed to light from a filtered xenon lamp (λ = 300–800 nm − Power = 250 mW) in a Suntest CPS+® (Atlas, Elancourt, France) to mimic the radiation and temperature of the sun in midsummer (Figure 1). No vitamins or trace elements were added to the samples tested. Smoflipid® syringes (standard or opaque) were exposed for 480 min and Numetah® G16% bags (with or without overwrap) were exposed for 420 min. For the Smoflipid® conditions, samples were collected after 180 and 480 min of exposure to filtered xenon lamps. For the Numetah® G16% conditions, samples were collected at the following times: 30, 60, 90, 120, 180, 240, 300, 360, and 420 min. The results are expressed as the lipid peroxidation concentration ratio obtained between the light overexposure condition and the light non-exposure condition (control group). The experiment was performed using three different batches of Smoflipid® and two different batches of Numetah® G16% and in triplicate for each condition.

Induction of lipid peroxidation during a realistic scenario in a hospital context

Samples of Smoflipid® in standard and opaque syringes were exposed to high-intensity blue light-emitting diodes (λ = 400–550 nm − Power = 4 mW/cm^2) in the experimental simulation laboratory located at the Faculty of Pharmacy of Nantes University. These conditions were chosen to as closely as possible mimic those of parenteral nutrition administration to premature newborns in a neonatal intensive care unit (Figure 2). The syringes were placed on an electric syringe pump (Vial Pilot A2, Fresenius Kabi) in the incubator. A Leddybloo® phototherapy lamp (Mediprema, Tauxigny-Saint-Bauld, France) was installed above the incubator as in clinical practice for 24 h. The study of lipid peroxidation was then performed after the following exposure times: 0, 2, 4, 6, 8, and 24 h according to the 2018 guidelines

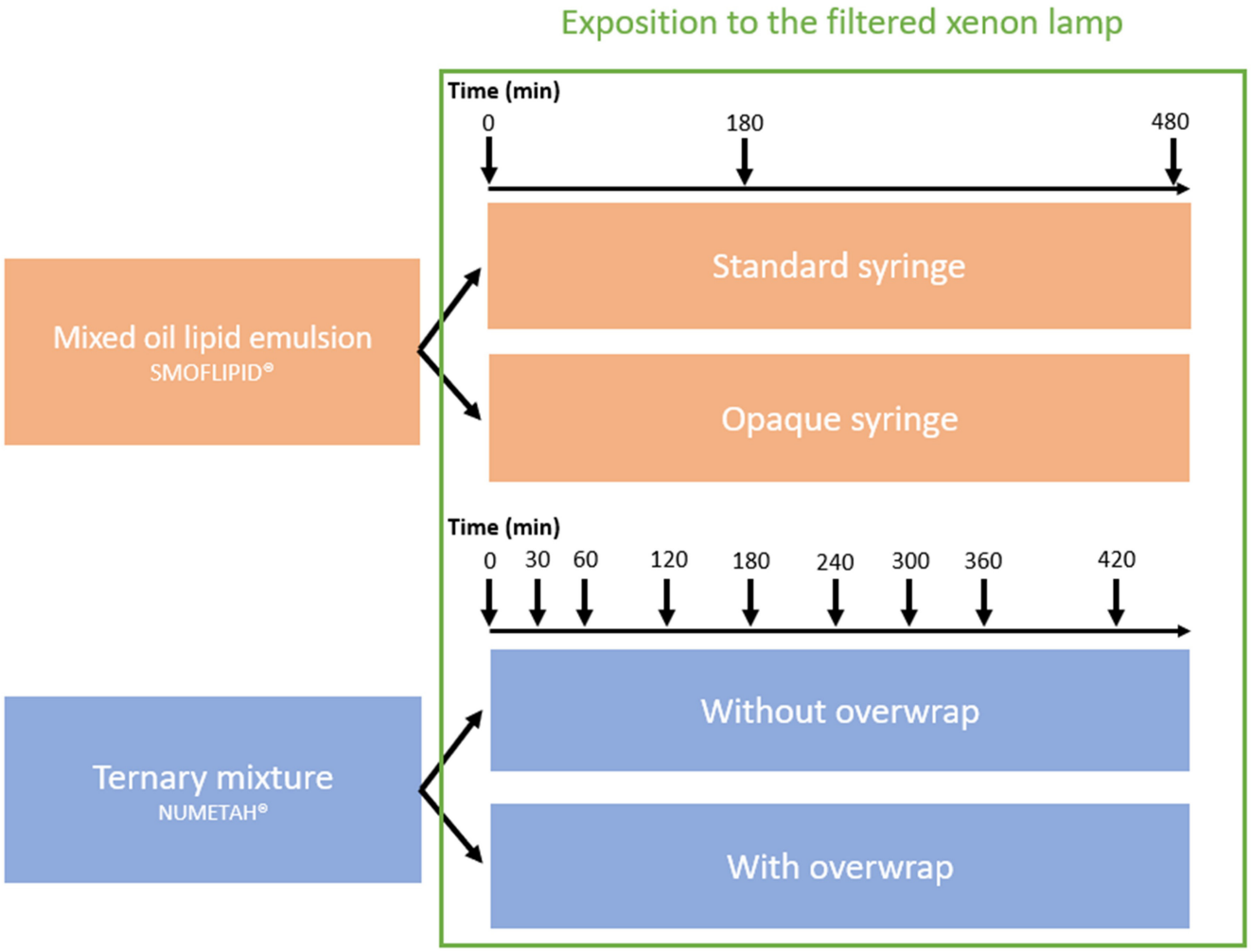

FIGURE 1 Induction of lipid peroxidation after deliberate light overexposure of the mixed oil lipid emulsion and ternary mixture vs unexposed conditions. Two independent experiments were performed to assess lipid peroxidation based on the quantification of their degradation products. Indeed, mixed oil lipid emulsion and ternary mixture were exposed to filtered xenon lamps ($\lambda = 300$–800 nm − Power = 250 mW) in a Suntest CPS + ® for a maximum of 480 min. Lipid peroxidation was determined by using the Peroxide Assay kit®. The experiments were performed in triplicate for each condition.

of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).[16] The results are expressed as the lipid peroxidation concentration ratio obtained between the blue light-exposure condition and the light non-exposure condition (control group). The experiment was performed using three different batches of Smoflipid® and in triplicate for each condition.

Evaluation of lipid peroxidation by measurement of the concentration of their degradation products (or hydroperoxides, HPO)

After dilution of the samples in a solvent composed of methanol/dichloromethane (80%/20%, v/v), HPO formation was determined using a Peroxide Assay kit® (# MAK311, Sigma-Aldrich, Saint-Louis, USA) following the manufacturer's instructions. Briefly, this method is based on the chromogenic Fe^{3+}-xylenol orange reaction.[17–19] The chromophore generated absorbs at 585 nm in spectrophotometry after 30 min of incubation at room temperature. The measured absorbance, using a Spectra Max® 190 UV/visible microplate reader (Molecular Devices), is proportional to the concentration of HPO in the sample.

Statistical analysis

GraphPad 8® software was used for all statistical analyses. Results are reported as means ± the standard error of the mean. A two-way unpaired ANOVA test was used followed by a Tukey's post-test, with *p*-values adjusted for multiple comparisons, to compare (1) the HPO concentration in

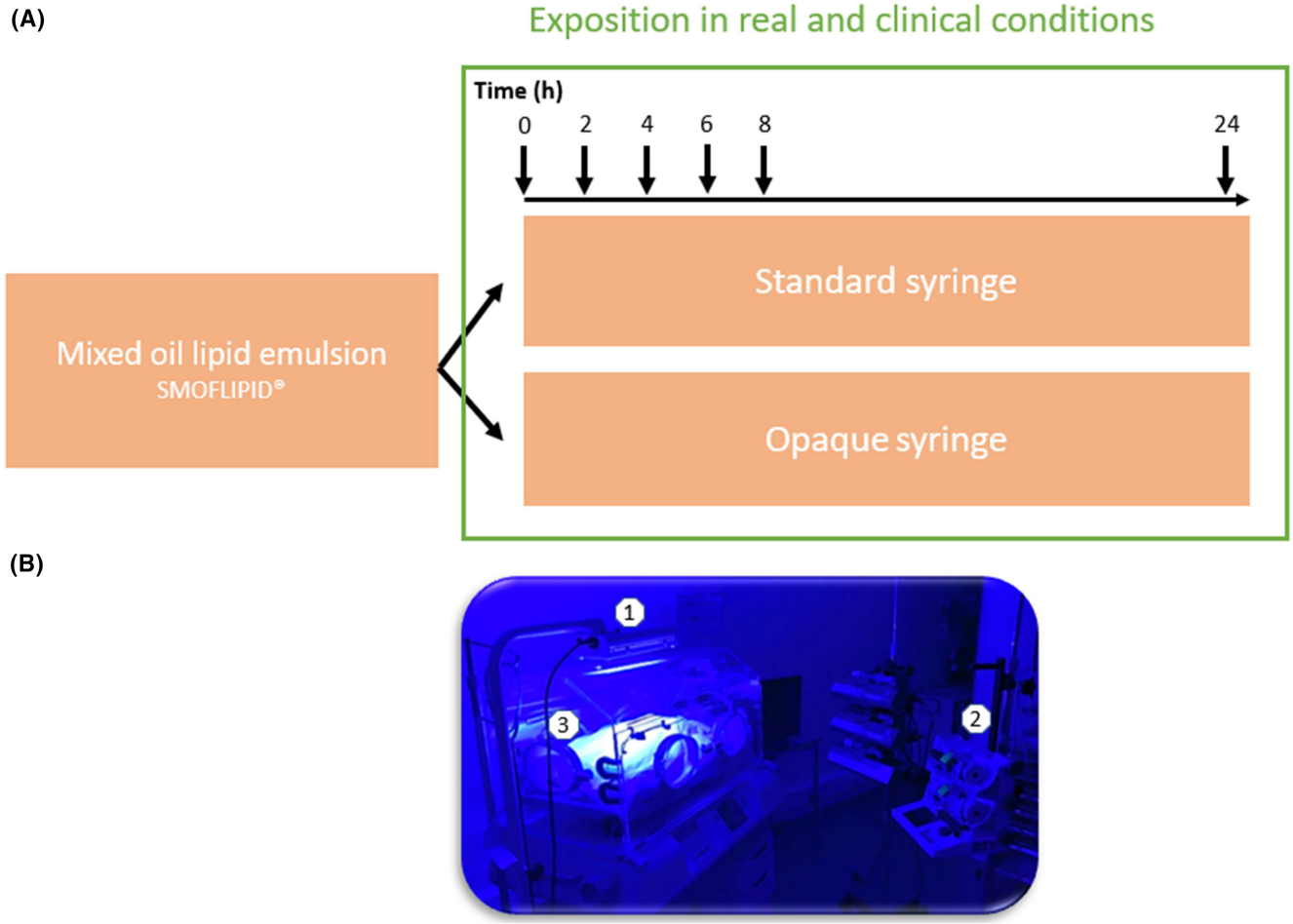

FIGURE 2 Induction of lipid peroxidation during a realistic scenario in a hospital context. (A) Mixed oil lipid emulsion was exposed to Leddybloo® phototherapy lamp for 24 h. Lipid peroxidation was determined by using the Peroxide Assay kit®. The experiments were performed in triplicate for each condition; (B) Representative picture of the assembly used in the experimental simulation laboratory located in the Faculty of Pharmacy in Nantes in order to reproduce the conditions of administration of mixed oil lipid emulsion in a neonatal intensive care room (1: Leddybloo® phototherapy lamp; 2: electric syringe pump; 3: incubator with low fidelity mannequin).

standard or opaque syringes after exposure of Smoflipid® to filtered xenon lamps; (2) the HPO concentration in Numetah® G16% bags protected or not from light by overwraps after exposure of bags to filtered xenon lamps; (3) the HPO concentration in standard or opaque syringes after exposure of Smoflipid® to high-intensity blue light-emitting diodes during a realistic scenario in a hospital context.

RESULTS

Hydroperoxide formation after deliberate light overexposure of mixed oil lipid emulsion and ternary mixture to filtered xenon lamps

In vitro, quantification of the HPO concentration ratio in Smoflipid® samples revealed an increase in lipid peroxidation when the Smoflipid® was exposed to light from a filtered xenon lamp in a standard syringe (1.7-fold at 180 min and 2.2-fold at 480 min) or an opaque syringe (1.4-fold at 180 min and 1.9-fold at 480 min) compared to a control group (Figure 3A). The use of opaque syringes for the administration of Smoflipid® reduced HPO formation by an average of 20% at 180 min after exposure to light from a xenon lamp (and by an average of 14% after 480 min) compared to the use of standard syringes (Figure 3A).

Quantification of the average HPO concentration ratio in Numetah® G16% revealed a difference in lipid peroxidation when the Numetah® G16% was exposed to light from a filtered xenon lamp and not protected or protected with opaque overwraps compared with an unexposed condition, with increases of 4.4-fold and 2.3-fold, respectively, at 180 min and 8.1-fold and 4.9-fold, respectively, at 420 min (Figure 3B). The use of opaque overwraps during the administration of Numetah® G16% reduced HPO

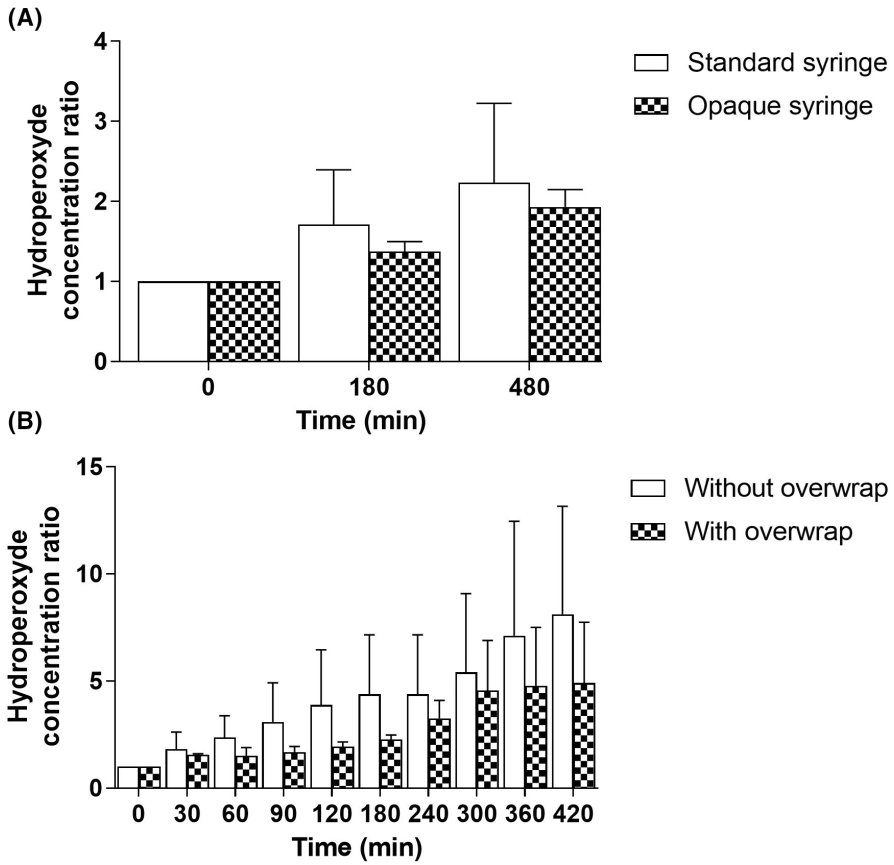

FIGURE 3 Hydroperoxide formation after deliberate overexposure of mixed oil lipid emulsion and ternary mixture to light from a filtered xenon lamp. (A) Mixed oil lipid emulsion samples contained in standard and opaque syringes and (B) a ternary mixture protected or not from light by opaque overwrap were, respectively, exposed during 480 min or 420 min to filtered xenon lamps ($\lambda = 300$–800 nm – Power = 250 mW). Then, lipid peroxidation was determined by using the Peroxide Assay kit® ($N = 3$, $n = 3$). These results were expressed as an HPO concentration ratio obtained between the light overexposure condition to the light non-exposure condition.

formation by an average of 48% after 180 min of exposure to light from a xenon lamp (and by an average of 40% after 420 min) compared to the condition where the Numetah® G16% samples were not protected (Figure 3B).

Even if the overall results of this experiment are not statistically significant, a tendency toward reduction of HPO formation under these conditions using this photoprotection MD was shown over time.

Hydroperoxide formation after exposure of mixed oil lipid emulsion to high-intensity blue light during a realistic scenario in a hospital context

These conditions used above do not reflect what happens in real conditions, especially because newborns are more often exposed to a high-intensity blue light from a phototherapy lamp, it is, therefore, essential to evaluate the effectiveness of these photoprotection MD during a realistic scenario in a hospital context.

During the 24-h phototherapy session in the experimental simulation laboratory, the mean concentration of HPO in standard Smoflipid® syringes was 233 ± 86 μM at 2 h, 347 ± 12 μM at 4 h, 848 ± 140 μM at 8 h, and 1610 ± 421 μM at 24 h. The mean concentration HPO in opaque Smoflipid® syringes was 242 ± 93 μM at 2 h, 320 ± 97 μM at 4 h, 626 ± 92 μM at 8 h, and 1230 ± 346 μM at 24 h (data not shown).

Moreover, when Smoflipid® samples were administered with standard syringes and exposed to phototherapy light, the HPO concentration increased compared with syringes unexposed to phototherapy light, with increases of 0.9-fold at 2 h, 1.4-fold at 4 h, 3.6-fold at 8 h, and 6.3-fold at 24 h. When Smoflipid® samples were administered with opaque syringes and exposed to phototherapy light, the HPO concentration increased compared with syringes unexposed to phototherapy light, with increases of 0.9-fold at 2 h, 1.2-fold at 4 h, 2.5-fold at 8 h, and 5.4-fold at 24 h (Figure 4). Under these conditions, the photoprotection MD did not appear to significantly reduce the amount of HPO produced over time.

DISCUSSION

According to the guidelines of the ESPGHAN, pediatric PN is used in hospitals when conventional or enteral feeding is not possible in patients due to impaired or immature gastrointestinal function.[16] Several types of PN used in hospitals: (1) mixed oil lipid emulsions; (2) binary mixtures, composed of dextrose monohydrate and amino acids, which can used in combination with a mixed oil lipid emulsion; (3) ternary mixtures composed of dextrose monohydrate, amino acids, and a lipid emulsion. These mixtures can be supplemented with vitamins, trace elements, and sometimes electrolytes within validated pharmaceutical limits. In our institution, it is important to note that no supplementation is added directly into the PN bag in order to limit microbiological risk. However, they are added in a Y-site using an extender. Like all health products, PN must be stored under optimal conditions (light, temperature), in particular mixed oil lipid emulsions and ternary mixture, due to their high polyunsaturated fatty acid composition. These fatty acids are a major source of HPO production during their administration as a result of their oxidation by radical oxygen species.

Even if, in the majority of living organisms, where all antioxidant systems interact with each other, the toxicity of HPO has not yet been fully proven, the toxicity of HPO has been documented in cellular and tissue models since the 90s. The toxicity of HPO contributes to a decrease in the intracellular adenosine triphosphate content, which is essential for providing energy for metabolic reactions,[20–22] decreases endothelial cell viability,[23,24] and interferes with eicosanoid production.[23] In isolated organs from rat and rabbit, HPO-containing solutions have previously been shown to affect organ function by increasing pulmonary vascular permeability,[25,26] decreasing myocardial contractility, and reducing coronary responsiveness.[27] Other animal studies have also shown that HPO administration can increase cell apoptosis, cause liver damage, steatosis,[8] and increase cholestasis, and can lead to the development of pulmonary fibrosis.[28] Thus, exogenous administration of HPO from PN directly to patients also leads to various clinical complications.[7,29,30] Preterm newborns, who are fed exclusively by regular PN during the first days or weeks of life, preterm newborns are particularly susceptible to these administered HPO.[5,31] Indeed, during their administration, the exposure of PN to light sources is one of the main causes of the formation of HPO.[32] In this context, we wished to verify that photoprotection MD used in neonatal intensive care units was associated with a reduction of HPO load formed during the administration of PN.

For the determination of HPO, we chose a colorimetric method based on the chromogenic Fe^{3+}-xylenol orange reaction. This method, that requires oxidation of ferrous ions in the presence of a ferric ion indicator xylenol, was described as a reference method for the determination of HPO by Wolff et al.[17] The main advantage of this method is that it does not require pretreatment of the samples, unlike chromatographic or spectroscopic methods.[33]

We used a qualified Suntest CPS+® to assess the intrinsic photostability characteristics of PN caused by solar radiation in a short period of time based on its xenon lamp. This technique is recommended by the International Council for Harmonization of Technical Requirements (ICH) for the registration of pharmaceuticals for human use for bench testing of photostability. The use of a Suntest CPS+® allowed us to accelerate the photodegradation of PN, validate the method of evaluation of lipid peroxidation, and begin to evaluate the photoprotection performance of the selected MD under conditions of light

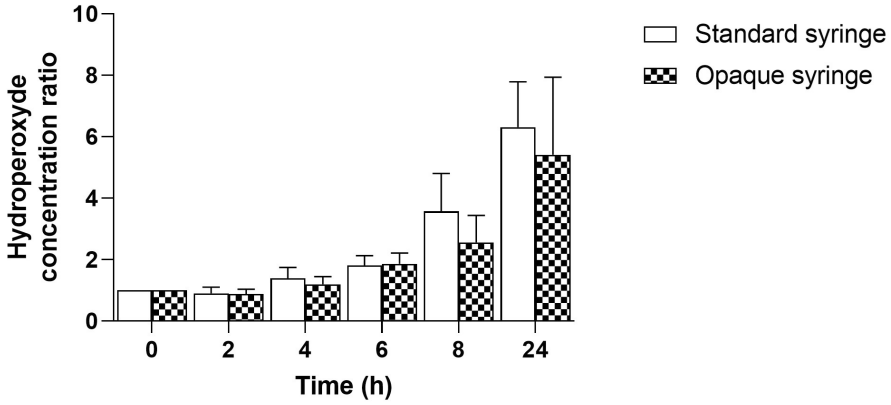

FIGURE 4 Hydroperoxide formation after exposure of mixed oil lipid emulsion to high-intensity blue light during a realistic scenario in a hospital context. Mixed oil lipid emulsion samples contained in standard and opaque syringes were exposed for 24 h to high-intensity blue light ($\lambda = 400–550$ nm – Power = 4 mW/cm^2) in conditions that reproduce those of a neonatal intensive care room. Then, lipid peroxidation was determined by using the Peroxide Assay kit® ($N = 3$, $n = 3$). These results were expressed as an HPO concentration ratio obtained between the blue light exposure condition to the light non-exposure condition.

overexposure. After 8 h of light exposure of mixed oil lipid emulsion and 7 h of light exposure of ternary mixture, we noted a tendency toward decreased HPO production in PN samples when administered with photoprotection MD vs control groups.

The second part of the work consisted of testing opaque syringe administration under "real" conditions close to clinical practice during phototherapy sessions performed in neonatal intensive care units. Indeed, Leddybloo® phototherapy lamps are used for the treatment of hyperbilirubinemia in neonates. They expose the whole body to intense light and act by interaction of the light with the bilirubin located in the skin, transforming it into photoderivatives directly eliminated in the stools and urine.[34–36] The hepatic stage of bilirubin transformation, which limits its elimination, is thus largely bypassed.[37] Therefore, to reproduce the conditions of administration of mixed oil lipid emulsion in a neonatal intensive care room, we created a realistic scenario using a low-fidelity mannequin in an incubator that was exposed for 24 h to the high-intensity blue light of a Leddybloo® phototherapy lamp. After 24 h of exposure of mixed oil lipid emulsion, we noted a tendency toward decreased HPO in the mixed oil lipid emulsion samples when administered with photoprotection MD (opaque syringe) compared to the standard syringe.

Although the results were not significantly different, our study suggests that the use of an opaque syringe for the administration of mixed oil lipid emulsion and a photoprotective overwrap for the administration of ternary mixture appears to limit the increase in HPO concentration under conditions of overexposure to light or under conditions that closely mimic clinical situations.

However, it is important to note that these HPO could also be generated during the storage of PN. Thus, vigilance is required to ensure that these products are protected from light. Given the recent recommendations of American Society for Parenteral and Enteral Nutrition (ASPEN),[38] other types of MD, that we did not test in this study, could be used, such as opaque tubing, for example, when administering PN to further limit light exposure of PN components during administration.

Limitations

Although this study appears to demonstrate a benefit of photoprotection MD during the administration of PN, it does not demonstrate a direct clinical benefit in subjects receiving PN. This study only evaluated partial photoprotection rather than complete photoprotection. Therefore, it appears essential to repeat these experiments on a larger scale with complete photoprotection. Indeed, our experiment was only repeated three times. Multiplication of these experiments could allow a significant relative difference to be discerned between the photoprotection and the non-photoprotection conditions. Only a prospective randomized clinical trial could determine whether photoprotection of PN during the multiple steps of the PN process (and not just the administration) could benefit the vital prognosis of the most immature neonates by measuring, for example, the concentration of HPO excreted in the urine. Finally, in addition to light, other meteorological factors that we did not measure in this study could act on lipid peroxidation, such as temperature and hygrometry during PN administration.

CONCLUSION

Although, under our tested conditions, the use of photoprotection DMs is associated with a non-significant reduction in HPO concentration, this empirical approach (no standards or specifications) appears to be a necessary option for slowing down HPO exposure in neonates during NP administration, as indicated in the ANSM safety information.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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