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Effects of phototherapy using different light sources on oxidant and antioxidant status of neonates with jaundice

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ABSTRACT

Background/aim: Neonates have limited antioxidant protective capacity. It has recently been demonstrated that phototherapy used for treatment of neonatal jaundice produces oxidative stress. Various phototherapy devices using different light sources are available for phototherapy. We aimed to investigate the effects of phototherapy applied with different light sources on the global oxidant/antioxidant status in neonates.
Methods: Term and late-preterm (≥35 weeks) newborn infants hospitalized to receive phototherapy for non-hemolytic jaundice in the 2–9 days of life were enrolled. Infants who received conventional phototherapy with fluorescent lamps were defined as group 1, intensive light emitting diode (LED) phototherapy as group 2, and fiberoptic phototherapy as group 3. The serum total antioxidant capacity (TAC) and total oxidant status (TOS) were measured before and 24 h after phototherapy. Oxidative stress index (OSI) was calculated.
Results: Twenty nine patients were included in each group. At the beginning of phototherapy serum TAC, TOS and OSI levels were similar in all groups. After phototherapy serum TAC decreased significantly in all three groups ($p < 0.001$). Total oxidant status increased significantly in group 1 ($p < 0.001$) and group 2 ($p = 0.001$) whereas a statistically insignificant increase was observed in group 3 ($p = 0.057$). After phototherapy OSI increased significantly in group 1 ($p < 0.001$), group 2 ($p = 0.001$), and group 3 ($p = 0.038$).
Conclusion: As indicated by increased OSI, oxidant/antioxidant balance is disturbed in favor of oxidants after blue fluorescent light, LED and fiberoptic phototherapy.

1. Introduction

Neonatal jaundice is a common condition and phototherapy is an accepted modality for its management [1,2]. Phototherapy converts unconjugated bilirubin to its oxidation products as well as to photo and structural isomers, which are easily eliminated through the gastrointestinal tract or lost in urine [2]. Phototherapy is generally considered as a safe and well-tolerated therapy in neonatal jaundice [3]. Recently phototherapy has been shown to be related to oxidative stress, lipid peroxidation and DNA damage [4–7]. Neonates have limited antioxidant protective capacity and oxidative damage plays an important role in pathogenesis of many diseases in the newborn period [8].

Effectiveness of phototherapy is dependent on the intensity and wavelengths of the light used. Bilirubin absorbs light most strongly in the blue region of the spectrum near 460 nm wavelength. Several devices using light sources with different wavelengths and intensities are available for phototherapy [9]. Conventional phototherapy given with fluorescent lamps has been shown to have a negative impact on oxidant/antioxidant defense system and leads to increased oxidative stress in hyperbilirubinemic infants [6,7,10]. Recently, high intensity gallium nitride light emitting diodes (LEDs) which deliver high intensity light of narrow wavelength spectrum have been developed and increasingly being used. Data related to the effects of LED based phototherapy on oxidant/antioxidant balance is limited. In this study we aimed to investigate the effects of two different LED based phototherapy systems (an overhead device and a fiberoptic pad) on oxidant and antioxidant status and compare them with conventional fluorescent tube phototherapy devices.

2. Methods

Term and late-preterm (≥35 weeks) newborn infants hospitalized for significant indirect hyperbilirubinemia requiring phototherapy in the 2–9 days of life were enrolled. The study was approved by the local Research Ethics Committee and informed consent was obtained from the parents. All infants were otherwise healthy with appropriate birth weights for gestational age (estimated by the last menstrual period and confirmed by ultrasound scan) and had no pathologic etiological factors for hyperbilirubinemia. Infants with severe congenital malformations,

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maternal diabetes, maternal eclampsia–preeclampsia, birth asphyxia, respiratory distress even mild or transient, sepsis, hemolytic type of hyperbilirubinemia (evidence of hemolysis on peripheral blood smear, reticulocyte count > 5%), ABO blood group or Rh incompatibility, positive direct Coombs test and those who are jaundiced within the first 24 h after birth were excluded from the study.

Criteria for starting phototherapy were based on the criteria defined by the American Academy of Pediatrics. For conventional phototherapy the IC-100 Phototherapy System (Ertunç Özcan, Ankara) consisting of four blue fluorescent lamps (Osram L 18W/67 Lumilux Blue, Germany, intensity: 10–15 μW/cm^2/nm, spectrum 430–470 nm). For LED phototherapy an overhead device the Tende Babyblue LED phototherapy system (Tende Electronics & Software Ltd. Company, Ankara, intensity: 30–120 μW/cm^2/nm, spectrum 450–470 nm), and a fiberoptic phototherapy device the BiliSoft LED Phototherapy System (Datex-Ohmeda, Inc. GE Healthcare, Finland, large pad with 35 μW/cm^2/nm intensity, spectrum 430–490 nm) were used. Regardless of the initial bilirubin levels infants requiring phototherapy were randomized with sequentially numbered sealed opaque envelopes to 3 different groups. Allocation to different groups was done at the same time period. Infants who received conventional phototherapy were defined as group 1, LED phototherapy as group 2, and fiberoptic phototherapy as group 3. Overhead LED based phototherapy units had 5 different levels of light intensity. For standardization purposes in group 2 LED phototherapy was given at level 3 which has an irradiance of 60–90 μW/cm^2/nm measured by the authorized technical service. During phototherapy all infants were kept completely unclothed with their eyes and genital regions covered in double walled incubators. Conventional and LED phototherapy units were placed over the incubators 25–30 cm away from the infants. Fiberoptic pads were placed under the infants. Phototherapy was interrupted only for feeding, cleaning, and blood sampling. Gestational age, sex, birth weight, age at phototherapy, serum total bilirubin (STB) level at initiation and termination of phototherapy were recorded.

Venous blood sampling (2 mL) was performed from a peripheral vein prior to and 24 h after phototherapy to determine total antioxidant and oxidant capacity. Samples were centrifugated at 1500 ×*g* for 10 min within 30 min of collection, stored at −80 °C until analysis. As the measurement of different oxidants and antioxidants separately is not practical, and their oxidant and antioxidant effects are additive, the total antioxidant capacity (TAC) and total oxidant status (TOS) were measured using a reliable and sensitive direct measurement method [11,12]. Total antioxidant capacity levels were measured by Erel's TAC method, which is based on the bleaching of the characteristic color of a more stable 2,2′-azino-bis(3-ethylbenz-thiazoline-6-sulfonic acid) (ATBS) radical cation by antioxidants. The results were expressed in mmol Trolox equiv/L. Relative antioxidant activities of individual antioxidants and their estimated contributions to TAC were reduced glutathione (52.9%), uric acid (33.1%), vitamin C (4.7%), total bilirubin (2.4%), vitamin E (1.7%) and others (5.2%) [11]. Total oxidant status serum concentrations were measured using Erel's TOS method, which is based on the oxidation of ferrous ion to ferric ion in the presence of various oxidative species in acidic medium and the measurement of the ferric ion by xylenol orange. The results were expressed in μmol H_2O_2/L. The main components of serum TOS were hydrogen peroxide and lipid hydroperoxide [12]. Erel's TAC and TOS methods are colorimetric and automated and the precision of this assay is less than 3%. The TOS to TAC ratio was used as the oxidative stress index (OSI). The OSI value was calculated as follows: OSI = [(TOS) / (TAC) / 100].

Statistical analyses were conducted using the SPSS version 17.0 (SPSS Inc., Chicago, IL). The chi-square test was used to compare categorical variables. For continuous variables with normal distribution One-Way ANOVA was used to compare three independent groups and Student's t-test was used to compare two independent groups. Normally distributed data were presented as means with respective standard deviations. Kruskal–Wallis test was used to compare three independent groups for continuous variables without normal distribution and data were presented as medians, minimum and maximum values. Wilcoxon test was used for comparison among dependent groups. Correlation analyses were performed by the Spearman test. Statistical significance was accepted at $p < 0.05$.

3. Results

Ninety term and late preterm infants hospitalized for indirect hyperbilirubinemia were enrolled in the study. Three patients were excluded; one because of termination of phototherapy before 24 h and two because of hemolytic blood sample. Finally 29 patients were included in each of the three study groups. Study groups were similar in terms of gestational age, birth weight, gender, mode of delivery, age and STB level at the beginning of phototherapy (Table 1). After 24 h of phototherapy STB was higher in group 2 compared to group 1 ($p = 0.002$) and group 3 ($p = 0.001$). Groups 1 and 3 have similar STB after 24 h of treatment ($p = 0.910$). Due to inadequate decline in STB with 24 h of phototherapy, three patients in group 3 and two patients in group 1 switched to LED phototherapy after blood samples for TAC, TOS and OSI measurement were obtained.

At the beginning of phototherapy serum TAC, TOS and OSI levels were similar in all groups (Table 2). After 24 h of phototherapy serum TAC decreased significantly in all three groups ($p < 0.001$) (Fig. 1). Serum TOS values were increased significantly in group 1 ($p < 0.001$) and group 2 ($p = 0.001$) after phototherapy. In group 3 TOS increased after phototherapy but the difference was not significant with a borderline p value ($p = 0.057$) (Fig. 2). Oxidative stress index values increased in group 1 ($p < 0.001$), group 2 ($p < 0.001$), and group 3 ($p = 0.038$) after phototherapy (Fig. 3). Serum TAC, TOS and OSI levels were similar among the study groups after phototherapy (Table 2). Decline in STB (STB before phototherapy–STB after phototherapy) was correlated to decrease in serum TAC (TAC before phototherapy–TAC after phototherapy) (rho = 0.287, $p = 0.007$), whereas no correlation was observed

Table 1
Clinical and laboratory data of study groups.

	Conventional phototherapy (n = 29)	LED phototherapy (n = 29)	Fiberoptic phototherapy (n = 29)	p
BW[a] (gr)	3060 ± 464	3171 ± 394	3036 ± 429	0.444
GA[b] (week)	38 (35–40)	39 (36–40)	38 (35–41)	0.163
Sex (F/M)	11/18	14/15	9/20	0.400
Cesarean section (n)	13 (45%)	12 (41%)	12 (41%)	0.954
Age at the beginning of therapy[b] (h)	136 (50–190)	120 (48–210)	140 (52–225)	0.419
STB at the beginning of therapy[a] (mg/dL)	19 ± 2.4	19.4 ± 3	18.6 ± 2.7	0.564
STB 24 h after therapy[a, c] (mg/dL)	12.8 ± 2.4	10.9 ± 2.2	12.9 ± 2.2	0.001

BW: Birth weight, GA: Gestational age, STB: Serum total bilirubin.
[a] Variables compared with One-Way ANOVA and data presented as mean ± SD.
[b] Variables compared with Kruskal–Wallis Test and data presented as median (min–max).
[c] Dual comparisons for STB 24 h after therapy with Student's t-test: Conventional phototherapy vs LED phototherapy, $p = 0.002$; conventional phototherapy vs fiberoptic phototherapy, $p = 0.91$; and LED phototherapy vs fiberoptic phototherapy, $p = 0.001$.