Gaziosmanpaşa Üniversitesi Tıp Fakültesi Dergisi 2021;13(1): 38-51

Orijinal Makale **Akçalı ve ark.**

Yenidoğan Sarılığında Fototerapinin Oksidan / Antioksidan Durum Belirteçleri Üzerine Etkileri

Effects of Phototherapy on Oxidant / Antioxidant Status Markers in Neonatal Jaundice

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Özet

Giriş: Fototerapi, hiperbilirubinemili yenidoğanlara kolayca uygulanabilen, invaziv olmayan,iyi tolere edilen, düşük maliyetli bir yöntemdir; bununla birlikte, fototerapinin oksidatif stresbelirteçlerinin seviyelerinde değişikliklere neden olduğu bildirilmiştir. Oksidatif stres vefototerapi arasındaki ilişkiyi değerlendirmek için birçok çalışma yapılsa da,hiperbilirubinemili yenidoğanlarda paraoksonaz (PON) ve arilesteraz aktivitelerini, lipithidroperoksit (LOOH) seviyelerini total oksidan durum (TOS) ve oksidatif stres indeksi (OSI)toplam antioksidan kapasite (TAC) hesaplarını aynı anda belirleyen yayınlanmış bir çalışmabulamadık. Bu çalışma, hiperbilirubinemili yenidoğanlarda bu biyobelirteçlerin tümünübelirleyerek fototerapinin oksidatif stres paneli üzerindeki etkilerini değerlendirmeyiamaçlamıştır.

Gereç-Yöntem: Fototerapi gerektiren hiperbilirubinemili kırk yedi term ve normal kiloluyenidoğan çalışmaya alındı. Serum PON ve arilesteraz aktiviteleri ile TAC, TOS, OSI veLOOH düzeyleri spektrofotometrik olarak ölçüldü.

Bulgular: Fototerapi sonrası serum PON ve arilesteraz aktiviteleri arttı ($p < 0,05$); oysa serumTAC, TOS, OSI ve LOOH düzeyleri düştü ($p < 0,05$). Serum trigliserit ve ürik asit düzeyleritedavi ile azalırken, serum LDL-C ve albümin düzeyleri arttı ($p < 0,05$).

Sonuç: Neonatal hiperbilirubinemiye bağlı fototerapi alan yenidoğanlarda PON, arilesteraz,TAC, TOS ve OSI düzeyleri ile lipit profilini birlikte değerlendiren ilk çalışmadır. Fototerapisonrası TAC, TOS, OSI, LOOH düzeylerinde azalma ve PON ve arilesteraz aktivitelerindekiartış, fototerapi ile tedavi sonrası yenidoğan sarılığında oksidatif stresin azaldığınıgösterebilir.

Anahtar Kelimeler: Hiperbilirubinemi, Paraoksonaz, arilesteraz, oksidatif stres, Fototerapi

Abstract

Background: Phototherapy is a non-invasive, well-tolerated, low-cost method that is easilyapplied to neonates with hyperbilirubinemia; however, phototherapy has been reported tocause variations in the levels of oxidative stress markers. Although many studies have beenconducted to assess the relationship between oxidative stress and phototherapy, we could notfind any published study that simultaneously determined paraoxonase (PON) and arylesteraseactivities, lipid hydroperoxide (LOOH) levels, and calculations of total antioxidant capacity(TAC), total oxidant status (TOS) and oxidative stress index (OSI) in newborns withhyperbilirubinemia. This study aimed to evaluate the effects of phototherapy on the oxidativestress panel by determining all of these biomarkers in neonates with hyperbilirubinemia.

Materials-Methods: Forty-seven full-term and normal-weight newborns withhyperbilirubinemia requiring phototherapy were enrolled the study. Serum PON andarylesterase activities and TAC, TOS, OSI and LOOH levels were measuredspectrophotometrically.

Results: Serum PON and arylesterase activities were increased after phototherapy ($p<0,05$);whereas, serum TAC, TOS, OSI and LOOH levels were decreased ($p<0,05$). Serumtriglyceride and uric acid levels were decreased with therapy, while serum LDL-C andalbumin levels were increased ($p<0,05$).

Conclusions: This is the first study to evaluate PON, arylesterase, TAC, TOS and OSI levelsand lipid profile together in neonates receiving phototherapy due to neonatalhiperbilirubinemia. Decrease in TAC, TOS, OSI, LOOH levels and increase in PON and1arylesterase activities after phototherapy can indicate decreasing oxidative stress in neonataljaundice after management with phototherapy.

Keywords: Hyperbilirubinemia, Paraoxonase, arylesterase, oxidative stress, Phototherapy

Introduction

Hyperbilirubinemia is a common condition in newborns, developing in around 60% of healthyfull-term newborns during first week of life, that possibly leads to neonatal morbidity andhospitalization (1). High serum bilirubin levels should be managed immediately, as they arerelated with cytotoxicity and neurotoxicity and may result with kernicterus –a conditioncharacterized with irreversible neurological damage (2). The most widely accepted modalityfor lowering bilirubin levels is phototherapy which uses light energy to alter the molecularconfiguration

of bilirubin and converts unconjugated bilirubin into oxidation products andhigher-polarity water-soluble isomers that are easily excreted through the gastrointestinal tractor urine without hepatic conjugation (3). Phototherapy is known to be a reliable and noninvasive method with few side effects including rash, dehydration, temperature instability; butit may also induce oxidative stress, lipid peroxidation and oxidative damage to DNA (4). It iswell-known through the reports of previous studies that bilirubin itself has strong antioxidantproperties (5). Bilirubin and biliverdin are potent scavengers of reactive singlet oxygen, theyreact with peroxyl radicals and superoxide anions, and are reducing substrates to peroxidasesin the presence of organic hydroperoxides and hydrogen peroxide (5). It is rather remarkablethat these features of a potentially toxic substance are particularly important (when undercontrol) in neonates; since their antioxidant capacity against circulating free radicals is limitedand neonatal erythrocyte membranes are more sensitive to oxidative damage due to higher

pro-oxidant potentials (4).Paraoxonase (PON) is a calcium-dependent esterase that is associated with high-densitylipoprotein cholesterol (HDL-C) and has protective functions against cellular oxidativedamage and atherogenesis (6). It also serves as a negative acute phase protein with reducedactivity in inflammatory conditions (7). Although PON and arylesterase are considered astwo separate enzymes, studies have shown that the enzyme formed from a single gene product5has both arylesterase and paraoxonase activity and is responsible for the hydrolysis of bothparaoxons, paraoxonase and phenylacetate (8). Reduced PON and arylesterase enzymeactivities have been demonstrated in patients with increased oxidative stress. Lipidhydroperoxide (LOOH) is a metabolic product that is generated as a result of oxidativedegradation of lipids caused by reactive oxygen species, and is a sensitive marker of lipidperoxidation and oxidative stress in tissues (9). In addition, oxidative stress index (OSI) is acombined measurement calculated as a ratio between total oxidant status (TOS) and totalantioxidant capacity (TAC), and has been demonstrated as a reliable biochemical markerreflecting the state of oxidative status (9). Although many studies have been conducted toassess the relationship between oxidative stress and phototherapy, we could not find a reportin literature examining PON and arylesterase activities, LOOH, TAC, TOS and OSI levelstogether in newborns with hyperbilirubinemia.

The study was aimed at evaluating the effects of phototherapy on the oxidative stress panel bysimultaneously measuring PON, arylesterase activities, and the levels of LOOH, TAC, TOSand OSI in neonates with hyperbilirubinemia.

Material and Methods

Study design

This prospective, observational study was conducted in the neonatal intensive care unit ofHarran University Training and Research Hospital from April 2008 to September 2008. Atotal of 47 full-term (between 37 and 42 weeks) and normal-weight (between 2.5 and 4 kg)newborns aged between 2–14 days exhibiting idiopathic unconjugated hyperbilirubinemiarequiring phototherapy were enrolled in this study. All newborns were breastfed followingspontaneous vaginal delivery and their APGAR scores at 1 and 5 minutes were above. Phototherapy was performed in all of these patients due to bilirubin levels that were in excessof reference ranges for age. Blood samples were obtained before and after the phototherapy.Infants' clinical data and demographic characteristics, including age of jaundice onset,gestational age, gender, birth weight, and APGAR score and mothers' data such as age, parity,pregnancy-related problems, and blood type were collected. Subjects with preterm or postterm birth, low birth weight or high birth weight, hyperbilirubinemia within the first 48 hoursof life, requirement for exchange transfusion due to higher bilirubin, congenital malformation,perinatal asphyxia, respiratoryistress, hypoalbuminemia, bilirubin-associated encephalopathyat presentation, ABO/Rh incompatibility, sepsis, dehydration, infection, positive directCoombs test, and the presence of any systemic or metabolic disorder were defined as criteriafor exclusion from the study.

Ethical Issues

All research procedures were evaluated and accepted by the Research Ethics Committee ofHarran University and were carried out in accordance with the ethical standards specified inthe Helsinki Declaration (28,02,2008/01/04). Written and verbal informed consent wasobtained from all parents before participating in this study.

Phototherapy

Infants with hyperbilirubinemia were treated with phototherapy based on AAP guidelines(10). Infants were placed naked (except for a diaper and eye patches) in an incubator with astandard Bilicrystal IV class 1 type B phototherapy device

comprised of 4 white and 4 bluefluorescent tubes (Bilicrystal, Medestime, Marcinelle, Belgium). Phototherapy was appliedwith 12-20 μW/cm²/nm irradiation from 40-cm above the infant. Phototherapy wascontinuously performed to neonates with jaundice except during feeding and necessary care(cleaning, repositioning). Phototherapy was terminated in patients whose total bilirubin levelsdecreased below 14 mg/dL. No side effects of phototherapy occurred in patients during andafter the procedure.

Biochemical Analyses

Blood samples were drawn from the antecubital vein before and after phototherapy. Afterclotting in serum separator tubes, samples were centrifuged at 4000 RPM for 10 minutes,serum was separated and aliquots were stored at -80°C until analyses were performed. Serumtriglyceride, cholesterol, High density lipoprotein-cholesterol (HDL-C), Low densitylipoprotein-cholesterol (LDL-C), uric acid, and albumin levels were determined bycommercially available assay kits with the routine clinical chemistry analyzer (Aeroset,Abbott Diagnostics, USA).

Measurement of Paraoxonase And Arylesterase Activities

Serum paraoxonase (PON) activity measurement was performed using paraoxon as a substrate(11). Paraoxonase activity was determined by measuring the formation of p-nitrophenolproduced as a result of enzymatic hydrolysis of paraoxon at 412 nm using 100 mM Tris-HClbuffer at pH 8 containing 5 mM CaCl2 and 7 mM paraoxon. The enzymatic activity wascalculated from the molar absorptivity coefficient of the generated p-nitrophenol (which was17,000 M−1 cm−1). One unit (U) of PON activity was described as 1 mol p-nitrophenolproduction/minute under the above conditions. Serum PON activity was expressed as U/L.Serum arylesterase activity was determined using phenyl-acetate as the substrate (11).Arylesterase activity was performed by monitoring the absorbance increase for the formationof phenol at 270 nm (from the enzymatic hydrolysis of phenyl-acetate) in 100 mM Tris-HCl(pH=8) buffer containing 2 mM CaCl2 and 13 Mm phentl-acetate. The enzymatic activity wascalculated from the molar absorptivity coefficient at pH 8, which was 1310 M−1 cm−1. Oneunit (U) of arylesterase activity was defined as 1 mol phenol production/minute under theaforementioned conditions. Serum arylesterase activity was represented as U/L.8All colorimetric measurements with these two methods were performed with

the use of aTechcomp 8500 11 UV/VIS spectrophotometer (Shanghai, China).

Measurement of Lipid Hydroperoxide Levels

Lipid hydroperoxide (LOOH) measurement was measured using the method developed byArab et al. (12). This method is based on the conversion of ferrous ions of lipidhydroperoxides into ferric ions in acidic medium and measurement of ferric ions formingcolor at 560 nm with Xylenol orange. Triphenyl phosphine, which is a specific agent forlipids, reduces LOOHs. The difference between the presence and absence of pretreatmentwith triphenyl phosphine was determined. Serum LOOH levels were expressed as μmol/L.

Measurement of Total Antioxidant Capacity and Total Oxidant Capacity

Serum total antioxidant capacity (TAC) was measured using an automated method developedby Erel et al (13). This method is based on Fenton-type hydroxyl radical production throughthe reaction of Fe-o-dianicide and hydrogen peroxide. The hydroxyl radical is reduced andreacts with the colorless o-dianisidine molecule at low pH to form yellow-brown dianisidylradicals. Dianisidyl radicals increase color formation by precipitation in further oxidationreactions. However, antioxidants in the samples suppress these oxidation reactions, and thus,the formation of color. This reaction is measured spectrophotometrically with an automaticanalyzer. Serum TAC levels were expressed as mmol Trolox equivalents/L.Total oxidant status (TOS) was determined in serum using a commercial kit (Rel AssayDiagnostics, Gaziantep, Turkey) (14). The oxidants that are present in the sample oxidize theferrous ion-o-dianicidine complex to the ferric ion. Ferric ions form a colored complex withxylenol orange in an acidic medium. The intensity of the color (associated with the amount ofoxidants present in the sample) was measured spectrophotometrically. The assay was9calibrated with hydrogen peroxide, and the results were expressed as the hydrogen peroxideequivalent per liter (μmol H2O2 equivalent/L).The oxidative stress index (OSI) was calculated through the TOS/TAC formula as follows:OSI (arbitrary unit) = (TOS, μmol/L)/(TAC, μmol Trolox equivalent/L) x100].

Statistical Analysis

All statistical analyses were processed and performed using the SPSS v11 (SPSS Inc.,

Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine whether variableswere normally

distributed. The comparisons of the differences between before and afterphototherapy were performed using the paired-samples t-test. Numerical data were shown asmean ± standard deviation. A p <0.05 value was accepted to be statistically significant in all

tests.

Results

A total of 47 infants, 25 males and 22 females, who presented with jaundice and were foundto have hyperbilirubinemia were included the study. The mean age of infants was 6 days andtheir mean weight was 3.21±0.41 kg. The mean duration of phototherapy applied to theinfants was 1.51±0.58 days. The demographic characteristics of the infants were shown inTable 1.

Table 1. Demographic and clinical characteristics of infants and mothers

Number of infants	47
Male/Female	25/22
Age (days)	6 ± 3
Weight (kg)	3.21 ± 0.41
Gestational age (week)	39 ± 1
Duration of phototherapy (hour)	1.51 ± 0.58
Maternal age (years)	27 ± 6
Number of pregnancies	3 ± 2

Data are given as mean ± standard deviation

Total and indirect bilirubin levels were decreased after phototherapy. The mean serum TAClevels were 1.08±0.10 µmol TroloxEqv/L before phototherapy, and 0.86 ± 0.13 µmolTroloxEqv/L after phototherapy. The decrease in TAC values after phototherapy wasstatistically significant (p<0.001). Furthermore, it was found that the mean serum TOS levelwas decreased significantly with phototherapy (25.11±14.05 µmol troloxEqv/L vs.15.78±6.70 µmol troloxEqv/L, p<0,001). OSI did significantly differ with phototherapy(2.50±1.80 vs. 1.80±0.67, p=0.01). There was a significant increase in serum PON activity10with phototherapy (40.00±30.93 vs. 55.14±37.63, p=0.003). Arylesterase levels were alsoincreased significantly after phototherapy (40.66±25.02 U/L vs. 53.38±30.47 U/L, p=0.003).

The mean LOOH levels were 10.24 ± 4.26 µmol/L before phototherapy and 7.28 ± 2.09µmol/L after phototherapy (p<0.001). Phototherapy was also significantly

effective onreducing triglyceride, VLDL-C and uric acid levels (p=0.005, p=0.005 and p=0.001,respectively). Serum LDL-C and albumin levels were found to increase with treatment(p=0.008 and p=0.002, respectively) (Table 2).

Table 2. Biochemical characteristics of infants

	Before phototherapy	**After phototherapy**	***p* value**
TAC (μmol Trolox Eqv./L)	1.08 ± 0.10	0.86 ± 0.13	**0.001**
TOS (μmol H_2O_2 Eqv./L)	25.11± 14.05	15.78 ± 6.70	**0.001**
OSI	2.50 ± 1.80	1.80 ± 0.67	**0.01**
Paraoxonase (U/L)	40.00 ± 30.93	55.14 ± 37.63	**0.003**
Arylesterase(U/L)	40.66 ± 25.02	53.38 ± 30.47	**0.003**
LOOH (μmol/L)	10.24 ± 4.26	7.28 ± 2.09	**0.001**
Triglyceride(mg/dl)	177.87 ± 51.99	152.21 ± 64.44	**0.005**
Cholesterol (mg/dl)	119.28 ± 39.74	130.59 ± 35.85	0.058
HDL-C(mg/dl)	41.17 ± 11.82	43.85 ± 10.99	0.099
LDL-C (mg/dl)	43.13 ± 30.50	56.06 ± 27.03	**0.008**
VLDL-C (mg/dl)	35.57 ± 10.38	30.44 ± 12.88	**0.005**
Total bilirubin(mg/dl)	19.04 ± 2.54	10.80 ± 2.02	**0.001**
Indirect Bilirubin (mg/dl)	18.02 ± 2.52	9.80 ± 2.04	**0.001**
Albumin (mg/dl)	3.67 ± 0.29	3.88 ± 0.35	**0.002**
Uric acid (mg/dl)	5.43 ± 3.15	3.45 ± 0.97	**0.001**

TAC: Total antioxidant capacity. TOS: Total oxidant status. H_2O_2: Hydrogen peroxide. OSI: Oxidative stress index. LOOH: Lipid Hydroperoxide. HDL-C: High density lipoprotein-cholesterol. LDL-C: Low density lipoprotein-cholesterol. VLDL-C: Very low density lipoprotein-cholesterol. Data given as mean ± standard deviation.

Discussion

The current study aimed to examine the effects of phototherapy on oxidative status inneonates with hyperbilirubinemia. We found significant a reduction in TAC, TOS, OSI andLOOH levels and an increase in PON and arylesterase activities in neonates afterphototherapy. To the best of our knowledge, this is the first study in the literature evaluatingall these parameters together in patients with neonatal hyperbilirubinemia.Hyperbilirubinemia arises as a result of excessive production of bilirubin, primarily due to therapid breakdown of erythrocytes and insufficient clearance of bilirubin by the immature liver,often leading to a requirement for phototherapy, or in severe cases, exchange transfusion (15).

Phototherapy is a non-invasive, well-tolerated, low-cost method that is easily applied toneonates with hyperbilirubinemia. The statistically significant decrease of bilirubin levelsafter management with phototherapy in our study supports phototherapy is an effectivemethod in the treatment of hyperbilirubinemia. Phototherapy has been suggested to havenegative impacts on oxidative status and may also cause photodynamic stress, lipidperoxidation and DNA damage (4). Oxidative stress can be defined as a deterioration ofoxidant-antioxidant balance due to an excess production of free radicals or a decrease in theability antioxidant defense system, leading to cellular/tissue damage with other negativeeffects, including protein modification, lipid peroxidation, oxidative DNA base modification,11and also impaired cellular signaling (16). Alterations in the balance of oxidative and antioxidative characteristics are considered to play a significant role in the pathogenesis of many

conditions including neurodegenerative diseases, autoimmune diseases, and metabolicdisorders (17). Previous studies have demonstrated that phototherapy may cause varyinglevels of oxidative stress in newborns undergoing the management of phototherapy; however,results are often conflicting (18). Some studies have revealed an augmentation in oxidativestress markers after phototherapy, while others demonstrate decreases. Ozture et al. Founddecreased malondialdehyde (MDA) levels after phototherapy, indicating that phototherapyreduces oxidative stress (19). Similarly, Torun et al. found that oxidative stress markers didnot increase after phototherapy (20). In contrast, a study conducted by Ayçiçek et al. in 36neonates receiving phototherapy demonstrated unaltered levels of TAC,

thiol content andalbumin, decreased levels of Vitamin C, uric acid, total bilirubin and MDA levels, and alsoincreased levels of TOS, LOOH and OSI after phototherapy (21). They also found positivecorrelations between total bilirubin and MDA, suggesting that low MDA may be the result ofthe suppression of pathways upstream of MDA formation by bilirubin and aldehydestructures. We demonstrated significantly decreased levels of oxidative stress markersincluding TOS, LOOH and OSI after treatment in our patients. It is possible that the decreasein free oxygen radical production resulting from a decrease in the synthesis of prostoglandinsafter phototherapy may be the cause of reduced oxidative stress. Furthermore, the reduction inthe oxidation of fatty acids (as a source of free oxygen radicals) during phototherapy couldexplain the decrease in oxidative stress markers. On the other side of the equation, a reductionin the levels of antioxidants has been demonstrated in neonatal hyperbilirubinemia in previousstudies. For instance, Dahiya et al. showed increased MDA and superoxide dismutase levelsand decreased antioxidant levels in hyperbilirubinemic neonates after phototherapy (22).

Additionally, Kurban et al. found decreased TAC levels after phototherapy in 40 full-term12newborn with jaundice (23). Consistent with these results, we found decreased levels of TACafter phototherapy in our study. This may be related to consumption of antioxidants, primarilybilirubin itself, during phototherapy. We found decreased bilirubin levels parallel todecreasing TAC levels. Studies have demonstrated that increased serum bilirubin levels mayprotect against diseases related to oxidative stress (5). We also found decreased levels of uricacid, which may have contributed to the decrease in TAC after phototherapy. Consistent withour study, Aycicek et al. reported significant decreases in uric acid after phototherapy (21). Itis not certain whether the decrease in serum uric acid is a direct effect of photo-oxidation or aresult of reduced oxidative stress. Another interesting finding of this study was the increase inalbumin levels after treatment. The increase in albumin, yet another molecule with antioxidantproperties, may be due to heat exposure and dehydration during phototherapy, as well as theexcretion of bilirubin from the circulation.The human serum paraoxonase enzyme is an ester hydrolase synthesized primarily in the liverand associated with lipoproteins including HDL-C and LDL-C (7). PON exerts paraoxonase,arylesterase and lactonase activities (8). PON functions as

an endogenous antioxidant bypreventing the oxidation of lipoproteins by reactive oxygen radicals (6). Its serum level isaffected by the levels of oxidized LDL and also other inflammatory and oxidative conditions.The ability of lipoprotein-associated PON1 to hydrolyze hydrogen peroxide can also play animportant role in eliminating oxidants that occur during arteriosclerosis (24). Altered levelsof PON activity have been shown in many diseases related with oxidative stress andinflammation. However, there is only one study in literature examining the relationshipbetween phototherapy and PON activities in neonatal hyperbilirubinemia. Kurban et al.showed in 40 full term infant with jaundice that PON1 activities did not significantly changeby phototherapy (23). In our study, we found an increase in PON and arylesterase activitieswith treatment. Our results may indicate an increase in PON and arylesterase activities due to13decreased oxidative stress and also increased hemolysis after phototherapy. However, as aresult of the reduction of bilirubin with phototherapy, it is possible that the liver experiences adecrease in load; thereby easing the synthesis of PON and arylesterase. In addition, we foundsignificantly increased LDL-C levels with treatment in our study. LDL-C levels may beelevated to balance increased PON and arylesterase activities. The small sample size of this study and its single-center characteristic are importantlimitations with regard to the generalizability of results. Secondly, we measured biochemicalmarkers once before and after treatment; however, a higher number of measurements duringtreatment in the same infants could be more informative. Thirdly, we performed our studywithout controls; however, phototherapy cannot be applied to healthy patients.In conclusion, this is the first study in the literature to evaluate the effects of phototherapy onPON, arylesterase, lipid profile, TAC, TOS and OSI in patients with neonatalhiperbilirubinemia. Decreased TAC, TOS, OSI, LOOH levels and increased PON and

arylesterase activities after phototherapy can be interpreted as an overall decrease in oxidativestress. Further comprehensive studies with large number of samples are needed to evaluate theeffects of phototherapy on oxidative balance.

Ethical Statement

The study was approved by the Research Ethics Committee of Harran University.

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