

## Fototerapi Alfa Melanosit Uyarıcı Hormon Seviyelerini Etkiler mi?

### Does Phototherapy Influence Alpha Melanocyte Stimulating Hormone Levels?

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#### ÖZ

**Amaç:** İlk kez bu araştırmayla indirekt hiperbilirubinemi (İHB) olan yenidoğanlarda fototerapinin plazma alfa-melanosit uyarıcı hormon ( $\alpha$ -MSH) üzerine etkisinin araştırılması amaçlanmıştır.

**Materyal ve Metot:** İHB nedeniyle yenidoğan yoğun bakım ünitesinde yatarak fototerapi tedavisi uygulanan 45 olgu, 1 Temmuz 2019-30 Eylül 2019 tarihleri arasında prospektif olarak çalışmaya dahil edildi. Fototerapi öncesi ve sonrası plazma  $\alpha$ -MSH ve bilirubin düzeyleri ölçüldü.

**Bulgular:** Çalışmaya 45 yenidoğan (19 kız, 26 erkek) dahil edildi. Ortalama doğum kilosu 3202 gr ve ortalama total bilirubin düzeyi 17,2 mg /dl idi. Fototerapi öncesi ve sonrası  $\alpha$ -MSH seviyeleri sırasıyla 326,2 (4,0-2228,0) ng/L ve 373,9 (8,7-2283,0) ng/L olup benzerdi ( $p > 0,05$ ).

**Sonuç:** Bu çalışmayla İHB için yenidoğanlara uygulanan fototerapinin, plazma  $\alpha$ -MSH üzerine etkisi olmadığı saptanmıştır.

**Anahtar Kelimeler:** Alfa-melanosit stimulan hormon, fototerapi, indirekt hiperbilirubinemi, yenidoğan

#### ABSTRACT

**Objective:** We aimed to investigate the effect of phototherapy on plasma alpha-melanocyte-stimulating hormone ( $\alpha$ -MSH) levels of newborns with indirect hyperbilirubinemia (IHB) for the first time.

**Materials and Methods:** A total of 45 cases, who were hospitalized in neonatal intensive care units between July 1, 2019, to September 30, 2019, and received phototherapy, were retrospectively included in the study. Plasma  $\alpha$ -MSH and bilirubin levels were measured before and after the phototherapy.

**Results:** A total of 45 newborns (19 girls and 26 boys) were included in to study. The average birth weight was 3202 grams and the mean total bilirubin level was 17.2 mg/dL.  $\alpha$ -MSH levels before and after phototherapy were 326.2 (4.0-2228.0) ng/L and 373.9 (8.7-2283.0) ng/L, respectively and did not represent a significant difference ( $p > 0.05$ ).

**Conclusion:** This study demonstrated that there was no effect between phototherapy applied for newborn IHB and plasma  $\alpha$ -MSH levels.

**Keywords:** Alpha-melanocyte stimulating hormone, indirect hyperbilirubinemia, newborn, phototherapy

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#### INTRODUCTION

Indirect hyperbilirubinemia (IHB) known as the main element of newborn jaundice.<sup>1,2</sup> IHB might cause irreversible brain damage and kernicterus in a small population of newborns.<sup>3</sup> Thus, the treatment of newborn IHB is extremely crucial and phototherapy is the key method for IHB.<sup>2</sup> The primary goal of

the phototherapy is to prevent the development of acute and reversible “acute bilirubin encephalopathy” and persistent “kernicterus” that occur in accordance with bilirubin toxicity in newborns.<sup>4</sup> It reduces; the elevation of indirect bilirubin levels in all newborns independent of the presence of hemolysis, maturity or pigmentation level of the skin.<sup>1</sup>

Phototherapy might be related with some unknown effects such as maculopapular skin eruption, dehydration, diarrhea, retina damage and skin bronzing.<sup>2</sup> Phototherapy might cause oxidative damage. Oxidation and free radicals are reported to trigger bronchopulmonary dysplasia, premature retinopathy, necrotizing enterocolitis and patent ductus arteriosus in low birth weight newborns. Phototherapy leads to the removal of antioxidants from blood circulation, which are essential in newborns. In vitro studies represented that DNA damage was caused by the same levels of radiation that is used in clinical phototherapy.<sup>4</sup>

Alpha-melanocyte stimulating hormone ( $\alpha$ -MSH) is released from the pituitary gland by the corticotropin-releasing hormone that is secreted from the hypothalamus and proteolysis of a precursor called proopiomelanocortin.<sup>5</sup>  $\alpha$ -MSH secretions are regulated by tuberohypophyseal dopaminergic neurons,  $\alpha$ -MSH is produced by keratinocytes and melanocytes following the exposure to ultraviolet (UV) radiation in the skin.<sup>6</sup> Apart from hair and skin pigmentation,  $\alpha$ -MSH is essential in regulating feeding behavior, energy homeostasis, protecting against ischemia and reperfusion and anti-inflammatory process.<sup>7</sup>  $\alpha$ -MSH induces pigmentation in order to reduce UV related DNA damage.<sup>7,8</sup> Previous studies demonstrated that  $\alpha$ -MSH protects UV induced skin damage.<sup>9</sup> MSH level was affected by different factors such as nutrition, newborn skin thickness, lighting, etc.<sup>7,8</sup>

According to our knowledge, there was no published English language study that focused on the effect of  $\alpha$ -MSH on newborn phototherapy, yet. Does phototherapy affect  $\alpha$ -MSH levels in newborns? As the  $\alpha$ -MSH level is directly related to the applied radiation, the phototherapy treatment might affect  $\alpha$ -MSH levels. For this purpose, we measured the  $\alpha$ -MSH levels before and after the phototherapy and aimed to investigate whether this protective mechanism has a protective effect for UV damage in babies receiving phototherapy. We aimed to investigate the effect of phototherapy on  $\alpha$ -MSH levels of newborns.

## MATERIALS AND METHODS

This study was conducted in Sakarya University Faculty of Medicine from June 1, 2019, to September 30, 2019. The individuals who were hospitalized to neonatal intensive care units (NICU) due to IHB and informed consents were obtained from the parents. This study was approved by Sakarya Univer-

sity Ethical Committee (Date: 01/06/2019, decision no:16214662/050.01.04/86).

**Exclusion and Inclusion Criteria:** In this study, babies with hyperbilirubinemia who needed phototherapy were included in the study prospectively. Babies with major congenital anomaly, chromosomal anomaly, sepsis, and direct hyperbilirubinemia were excluded from the study.

**Phototherapy and Blood Specimen Collection:** Phototherapy has been applied according to the total serum bilirubin (TSB) levels proposed by the American Academy of Pediatrics.<sup>10</sup> Phototherapy was discontinued when phototherapy was 2 mg/dl below the starting limit.

Blood specimens were collected before and after the phototherapy.

Patients were put on eye patches and treated with LED (Light-emitting diode) phototherapy from 40 cm for 12-30 hour time periods. Phototherapy was applied using a Babyblue LED phototherapy system (TENDE, Ankara, Turkey; spectrum 460-490 nm). Phototherapy was applied to the naked body, apart from covered genital areas and eyes. During feeding, phototherapy sessions were ceased. Intensive phototherapy was given to patients whose total bilirubin level was at the threshold of exchange transfusion or whose bilirubin increased rapidly.

When the specimens clotted completely, they were centrifuged for 10 minutes at 4000 G. Serum fractions were collected and frozen at -40°C until further usage.  $\alpha$ -MSH levels were studied with commercial double antibody enzyme-linked immunosorbent assay using YLBiont brand Sandwich ELISA (Shanghai YL Biotech Co., Ltd.).

**ELISA Test:** Specimens were pipetted into monoclonal antibody-coated wells. Next, anti- $\alpha$ -MSH monoclonal antibodies were added. Streptavidin-HRP conjugates were added to all wells except the blind well and incubated at 37°C for 60 minutes. After the incubation, a washing step was performed in order to remove unbound antibodies. Chromogen was added to colorize and incubated at 37°C for 10 minutes. Blue colour occurred after the reaction and a stop solution was added to terminate it. The reaction termination was observed by blue to yellow colour change. The intensities of the yellow colour were directly proportional to  $\alpha$ -MSH concentration. The colorimetric readings were performed with a micro ELISA reader inappropriate wavelength. Standard values and related optical density values were matched, then a linear regression equation graph was

drawn. Sample concentrations were calculated. The results were represented in ng/L. **Statistical Analysis:** Statistical evaluation was performed using Statistical Package for Social Sciences (SPSS) 20 (Inc, Chicago, Illinois, USA) statistical analysis program. Frequency distributions, descriptive statistics were applied in statistical analysis. Normal distribution was tested using the Kolmogorov-Smirnov test. Since the quantitative value, parametric test conditions were not provided, the Mann-Whitney U test was performed in groups, whereas Wilcoxon Signed Ranks Test was conducted before and after therapy results of dependent groups. P-value was below 0.05 defined as statistically significant.

## RESULTS

A total of 45 newborn babies (19 girls and 26 boys) were included in the study. A total of 19 of them were born through vaginal delivery whereas 26 were delivered by caesarian. A total of 39 of the participants were term and six were premature birth. The demographic characteristics including birth weights, gestational weeks, admission and discharge weights, duration of phototherapy and blood parameters of the patients were represented in [Table 1](#). According to phototherapy,  $\alpha$ -MSH levels were represented in [Table 2](#). MSH levels did not represent a significant difference before and after phototherapy ( $p>0.05$ ). Also, there was no difference in  $\alpha$ -MSH levels when the bilirubin measurements were compared before and after phototherapy ( $p>0.05$ ).

## DISCUSSION AND CONCLUSION

Neonatal jaundice occurs due to the elevation of bilirubin which is the final product of the catabolism, in the bloodstream. Increased indirect bilirubin leads to yellowing in the skin and sclera of a baby. Additionally, the rise in bilirubin level is toxic for the central nervous system. In babies, it also causes bilirubin encephalopathy and then kernicterus. For this reason, neonatal jaundice is critical and the most commonly used treatment is phototherapy, in which the light energy alters the molecular structure of bilirubin and enables its excretion by bile and urine.<sup>11</sup>

Liquid electrolyte breakdown, bronze baby syndrome, circadian rhythm disorder, disruption in the balance between oxidant and antioxidant were observed among the negative effects of phototherapy.<sup>12</sup>  $\alpha$ -MSH is significantly crucial in protecting the melanocytes from oxidative damage, as an immunomodulator and anti-inflammatory.  $\alpha$ -MSH decreases

oxidative damage by reducing the UV related hydrogen peroxide amounts. For example melanocytes of vitiligo patients possess low levels of  $\alpha$ -MSH. Accordingly, melanocytes cannot be protected from oxidative stress sufficiently.<sup>13</sup> However Spiro et al. examined the effect of  $\alpha$ -MSH on patients with mycosis fungoides and psoriasis who receive UV and demonstrated that  $\alpha$ -MSH levels were not significantly different before and after 3-week UV treatment.<sup>14</sup>

Melanogenesis is regulated by partial binding of  $\alpha$ -MSH to its receptor, which leads to elevated melanin production.<sup>15</sup> Theoretically it might be concluded that MSH levels alter before and after the phototherapy. For this, we investigated the  $\alpha$ -MSH level in neonatal jaundice before and after the phototherapy. In our study, we did not detect a significant difference between before and after  $\alpha$ -MSH levels ( $p>0.05$ ). To the best of our knowledge, no study has focused on the effect of phototherapy on plasma  $\alpha$ -MSH levels of newborns yet.

The major limitation of our study is the relatively low subject count. This study would have been more robust with more participants. Another limitation of our study was preterm infants were not excluded from our study. It is possible that there is a difference between the skin thickness or brain maturation level of premature and term babies and their MSH levels. Newborns may have encountered other factors that affect their MSH level (eg day-night cycle, other light exposure). Our inability to control these factors is also a limitation.

This study is the pioneer in terms of investigating the influence of phototherapy on  $\alpha$ -MSH levels of neonates and indicated that phototherapy, which is applied to newborn babies have no effect on plasma  $\alpha$ -MSH levels.

**Ethics Committee Approval:** This study was approved by the Sakarya University Faculty of Medicine Ethics Committee (Date: 01/06/2019, decision no:16214662/050.01.04/86).

**Conflict of Interest:** No conflict of interest was declared by the author.

**Author Contributions:** Concept – MK; Supervision – MK, EÇ; Materials – MK; Data Collection and/or Processing – MK, EÇ; Analysis and/ or Interpretation – MK; Writing – MK.

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**Table 1.** Demographic characteristics of patients.

<b>Parameters</b>	<b>N</b>	<b>Minimum</b>	<b>Maximum</b>	<b>Mean±SD</b>
<b>Birth weight (g)</b>	45	2060.0	4190.0	3202.2±477.8
<b>Admission weight (g)</b>	44	1960.0	3900.0	3016.4±445.2
<b>Gestational week</b>	45	35	41	38±3
<b>Discharge weight (g)</b>	44	2000.0	3910.0	3074.5±440.9
<b>Duration of phototherapy (hour)</b>	45	12.0	30.0	21.0±3.9

SD: Standard deviation; N: Number.

**Table 2.**  $\alpha$ -MSH and bilirubin levels of patients.

Parameters	Before Phototherapy		After Phototherapy Median (min-max)		p
	Median (25P-75P)	min-max	Median (25P-75P)	min-max	
<b>Total bilirubin (mg/dl) (n=45)</b>	17.2 (13.9-20.4)	7-27	10.6 (8.9-12.8)	6-15	NS
<b>Indirect bilirubin (mg/dl) (n=45)</b>	16.3 (12.6-19.2)	6.4-26.0	9.8 (7.9-11.6)	5-13	NS
<b><math>\alpha</math>-MSH (ng/L) (n=45)</b>	326.2 (48.2-298.1)	4.01-2228.0	373.9 (17.1-393.3)	8.7-2283.0	NS

NS: Not significant;  $\alpha$ -MSH: Alpha-melanocyte stimulating hormone. Data expressed as median [25P(Percentile)-75P], minimum and maximum.