*Araştırma Makalesi / Research Article*

# Effectiveness of light emitting diode phototherapy for direct coombs positive newborns

## Direkt coombs pozitif yenidoğanlarda light emitting diode fototerapinin etkinliği

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Abstract

Background: Phototherapy is the most frequently used treatment when serum bilirubin levels exceed physiological limits. The direct antiglobulin titer (DAT) test is regarded as the cornerstone of diagnosis of immune hemolytic disease of the newborn.
Methods: Patients with hyperbilirubinemia who were born in our hospital and whose gestational age was over 35 weeks were enrolled. DAT positive and DAT negative patients were compared in terms of light emitting diode (LED) phototherapy efficacy.
Results: Seventy-seven cases were DAT-negative and 72 were DAT-positive. No statistically significant differences were found for the duration of phototherapy and hospitalization between the DAT-positive and negative groups. In the DAT-positive group, the phototherapy needs of the patients were determined to occur at an earlier stage (postnatal age 1.4 day, $p<0.05$), and the rate of patients requiring exchange transfusion, blood transfusion and intravenous immunoglobulin was found to be statistically significant higher in DAT-positive infants.
Conclusions: Although LED phototherapy is effective in DAT-positive patients, the need for exchange transfusion and intravenöz immunoglobulin (IVIG) shows that there is still a need for more effective phototherapy in these patients.

Key Words: Direct antiglobulin, Hyperbilirubinemia, Newborn, Phototherapy

Öz

Amaç: Fototerapi, serum bilirubin düzeyleri fizyolojik sınırları aştığında en sık kullanılan tedavi yöntemidir. Direkt antiglobulin titresi (DAT) testi yenidoğanın immün hemolitik hastalığı tanısının temel taşı olarak kabul edilir.
Materyal ve Metot: Hastanemizde doğan ve gebelik yaşı 35 haftadan fazla olan hiperbilirubinemili hastalar çalışmaya alındı. DAT pozitif ve DAT negatif hastalar light emitting diode (LED) fototerapi etkinliği açısından karşılaştırıldı.
Bulgular: Yetmiş yedi olgu DAT negatif, 72 olgu DAT pozitif idi. DAT pozitif ve negatif gruplar arasında fototerapi ve hastanede yatış süresi açısından istatistiksel olarak anlamlı bir fark bulunmadı. DAT pozitif grupta hastaların fototerapi gereksinimlerinin daha erken bir aşamada (doğum sonrası yaş 1.4 gün, $p <0.05$) olduğu tespit edildi, exchange transfüzyon ve intravenöz immunoglobulin (IVIG) gerektiren hastaların oranı DAT pozitif bebeklerde istatistiksel olarak anlamlı derecede yüksekti.
Sonuç: LED fototerapi DAT pozitif hastalarda etkilidir ancak kan değişimi ihtiyacı ve IVIG bu hastalarda hala daha etkili fototerapiye ihtiyaç olduğunu göstermektedir.

Anahtar Kelimeler: Direkt antiglobulin, Hiperbilirubinemi, Yenidoğan, Fototerapi

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## Introduction

Direct antiglobulin titer (DAT) test is an important tool in the evaluation of immunohemolytic patients (1). The DAT test can be used to describe the sensitivity of erythrocytes in vivo, positive results may show hemolytic disease of the newborn (HDN) (2).

Some studies suggest that this is a weak marker in severe hyperbilirubinemia (3,4) and is rarely detected in patients hospitalized for jaundice (5).

But, American Academy of Pediatrics (AAP) subgroup of hyperbilirubinemia; stated that blood group mismatches with DAT positivity are risk factors for the development of severe hyperexemia and hence neurotoxicity (6,7). Investigators have recently emphasized that the DAT strength could be a significant risk factor in the development of hyperbilirubinemia that newborns with DAT strength ++ (or more) are especially at high risk and this factor should be considered in the treatment of a newborn with hemolytic disease (8).

Phototherapy is the most common method in the treatment of hyperbilirubinemia. The effectiveness of phototherapy depends on the wavelength, radiation, exposed surface area, exposure time and distance from phototherapy to surface. Intensive phototherapy is achieved by using a high level of radiation in the 430-490 nm band (usually 30WW/cm2). The light emitting diode (LED) may be more effective than conventional phototherapy due to phototherapy, high light intensity and narrow wavelength. It can also be more cost-effective due to the longer life of the light source and lower energy consumption (9). In the literature, most of the LED phototherapy studies are generally related to the duration and effectiveness of treatment in neonates with nonconjugated hyperbilirubinemia. However, there is no study comparing the efficacy of LED phototherapy with immune hemolytic patients non-hemolytic jaundice. The aim of this study was to investigate the efficacy of LED phototherapy, which is currently the most effective treatment in hyperbilirubinemia, in DAT positive patients.

## Materials and Methods

Consecutive newborns were evaluated at our hospital between October 2014 and 2015. This study was a prospective cohort. The study was approved by the local ethics committee.

*Patients*

Between January 2014 and August 2015, in the first week of life, term and late preterm (≥ 35 weeks) patients with high bilirubin levels requiring phototherapy were enrolled in the study. All infants were healthy in other respects, and birth weights were consistent with gestational ages. Infants with major congenital malformations, perinatal asphyxia, sepsis, cephalohematoma, adrenal hemorrhage, anemia, or those with increased bilirubinemia potential, such as glucose-6-phosphate dehydrogenase deficiency or positive DAT; except AB0 and Rh heterospecific were excluded from the study.

Methods

Significant hyperbilirubinemia; the serum bilirubin values above the 75th percentile were defined according to the AAP criteria (6). Neoblue® LED phototherapy (Natus Medical Inc., San Carlos, CA, USA, density: 30 μW/cm2/nm, spectrum 450-470) was applied to phototherapy with devices. The device was placed 30 cm above the infants. Once a week and if necessary lamps were changed. After hospitalization, phototherapy was started rapidly. Phototherapy was terminated when the bilirubin level fell to the safe limit according to AAP criteria direct antiglobulin (6). When the level of bilirubin was above the limits determined by AAP, exchange transfusion was performed (6).

Blood type typing was performed by standard blood bank technique. For the detection of ABO/Rh /minor blood groups and DAT, DiaMed AHG (Dia Med-ID, Cressier, Switzerland) gel method was used in blood bank. 50 μL of 0.8% erythrocyte suspension was centrifuged for 10 minutes and agglutination; rated negative, 1+, 2+, 3 +, 4+. Bilirubin levels were measured using the Unistat Bilirubinometer (AO Scientific Instruments, Buffalo, NY).

Data collected included gestation week, birth weight, DAT status, DAT grade, serum bilirubin levels, duration of phototherapy and hospitalization, re-admission, and treatment for hyperbilirubinemia, IVIG, exchange transfusion, or blood transfusion. The side effects of phototherapy, such as hypothermia, hyperthermia, dehydration, and skin rash were recorded.

Statistical analyses

Statistical analysis were performed using the statistical package SPSS for of Windows v. 17.0 (SPSS Inc., Chicago, Illinois). Paired-samples t test and independent samples t test were used for continuous variables. For categorical variables x2 test was used. Continuous variables were given as mean ± standard deviation and categorical variables were given as frequency and percentage. $P < 0.05$ was considered statistically significant. Written informed consent was obtained from the parents of the patients included in the study.

## Results

A total of 149 patients completed the study, and 12 were excluded because of major congenital malformations (n = 3), sepsis (n=3), perinatal asphyxia (n=2), and other conditions with the potential of increasing hyperbilirubinemia (n=4). The demographic and clinical characteristics of the patients are summarized in Table 1.

Among all the cases, 77 were DAT-negative and 72 were DAT-positive. Birth weight, gestation, and other demographic variables were similar in the neonates enrolled in the DAT-positive or negative groups. The DAT-positive group

comprised 51 (70.8%) patients with AB0 blood group incompatibility and 21 (29.2%) with Rh incompatibility. The DAT-negative group comprised 33 (42.8%) patients with AB0 blood group incompatibility. The comparison of the effectiveness of LED phototherapy between DAT-positive and DAT-negative patients is presented in Table 1.

No statistically significant differences were found for the duration of phototherapy and hospitalization between the DAT-positive and negative groups. In the DAT-positive group, the phototherapy needs of the patients were determined to occur at an early stage (postnatal age 1.4 day, $p < 0.05$), and the rate of patients requiring exchange transfusion, blood transfusion, and intravenous immunoglobulin was found to be statistically significantly higher in DAT-positive infants (Table 2). Weight loss and reticulocyte count were found to be statistically significantly different between the two groups. Weight loss was higher ($p < 0.05$) and the reticulocyte count was lower in the DAT-negative group ($p < 0.05$).

DAT-positive patients were classified according to DAT strength. Thirty (41.7%) patients were included in the DAT 1+ group and 42 (58.3%) in the DAT 2+≤ group. No statistically significant differences were found for duration of phototherapy and hospitalization, need for exchange transfusion, blood transfusion, intravenous immunoglobulin, and re-admission between the two groups (Table 2).

A total of eight (5.3%) infants and nine re-admission events for hyperbilirubinemia were found during the study period ($p=0.021$) (Table 1). One infant with AB0 incompatibility and a positive DAT was re-admitted because of prolonged hyperbilirubinemia.

No side effects of phototherapy such as erythema were noted in either of the groups. The nurses did not complain of nausea or dizziness when they were looking at babies under the blue LED light.

Table 1. Clinical Characteristic and Efficacy of LED phototherapy in patients with positive and negative DAT

| | DAT positive (n=72) | DAT negative (n=77) | p |
|---|---|---|---|
| Gestation age (mean±SD) (week) | 38.2±2.1 | 37.8 ±2.4 | 0.41 |
| Birth weight (mean±SD) (g) | 3125 ±528 | 3129± 470 | 0.96 |
| Male, n (%) | 34 (47.2) | 44 (57.1) | 0.25 |
| C/S, n (%) | 35 (48.6) | 25 (32.5) | 0.047 |
| Age at the onset of phototherapy (mean±SD) (day) | 1.4±0.76 | 3.9±2.2 | <0.001 |
| Duration of phototherapy (mean±SD) (h) | 57.1±52 | 46.9±27.3 | 0.64 |
| Duration of hospitalization (mean± SD) (h) | 90.7±68.8 | 81.2±52.0 | 0.399 |
| Exchange transfusion , n (%) | 8 (11.1) | 2 (2.6) | 0.038 |
| Blood transfusion , n (%) | 8 (11.1) | 1 (1.3) | 0.012 |
| Intravenous immunoglobulin, n (%) | 20 (27.8) | 1 (1.3) | 0.000 |
| Re-admitted for phototherapy, n (%) | 7 (9.7) | 1 (1.3) | 0.021 |

*mean±SD ; mean±standart deviation, n ; number, h;hour DAT; Direct antiglobulin titer, LED; Llight emitting diode, C/S;C-section*

Table 2. Comparison of the DAT 1 and 1< positivity

| | DAT 1 positive (n=30) | DAT 1< positive (n=42) | p |
|---|---|---|---|
| Admitted for phototherapy (day) (mean±Std) | 1.4±0.12 | 1.4±0.12 | 0.77 |
| Duration of phototherapy (h) (mean±Std) | 60.9±8.1 | 54.1±8.8 | 0.22 |
| Duration of hospitalization (h) (mean± Std) | 89.5±9.6 | 91.6±12.1 | 0.65 |
| Exchange transfusion, n (%) | 2 (6.6) | 6 (14.3) | 0.31 |
| Blood transfusion, n (%) | 3 (10) | 5 (12) | 0.8 |
| Intravenous immunoglobulin, n (%) | 6 (20) | 14 (33.3) | 0.21 |
| Re-admitted for phototherapy, n (%) | 1 (3.3) | 6 (14.3) | 0.22 |

*mean±SD ; mean±standart deviation, n ; number, h;hour, DAT; Direct antiglobulin titer*

## Discussion

We investigated the efficacy of LED phototherapy in patients with isoimmune hemolysis. To our knowledge, this is the first study investigating the efficacy of LED phototherapy in patients with isoimmune hemolysis in the literature. We consider the probable outcome to be due to the unsuccessful elimination of maternal antibodies within the circulation of the baby through LED phototherapy. LED phototherapy is capable of detoxifying the bilirubin produced as a result of hemolysis, but it cannot inhibit the mechanism

of ongoing hemolysis because of the circulating maternal antibodies.

The isoimmune hemolytic disease is listed by the AAP in the 2004 Clinical Practice Guideline for the management of hyperbilirubinemia as an important risk factor for the development of severe hyperbilirubinemia. According to this guideline, DAT positivity is also shown as a risk factor for a bilirubin neurotoxicity (7). However, a positive DAT is usually regarded as only weakly predictive of hyperbilirubinemia (3,10,11). The direct Coombs test is used to determine the autoantibodies produced against erythrocyte antigens due to various reasons. This parameter is used to define the presence of an immune etiology in patients with hemolysis. Autoimmune hemolytic anemias, drug-related hemolysis, and delayed or acute transfusion reactions are characterized by a positive DAT test (12-14). In our study, we only investigated DAT-positive patients with AB0 and Rh incompatibility and compared the effect of LED phototherapy according to DAT strength on the patients. Dillon et al. (15) that low or high DAT power strongly predicted whether a baby needed phototherapy, and that an intermediate DAT force required concomitant bilirubin measurements to determine the need for phototherapy. It has been reported that the positive DAT power for jaundiced infants has a duration of phototherapy twice as long as control babies. A limited number of studies have been found about DAT strength with DAT power and a positive correlation was found between DAT power and phototherapy treatment (9,16,17). As commonly reported in studies, 4+≤ DAT strength was positively correlated with the duration of phototherapy (15,17). In our study, all DAT-positive patients were below 3+. Thus, we grouped our patients as 1+ and 2+≤ only. No difference was observed between the groups in terms of initiation time of phototherapy, duration of phototherapy, exchange transfusion, and the need for IVIG or blood transfusion in LED phototherapy. This result may be due to the lack of high-grade, DAT-positive patients in our study group. Nevertheless, the outcomes of our study demonstrate that DAT positivity is an important indicator in determining hemolysis.

Phototherapy converts bilirubin into water-soluble products that can bypass the hepatic conjugation system and which can be removed without any other metabolism (18). Intensive phototherapy provides radiation in the 430–490 nm band. Recently, LEDs have been included into phototherapy units. LEDs generate low heat, and thus they can be kept close to the baby's skin without undesirable effects. The serum rapidly reduces the level of bilirubin, and the exchange transfusion rate decreases (5,9,19). LED instruments are routinely used for phototherapy in our unit. In recent years, the exchange transfusion application in our unit has dramatically decreased with the help of LED instruments. However, its efficacy on DAT-positive patients was limited to our observations only. In this study, we determined that the need for exchange transfusion, IVIG, and blood transfusion was not eliminated in DAT-positive patients despite the LED application. The need for exchange transfusion, IVIG, and blood transfusion was 6%, 14.1%, and 6% for all patients, respectively. Studies reported a need of over 20% for exchange transfusion, IVIG, and blood transfusion in DAT-positive patients with AB0 and Rh incompatibility who had undergone conventional phototherapy (20). In a recent study, the need for blood transfusion in DAT-positive AB0 patients was reported to be lower than that in previous studies, and the authors attributed it to the use of LED instruments in phototherapy (21). The rates observed in our study are similar to those in this study. Furthermore, the duration of phototherapy and hospital stay was similar. These results indirectly indicate that LED phototherapy is effective in detoxifying the bilirubin deposits in isoimmune hemolytic disease. Therefore, we consider LED phototherapy to decrease the need for blood transfusion and IVIG in DAT-positive patients but to be unable to eliminate it.

In our study, weight loss was more significant in the DAT-negative patient group. An important etiology of jaundice in this group was dehydration in the early period. As the jaundice was noted late, the initiation time of therapy was later compared with that in the DAT-positive group.

A limitation of our study is the lack of a DAT-positive group that had undergone conventional phototherapy. Another limitation is that our study did not include high-grade, DAT-positive patients, and thus the effect of LED phototherapy could not be considered for these patients. The strengths of our study are the fact that it is the first work to evaluate the efficacy of LED phototherapy in DAT-positive patients with isoimmune hemolytic disease and that it has a large sample size.

In conclusion, although LED phototherapy is effective in DAT-positive patients, the need for exchange transfusion and IVIG shows that there is still a need for more effective phototherapy in these patients.

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