

## Effect of Neonatal Phototherapy on Serum Levels of Interleukin 1, 6, 8, TNF $\alpha$ and White Blood Cell Count

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### Abstract

**Background:** Recent progress in medical sciences approved Phototherapy (PT) as a standard method of treatment and care for hyperbilirubinemia in the neonatal period. Some investigations have expressed concern about potential toxic effects of phototherapy, one possible harmful is affection of cytokines production, which can affect the function of neonatal immune system.

**Aim of the Study:** This work aimed to investigate the effect of PT on serum levels of interleukin 1, 6, 8, TNF  $\alpha$  and WBCs count in neonates with hyperbilirubinemia and in normally healthy neonates.

**Material and Methods:** The present study was carried out at Al-Azhar University Hospital (Damietta) during the period from January 2017 to March 2018, the study included 90 Egyptian term neonates with neonatal jaundice who had total bilirubin levels higher than 15mg /dl, and 30 normal healthy neonates were selected as control group. Venous blood samples were obtained from newborn with jaundice before exposure and at 72h after exposure to PT and from controls at the time of examination for estimation of interleukins 1, 6, 8, TNF $\alpha$  and WBCs count.

**Results:** The mean level of IL-1 before PT was (1.84 $\pm$ 0.89) and decreased slightly after PT (1.75 $\pm$ 0.63) with no statistically significant difference, ( $p$ -value=0.43). The mean value of IL-6 before PT was (38.7 $\pm$ 19) and decreased slightly after PT (34.6 $\pm$ 16.8) with no statistically significant difference ( $p$ -value=0.13). The mean level of IL-8 before PT was (376.4 $\pm$ 84.7) and decreased slightly after PT (353.7 $\pm$ 94.6) with no statistically significant difference, ( $p$ -value=0.09). The mean level of TNF $\alpha$  before PT was (8.63 $\pm$ 4.6) and increased after PT (17.6 $\pm$ 3.2), with statistically significant difference,  $p$ -value (<0.0001). The mean level of WBCs count before PT was (11300 $\pm$ 1987) and increased after PT (12500 $\pm$ 2281) with statistically significant difference, ( $p$ -value=0.0002).

**Conclusion:** Our findings demonstrate that an increased levels of serum TNF $\alpha$  and WBCs count in healthy term

neonates after PT could be considered as complications. Therefore, it seems that PT can alter the function of the immune system. Otherwise, the levels of interleukins 1, 6, 8 were very slightly decreased after PT.

**Key Words:** Phototherapy – Interleukins – Tumor necrosis factor  $\alpha$  – Jaundice.

### Introduction

NEONATAL jaundice is one of the most frequent conditions confronting pediatricians daily. About 70% of preterm infants develop jaundice in the first days of life. Bilirubin above a certain concentration, can deposit in the brain causing encephalopathy which is a devastating brain injury that can complicate the jaundice and may potentially lead to a serious nervous and developmental handicaps [1-3].

Phototherapy can affect the synthesis and release of cytokines from the peripheral immune system [4]. Exposure to Ultraviolet (UV) radiation initiates a complex cascade of responses that affect the immune system. Various immune mediators such as interleukin IL-1, IL-6, IL-10 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) are secreted by the immune system of skin to support the systemic immunologic response [5-6].

TNF- $\alpha$  is a glycoprotein hormone with important functions in inflammation and apoptosis. It plays a significant role as a proinflammatory cytokine in the defense against viral, bacterial and parasitic infections and autoimmune disorders [8].

Recent progresses in medical sciences mentioned Phototherapy (PT) as a standard method of treatment and care for jaundice in the neonatal period. PT uses the Ultraviolet (UV) radiation that

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makes a surge of immune responses. Commonly, the immune system of the skin secretes a variety of immune mediator cytokine such as interleukin (IL)-1, IL-6, IL-10, and tumor necrosis factor  $\alpha$  to enhance the systemic immunologic responses [9-11].

Despite the prolonged use of PT, its exact mechanism of action is unknown yet and different studies noted inconsistent results on cytokines levels and WBCs count after PT [12,13].

IL-6 appears to act primarily as a differentiation factor that increases the production of antibodies by activated B cells.

It increases platelet production and induces acute phase reactant protein production by liver cells [14,15].

We carried out this study to investigate the influence of phototherapy on the levels of IL-1, IL-6, IL8 and TNF as cytokines expressed from keratinocytes, and their effect on White Blood Cells (WBC) in the peripheral blood of babies with hyperbilirubinemia.

### Patients and Methods

The present study was carried out at Al-Azhar University Hospital (Damietta) during the period from January 2017 to March 2018. The study included 90 Egyptian term neonates with neonatal jaundice who had total bilirubin levels higher than 15mg/dl, and 30 normal healthy neonates were selected as a control group.

Parental informed consent was taken prior to inclusion and the study was approved by the Local Ethics Committee. Inclusion criteria for this study group were cases of neonatal indirect hyperbilirubinemia where the use of phototherapy had begun according to the guidelines of the American Academy of Pediatrics [16]. Exclusion criteria were premature babies, congenital malformations, congenital infections associated with TORCH, hypoxia, respiratory distress, neonatal hemolytic disease, sepsis, exchange transfusion, and any surgical problems. In mothers, the exclusion criteria were diabetes mellitus, preeclampsia, steroid treatment, and use of drugs. Blood samples were obtained from hyperbilirubinemia term newborns before and at 72h after exposure to phototherapy. Phototherapy was administered by five blue lights with wavelengths of 400-500nm, placed 30cm above the infants. Four milliliters of blood were obtained for cytokine analysis. The serum layer was separated by centrifugation and was frozen at  $-20^{\circ}\text{C}$ .

Samples were studied by Enzyme-Linked Immunosorbent Assay (ELISA) for TNF- $\alpha$ , IL-1 $\alpha$ , and IL-6 levels with human cytokine kits (Bender Med systems, A-1030 Vienna, Austria, and Europe). The assays were done according to the manufacturer's instructions, and absorbance measurements were made on Stat Fox Microplate Reader. All measurements described above were carried out with kit control. One milliliter of blood was collected before and after phototherapy in glass tubes containing ethylenediaminetetraacetic acid. WBCs count measurement with cell counter (ESI Sysmex KX-21) was conducted in the laboratory.

Data were reported by descriptive statistics such as frequency, percent, mean, standard deviation, and analyzed by paired sample *t*-test and Pearson's correlation coefficient in SPSS software Version 19.  $p < 0.05$  was considered statistically significant, and 95% confidence interval was noted.

### Results

The study included 90 Egyptian term neonates with neonatal jaundice who had total bilirubin levels higher than 15mg/dl, and 30 normal healthy neonates were selected as a control group. The mean gestational age of cases and control group was ( $37.71 \pm 1.38$ ,  $37.37 \pm 0.744$ ) respectively with no statistically significant difference  $p$ -value (0.6). With a mean of post-natal days of cases and control group was ( $3.83 \pm 0.75$ ,  $4 \pm 0.81$ ) respectively with no statically significant difference  $p$ -value (0.38). Mean birth weight of cases and control group was ( $2.7 \pm 0.89$ ,  $3.1 \pm 0.83$ ) respectively with no statically significant difference with  $p$ -value (0.1).

According to sex distribution in cases (39 males, 31 females) and control group (15 males, 15 females). The mean level of head circumference of cases and control group ( $36.4 \pm 5.6$ ,  $34.5 \pm 3.5$ ) respectively with no statistically significant difference. The mean level of the length of cases and control group ( $44.5 \pm 3.2$ ,  $45 \pm 4.8$ ) respectively was with no statistically significant difference (Table 1).

According to laboratory data of cases before and after PT, the mean level of serum bilirubin before and after PT was ( $18 \pm 2.5$ ,  $14 \pm 1.4$ ) respectively with statistically significant difference  $p$ -value ( $< 0.0001$ ), the mean level of Hb before and after PT was ( $14.5 \pm 2.3$ ,  $12 \pm 3.1$ ) respectively with statistically significant difference  $p$ -value ( $< 0.0001$ ), the mean level of WBCs before and after PT was ( $11300 \pm 1987$ ,  $12500 \pm 2281$ ) respectively with statistically significant difference  $p$ -value (0.0002) (Table 5).

The mean level of IL-1 before PT was (1.84 ± 0.89) and decreased after PT (1.75 ± 0.63) with no statistically significant difference, *p*-value (0.43). The mean value of IL-6 before PT was (38.7 ± 19) and decreased after PT (34.6 ± 16.8) with no statistically significant difference *p*-value (0.13). The mean level of IL-8 before PT was (376.4 ± 84.7) and decreased after PT (353.7 ± 94.6) with no statistically significant difference, *p*-value (0.09). The mean level of TNF before PT was (8.63 ± 4.6) and increased after PT (17.6 ± 3.2), with a statistically significant difference, *p*-value (<0.0001). The mean level of WBCs count before PT was (11300 ± 1987) and increased after PT (12500 ± 2281) with a statistically significant difference, *p*-value (0.0002) (Table 3).

Table (1): Demographic data of cases and control group.

Parameter	Cases N=90	Control N=30	<i>p</i> - value
Gestational age	37.71 ± 1.38	37.37 ± 0.744	0.6
Post-natal days	3.83 ± 0.75	4 ± 0.81	0.38
Sex:			
Male	39	15	0.27
Female	31	15	
Mode of delivery:			
NVD	44	12	0.06
CS	36	18	
Weight (kg)	2.7 ± 0.89	3.1 ± 0.83	1.0
Length	44.5 ± 3.2	45 ± 4.8	0.44
HC	36.4 ± 5.6	34.5 ± 3.5	0.9

Table (2): Concentration of IL- α, IL-6, IL-8 and TNF-α in serum of cases before phototherapy and control group.

	Cases N=90	Control N=30	<i>p</i> - value
IL-1 α (pg/ml)	1.84 ± 0.89	1.52 ± 0.54	0.06
IL-6 (pg/ml)	38.7 ± 19.3	34 ± 12.7	0.21
IL-8 (pg/ml)	376.4 ± 84.7	363.6 ± 74.2	0.46
TNF-α (pg/ml)	8.63 ± 4.6	12.4 ± 5.2	0.0003**

\*\* : Indicates statistically significant difference.

Table (3): Concentration of IL- α, IL-6, IL-8 and TNF-α in serum of cases before and after phototherapy.

	Before phototherapy	After phototherapy	<i>p</i> - value
IL-1 α (pg/ml)	1.84 ± 0.89	1.75 ± 0.63	0.43
IL-6 (pg/ml)	38.7 ± 19.3	34.6 ± 16.8	0.13
IL-8 (pg/ml)	376.4 ± 84.7	353.7 ± 94.6	0.09
TNF-α (pg/ml)	8.63 ± 4.6	17.6 ± 3.2	<0.0001 **

\*\* : Indicates statistically significant difference.

Table (4): Laboratory data of cases before phototherapy and control.

	Cases N=90	Control N=30	<i>p</i> - value
WBCs X 10 <sup>3</sup> /mm <sup>3</sup>	11345 ± 2123	11643 ± 1423	0.47
Hb (g/dl)	14.5 ± 2.1	15 ± 3.1	0.32
Hct (%)	44 ± 6	45 ± 7	0.45

Table (5): Laboratory data of cases before and after phototherapy.

	Before	After	<i>p</i> - value
Hb (g/dl)	14.5 ± 2.3	12 ± 3.1	<0.0001**
Hct (%)	44 ± 12	36 ± 7	<0.0001**
Total bilirubin	18 ± 2.5	14 ± 1.4	<0.0001**
WBCs X 10 <sup>3</sup> /mm <sup>3</sup>	11300 ± 1987	12500 ± 2281	0.0002**

### Discussion

Phototherapy has been effectively used as a relatively inexpensive and noninvasive method of treating neonatal hyperbilirubinemia. The decline in the number or exchange transfusions in recent years is, at least in part, likely a direct reflection of the effectiveness of phototherapy at treating hyperbilirubinemia [20].

The mechanism of action of phototherapy involves changing the original compound bilirubin into other isomer compounds that can be broken down and consequently excreted by the body via the urine and feces. Specific wavelengths of fluorescent light can change bilirubin into two other compounds, called photobilirubin and lumirubin. Which are isomers of bilirubin, this means that they are made of the same number of atoms, but their structures have been rearranged. When these specific wavelengths penetrate the skin, they convert the bilirubin into these isomers, which can be removed from the body without or with the involvement of the liver [17].

The liver also can excrete these isomers, and so the significant increase in the rate of biliary excretion of unconjugated, as well as the normally conjugated, forms of bilirubin and related bile pigments when either jaundiced rats or humans are irradiated with visible light of appropriate wavelength [18].

Phototherapy is generally considered a safe method for the treatment of hyperbilirubinemia, the reported side effects are controversial debate and include rash, loose green stools, dehydration, Increased susceptibility to childhood asthma and allergic conditions, water loss, oxidative injury and ocular hazards [5].

However, recently some investigations have expressed increasing concern about potential toxic side effects of phototherapy on the blood cells and the immune system, one possible harmful consequence is the affection of cytokines rate of production and the percentage of lymphocyte subtypes, which can eventually affect the function of the immune system of the newborn [19].

Different studies have shown that cytokine production may be changed after exposure to phototherapy [21].

Kurt et al., [21] studied the level of cytokines in 21 newborns before and after 72 h of phototherapy and concluded that TNF- $\alpha$ , IL-8, and IL-1b levels increased after phototherapy, while the serum IL-6 level did not significantly change, and the lymphocyte subset decreased.

In our study, IL-1, IL-6 and IL-8 were slightly decreased after PT, but these changes were not statistically significant. Moreover, our results agree with that of Sirota et al., [22] who stated that phototherapy affects the function of the immune system in newborns by alterations in cytokine production. Exposure to UV radiation results in higher TNF- $\alpha$  production and suppression of many cell-mediated immune responses.

Mrkaić et al., [23] observed that phototherapy may cause a disturbance in the behavior and higher incidence of infections in neonate. They examined the effects of phototherapy on the immune system of neonates without signs of infection, anoxia, or birth injury. Their results showed an increase in the total number of peripheral WBCs, polymorphonuclears, lymphocytes, and monocytes, as well as a delay in the chemo-luminescence response of the peripheral blood phagocytes. They concluded phototherapy may complicate the existing infection, though those findings were temporary.

Comparison between patients and controls regarding TNF- $\alpha$  level showed no statistically significant difference. These results suggest that neonatal hyperbilirubinemia does not influence the serum levels of TNF- $\alpha$ . These results are in agreement with that of Kurt et al., [21].

In our study, comparison of WBCs count in patients before and after phototherapy showed statistically significant difference, these results are in agreement with that of Kurt et al., [21], and with Jahanshahifard et al., [12] stated that phototherapy in term neonate can raise peripheral WBC count.

Hemoglobin levels and hematocrit values were statistically significantly lowered after phototherapy. These results may be explained by frequent blood sampling, besides the physiological decrement postnatally. Total serum bilirubin levels were highly statistically significantly lowered after phototherapy among patients ( $p \leq 0.001$ ). This means that UV phototherapy has lowered neonatal hyperbilirubinemia and these results are in agreement with that of Sirota et al., [22].

Serum TNF- $\alpha$  level in both patients before Phototherapy and the control group did not differ significantly. Serum TNF- $\alpha$  level significantly increased after 72h of exposure to phototherapy and this change was statistically significant  $p$ -value 0.0003 as shown in (Table 2), indicating the strong effect of phototherapy on TNF- $\alpha$  serum level. These results agree with that of Narbutt et al., [24] who stated that exposure of healthy term neonates to repeated doses of UV radiations shows a statistically significant increase in serum level of TNF- $\alpha$ .

In contrast, our results are not in agreement with that of Procianoy et al., [25] who studied the influence of phototherapy on serum cytokine concentrations in newborn infants; there were no statistically significant differences in TNF- $\alpha$  concentration before and after 24h of phototherapy.

In 2014, Beken et al., stated no significant difference between the blood cell count including leukocytes, lymphocytes, neutrophils, and platelets, before and after PT, but elevated eosinophil levels were noted. Therefore, they mentioned allergic diseases in later life according to higher levels of eosinophils in the neonatal period [26].

On the other hand, lipopolysaccharide-induced TNF- $\alpha$  production was higher in the newborns by phototherapy. The synthesis of IL-3 and IL-6 did not change significantly. Phototherapy affects the function of the immune system in newborns by alterations in cytokine production [22].

Despite the long-term use of phototherapy, the mechanisms of action on the blood and immune cells are quite unclear. Many of its effects are certainly mediated by induction of apoptotic cell death and another major mechanism is the induction of immunosuppression [13].

It is hypothesized that the effect of PT on immune regulation may partly be due to degrading bilirubin. Unconjugated bilirubin inhibits complement activation through the classical pathway [19]. And prevents leukocyte migration [28].

It is also hypothesized that it involves affection of the DNA and causing strand breaks eventually leading cellular injury with the subsequent activation of the immune system. Increasing the rate of production of white blood cells and various cytokines. DNA abnormalities will exert a more marked effect on the rapidly dividing cells as blood cells, gastrointestinal and skin cells. Recent researches have shown that when DNA-bilirubin complex in mammalian cells is irradiated by visible light of broad spectral output, the bilirubin moiety is photo-activated. This causes cleavage of bonds within the DNA. Permanent cellular damage has not yet been observed in the photo irradiated infant, but the potential for injury to cells must be considered [12].

#### *Conclusion:*

Our findings demonstrate that an increased levels of serum TNF $\alpha$  and WBCs count in healthy term neonates after PT but the levels of interleukins 1, 6 and 8 were non significantly decreased after PT. Therefore, it seems that PT can alter the function of the immune system.

#### *Conflict of interest:*

The authors of this study declare that they have no conflict of interests regarding this study.

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## تأثير المعالجة الضوئية في المواليد على مستويات المصل من الإنترلوكين ١ و٦ و٨ ومستوى المصل من عامل نخر الورم من النوع ألفا وعدد خلايا الدم البيضاء

التقدم الحديث في الأبحاث الطبية قد أثبت فعالية العلاج بالضوء كوسيلة قياسية للعلاج في حالات زيادة مستويات بيليروبين الدم الناتجة عن مرض الصفراء في المواليد حديثي الولادة. ولكن أعربت بعض الأبحاث الحديثة عن وجود بعض الآثار السمية المحتملة للعلاج بالضوء، أحد الآثار الضارة المحتملة هو الميل لإنتاج بعض الجزيئات ذات الوظائف المناعية والسيتوكينات، والتي يمكن أن تؤثر على وظيفة جهاز المناعة عند المواليد.

الهدف: يهدف هذا البحث إلى التحقق من تأثير العلاج بالضوء على مستويات المصل من الإنترلوكينات ١ و٦ و٨ وعامل نخر الورم من النوع ألفا بالإضافة إلى عدد خلايا الدم البيضاء الذين يعانون من زيادة مستويات بيليروبين الدم الناتج عن مرض الصفراء وفي المواليد الأصحاء.

طرق البحث: أجريت الدراسة الحالية في مستشفى جامعة الأزهر بمدينة دمياط خلال الفترة من يناير ٢٠١٧ إلى مارس ٢٠١٨، وقد شملت الدراسة ٩٠ وليدا حديثي الولادة مصابين باليرقان الدموي الوليدي، لديهم مستويات بيليروبين كاملة أعلى من ١٥ ملليجرام/ديسيلتر. وتم الحصول على عينات الدم الوريدي من المواليد قبل التعرض للعلاج بالضوء بالإضافة إلى الحصول على عينات دم وريدية أخرى بعد التعرض للعلاج بالضوء بفترة ٧٢ ساعة. كما تم إختيار ٣٠ من المواليد الأصحاء كمجموعة ضابطة وتم الحصول على عينات من الدم الوريدي لهم مع إجراء الفحص الطبي. وقد تم استخدام عينات الدم لقياس مستويات بيليروبين الدم، عدد خلايا الدم البيضاء، مستويات الإنترلوكينات ١ و٦ و٨ بالإضافة إلى مستوى المصل من مادة عامل نخر الورم من النوع ألفا.

النتائج: إنخفض مستوى مركب الإنترلوكينات ١ و٦ و٨ إنخفاضا طفيفا بعد العلاج الضوئي مع عدم وجود فروق ذات دلالة إحصائية وزاد مستوى المصل من مادة عامل نخر الورم من النوع ألفا بصورة كبيرة ذات دلالة إحصائية كما زاد عدد كرات الدم البيضاء بصورة ذات دلالة إحصائية.

الخلاصة: تؤكد نتائج الدراسة الحالية على وجود تأثير للعلاج الضوئي المستخدم في حالات اليرقان على الجهاز المناعي الخاص بالأطفال حديثي الولادة بدليل وجود زيادة ذات دلالة إحصائية في عدد كرات الدم البيضاء وفي مستوى المصل من مادة عامل نخر الورم من النوع ألفا.