

Effect of Phototherapy on Peripheral Blood Cells in Hyperbilirubinemic Newborns

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ABSTRACT

This study was conducted to determine the neutrophil/lymphocyte ratio, lymphocyte/monocyte ratio, platelet/lymphocyte ratio; and to evaluate the effect of phototherapy on the peripheral blood cells in newborns with indirect hyperbilirubinemia. A total of 180 newborns consisting of 119 hyperbilirubinemic newborns, who received phototherapy; and 61 healthy newborns were included in the study. A statistically significant difference was present only between the patient group and healthy newborn white blood cell values after phototherapy. The differences found for pre-phototherapy neutrophil/lymphocyte ratio and lymphocyte/monocyte ratio values were statistically significant, but no statistical significance was present for the values after phototherapy. These results suggest that phototherapy may have an effect on peripheral blood cells by directly decreasing both the cytokine and bilirubin levels. The decrease in neutrophil/lymphocyte ratio and lymphocyte/monocyte ratio after phototherapy could potentially be used in the evaluation of phototherapy's effect on peripheral blood cells. New studies on this subject are, therefore, required.

Key Words: *Newborn, Phototherapy, Inflammation, Peripheral blood cells.*

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Indirect hyperbilirubinemia (IHB) can be detected in at least two-thirds of newborns in the first week of life. There is evidence that phototherapy can directly affect the expression and function of cell surface receptors including adhesion molecules, cytokines, and growth factor receptors.¹⁻⁵ The ratios between various white blood cells (WBC) are now used to determine the prognosis of various disorders and as markers of possible inflammation. The aim of this study was to determine the neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), and platelet/lymphocyte ratio (PLR) in newborns who received phototherapy for IHB; and to investigate the effect of phototherapy on inflammation and peripheral blood cells.

The study was planned retrospectively and included patients admitted to the neonatal intensive care unit for phototherapy with a diagnosis of IHB from May 2016 to May 2018. The criteria for inclusion in the study and initiating phototherapy for patients were determined according to American Academy of Pediatrics.¹ Newborns >37 weeks and <15 days were included in the study. Premature infants, newborns with a congenital malformation/anomaly, congenital infection, hypoxia, respiratory distress, patients with severe neonatal hemolytic disease requiring transfusion or other systemic disease or who had suffered from sepsis, had undergone exchange transfusion or surgery, or whose file

information could not be accessed or had missing information, and the infants of mothers with preeclampsia or diabetes, or of mothers who were receiving steroid therapy or other medication, were excluded from the study. Phototherapy treatment was administered according to the guidelines published by the American Academy of Pediatrics.¹ Blue light phototherapy at a wavelength of 420-490 nm was administered from a distance of 30 cm to the newborns with hyperbilirubinemia. The treatment duration was at least 48 hours and patients who received phototherapy for less than 48 hours; were excluded from the study. Blood samples were taken within 12 hours before and after phototherapy. Approval was obtained from the Ethics Committee of the Hospital for the study.

The age, gender, gestational weight / week, bilirubin values of all subjects and the pre-phototherapy and post-phototherapy whole blood count parameters [hemoglobin (Hb), hematocrit (Htc), WBC, lymphocyte, monocyte, neutrophil, and platelet count] of the patient group were recorded from the charts. The NLR, LMR and PLR were calculated. The peripheral blood count results of the patient group were compared with those of the control group created from healthy newborns. The control group consisted of newborns who presented to the outpatient department, with a whole blood count result for any reason, but without any disease on the history, physical examinations or tests, and who were accepted as normal/healthy. Any side effects seen during phototherapy were recorded.

The data of the patient group were evaluated with the SPSS version 21 software programme. The measurement data were presented as mean \pm standard deviation or incorporate median (IQR) values. The compliance of the data with the normal distribution were evaluated with the Kolmogorov-Smirnov test.

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Table I: Results of patients and control group.

	Pre-phototherapy n=119 Mean \pm SD or Median \pm IQR	Post-phototherapy n=119 Mean \pm SD or Median \pm IQR	Control n=61 Mean \pm SD or Median \pm IQR	p-value (pre PT-control) (post PT-control)
Total bilirubin (mg/dl)	17.9 \pm 3.42	10.4 \pm 2.6	10.6 \pm 2.8	p* = .000 (prePT-control) p* = .705 (postPT-control)
Hemoglobin (g/dl)	16.8 \pm 2.4	15.2 \pm 2.7	15.1 \pm 2.0	p* = .000 (prePT-control) p* = .820 (postPT-control)
Hematocrit (%)	51.3 \pm 7.5	46.2 \pm 8.3	46.2 \pm 6.7	p* = .000 (prePT-control) p* = .888 (postPT-control)
WBC ($\times 10^9$ /L)	11.6 \pm 3.8	11.0 \pm 3.25	10.0 \pm 2.8	p* = .005 (prePT-control) p* = .048 (postPT-control)
Lymphocytes ($\times 10^9$ /L)	4.53 \pm 1.47	4.92 \pm 1.77	4.7 \pm 1.7	p* = .374 (prePT-control) p* = .535 (postPT-control)
Neutrophils ($\times 10^9$ /L) (median \pm IQR)	4.13 \pm 2.92	3.95 \pm 3.15	3.07 \pm 2.37	p** = .001 (prePT-control) p* = .051 (postPT-control)
Monocytes ($\times 10^9$ /L) (Median \pm IQR)	1.17 \pm 0.63	1.08 \pm 0.76	0.97 \pm 0.74	p** = .028 (prePT-control) p* = .103 (postPT-control)
Platelets ($\times 10^9$ /L) (median \pm IQR)	303.0 \pm 136.5	354.0 \pm 167.5	348.0 \pm 170	p** = .003 (prePT-control) p* = .999 (postPT-control)
NLR (Median \pm IQR)	0.83 \pm 1.19	0.75 \pm 0.63	0.64 \pm 0.68	p** = .002 (prePT-control) p* = .209 (postPT-control)
LMR (median \pm IQR)	3.71 \pm 2.5	4.38 \pm 3.25	4.27 \pm 3.33	p** = .007 (prePT-control) p* = .472 (postPT-control)
PLR (median \pm IQR)	72.97 \pm 35.96	78.57 \pm 33.69	82.22 \pm 36.94	p** = .051 (prePT-control) p* = .281 (postPT-control)

The non-parametric and parametric tests chosen according to the distribution of the data on statistical evaluations were the Wilcoxon and Paired t-tests for dependent variables, the Mann-Whitney U-test and Independent t-test for independent variables, and the chisquare test for the comparison of categorical data, and expressed by frequency along with percentage. P-values <0.05 were considered significant.

Pre-phototherapy and post-phototherapy whole blood count parameters of the patients and the statistical evaluation results are presented in Table I. No significant side-effect was observed during phototherapy.

In this study, while a statistically significant difference was present between the peripheral whole blood cell counts of the pre-phototherapy patient group and healthy newborns, no such statistical significance was found after phototherapy except for WBC. A study has reported that phototherapy did not affect cytokine levels, but did cause a significant increase in peripheral white blood cell count; and believed this effect could be related to the stress of newborns admitted to the hospital or to the onset of infection.³ Another study was found no direct effect of phototherapy on B and T lymphocytes in newborns, but the treatment decreased total serum bilirubin levels and increased the percentage of CD19 + lymphocytes after 72 hours of exposure with the patient groups reaching values close to the control group.⁴ Another study reported an increase in WBC, polymorphonuclear leucocytes, lymphocytes and monocytes after phototherapy,⁶ Another study has shown that phototherapy could influence the immune system by altering cytokine production.³ Some have reported an increase in peripheral blood cells and WBC with phototherapy^{2,6} while other studies reported a decrease in WBC.^{3,4} In this study, it was found a decrease in WBC, neutrophil and monocytes, and an increase in lymphocytes with phototherapy. Physiological

changes occur in the peripheral blood cells in newborns in the first few days of life. Phototherapy may have contributed to this physiological decrease. Newborns with IHB were included in this study, while those with other disorders were excluded. A statistically significant difference was present for almost all the pre-phototherapy patient group peripheral blood values when compared with the values of healthy newborns. The peripheral blood cell results after phototherapy were similar to the results of healthy newborns. Phototherapy may possibly show its effect on peripheral blood cell regulation by stimulating the cytokine response. However, considering the physiological changes in the peripheral blood count in the first few days of newborns, it can be difficult to determine the level of this phototherapy effect. Further studies are, therefore, required.

A study showed that IHB in rats has an inhibitory effect on B lymphocytes as a result of the stimulation of apoptosis and necrosis in mature immune cells.⁵ They also reported that high levels of IHB especially resulted in increased splenic atrophy, bone marrow suppression, leukopenia, lymphocytopenia and a mitogenic response of T and B cells when administered *in vivo* (>25 kg/kbw). Another finding was that IHB-induced oxidative stress and cell death in mice splenocytes *in vivo*. Their final finding was that IHB stimulates apoptosis and necrosis of immune cells by decreasing the glutathione level within it.⁵ Various studies have evaluated the effects of phototherapy on the antioxidant/oxidant balance and reported that phototherapy could stimulate oxidative stress and have negative effects on the antioxidant/oxidant system.⁵ Mild bilirubin elevation has also been reported to be related to a decrease in the risk factors associated with cardiovascular disorders, diabetes and cancer development.^{5,6} IHB has an inhibitory effect on the classical complement pathway and leukocyte migration.^{5,6} The effect of phototherapy on the immune system may partially be

related to bilirubin degradation.^{5,6} This may indicate an association between high total bilirubin levels and peripheral blood cells by affecting both cytokine and bilirubin levels. The decrease in bilirubin levels with phototherapy may also have an effect on the cellular level by shifting the oxidant-antioxidant balance towards oxidant damage. In this study, it is evident that after phototherapy, peripheral blood counts of the patients were similar to those of healthy newborns. This may suggest that the effect of phototherapy on peripheral blood counts is through cytokine-mediated and/or by effecting the oxidant-antioxidant level by lowering the total bilirubin level. It is also possible that higher levels of bilirubin have an effect on the peripheral blood count, thus further studies on this subject are required.

CONFLICT OF INTEREST:

Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

AK: Data acquisition and analysis, interpretation, drafting and final approval.

MST: Conception and design, Interpretation, critical revision and final approval.

NA: Design, critical revision and final approval

SE: Interpretation, critical revision and final approval.

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