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Peripheral Blood Count Changes in Neonates with Indirect Hyperbilirubinemia after Phototherapy

Reem Medhat Mourad [1], Nevien Maher Waked [1], Manar Aref El Desouky[1], Khaled Mohamed Abdelhamid El-Khashab [2], Ahmed Saad El-Gayed [1]

[1] Department of Pediatrics, Faculty of Medicine, October 6th University, Egypt

[2] Department of Pediatrics, Faculty of Medicine, Cairo University, Egypt

Correspondence to: Ahmed S. El-Gayed, Egypt. Tel: (020)1005098331; ORCID 0000-0003-1011-6165;

E-mail: ahmedgayed.med@o6u.edu.eg

ABSTRACT

Background: Phototherapy (PT) is the mainstay treatment for jaundiced neonates, regardless of the cause. Concerns about phototherapy effects on the blood and immune system have been raised with inconsistent results**.**

Objectives: The aim of the current work was to assess the effect of phototherapy on peripheral blood count in jaundiced neonates and determine the effectiveness of double phototherapy based on changes in hemoglobin concentration and platelet count in studied neonates. **Patients and methods:** This longitudinal cohort study was conducted on 60 neonates, 26 preterm (43.3%) and 34 full-term (56.7%) who had physiological jaundice treated with phototherapy. Neonates with hemolytic jaundice or direct hyperbilirubinemia, and parents refusing the assent were excluded.

Venous blood samples were obtained from newborns with jaundice before PT and 48 hours after exposure to PT in all studied neonates. Complete blood count (CBC), Total and indirect Bilirubin, CRP were measured before initiating Phototherapy, 48 hours after PT for all neonates, and CBC within 5-7 days of PT for neonates with a change in blood count. The blood count before starting PT was considered the control value for individual neonates.

Results: In studied neonates, the mean age at presentation was 3.27±1.7 days and the mean weight was (2.56±0.42) kg. For all neonates after 48 hours of PT, the mean hemoglobin concentration, RBCs, and platelet counts were significantly decreased ($p< 0.05$). In Full term neonates, RBCs count was significantly decreased ($p<0.01$). Among preterm neonates, RBCs and hemoglobin concentration were significantly decreased (p-value<0.01), with no significant decrease in platelet count after 48 hours of PT. Total bilirubin inversely correlated with double PT in all studied neonates ($p=0.02$). Double PT also displayed a negative correlation with hemoglobin concentration and platelet count ($p=0.02$). This indicates that the use of double PT was associated with a significant decrease in hemoglobin and platelet count in cohorts studied**.**

Conclusion: It could be concluded that in neonates, phototherapy causes a temporary decrease in hemoglobin concentration, RBCs, and platelet counts. Hemoglobin concentration and platelet count in newborns are important factors that would predict the ability of phototherapy to reduce bilirubin in newborns with hyperbilirubinemia.

Keywords: Phototherapy, newborns, hemoglobin, platelet count, bilirubin, jaundice

INTRODUCTION

Neonatal jaundice is a frequent disease that affects more than 50% of full-term and premature newborns [(1)]. The breakdown of red blood cells elevates serum bilirubin levels, resulting in jaundice. Bilirubin is mostly coupled to albumin and is transported as 'unconjugated' bilirubin in the blood. Unconjugated bilirubin at high levels can be neurotoxic, resulting in acute or permanent encephalopathy that may lead to developmental delay, hearing loss, and seizures [(2)]. Severe hyperbilirubinemia accounted for 33% of all NICU admissions in Egypt in 2016, with approximately 10 cases complicated by kernicterus each year [(3)].

Unconjugated hyperbilirubinemia can be treated with phototherapy, exchange transfusion, and IVIG. Regardless of the cause, phototherapy (PT) remains the standard treatment for newborns with jaundice [(4)].

In general, phototherapy is safe and may have no harmful effects on newborns. Skin lesions, thermal and electrolyte imbalances that might lead to insensible water loss or dehydration, disturbance in the maternal-infant bond, and circadian cycle problems are among the short-term effects[(5)].

In the past years, there has been increased concern about phototherapy's effects on the immune and inflammatory systems, as well as its potential genotoxic side effects, which have been linked to neoplasms, melanocytic nevi, and allergic diseases, indicating that phototherapy is not as harmless as previously assumed [(5)].

Several published studies link phototherapy to neonatal harm. The expression of adhesion molecules, cytokines, and lymphocyte surface markers has been used in certain studies to measure the immunological and inflammatory response [(6,7)]. Others have investigated DNA damage in newborns exposed to phototherapy [(8,9,10)].

In terms of the effects on blood cells, **Mrkaić *et al.*** [(11)] noted a brief increase in the total number of leukocytes, while **Zarkesh *et al.*** [(12)] and **Jahanshahifard *et al.*** [(13)] observed an increase in circulating leukocytes in newborns with jaundice upon phototherapy. Since phototherapy effects are difficult to assess in the presence of baseline disease, **Mrkaić *et al.*** [(11)] investigation into the

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effect of phototherapy on newborns without signs of infection or hypoxia may help explain why this is merely a temporary response.

This study aims to investigate the impact of phototherapy on peripheral blood counts and to assess the effectiveness of double-surface phototherapy based on blood count changes.

PATIENTS AND METHODS

This longitudinal cohort study included a total of 60 neonates (26 preterm; 43.3% and 34 full-term; 56.7%) newly diagnosed with neonatal jaundice, treated at Neonatal Care Unit, October 6th University Hospital, Faculty of Medicine, October 6th city This study was conducted between February 2022 to July 2022.

Inclusion criteria: all apparently healthy neonates of both genders with indirect hyperbilirubinemia, within the first three weeks of life with normal Reticulocyte count for age, and negative CRP before starting phototherapy.

Exclusion criteria: Neonates with pathological jaundice due to hemolytic jaundice or direct hyperbilirubinemia, neonatal sepsis, and parents refusing the assent were excluded.

All participants were subjected to careful history taking that included a history of maternal disease, pregnancy complications, mode of delivery, and family history (previous sibling (s) with jaundice, and/or required phototherapy).

Clinical examination of all jaundiced newborns included pallor, jaundice, skin rash, ecchymosis, or cephalhematoma.

Laboratory Investigations:

All studied neonates were subjected to baseline investigations including complete blood count (CBC), reticulocyte count, ABO, and Rh determination. Total and indirect bilirubin, CRP, and serum albumin were determined.

Routine chemistry tests were done in the Chemical Pathology Unit of October 6th university hospital. CBC was done on an automated Beckman Coulter Synchron CX9 PRO analyzer), total serum Bilirubin was measured by the Diazo method, and Direct Bilirubin by colorimetric assay.

Phototherapy was started when neonate serum bilirubin reached a level requiring PT, according to the American Academy of Pediatrics guidelines 2004 [(14)] **.**

Serum bilirubin and CBC were measured before initiating phototherapy, 48 hours after PT for all neonates, CBC was repeated within 5-7days of terminating phototherapy for neonates that showed a change in blood count. The blood count before starting PT was considered the control value for individual neonates.

Ethical Consideration:

This study was ethically approved by Local Medical Ethics Committee, October 6th University (PMC-Me -2112010 /FWA00017585) and approved on 28-12-2021. Written informed consent of all the participants' parents was obtained. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical Analysis

Data recorded were analyzed using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Quantitative data were expressed using mean, standard deviation, minimum and maximum, and categorical data as frequency and percentage. Student t-test was performed to compare parametric quantitative variables. One-way ANOVA was used for the comparison of three groups and post hoc pairwise comparison when a significant difference was found. Chi-square test was done for categorical data, and Correlations between quantitative variables were done using the Spearman correlation coefficient. A P-value smaller than 0.05 was considered statistically significant.

RESULTS

Descriptive and baseline laboratory data of all studied neonates are depicted in Table 1.

The current study was carried out on 60 neonates who had physiological jaundice treated with phototherapy.

Their mean age at presentation was 3.27±1.7 days and their body weight was 2.56±0.42) kg; the mean total bilirubin was 16.39 ±2.48 mg /dl on admission.

The mean hemoglobin, RBCs, and platelet count significantly decreased (p-value < 0.05) after 48 hours of phototherapy for all studied neonates, Table 2.

Of all neonates, 13.3% had mild thrombocytopenia, and 1.7% had moderate thrombocytopenia that occurred after 48 hours of phototherapy.

Concerning Full term neonates, RBCs significantly decreased ($p<0.01$), and Hemoglobin and platelet counts also decreased after 48 hours of phototherapy ($p>0.05$), as shown in Table 4. Mean RBCs and Hemoglobin was (17.13±1.56gm/dl) before PT and significantly decreased (15.39±2.0, p-value<0.01) among preterm neonates after 48 hours of PT. However, the platelet decrease was not significant (p=0.06).

Total bilirubin inversely correlated with double PT in all studied neonates (p=0.02). Double PT also displayed a negative correlation with hemoglobin and platelet counts (p=0.02). this indicates that the use of double PT was associated with a significant decrease in hemoglobin and platelet count in cohorts studied.

In the full-term cohort of neonates, hemoglobin negatively correlated with double PT (r= -0.09, *p*>0.05) and platelet count (r= -0.12, p=0.2). However Single PT directly correlated with hemoglobin (r=0.1, p=0.17) and platelet counts (r=0.11, p=0.15) in all neonates

Table 1: Demographic data of neonates studied on admission

Parameter	No (%)
Gender	
Male	33 (55%)
Female	27 (45%)
Mode of delivery	
CS	41 (68.3%)
NVD	19 (31.6%)
Gestation	
Full Term	26 (43.3%)
Preterm	34 (56.7%)
Mean age at presentation (Days)	
Full term	83.49± 14.6
Preterm	70.36± 14.1
Neonates	
On Single PT	15 (25%)
On Double PT	45 (75%)

Table (2): Laboratory data of all studied neonates before starting phototherapy.

CBC Parameters	**Before Phototherapy (PT)**	
	Mean	SD
RBCs (10^6/ µL)	4.80	±0.63
Hb (g/dl)	16.86	±1.80
WBCs (10^3 /mm^3)	10.99	±2.21
Platelets (10^3 /mm^3)	307.05	±8.12
Reticulocyte count (%)	1.33	±.11
Total Bilirubin (mg/dl)	16.39	±2.48
CRP (-ve)	60 (100 %)	

Table (3): CBC & bilirubin values before phototherapy (PT) and after 48 hours of phototherapy for all studied neonates:

Parameters	**Before Phototherapy**		**After 48 hours of Phototherapy**		**P-value**
	Mean	±SD	Mean	±SD	
RBCs (10^6/µL)	4.80	0.63	4.33	0.66	0.0001*
Hb (g/dl)	16.86	1.80	15.59	2.33	0.0001*
WBCs (10^3 /mm^3)	10.99	2.21	12.17	3.75	0.14
Platelet (10^3 /mm^3)	307.05	8.12	265.41	10.39	0.01*
Bilirubin (mg/dl)	16.39	2.48	10.46	1.90	0.0001*

*Significant at p-value<0.05

Table (4): CBC values before PT and after 48 hours of PT in full-term neonates

CBC Parameters	**Before PT**		**After 48 hours PT**		
	Mean	±SD	Mean	±SD	P-value
RBCs (10^6/µL)	4.81	0.64	4.35	0.67	0.005*
Hb (g/dl)	16.77	1.88	15.82	2.55	0.08
WBCs (10^3 /mm^3)	10.97	2.65	12.32	2.47	0.17
Platelet (10^3/mm^3)	328.85	8.83	292.44	9.64	0.09

*Significant at p-value<0.05, PT (phototherapy)

Table (5): CBC values before PT and after 48 hours of PT for preterm neonates

CBC	**Preterm (n= 26)**				
	Before PT		**After 48 hours PT**		
	Mean	±SD	Mean	±SD	*P value*
RBCs (10^6/µL)	4.83	0.60	4.37	0.60	0.008*
Hb (g/dl)	17.13	1.56	15.39	2.00	0.001*
WBCs (10^3 /mm^3)	11.09	2.96	11.96	2.26	0.54
Platelet (10^3/mm^3)	276.46	8.50	227.81	9.2	0.06

Significant at p-value<0.05, PT (phototherapy)

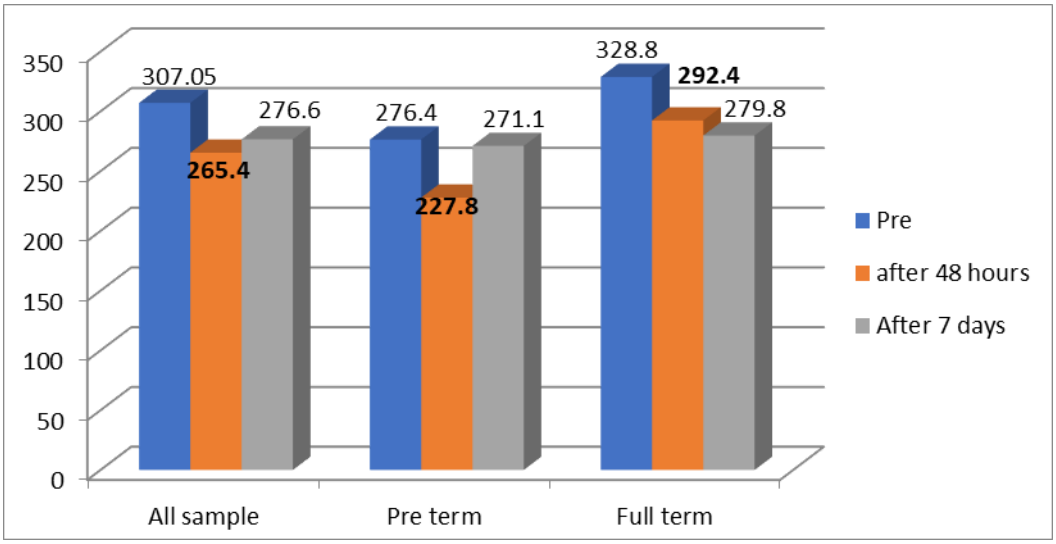

Figure (1): Mean platelet count values for all **neonates** studied after 48 hours of starting PT and 7 days of stopping PT

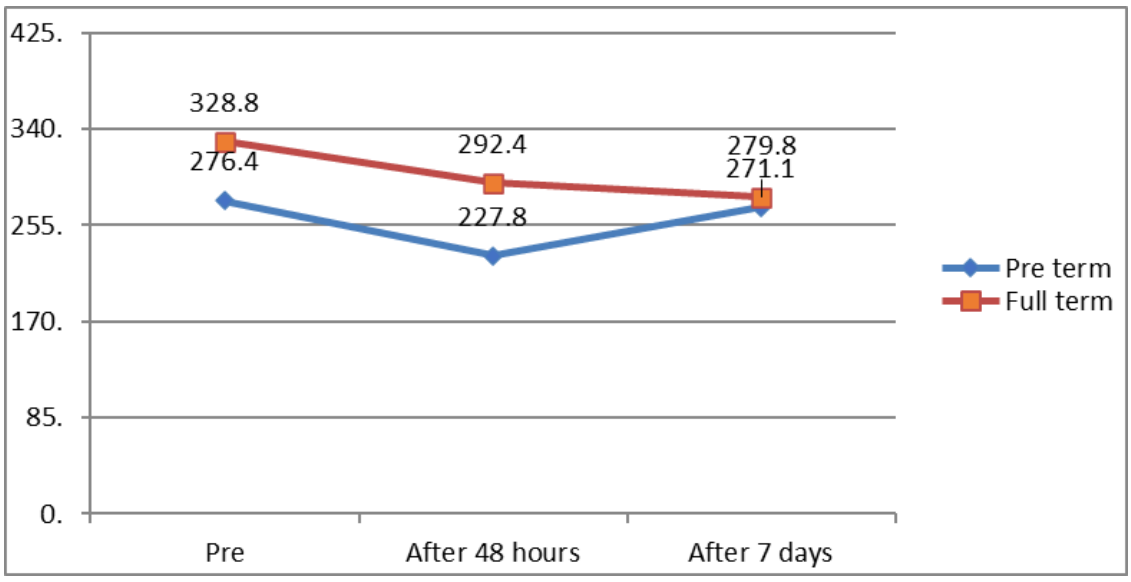

Figure (2): Mean platelet count values for preterm & full-term cohorts before PT, after 48 hours of starting PT and 7 days of stopping PT

Table (6): Effect of phototherapy Type (*Single PT Vs Double PT*) on CBC parameters after 48 hours for all studied neonates

CBC	Single PT		Double PT		P-value
	Mean	SD	Mean	SD	
RBCs (10^6/µL)	4.39	0.38	4.3	0.845	0.59
Hb (g/dl)	16.47	1.47	15.13	2.845	0.02*
WBCs (10^3 /mm^3)	10.62	2.52	12.81	2.08	0.07
Platelet (10^3/mm^3)	273.53	7.19	244.22	9.045	0.20

*Significant at p-value<0.05

Table (6) shows that double phototherapy (DP) significantly decreases hemoglobin values compared to single phototherapy (SP) respectively, p=0.02.

Table (7): Correlation between hemoglobin and bilirubin in all neonates and in full term cohort

Hemoglobin (g/dl)	**Bilirubin**(mg/dl)	
	R	**P-Value**
All neonates	0.19	0.01*
Full term	0.18	0.06

*Significant at p-value<0.05

Table (8): Regression analysis for the effect of double phototherapy on platelet count in all neonates

Independent variables	**Platelet count**			
	Coefficient	**Standard error**	**T**	**P**
Constant	287.506	7.268	39.559	.000*
Double phototherapy	-52.895	22.983	-2.301	.023*

*Significant at p-value<0.05

DISCUSSION

Phototherapy has been shown to be an effective noninvasive and limited-cost treatment option for neonatal hyperbilirubinemia. Although phototherapy has been utilized for a long time, the mechanism of its effects on blood cells is uncertain.

The effects of UV light on cells have been attributed to direct cellular damage, the induction of apoptotic cell death, and the development of immunosuppression, among other causes **[15].**

In our study, mean hemoglobin concentration and RBC count were significantly decreased (p< 0.05) after 48 hours of phototherapy for all studied neonates and cohorts of term neonates.

After exposure to phototherapy, WBCs and platelet counts may be changed. Peripheral WBC count showed a significant increase after phototherapy exposure **[16,17]**. This agreed with our study, which showed an increase in WBC count after PT (p=0.14), in term & preterm cohorts (P>0.05).

Mrkaić *et al.*[11] indicated that phototherapy may increase the behavior or likelihood of infections in newborns. They investigated how phototherapy affected the immune systems of newborns who had no signs of infection, anoxia, or birth injury. Their findings revealed an increase in peripheral WBCs as well as a postponement of the chemo-luminescence response of peripheral blood phagocytes. Even though the results were only temporary, they concluded that phototherapy could exacerbate the infection. However**, Kurt *et al* [17] and Eyada *et al* [18]** reported a decrease in WBC after PT.

In the current study, platelet count was significantly decreased (p-value < 0.05) after 48 hours of phototherapy for all studied neonates, while mild thrombocytopenia (platelet count 100-150×10^3/mm^3) occurred in 13.3% of all neonates and moderate

thrombocytopenia (count 50-<100×10^3) was detected in 1.7% of neonates.

Abd El Moktader et al. [19] reported that out of 120 neonates included in their study, nine neonates (7.5%) had thrombocytopenia after the first 24 hours of exposure to phototherapy. **Khera and Gupta** [20] noticed thrombocytopenia in 35% of patients after 48 hours of phototherapy in their research.

The platelet decline was ascribed by aforementioned authors to a photochemical reaction in the vascular bed and direct platelet damage caused by phototherapy's ultraviolet light, resulting in a reduction in platelet span and an increase in platelet turnover.

The standard textbooks do not list thrombocytopenia as a side effect of phototherapy, even though many authors have made attempts to investigate this effect [20.21]**.**

Sarkar *et al*. [22] found in their study that (31.1%) of newborns receiving phototherapy had moderate thrombocytopenia (100.000-150.000) shortly after phototherapy without any bleeding manifestation.

Platelets that were temporarily exposed to light following hematoporphyrin photosensitization lost their ability to aggregate and released potassium, acid phosphatase, serotonin, and adenosine triphosphate. Electron photomicrographs of these modified platelets displayed cytoplasmic material depletion and concealed membrane borders [21].

Concerning Full term neonates, WBCs & platelet counts also decreased after 48 hours of phototherapy (p>0.05), Table 4.

Term neonates may develop mild to severe asymptomatic thrombocytopenia after 48 hours of PT[23]**.** Platelet counts can be measured serially at 24-hour intervals after starting phototherapy to diagnose phototherapy-induced thrombocytopenia. Thrombocytopenia is diagnosed when the platelet count falls below 150000/mm3 following 24 hours of phototherapy [20].

On the other hand, **Monsef A and Eghbalian**[24] noticed a rise in platelet count under phototherapy in full-term newborns; they related this increase to enough bone marrow reserves and production in response to the accelerated platelets turnover in the peripheral microvasculature.

The mean Hemoglobin and RBC count significantly decreased (p-value<0.01) among the preterm cohort after 48 hours of PT. However, the platelet decrease was not significant (p=0.06).

If platelet bone marrow compensation is adequate, there will be no difference in platelet count before and after phototherapy [20]. It was observed that preterm neonates had a greater decline in platelet count [25]**.**

Our study revealed that total bilirubin negatively correlated with double phototherapy in all studied cohorts (p=0.02).

A recent Metanalysis by Nizam *et al* [26] concluded that a decline of TSB per hour and TSB levels at 24 hr. involving preterm infants weighing ≥ 1500gm overall significantly favored double phototherapy.

The most significant finding concerns preterm infants, who are more prone to kernicterus, and double phototherapy is effective in reducing TSB in infants of different gestational ages and birth weights.

In the current study, platelet counts showed a negative correlation with double PT (p=0.02) in all cohorts, which indicates that double PT use was associated with a significant decrease in platelet counts. This is in accordance with the findings of **Abdelhakeem *et al*** [16], who analyzed 40 newborns on single PT, 30 neonates on double PT, and 30 others on intense PT. They reported that after 72 hours of double PT, compared to single PT or intensive PT, neonates' platelet counts significantly decreased**.**

Hemoglobin negatively correlated with double PT (r=-0.06) in our study, which indicates that double PT was associated with a significant decrease in hemoglobin and an increase in hemoglobin count suggests less effective phototherapy.

The direct association between hemoglobin and bilirubin in all newborns (r=0.19, p=0.01) and the full-term cohort (r= 0.18,p=0.06), however, indicates that a decrease in hemoglobin levels was also accompanied by a decline in bilirubin levels.

Our finding that phototherapy and hemoglobin were negatively correlated may be explained by the intravascular effect of phototherapy on bilirubin isomerization [27]**.** The amount of light that reaches the bilirubin molecules will be reduced because the hemoglobin in erythrocytes absorbs some of the light; in other words, hemoglobin in erythrocytes will outcompete the bilirubin molecules, which will impact how well phototherapy works.

A substantial effect of hemoglobin concentration on the decrease in TSB was observed in a trial of 93 newborns, 33 weeks gestation age, treated with phototherapy by LED light for 24 hours for uncomplicated hyperbilirubinemia. They revealed that hemoglobin concentration has a significant impact on phototherapy efficacy. During 24 hours of phototherapy, TSB was reduced by 3.61 mmol/l for every 1.0 mmol/l increase in hemoglobin concentration [27]**.**

From a clinical viewpoint, our study results may benefit clinicians treating hyperbilirubinemia newborns with phototherapy. Newborns with high hemoglobin concentration are likely to need a longer duration of treatment, or a larger body-surface area exposed to phototherapy, compared with infants with a lower hemoglobin concentration, to achieve the same decrease in TSB. This could be important for the decision of when to draw the next blood sample.

STUDY LIMITATION

Our study has some limitations. Phototherapy irradiance was difficult to measure due to the lack of irradiance equipment at our unit. Another drawback is that a higher hemoglobin level may be linked to a higher bilirubin production rate. The observed positive correlation between high mean bilirubin and hemoglobin may be explained by a higher rate of bilirubin production at higher hemoglobin concentrations. The rise in TSB and postnatal age are inversely correlated during the first few days of life.

The cases studied were limited due to a shortage of neonates fulfilling inclusion criteria during the period of study

Author Contributions:

All authors shared in supervising, data analysis, writing the original draft, data interpretation, writing, and revising the original draft. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the study.

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