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ORIGINAL ARTICLE

A new approach to an old hypothesis; phototherapy does not affect ductal patency via PGE_2 and PGI_2

Ozge Surmeli-Onay[1], Murat Yurdakok[1], Tevfik Karagoz[2], Pinar Erkekoglu[3], Ilker Ertugrul[2], Sahin Takci[1], Belma Kocer Giray[3], Hayrettin Hakan Aykan[2], Ayse Korkmaz[1], and Sule Yigit[1]

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Abstract

Objective: Numerous investigations have demonstrated that phototherapy (PT) directly or indirectly causes ductal patency by photorelaxation effect. In this observational study, we aimed to assess the effect of PT on the incidence of patent ductus arteriosus (PDA) together with prostaglandins (PGE2) and (PGI2) levels in preterm infants.

Methods: Preterm infants whose gestational age < 34 weeks and who required PT in the first 3 d of life were enrolled in this prospective study. The clinical signs of PDA, the data of detailed echocardiographic study were recorded and plasma PGE_2 and PGI_2 levels were measured before and after PT. The outcome measures were the status of ductus arteriosus and alterations of PGE_2 and PGI_2 levels under the effect of PT.

Results: A total of 44 preterm infants were enrolled in the study, of these 21 (47.7%) were in Group 1 (Non-PDA Group) and 23 (52.3%) were in Group 2 (PDA Group). After PT, ductal reopening occurred in three infants (14.3%) in Group 1, while ductus closed in four infants in Group 2 (17.3%). PT does not seem to effect ductal patency for both groups ($p = 0.250$ and $p = 0.125$, respectively). PGE_2 levels were not different before and after PT for both groups ($p = 0.087$, $p = 0.408$, respectively). However, PGI_2 levels were significantly decreased after PT in both groups ($p = 0.006$, and $p = 0.003$, respectively).

Conclusion: There was no effect of PT on ductal patency. We can conclude that PGs were eliminated simultaneously with ductal closure and photorelaxation effect did not influence PG levels.

Keywords

Patent ductus arteriosus, preterm infant, phototherapy, prostaglandin

History

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Introduction

Phototherapy (PT) is widely used for the management of neonatal indirect hyperbiliribunemia. Although it is known as safe and effective treatment, short- and long-term side effects including interference with mother–infant bonding, imbalance of thermal environment and water loss, electrolyte disturbances, hypocalcemia, disorder of circadian rhythm, bronze baby syndrome, allergic diseases (asthma, allergic rhinitis, and conjunctivitis), melanocytic nevi, melanoma, skin cancer, retinal damage and patent ductus arteriosus (PDA) have been reported [1]. PT is commonly required in the first week of life when PDA may also be a clinical problem in preterm infants. In a preterm infant, a hemodynamically significant PDA, can lead to pulmonary overflow and systemic hypoperfusion which may result with cerebral hypoxia, acute renal failure and necrotizing enterocolitis [2].

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Photorelaxation of smooth muscle of the rabbit aorta was first described in 1961 [3]. Subsequently, Clyman and Rudolph [4] demonstrated that exposure of isolated lamb ductal rings to light resulted in photorelaxation and prevention of ductal closure despite stimulation with O_2. In the light of these *in vitro* studies, first in 1986, a positive relationship between PT and PDA was reported in preterm infants with respiratory distress syndrome (RDS). The authors reported that chest shielding resulted with significant reduction in the incidence of PDA [5]. Afterwards, Barefield et al. [6] showed similar results in extremely low birth weight infants. Infants who received PT had a significantly increased incidence of PDA compared to those not receiving PT (76% versus 53%). Another investigator reported ductal reopening during PT in preterm infants who had a closed ductus arteriosus before PT [7]. Although the exact mechanisms preventing ductal closure are uncertain, it was hypothesized that light could penetrate the thin chest wall of preterm infants and caused vasodilation. The light photon may give rise to photorelaxation on aortic smooth muscle directly or indirectly, through the activation of the nitric oxide–cyclic GMP pathway and Ca^{2+}-dependent K^+ ion channels [8,9].

After birth, the balance between vasoconstricting and vasodilating forces regulates ductus contractility. Prostaglandins (PGs) and nitric oxide which are locally produced in endothelial cells of the ductus contribute to ductal patency [10]. Among vasodilator prostaglandins (PGE2, PGI_2), particularly PGE_2, plays an important role in maintaining the patency of the ductus during fetal and neonatal life. PGE_2 is metabolized in the lungs and its concentration declines rapidly within 3 h after birth. The key point is, PG-related ductal dilation is developmentally regulated. It was shown that the immature ductus generates more PG and is also more sensitive to the vasodilator effects of PGs [11–13]. On the other hand, PGI_2 acts as a vasodilator and has antiaggregatory properties [14].

Numerous investigations have demonstrated that PT directly or indirectly causes ductal patency by photorelaxation effect [4–7]. Different from the previous studies, we hypothesized that PGs may play a role in photorelaxation mechanisms. Concerning this knowledge and background, this study was designed to investigate the effect of PT on ductal patency together with levels of vasodilator PGs in preterm infants. The questions were ''does PT cause ductal patency? And if it is true is the photorelaxation effect related with PGE_2 and PGI_2?''

Material and methods

This prospective study was conducted in the neonatal intensive care unit (NICU) of Hacettepe University Ihsan Dogramaci Children's Hospital, Ankara, Turkey between September 2011–May 2012. Institutional Ethics Committee approved the study (No: HEK 11/119) and informed consent form was obtained from each patient's family before inclusion in the study.

Study population

Preterm infants (gestational age < 34 weeks) who were admitted to NICU after birth and required PT in the first 3 d of life were enrolled in the study. Exclusion criterias were severe perinatal asphyxia (defined as a 5-min Apgar score < 4), congenital heart disease, primary persistent pulmonary hypertension, congenital or chromosomal abnormalities, inherited metabolic diseases, hydrops fetalis, maternal–fetal Rh incompatibility and drug administration (indomethacin, ibuprofen, steroid) in the first 3 d of life which could effect PG metabolism.

Study design

As part of routine clinical care, serum bilirubin concentrations were determined at least once a day according to signs of jaundice in preterm infants. Pathologic hyperbilirubinaemia was defined as any serum indirect bilirubin level requiring treatment with PT during the first week of life which was based on the 2004 American Academy of Pediatrics hyperbilirubinemia treatment guidelines [15]. After written informed consents were obtained from the parents, eligible preterm infants were prospectively enrolled in the study. A detailed echocardiographic study including two-dimensional imaging, color flow, pulsed- and continuous-wave Doppler examination were performed by a skilled pediatric cardiologist to monitor PDA. The infants who did not have PDA at the begining of the study were defined as Group 1, those who had PDA were defined as Group 2. The echocardiographic study was performed using a Siemens Acuson Cypress Echo Portable Ultrasound Machine, 7V transducer (Siemens Medical Solutions, Mountain View, Santa Clara, CA). Detailed information related with the ductus arteriosus were minimum size using color flow and imaging, direction of the shunt, left atrial/aortic root (LA/Ao) ratio, and left ventricular end-diastolic dimension. The hemodynamically significant PDA (hsPDA) was defined as ductal diameter over 1.5 mm and/or LA/Ao ratio >1.5 in the absence of atrial septal defect [16]. These assessments were obtained just before the initiation (T0) and just after the discontinuation (T1) of PT. Also, clinical signs of PDA including respiratory distress consisting of tachypnea, retractions and cyanosis, increased requirement of respiratory support, continuous or systolic murmur, hyperactive precordium, bounding pulses, hypotension, hypercapnia ($pCO_2 > 60$ mmHg in arterial blood gas analysis), respiratory acidosis (pH$<$7.20 and $pCO_2 > 60$ mmHg in arterial blood gas analysis) were observed by the same neonatologist at the time of T0 and T1. Blood samples (1 ml) to analyze plasma PGE_2 and PGI_2 levels were collected at the time of T0 and T1 either by venepuncture from a peripheral vein or from aortic/caval blood via an umbilical catheter. The blood was drawn into tubes containing EDTA. Plasma was separated immediately by centrifugation in room temperature and stored frozen ($-20\,^{\circ}C$) until assayed for PGE_2 and PGI_2 with ELISA. After these assessments were completed, infants were placed in incubators unclothed except for a diaper and with eyes covered. PT was applied with a new LEDs device (neoBLUE® LED Phototherapy System, Natus Medical Inc., San Carlos, CA) with a wavelength of 450 to 470 nm, placed 30 cm above the infant. PT was discontinued when serum indirect bilirubin level decreased under the PT level on the indicated curve. Brief periods of discontinuation of PT for feeding or diaper care of the infants were not excluded while calculating the total duration of PT.

Clinical data included prenatal steroid therapy, gender, gestational age, birth weight, mode of delivery, 5-min Apgar score, neonatal morbidities such as RDS, surfactant therapy, congenital pneumonia, neonatal sepsis (culture-proven), necrotising enterocolitis (NEC), intraventricular hemorrhage (IVH), the day of study enrollment, duration of PT, durations of nasal continuous positive airway pressure (nCPAP), mechanical ventilation (MV), supplemental oxygen and hospitalization and rate of mortality were recorded. Respiratory support was administered according to the severity of respiratory distress via nCPAP or MV. The increased requirement of respiratory support was defined as if the patient needed nCPAP while there had been no need of respiratory support, or MV while the infant was on nCPAP. All infants received total/partial parenteral nutrition beside enteral feeding according to NICU protocol. Daily fluid intake was also noted. Hypotension was treated with dopamine and dobutamine in case of the failure of fluid treatment. The patients were given ampicillin and gentamicin, empirically.

Diagnostic criterias of clinical data were as follows: (1) RDS: the presence of clinical signs of respiratory distress, supplemental oxygen and/or positive pressure ventilation (PPV) requirement, typical chest X-ray findings with reticulogranular patterns, air bronchograms and ground glass appearance in the *absence of* all signs of suspected/proven infection [17]. (2) Congenital pneumonia: the presence of clinical signs of respiratory distress, supplemental oxygen and/or PPV requirement, extra-pulmonary clinical signs of sepsis beginning from birth; typical chest X-ray findings in the *presence of* any suspected/proven infection. (3) Proven sepsis: clinical symptoms and signs of sepsis and a positive blood bacterial culture. (4) NEC: Clinical and radiological findings of NEC was defined according to modified Bell's criteria [18]. (5) IVH: defined by cranial ultrasound according to Volpe's grading systems [19]. (6) BPD: was defined as a persistent oxygen requirement at 36 weeks postmenstrual age.

Primary clinical outcomes were the incidence of PDA before and after PT and the alterations in the levels of PGE_2 and PGI_2 under the effect of PT.

Chemicals and reagents

PGE_2 ELISA kit was obtained from Cayman Chemicals (Ann Arbor, MI). Prostacyclin (PGI_2) enzyme-linked immunosorbent assay (ELISA) kit was from Cusabio Biotech Co. (Wuhan, China).

PGE_2 and PGI_2 determination

PGE_2 analysis

In the assay, to determine PGE_2 levels, the measurement of PGE_2 metabolites was performed because of the rapid metabolism of PGE_2. This assay converts all the major metabolites of PGE_2 into a single derivative, which is easy to measure by ELISA technique. The procedure was applied according to manufacturer's instructions. Briefly, 50 µl of sample or standard and 50 µl of PGE_2 monoclonal antibody were added to each well. Besides, blank, total activity, non-specific binding, and maximum binding (B_0) wells were also prepared. Plate was incubated for 60 min at room temperature. Wells were emptied and washed. Later, 200 µl Ellman's reagent was added to each well and plate was kept in dark for 90 min. The color development was measured spectrophotometrically at a wavelength of 420 nm. % Bound/Maximum bound (% B/B_0) ratio which indicates the ratio of the absorbance of a particular sample or standard well to that of the B_0 well, was calculated. Later, a standard curve was prepared that plotted the % B/B_0 values versus concentration of a series of wells containing various amounts of the analyte. Results were calculated by a computer program which was capable of generating a four parameter logistic (4-PL) curve-fit. Recovery studies were performed on two samples and average recovery was calculated as 81% ± 4.57. The minimum detectable dose of human PGE_2 was 36 pg/ml.

PGI_2 analysis

Plasma PGI_2 levels before and after PT were determined by using an ELISA kit according to manufacturer's instructions. The microtiter plate provided in this kit has been pre-coated with a goat-anti-rabbit antibody. Briefly, standards or samples were added to the appropriate microtiter plate wells (50 µl). Later, horseradish peroxidase (HRP)-conjugate and antibody preparation specific for PGI2 (50 µl) were added into wells and plate was incubated for 1 h at 37 °C. Then, wells were washed and substrate solutions A and B (for 1 h at 37 °C) were added to each well and plate was incubated for 15 min at 37 °C. The enzyme–substrate reaction was terminated by the addition of a sulphuric acid solution (stop solution) and the color change was measured spectrophotometrically at a wavelength of 450 nm. The concentration of PGI_2 in the samples was then determined by comparing the optical density (O.D.) of the samples to the standard curve. Results were calculated by a computer program which was capable of generating a four parameter logistic (4-PL) curve-fit. Recovery studies were performed on two samples and average recovery was calculated as 110.53% ± 9.24. The minimum detectable dose of human PGI_2 was <2 ng/ml.

Statistical analysis

Statistical data were analyzed by using SPSS 16.0 software on a personal computer. All data were initially controlled for normality of distribution according to the Kolmogorov–Smirnov test. The data were presented as mean ± standard deviation (SD) of the mean, frequency, and percentage for categorical variables, median, interquartile range, minimum–maximum for continuous variables. Continuous variables were compared by using Wilcoxon test for dependent data. Categorical variables were analyzed by McNemar test. Mann–Whitney *U* test was used for comparison of two independent samples. A p value of <0.05 was accepted as statistically significant.

Results

A total of 134 infants who were between 27 and 34 weeks gestation were admitted to our NICU during study period. Finally, the study was completed with a total of 44 preterm infants, of these 21 (47.7%) were in Group 1 (Non-PDA Group) and 23 (52.3%) were in Group 2 (PDA Group) (Figure 1). The demographic and clinical characteristics of the two study groups were given in Table 1. In Group 1, the mean gestational age, birth weight and 5-min Apgar score were significantly lower while the incidence of RDS, surfactant therapy, pneumonia and intraventricular hemorrhage were higher than Group 2 as expected. The comparison of clinical signs, echocardiographic data and PG levels of two groups before and after PT were given in Table 2. The day of initiation, duration of PT and fluid intake during PT were similar in both groups ($p = 0.218$, 0.719, 0.088, respectively). After PT, ductal reopening occurred in 3 (14.3%) infants in Group 1, while ductus closed in 4 (17.3%) infants in Group 2. Therefore PT does not seem to effect ductal patency in both Group 1 and 2 ($p = 0.250$ and $p = 0.125$, respectively). PGE_2 levels were not statistically significant before and after PT in both groups ($p = 0.087$, $p = 0.408$, respectively). However, PGI_2 levels were significantly decreased after PT in both groups ($p = 0.006$ and $p = 0.003$, respectively) (Figure 2). Between Group 1 and 2 PGE_2 and PGI_2 levels before PT were similar ($p = 0.257$ and $p = 0.059$, respectively) (Table 2).

Figure 1. Flow chart of the study.

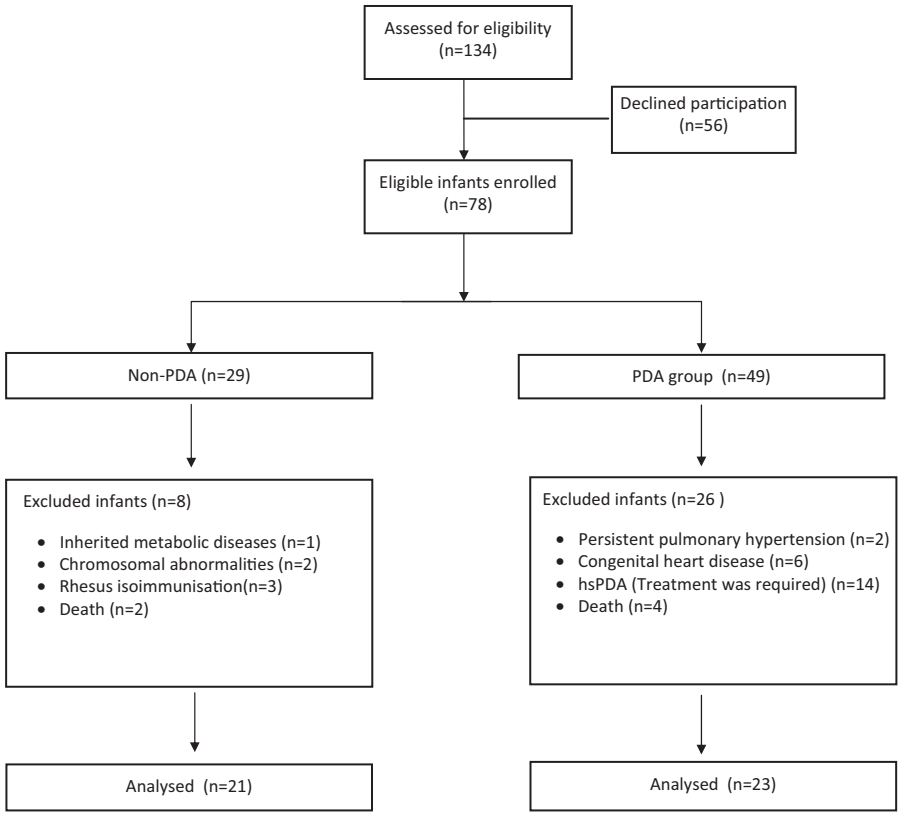

Table 1. Demographic and clinical characteristics of preterm infants with and without PDA in the first week of life.

	Group 1 (Non-PDA) ($n=21$)	Group 2 (PDA) ($n=23$)	p
Gestational age (wk), mean ± SD (min−max)	31.4 ± 1.7 (−)	29.5 ± 1.7 (−)	**0.001**
Birth weight (g), mean ± SD (min−max)	1486 ± 294 (−)	1272 ± 342 (−)	**0.034**
Gender (M/F), *n* (%)	7 (33.3)/14 (66.7)	19 (82.6)/3 (17.4)	**0.001**
Prenatal steroids, *n* (%)	15 (71.4)	12 (54.5)	0.250
Cesarean section, *n* (%)	19 (90.4)	20 (90.9)	0.961
Apgar score (5-min.), mean ± SD (min−max)	7.9 ± 1.0 (6–10)	6.8 ± 1.0 (6–9)	**0.001**
Respiratory distress syndrome, *n* (%)	5 (23.8)	15 (68.2)	**0.009**
Surfactant therapy, *n* (%)	5 (23.8)	15 (68.2)	**0.009**
Pneumonia, *n* (%)	1(4.8)	9 (40.9)	**0.009**
Necrotizing enterocolitis, *n* (%)	4 (19)	4 (18.2)	1.000
Early neonatal sepsis	3 (14.3)	7 (31.8)	0.281
Intraventricular hemorrhage, *n* (%)	–	5 (22.7)	**0.048**
Mortality, *n* (%)	–	1 (4.3)	1.000

The bold values represent statistical significance.

Discussion

This is the first study investigating the vasodilator effect of PT on ductal patency combined with serum PGE_2 and PGI_2 levels in preterm infants. Our study revealed that PT does not alter the course and incidence of ductal patency. In Group 1 (infants without PDA), ductal opening was detected in three among 21 infants (14.3%) and none of them was hsPDA. On the contrary, ductus of four infants in Group 2 (infants with PDA) closed and the ductus diameter of the other infants decreased after PT. Benders et al. [7] reported the echocardiographic data of 27 preterm infants (<32 weeks of gestation) before, during and after PT. Ductal reopening was detected in 14 (52%) infants, but none of them had hsPDA. This was a very high ratio when compared with ours. Moreover, our results differed from the report of Rosenfeld et al. [5] which has shown a reduction in the incidence of ductal patency with chest shielding. The authors have speculated that if shielding reduces the occurence of PDA, then PT may have a role in ductal patency. However in this study, the evaluation of ductal patency was based on presence of murmur. Echocardiographic evaluation was performed only in those with a murmur consistent with PDA. So, the real incidence of PDA was not definite in this randomized, non-blinded study. Another study on chest shielding in extremely preterm infants revealed that chest shielding did not have any effect on the incidence or severity of PDA, ductal diameter and LA/Ao ratio. The limitation of this prospective study was the usage of indomethacin which has lead to interference while evaluating the data. Despite some limitations the data of ''no shield'' group in this study was similar with Group 2 in our study. Similarly, no statistical difference was detected

Table 2. Comparison of the clinical and echocardiographic findings and PG levels of preterm infants with and without PDA before and after PT.

	Group 1 (Non PDA) $n=21$			Group 2 (PDA) $n=23$		
	Before PT	After PT	*p*	Before PT	After PT	*p*
Respiratory distress, (*n*, %)	1 (4.8)	5 (23.8)	0.125	9 (39.1)	10 (43.5)	1.000
Increase in respiratory support, *n* (%)	1 (4.8)	5 (23.8)	0.125	3 (13.0)	6 (26.1)	0.453
Hypotension, *n* (%)	–	–	–	–	3 (13.0)	0.250
Hyperactive precordium, *n* (%)	–	–	–	4 (17.4)	5 (21.7)	1.000
Bounding pulses, *n* (%)	–	1 (4.8)	1.000	4 (17.4)	7 (30.4)	0.250
Murmur, *n* (%)	–	2 (9.5)	0.500	6 (26.1)	8 (34.8)	0.687
Hypercapnia, *n* (%)	1 (4.8)	1 (4.8)	1.000	4 (17.4)	5 (21.7)	1.000
Respiratory acidosis, *n* (%)	1 (4.8)	–	1.000	4 (17.4)	4 (17.4)	1.000
Ductal patency, *n* (%)	–	3 (14.3)	0.250	23 (100.0)	19 (82.6)	0.125
Ductus diameter (mm)*	–	1.8 ± 1.0 (1.2–3.0)	–	1.5 (0.6–2.4)	1.00 (0.5–2.7)	0.141
Left atrium/aortic root ratio†	1.35 (0.65–1.66)	1.36 (0.65–1.78)	0.256	1.48 (1.2–2.0)	1.42 (1.2–1.8)	0.456
Left ventricle end-diastolic diameter†	13.00 (10–16)	13.0 (10–16)	**0.012**	13.0 (9.9–17.0)	13.4 (9.9–18.0)	0.148
PGE_2 level, (pg/ml) median (min−max)†	69.8[a] (53.7–713.1)	133.5 (60.9–1076.5)	0.087	104.4[b] (38.5–551.2)	69.2 (21.4–457.4)	0.408
PGI_2 level, (ng/ml) median (min−max)†	436.3[c] (247.9–755.8)	349.2 (183.6–586.9)	**0.006**	559.4[d] (272.3–1027.1)	462.5 (254.5–796.5)	**0.003**

The bold values represent statistical significance.
PG, prostaglandin; PDA, patent ductus arteriosus; PT, phototherapy.
*Mean ± SD (min−max), †Median (min−max), a and b: $p=0.257$, c and d: $p=0.059$.

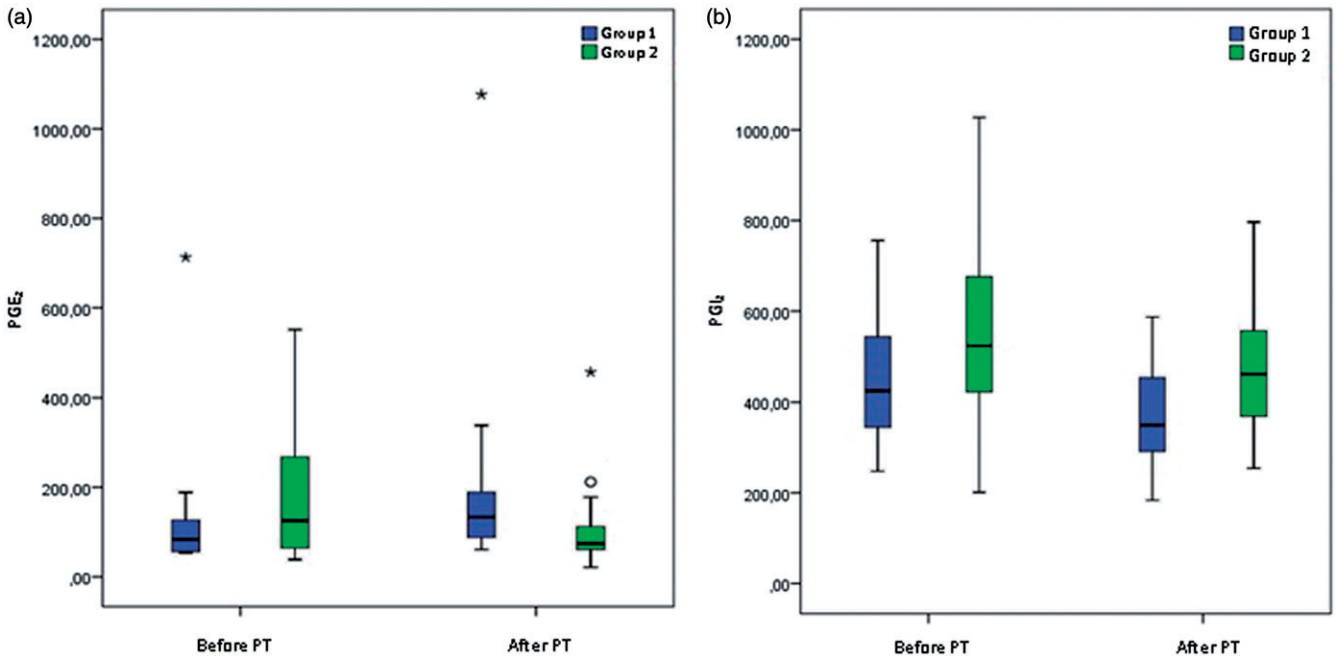

Figure 2. (a) The alterations in levels of PGE_2 before and after PT. (b) The alterations in levels of PGI_2 before and after PT. *Represents abnormal high results.

in ductal patency, ductal diameter, LA/Ao ratio before and after PT. In addition, the clinical trial of National Institute of Child Health did not support the hypothesis of Rosenfeld et al. [5]. This study revealed an incidence of 6.7% in 672 infants of PT group while it was 7.0% among 667 infants of the control group [20].

The frequency of clinical findings including respiratory distress, increased need for respiratory support, presence of murmur, hyperactive precordium, bounding pulses, hypotension, hypercapnia, and respiratory acidosis were not different before and after PT in both groups (Table 2). These results were compatible with echocardiographic results. However, our study revealed that left ventricle end-diastolic diameter was significantly increased after PT in Group 1, while there was no difference in Group 2. This result may be related to three infants whose ductus opened in Group 1. Three infants in Group 2 developed hypotension after PT. This finding may be related with the steal phenomen of PDA as all of them were hsPDA and with the vasodilation effect of PT.

PGs, especially PGE_2 is known as a potent vasodilator which plays a major role in maintaining the patency of the ductus arteriosus during fetal and neonatal life [11–13]. Various reports claimed that the ductus arteriosus of the preterm infant is more sensitive to these vasodilator effects [12,13]. Since blood vessels have been shown to be capable of PG synthesis, the superficial vessels underlying the skin surface which exposed to PT might affect the synthesis and plasma levels of PG [21,22]. According to our hypothesis, if PT keeps ductus open by photorelaxation effect, PG levels will be increased in parallel with the patency of ductus after PT. However, PT did not effect ductal patency and did not have any enhancing effect on PGE_2 and PGI_2 levels.

In addition, no statistically significant difference was detected between PGE_2 levels before and after PT. Although there is no statistical difference, PGE_2 levels increased after PT in Group 1. This increase may be a result of ductal reopening in three infants. The median of PGE_2 increased in parallel with ductal reopening (Table 2). On the other hand, the median of PGE_2 in Group 2 decreased compatible with the ductus diameter which showed a tendency to close. In 1979, a methodologically similar study which investigated immunoreactive prostaglandin A (iPGA) values of 14 preterm infants before and after PT was reported. However, echocardiographic evaluation was lacking in this study. PGA is a potent vasodilator which represents an extraction by product of PGE. The authors reported that plasma iPGA values significantly decreased after 48 h of PT. It was speculated that PT might have increased the catabolism of PGs. Despite a significant decrease in PGA levels, the authors could not conclude an effect of PT on ductal patency through PG levels [23]. An animal study demonstrated that PGE_2 affects ductus arteriosus tone by EP4 modulating Kv channels in different oxygen tension of preterm and term. However, PGE_2 or its analogue PGE_1 was found less effective to PDA of preterm infants [24].

Published data on plasma concentrations of PGs in preterm infants are limited. Clyman et al. [25] reported rather lower mean values of arterial PGE_2 levels (12.4–18.9 pg/ml in the presence and absence of PDA) in 29 preterm infants when compared with our results. In a study, plasma PGE_2 levels ranged from <50 to 354 pg/ml in 16 preterm infants with PDA [26]. Another study ($n=27$) demonstrated a lack of correlation of plasma PGE_2 and gestational age, birth weight, RDS or PDA [27]. A research on the effect of chorioamnionitis on plasma PGE_2 revealed that levels of PGE_2, although much higher than adult values, essentially remain unchanged during the first week. Infants with a PDA during the first week of life had elevated PGE_2 levels on day 3, 486 (78) versus 280 (34) ($p=0.02$), compared with those who did not [28]. These results are similar with us possibly due to the methodological similarity as the usage of ELISA. However, another study which investigated the change of PGE_2 in urinary samples in preterm infants, reported the results under the effect of ibuprofen treatment. The results revealed that urinary PGE_2 decreased significantly both in ibuprofen-treated infants (66.95 ± 16.78 versus 27.15 ± 17.92 pg/ml, $p<0.001$) and in not treated infants (71.7 ± 16.2 versus 53.2 ± 18.4 pg/ml, $p<0.001$) [29]. As predicted, ibuprofen treatment resulted in a significant reduction in urinary PGE_2 but we can not compare these results with ours due to the sample difference and treatment effect. None of the infants in our study was treated with ibuprofen for PDA.

In our study, the levels of PGI_2 significantly decreased correlating with the tendency of ductal closing. There is limited data on PGI_2 levels of preterm infants in literature. One of them showed that in preterm infants, 6-keto-$PGF_{1\alpha}$ levels (a metabolite of PGI_2 in peripheral blood) were lower than those of term infants on the first 4 d of life ($p<0.05$) and later no difference was detected [30]. Adversely, a study which examined the 6-keto-$PGF_{1\alpha}$ levels in relation to echocardiographic measurements revealed that 6-keto-$PGF_{1\alpha}$ levels were markedly raised in preterm infants compared with older children and adults. Afterwards, a rapid reduction in these high values was detected by 24 h of age. The highest concentrations were shown in infants who were mechanically ventilated, with lung parenchymal pathology such as RDS or pneumonia [31]. Our results directly represent PGI_2, so the levels could not be compared with these studies. PGI_2 seems to be correlated with ductal patency in Group 2, as PDA of four infants closed and diameter of the others diminished. However, although ductal reopening developed in three infants in Group 1, PGI_2 levels decreased significantly ($p=0.006$). So, it may be speculated that PGE_2 was more dominant in ductal reopening. Shortage of our study is the limited number of enrolled infants.

In conclusion, we did not reach any data supporting our hypothesis as PT was not a determining factor for ductal patency. In addition, no difference was detected between PGE_2 levels before and after PT. PGI_2 levels were significantly decreased after PT for both groups. We can conclude that PGs were eliminated simultaneously with ductal closure and photorelaxation effect did not influence PG levels.

Declaration of interest

All of the authors declared that they have no conflict of interests.

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