Does Perfusion Index in Term Neonate with Late-Onset Pneumonia Predict Disease Severity and Prognosis?

Geç Başlangıçlı Pnömonili Yenidoğanlarda Perfüzyon İndeksi Hastalığın Şiddeti ve Prognozu Öngörebilir mi?

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ABSTRACT

Objective: Pneumonia is an important disease that causes sepsis in newborns and constitutes the majority of deaths due to infections, especially in developing countries. Pulse oximeters that are widely used in clinics, can determine heart rate, arterial oxygen saturation, additionally perfusion index (PI). In this study, the role of PI in determining the severity and prognosis of the disease in newborns with late-onset pneumonia (LOP); the relationship between PI and respiratory support need and Silverman Anderson Retraction Score (SAS) were aimed to determine.

Material and Methods: In this prospective study, 30 term newborns diagnosed with late-onset pneumonia (LOP) were at the time of hospitalization,at the 24th hours of their treatment, and discharge; in the control group, PI measurements were made from the right upper extremity every 10 seconds for 3 minutes at the discharge of 30 term healthy newborns between December 2017 and June 2018. By comparing the data, it was aimed to determine the relationship of PI with the severity of the disease, prognosis, need for respiratory support and Silverman Anderson Retraction Score (SAS).

Results: Their mean birth weights was 2000 - 4600 g the mean was 3570 g in the study, 2800 - 4100 g the mean was 3610 g in the control group and there was no significant difference (p>0.05); Gestational ages were $36^{5/7}$ – $41^{3/7}$, mean $39^{2/7}$ in the study group, $37^{3/7}$ – $40^{5/7}$ in the control group, mean $39^{6/7}$ weeks, and the statistical difference between the groups was not significant (p>0.05). The ratio of female/male was similar in the groups. Their median age was 9.5 days (3-27) in the control, 21 days (5-28) in the study group, and higher in the study group (p<0.05). The median capillary refill time was 1.7 seconds in the control, 1.6 seconds in the study group, and similar between the groups. The mean PI was 2.3±0.9 in the control group. In the study group, it was 3.6±1.2 on hospitalization, 3.2±1.2 on the first day, 3.4±0.7 at discharge. In the study group, PI values on hospitalization and first day were higher (p<0.05).

There were reticular infiltration 50% bilateral, 30% right paracardiac, 10% left paracardiac, 3.3% right lower lobe. Alpha hemolytic streptococci in 1 (3.3%), *Acinetobacter iwoffii* in 1 (3.3%), Respiratory syncytial virus 6 (20%), Coronavirus 4 (13.3%), Rhinovirus 2 (6.7%) and Influenza A 1 (3.3%) patient were determined. We applied free flow oxygen 17 (56.7%), oxygen by hood 5 (16.7%), heated humidified high-flow nasal cannula 1 (3.3%), nasal continuous airway pressure 4 (13.3%), nasal intermittent positive pressure ventilation 4 (13.3%) cases. PI was higher in the patients needing positive pressure on admission (p<0.05). A positive correlation was found between SAS and PI on admission in the study group (p=0.008). The number of patients whose PI decreased during hospitalization increased over time.

Conclusion: In the neonates with LOP, the severity of the disease, the need for respiratory support and prognosis cannot be predicted by PI. There was no relation between SAS and PI.

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It was concluded that more accurate results can be achieved by measuring PI using more patients, more sensitive probes and technically more advanced monitors. New studies should be conducted to determine the role of PI in demonstrating well-being and early detection of life-threatening conditions in the healthy newborns.

Key Words: Late-onset pneumonia, Newborn, Perfusion index

ÖZ

Amaç: Pnömoni yenidoğanlarda sepsise neden olan önemli bir hastalık olup özellikle gelişmekte olan ülkelerde enfeksiyonlara bağlı ölümlerin çoğunluğunu oluşturmaktadır. Kliniklerde yaygın kullanılan nabız oksimetreler kalp atım hızı, arteriyal oksijen doygunluğu yanında perfüzyon indeksini (PI) de belirleyebilmektedir. Bu çalışmada geç başlangıçlı pnömoni (GBP) gelişen yenidoğanlarda PI'nin hastalığın şiddeti ve prognozunu belirlemedeki rolü;PI ile solunum destek ihtiyacı ve Silverman Anderson Retraksiyon Skorlaması(SAS) arasındaki ilişkinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu prospektif çalışmada Aralık 2017 - Haziran 2018 arasında geç başlangıçlı pnömoni (GBP) tanılı 30 term yenidoğanın yatışında, tedavininin 24.saati ve taburculuğunda; kontrol grubunda ise 30 term sağlıklı yenidoğanın taburculuğunda 3 dakika boyunca 10 saniyede bir sağ üst ekstremiteden PI ölçümleri yapılmıştır.Veriler karşılaştırılarak PI'nin hastalığın şiddeti, prognozu, solunum destek ihtiyacı ve Silverman Anderson Retraksiyon Skorlaması (SAS) ile ilişkisinin belirlenmesi amaçlanmıştır.

Bulgular: Olguların doğum ağırlığı ortalama çalışma grubunda 3570 g (2000-4600), kontrol grubunda 3610 g (2800–4100)olup aralarında fark yoktu (p>0.05). Gebelik yaşları ortalama çalışma grubunda $39^{2/7}$ ($36^{5/7}$–$41^{3/7}$), kontrol grubunda $39^{6/7}$ ($37^{3/7}$-405/7) hafta olup aralarındaki fark anlamlı değildi (p>0.05). Gruplarda kız/erkek oranı benzerdi. Yaş ortancası kontrol grubunda 9.5 (3-27), hasta grubunda 21 gün (5-28) olup hasta grubunda daha yüksekti (p<0.05). Ortanca kapiller dolum zamanı kontrol grubunda 1,7; hasta grubunda 1.6 saniye olup aralarında fark yoktu (p>0.05). Ortalama PI kontrol grubunda 2.3±0.9; çalışma grubunda yatışta 3.6±1.2, birinci gün 3.2±1.2, taburculukta 3.4±0.7'di. Çalışma grubunun yatış ve birinci gün PI değerleri, kontrol grubundan yüksekti (p<0.05).

Hastalarda %50 bilateral, %30 sağ parakardiyak, %10 sol parakardiyak, %3.3 sağ alt lobda retiküler infiltrasyon vardı. Kan kültürlerinde alfa-hemolitik streptokok 1 (%3.3), *Acinetobacter iwoffii* 1 (%3.3); solunum yolu sekresyonlarında Solunum Sinsityel Virus 6 (%20), Coronavirüs 4 (%13.3), Rhinovirüs 2 (%6.7) ve İnfluenza A 1 (%3.3) olguda gösterildi.

Serbest akış oksijen 17 (%56.7), hoodla oksijen 5 (%16.7), ısıtılmış nemlendirilmiş yüksek akışlı nasal kanül 1 (%3.3), nasal sürekli hava yolu basıncı 4 (%13.3), nasal aralıklı pozitif basınçlı ventilasyon 4 (%13.3) olguya uygulandı. Yatışta basınç ihtiyacı olanlarda PI daha yüksekti (p<0.05). Çalışma grubunda yatıştaki SAS ile PI arasında pozitif korelasyon saptandı (p=0.008). Yatış süresince PI düşen hasta sayısının arttığı saptandı.

Sonuç: Yenidoğanlarda GBP'lerde hastalığın şiddeti, solunum destek ihtiyacı ve prognozun PI ile öngörülemediği; SAS ile PI arasında ilişki olmadığı gösterildi. Güvenilir veriler için daha çok olgu, hassas prob ve monitörlerle çalışma yapılması gerektiği sonucuna varıldı. Ayrıca, sağlıklı yenidoğanlarda PI'nin iyilik halini gösterme ve hayati tehlikeyi erken saptamadaki rolünün belirlenebilmesi için yeni çalışmalar yapılmalıdır.

Anahtar Sözcükler: Geç başlangıçlı pnömoni, Yenidoğan, Perfüzyon indeksi

INTRODUCTION

Pneumonia is an important disease that causes sepsis in newborns and accounts for more than 96% of deaths due to neonatal infections in developing countries (1,2). According to the data of the Turkish Statistical Institute, pneumonia constitutes 11% of the reasons for admission to the hospital in children aged 0-6(3). Neonatal pneumonia is classified as early (first 72 hours) or late-onset (GBP, after 3 days).

Non-invasive techniques are widely used for diagnosis and treatment of diseases. These techniques accelerate the determination of invasive intervention requirements in patients and the decision of intervention. Pulse oximeters (PO) are devices that are widely used in the healthcare field and can determine the perfusion index (PI) in addition to heart rate (HR) and arterial oxygen saturation (SpO2). Pulse oximeters basically work on the principle of measuring the amount of absorption of infrared and infrared rays sent from the device to the tissues. PI, a non-invasive indicator, is calculated by the ratio of the non-pulsatile signal (static blood flow, skin and other tissues) to the pulsatile signal (arterial blood flow) and indicates peripheral perfusion (4). Since the non-pulsatile blood flow is constant in the tissues and in the venous bed, changing the amount of pulsatile blood flow in the peripheral tissues changes the PI. That is, PI is more related to the amount of arterial blood flow, not SpO2 in the blood (5). Normal values were found to be 0.02 - 20. Low PI values p<1.24) in newborns have been reported as a good indicator for determining the severity of the disease (5,6).

In this study, it was aimed to determine the severity of the disease and the need for respiratory support by using PI in term newborns diagnosed with GBP. In addition, it was aimed to evaluate the validity in determining the prognosis by comparing the PI with the Silverman Anderson Retraction Score (SAS).

MATERIALS and METHODS

This study was carried out by T.C. The study was conducted prospectively with 30 patients and 30 control groups after obtaining the approval of the local ethics committee of Health Sciences University Ankara Pediatrics Hematology Oncology

Training and Research Hospital dated 19/03/2018 and numbered 2017/131. Term newborns diagnosed with LOP and hospitalized in the neonatal intensive care unit (NICU) in our hospital between December/2017 and June/2018 were determined as the study group; The same number of term, healthy, non-respiratory problems newborns followed up with the mother were included as the control group. Age (days), gender, physical examination findings, capillary refill time, complete blood count parameters, C-reactive protein (CRP), blood gas parameters, SpO2, SAS at the time of hospitalization of the patients were recorded. In addition, the oxygen needs, respiratory support needs and total hospitalization times of these patients were determined. Non-invasive PI measurement is the ratio of pulsatile arterial flow in the peripheral area of infrared signals to non-pulsatile tissue components (venous blood, connective tissue, skin, bone, etc.) and provides important information in terms of hemodynamics, as it reflects instantaneous changes (7). In the study group, PI values were determined 3 times at admission, on the first day and at discharge.Values at discharge were recorded for the PI value of the control group. Nellcor Pulse Oximeter probe and Biolight Q5 (Made in Germany) patient monitor were used for peripheral PI measurement. To determine the PI value of the patients, a measurement was taken from the right hand every 10 seconds for 3 minutes. The value found by taking the average of the 18 measurements obtained was recorded as the PI value.The relationship between age, gender, complete blood count parameters, CRP, blood gas parameters, SpO2, SAS of the patients and during of hospitalization, oxygen demand, respiratory support needs and total hospitalization times and PI were evaluated.

Data analysis in our study was done with SPSS Computer Package Program version 22. Kolmogorov-Smirnov test in the evaluation of the distribution width of the data, mean and standard deviation in the representation of the data conforming to the parametric distribution; median, minimum and maximum values were used for those who did not comply. Categorical variables were shown as number of cases and percentile. Student t and Anova tests in the analysis of parametric data with categorical variables; Mann Whitney U Test from analysis of non-parametric data; Pearson Chi-square test in the analysis of categorical variables with each other; Pearson correlation test was used to compare quantitative data with each other. The variation of the data over time was analyzed by Paired samples test and Wilcoxon test. Significance level was accepted as $p<0.05$.

RESULTS

In our study, the mean birth weight was 3570 g (2000–4600) in the study group and 3611 g (2800–4100) in the control group, and there was no difference between them ($p>0.050$). The mean gestational age was $39^{2/7}$ weeks ($36^{5/7}$–$41^{3/7}$) in the study group, and $39^{6/7}$ weeks ($37^{3/7}$–$40^{5/7}$) in the control group, and there was no difference between the groups ($p>0.050$).

Table I: Pathological history and physical examination findings of the patients.

Pathological feature	n (%)
History	
Respiratory infection in family	8 (26.7)
Cough / Wheesing	25 (83.3)
Runny nose/ nasal congestion	6 (20)
Fever	2 (6.7)
Reduction in suction	2 (6.7)
Groaning	1 (3.3)
Hoarseness	1 (3.3)
Respiratory system examination findings	
Tachypnea	28 (93.3)
Ral / ronchus	25 (83.3)
Forced expiration	1 (3.3)
Use of accessory respiratory muscles,withdrawal	6 (20)
SpO2* (%)	82-94
Respiratory rate* (/per minute)	48-74

Minimum-maximum **Sp02: Arterial Oxygen Saturation*

Table II: Perfusion indices with Silverman Anderson Scores.

Parameter	PI at the time of hospitalization		PI on the first day		PI at discharge
	r	p	r	p	r
SAS	0.475*	0.008	0.243	0.196	0.144

The female/male ratio of the cases was 0.5 (10/20) in the control group and 0.7 (12/18) in the patient group, and there was no difference between the groups in terms of gender ($p>0.050$).

The median length of stay of the patient group was 9 days. The median age of the cases was 9.5 days (3-27) in the control group and 21 days (5-28) in the study group, which was higher in the study group ($p<0.050$). The pathological history and physical examination findings of the subjects in the study group are shown in Table I.

The median capillary refill time was 1.7 seconds in the control group and 1.6 seconds in the patient group, and there was no difference between the groups ($p>0.050$). The mean PI in the control group was 2.3±0.9; In the patient group, it was 3.6±1.2 during hospitalization, 3.2±1.2 on the first day, and 3.4±0.7 at discharge. Hospitalization and first day PI values of the study group were higher than the control group ($p<0.050$). PI changes of the cases during their hospitalization were not significant ($p>0.050$). However, it was found that the number of patients with PI increased over time.

The mean SAS values of the subjects in the study group at the time of hospitalization were 0.6 (0-2) A positive correlation was found between SAS and PI during hospitalization in this group ($p=0.008$) (Table II).

Complete blood count and CRP results of the study and control groups are given in Table III.

Table III. Complete blood count and CRP results of the study and control groups.

Laboratory findings	Patient group	Control group	p
Hemoglobin	14.0±2.8	16.0±2.9	0.008
Hematocrit	41.0±8.3	48.4±8.6	0.002
White blood cell count	9400 (5300-28500)	11050 (3700-26400)	0.185
Neutrophil count	3380 (700-8500)	3300 (1500-18400)	0.717
Lymphocyte sayısı	4400 (2200-11200)	3800 (2400-8700)	0.131
CRP	0.43 (0.05-15.5)	0.15 (0.02-1.12)	<0.001
I/T index	0.31 (0.12-0.9)	0.14 (0.04-0.60)	<0.001

I/T: *İmmmature/total neutrophil ratio,* ***CRP:*** *C-reactive protein.*

Table IV: Comparison of pressure and oxygen need with perfusion index.

Perfusion index	Pressure and oxygen need		p
	Yok (n: 22)	Var (n: 8)	
At the time of hospitalization	3.35±1.14	4.34±1.25	0.049
On the first day	3.10±1.20	3.29±1.36	0.729
At discharge	2.62±0.67	2.98±1.26	0.313

Data are expressed as mean±standard deviation, analysis by Student's t-test.

Hemoglobin and hematocrit levels of the study group were lower than the control group, and CRP and I/T ratios were higher (p<0.050); white blood cell, neutrophil and lymphocyte counts were similar (p>0.050).

Median pO2 level was 46 mmHg, mean pCO2 level was 39.6±6 mmHg, lactate level was 2.1 mmol/L, SpO2 was 78.3±11.5% in the study group. The median pO2 level was 58 mmHg, lactate level was 1.65 mmol/L, mean pCO2 level was 30.6±5.1 mmHg, SpO2 was 86.4±11% in the control group. The pO2 and SpO2 levels of the study group were low, pCO2 levels were high (p<0.050), and the lactate levels of both groups were similar (p>0.050).

In the chest radiographs of the patients in the study group, 50% bilateral reticular, 30% right paracardiac, 10% left paracardiac, and 3.3% right lower lobe reticular infiltration were detected; 6.7% were evaluated as normal. In blood cultures, alpha hemolytic streptococcus was isolated in 1 (3.3%) and *Acinetobacter iwoffii* in 1 (3.3%) patient. Respiratory Syncytial Virus (RSV) 6 (20%), Coronavirus 4 (13.3%), Rhinovirus 2 (6.7%) and Influenza A 1 (3.3%) cases by polymerase chain reaction (PCR) in respiratory tract secretions shown.

In the study group, free flow oxygen 17 (56.7%), in-hood oxygen 5 (16.7%), heated humidified high-flow nasal cannula (HHHFNC) 1 (3.3%), nasal continuous airway pressure (nCPAP) 4 (13.3%), nasal gap positive pressure ventilation (nIPPV) was applied to 4 (13.3%) cases.The maximum duration of oxygen administration to the patients in the study group was 11 days. In-hood oxygen was applied for 5 days, nIPPV for 6 days, and mechanical ventilation for a maximum of 0.25 days. Antibiotherapy was given to 18 (60%), antiviral treatment (oseltamivir) was given to 2 (6.7%) cases, and the mean duration of these treatments was 5-10 days. Eight (26.7%) of the subjects in the study group required positive pressure and oxygen support. The PI was higher in the patients who were given pressure and oxygen support (p<0.050).A positive correlation was found between the duration of support and the PI on the first day of treatment in patients who were given oxygen support with Hood (p<0.050) (Table IV).

There was no significant relationship between PI at hospitalization, first day and discharge of the study group and age, Hb, Hct, white blood cell,neutrophil,lymphocyte counts, CRP, pO2, pCO2, lactate levels, capillary refill time, hospitalization stay, free flow oxygen,nCPAP,nIPPV support times (p>0.050). There was a positive correlation between PI and pCO2 levels in the study group on hospitalization and on the first day (p<0.050).Again, a positive correlation was found between SAS and PI at the time of hospitalization (p<0.050). There was a positive correlation between the duration of support and PI on the first day in the patients applied in-hood oxygen(p<0.050).A positive correlation was found between SAS and PI at the hospitalizations of the subjects in the study group (p<0.050).

DISCUSSION

The studies related to PI in newborns are increasing in the literature. Granelli et al. reported that PI values did not change with age in their study on infants aged between 1 hour and 5 days (5). In this study, no significant relationship was found between PI and age and gender, in line with the literature.Unal et al. (8) reported that PI was similar to the control group in newborns with transient tachypnea and delayed labor. Lima et al. (4) stated that PI may be low in critically ill patients and highly variable in the normal population. In this study, PI

of term newborns with LOP was found to be higher on the first day of hospitalization and treatment. It was thought that this might be related to the follow-up of the cases in the emergency department or given supplemental oxygen before hospitalization. Thus, oxygen support might have increased oxygen transport to the tissues.

In this study, hemoglobin and hematocrit levels were low in newborns with LOP; CRP and I/T ratios were found to be higher, which was thought to be due to infection. Besides, no correlation was found between hemoglobin, hematocrit,CRP values, white blood cell-neutrophil and lymphocyte counts and PI in newborns diagnosed with LOP. A negative correlation was found between PI and I/T ratio at the time of hospitalization of the patients. Since perfusion is a measure of the blood flow to the region rather than the formed elements in the blood, it can be thought that there is no relationship between the parameters in the complete blood count and PI. Nutrition, intravenous therapy, jaundice, sleep-wake state, sleeping position, agitation, tremor, hypothermia, hypotension, arrhythmia, high carboxyhemoglobin and methemoglobin levels, nail paint (nail polish, henna, methylene blue, etc.), excessive light exposure (sun, heater and phototherapy lights), low perfusion, and improper placement of the probe have been reported to cause false peripheral PI readings (9-11). It is also reported that PI gives information about peripheral vasomotor tone. PI is different between the extremities and the highest value is obtained in the right upper extremity.Wide differences between extremity readings are thought to be most likely related to transitional circulation changes (12).

The arterial blood oxygen level in the primarily monitored area is affected by the amount of arterial blood flow rather than SpO2 (5). Since the non-pulsatile blood flow is the same in tissues, an increase or decrease in pulsatile arterial blood flow causes changes in peripheral perfusion. Serial measurements of serum lactate can be used to detect hypoperfusion and evaluate response to therapy, and above ≥4 mmol/L is considered critical for tissue oxygenation. Ramsey et al. (13) they reported that lactate level was significantly higher and PI was low in cases with severe sepsis. Kroesse et al. (14) did not find a relationship between lactate and PI in their study in newborns. In this study, lactate levels of the cases were not different in the control and study groups. This may be related to early admission of the cases, no patients with severe infection that impaired tissue oxygenation, or implementation of oxygen and circulatory supportive therapies during transport, in the emergency service and other centers before infant's hospitalization.

In this study, newborns with LOP had lower pH, pO2 and SpO2; but pCO2 level was found to be higher. However, there was no significant relationship between PI and pO2, pCO2, lactate levels. Pneumonia in newborns, increasing pCO2 by disrupting gas exchange and ventilation-perfusion in alveoli; it causes a decrease in pH, pO2 and SpO2. By developing tachypnea, the patient tries to compensate this situation by using accessory respiratory muscles and to keep the pH normal.If oxygenation is provided with these mechanisms and treatment, peripheral circulation may improve and PI may return to normal. In addition, it can be thought that supplemental oxygen applied to the patient may increase SpO2, PI and saturation.

Granelli et al.(5) evaluated PI with a single measurement and suggested that serial measurements may be more valuable for monitoring changes in peripheral perfusion. Cresi et al. (15) reported that while there was a significant difference between the first and the 3rd days in the median PI values, they did not detect a significant difference between the 3rd and 7th days. De Felice et al. (16) did not report any difference between the PI values measured immediately and in the first minutes and the first-fifth minutes after birth (16). This suggested that the waveforms in the preductal arteries remained stable despite the hemodynamic changes that occurred during transit the infants' PI remained stable. Unal et all reported that PI valueS decreased significantly during crying and increased activity in infants with transient tachypnea of the newborn (8). In our study, PI did not change significantly in term newborns with LOP, but the number of patients with decreased PI increased over time.While trying to reduce supportive treatments (oxygen, iv fluid, etc.) over time, PI may have decreased. The fact that the infants were sluggish at the time of admission due to respiratory distress, their activities increased after clinical improvement and their crying more may also have caused a decrease in PI.

Lima et al. (17) thought that PI could be used in the evaluation of hypoperfusion in critically ill patients, and reported that a PI value less than 1.4 showed a strong correlation with capillary filling time. However, these results are for adult patients and the authors found no association between changes in cardiac output and peripheral PI or poor peripheral perfusion. These findings were associated with possible heterogeneity in the regulation of skin blood flow during changes in blood flow, and were thought to be related to sympathetic nerve activity (18). In this study, there was no difference between the groups in terms of capillary refill time.In addition, no correlation was found between PI and capillary filling in the study group. The results were not considered reliable because of the low number of patients with severe pneumonia, in shock and in need of intubation.

Although the need for oxygen support was high (56.7%) in newborns who developed LOP in our study, no relationship was found between oxygen requirement, hospital stay and PI. Again, it was shown that administration of HHHFNC, nCPAP and nIPPV had no effect on PI. This may be related to no cases with severe pneumonia and the small number of patients undergoing invasive mechanical ventilation. A positive correlation was found between the PI and SAS scores of the patients during their hospitalization. It was thought that this might be related to the administration of additional oxygen and other supportive treatments to the patients in the emergency room, other centers or during transport.

The fist limitation of the study is the small number of cases. Another limitation is the low sensitivity of the monitors used in the study. It is thought that more reliable data can be obtained by using FDA approved monitors with a lower margin of error and filtering feature against artifacts.

In conclusion, although PI is known as a quotable, inexpensive, effective and non-invasive method that can be used to demonstrate the hemodynamic status and well-being of the newborn.Nevertheless, PI has not been found to be reliable in determining the severity and prognosis of the disease in term newborns with LOP. In order to use PI in the diagnosis and treatment of pneumonia in newborns, it was thought that studies involving patients with more and severe infections should be conducted.

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