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Original Article

Procalcitonin as a marker of respiratory disorder in neonates

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Abstract ***Background***: Serum procalcitonin (PCT) increases in various respiratory disorders such as acute respiratory distress syndrome. Elevated PCT is also observed in healthy neonates. In this study, we investigated whether PCT is a good marker of respiratory disorder in neonates.

Methods: A total of 155 neonates with or without respiratory disorder, were eligible for the study. PCT was measured on electrochemiluminescence immunoassay. Each neonate was allocated to the non-respiratory disorder (control) group ($n = 95$), or a respiratory disorder group ($n = 60$). PCT was compared between the groups, and association with other markers, including C-reactive protein (CRP) and white blood cell (WBC) count, was analyzed.

Results: Of the 60 neonates in the respiratory disorder group, 39, 10, five, one, two, two, and one neonates had transient tachypnea of the newborn, respiratory distress syndrome, air leak syndrome, meconium aspiration syndrome, 18-trisomy, neonatal asphyxia, and congenital diaphragmatic hernia, respectively. Mean PCT, CRP and WBC count in the respiratory disorder group were 9.01 ng/mL, 0.26 mg/dL, and 16 100 cells/μL, respectively. The area under the curve obtained for PCT in distinguishing between the respiratory disorder and control groups was 0.85 (sensitivity, 66.7%; specificity, 93.0%; optimum cut-off, 3.73 ng/mL), that for CRP was 0.72 (sensitivity, 75.0%; specificity, 64.6%; optimum cut-off, 0.14 mg/dL), and for WBC it was 0.44 (sensitivity, 60.0%; specificity, 29.6%; optimum cut-off, 15 000 cells/μL).

Conclusions: PCT is more susceptible, as a diagnostic parameter of infection, to the effect of respiratory disturbance than CRP and WBC.

Key words C-reactive protein, neonate, procalcitonin electrochemiluminescence immunoassay, white blood cell count.

Procalcitonin (PCT) is a 116-aminoacid peptide and a precursor of calcitonin, which is normally secreted by the C-cells of the thyroid gland in response to hypercalcemia. Although serum PCT is negligible under normal conditions, PCT is secreted into the blood during infection without an increase in calcitonin level.[1] PCT increases rapidly within 3–4 h in response to bacterial endotoxins, peaks at approximately 18–24 h, and remains high for at least 24–48 h. The half-life of PCT is approximately 24 h in the peripheral blood.[2–4] Serum PCT increases significantly during systemic bacterial and fungal infections but not during viral infection.[5,6] In contrast to findings in infants and children, elevated PCT has been observed even in uninfected and healthy neonates within the first 4 days of life.[2–7] Most studies that have investigated the kinetics of PCT during the first few days of life (predominantly in term neonates) failed to identify high PCT at birth in septic neonates.[4,5,7]

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In this study, serum PCT level was analyzed and compared with that of other markers, including C-reactive protein (CRP) level and white blood cell (WBC) count, in neonates with and without respiratory disorders to confirm whether PCT could be a useful marker for the diagnosis of respiratory disorder in neonates.

Methods

Subjects

A total of 155 neonates who were treated in the neonatal intensive care unit (NICU) of Ehime University Hospital between April 2009 and February 2012 were deemed eligible for the study. Each neonate met the following criteria: negative for congenital malformation or toxoplasmosis, other (syphilis and HIV), rubella, cytomegalovirus, and herpes simplex virus (TORCH) infection, negative for bacterial infection with various cultures, no history of antibiotic treatment, and no maternal infection or acute circulatory failure. Any neonate who met the newborn systemic inflammatory response syndrome (SIRS) criteria was also excluded.[8] Respiratory disorder was diagnosed if the following features were present: apnea for at least 10 s, tachypnea defined as respiratory rate >70/min in preterm and >60/min in term neonates, nasal flaring, retractions, cyanosis, or respiratory distress.

Before the study, written informed consent was obtained from the parents of the neonates, in accordance with the Declaration of Helsinki.

Methods

Blood samples were obtained from the vein or heel of each neonate within the first 12 h of life and on the first, second, and third days of life. PCT was measured on electrochemiluminescence immunoassay (Brahms PCT; Roche Diagnostics Japan, Tokyo, Japan). CRP and WBC count were also measured using the same blood samples. The neonates were divided into two different groups as follows: the respiratory disorder group consisted of all neonates with respiratory disorder (group A), whereas the non-respiratory disorder group (controls) consisted of those without any respiratory disorder (group B). PCT, CRP, and WBC count on each day of life were compared using receiver operating characteristic (ROC) curves. The neonates with respiratory disorders were divided into two subgroups, namely a term neonate group (group A1) and a preterm neonate group (group A2). Maximum PCT was compared between these two groups from birth to day 3 of life. Maximum PCT in group A was also compared from birth to day 3 of life according to treatment (oxygen, mechanical ventilation, and directional positive airway pressure).

Statistical analysis

Statistical analysis was carried out using SPSS Statistics for Windows version 20 (IBM, Armonk, NY, USA). For univariate analysis of non-normally distributed variables, median (50th percentile) and interquartile range (25th–75th percentile) were used. For continuous variables, Student's *t*-test was used to compare two groups. All results are expressed as mean ± SD. Fisher's exact probability test was used to analyze categorical data. Mann–Whitney *U*-test was used to compare two independent samples for serum PCT, CRP, and WBC count. Univariate analysis of the predictive accuracy of continuous predictors (PCT, CRP, and WBC) was performed using ROC curves. Differences with (two-sided) $P < 0.05$ were considered statistically significant.

Results

A total of 155 neonates were eligible for the study, of whom 60 were classified into group A and 95 were classified into group B. The underlying disease in group A was transient tachypnea of the newborn (TTN; $n = 39$), respiratory distress syndrome (RDS; $n = 10$), air leak syndrome ($n = 5$), meconium aspiration syndrome (MAS; $n = 1$), 18-trisomy ($n = 2$), severe neonatal asphyxia ($n = 2$), or congenital diaphragmatic hernia ($n = 1$).

The clinical characteristics of both groups were similar in terms of sex, birthweight, frequency of emergency surgery and respiratory rate at birth (Table 1). The gestational age at birth and Apgar score at 1 and 5 min were significantly lower in group A than in group B. Cesarean delivery was also higher in group A than group B.

Serum PCT, CRP, and WBC count at birth and at days 1, 2, and 3 of life in both groups are shown in Figure 1. Serum PCT from birth to day 3 of life was significantly higher in group A than in group B. CRP at birth and at day 1 of life were slightly higher in group A than in group B. There was no significant difference in CRP at days 2 and 3 of life, and in WBC count from birth to day 3 of life. Serum PCT was maximum on day 1 of life in all neonates regardless of the presence of respiratory disorder; PCT then decreased to normal without antibiotics as respiratory symptoms improved. Maximum PCT from birth to day 3 of life in term infants (group A1) was 13.186 ng/mL (range, 0.192–60.2 ng/mL; $n = 41$), while that in preterm infants (group A2) was 14.691 ng/mL (range, 0.971–57.1 ng/mL; $n = 41$). There were no significant differences between groups A1 and A2 ($P = 0.555$).

Figure 2 shows the ROC curves for serum PCT, CRP, and WBC count. The area under the curve (AUC) obtained for PCT level on day 1 of life to distinguish between the neonates with respiratory disorders and the controls was 0.85 (sensitivity, 66.7%; specificity, 93.0%; optimum cut-off, 3.73 ng/mL), whereas that for CRP level was 0.72 (sensitivity, 75.0%; specificity, 64.6%; optimum cut-off, 0.14 mg/dL) and that for WBC count was 0.45 (sensitivity, 60.0%; specificity, 29.6%; optimum cut-off, 15 000 cells/μL).

Maximum serum PCT in the neonates according to respiratory disorder or treatment from birth to day 3 of life is shown in Figure 3. Maximum PCT was high in some of those with TTN, RDS, or air leak syndrome, but there were no significant differences among the different respiratory disorders (Fig. 3a). Serum PCT was significantly higher in the neonates who were treated with any respiratory management procedure (oxygen,

Table 1 Clinical characteristics vs presence of respiratory disorder

	Group A ($n = 60$) n (%) or mean ± SD	Group B ($n = 95$) n (%) or mean ± SD	P
Male	40 (66.7)	50 (52.6)	0.97‡
Gestational age at birth (weeks)	36.7 ± 3.0	37.9 ± 2.0	<0.01§
Birthweight (g)	2409 ± 610	2578 ± 518	0.07§
Apgar score (1 min)†	6.4 ± 2.2	7.6 ± 1.3	<0.01§
Apgar score (5 min)†	7.9 ± 1.6	8.6 ± 1.1	<0.01§
Cesarean section	43 (71.7)	41 (43.2)	<0.01‡
Emergency surgery	20 (46.5)	18 (43.9)	0.83‡
Respiratory rate at birth (/min)	56.4 ± 26.9	53.4 ± 14.2	0.22§

Group A, respiratory disorder group; group B, non-respiratory disorder group. †Neonatal condition in the first and fifth minute after birth, including appearance, heart rate, muscle tone, and respiratory effort. ‡Fisher's exact probability test. §Student's *t*-test.

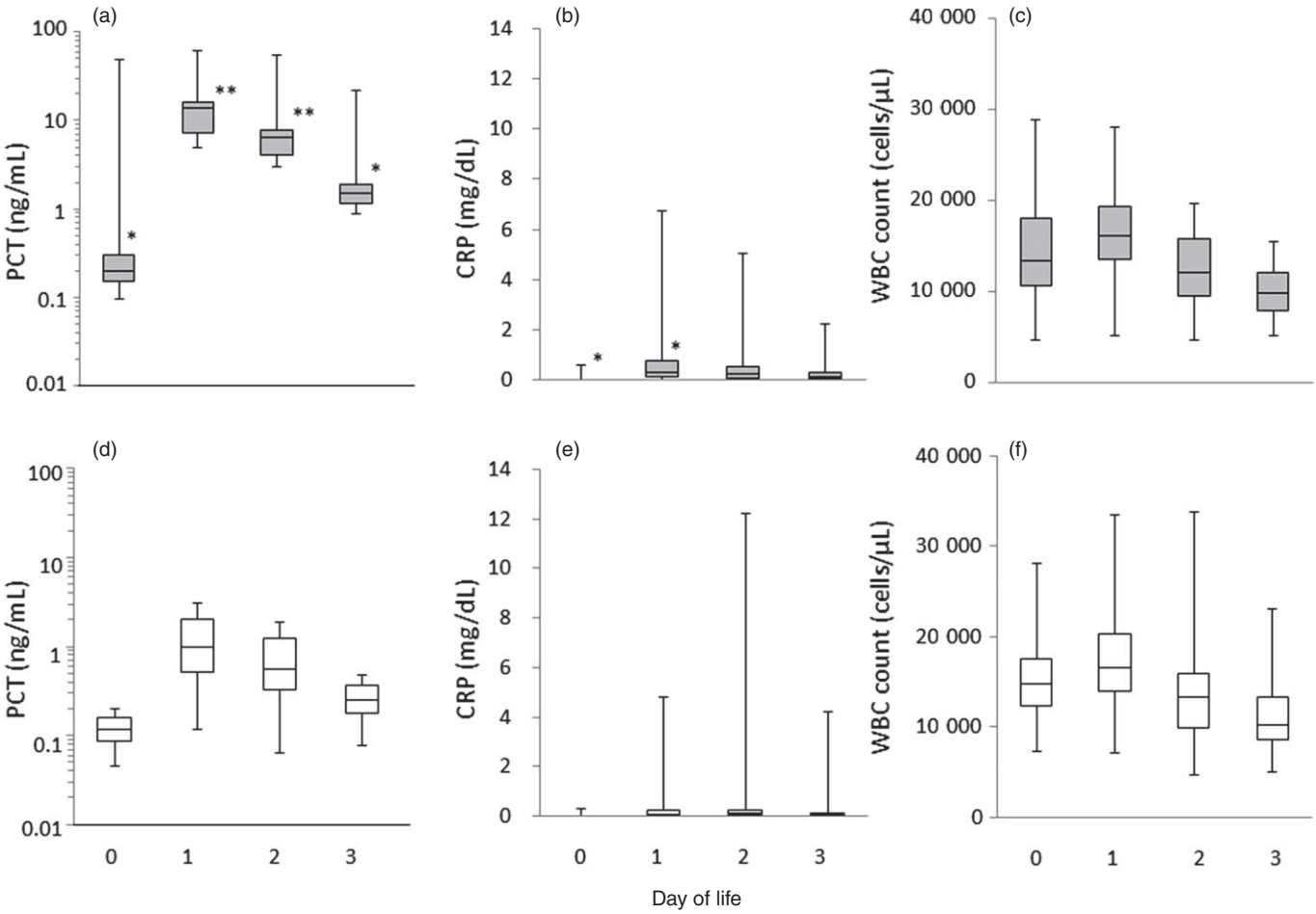

Fig. 1 Serum procalcitonin (PCT), C-reactive protein (CRP), and white blood cell (WBC) count from birth to day 3 of life in (a–c) group A and (d–f) group B. Data given as median and range. *$P < 0.05$, **$P < 0.01$.

mechanical ventilation, or directional positive airway pressure) than in the others ($P < 0.001$; Fig. 3b).

With regard to correlation between PCT level and severity of respiratory disturbance, maximum PCT was compared in respiratory disorder ($n = 60$)/TTN ($n = 39$) neonates for oxygen treatment period (Fig. 4). There was a positive correlation between PCT and period of oxygen requirement ($r = 0.246$). In TTN neonates, there was a strong correlation between PCT (ng/mL) and period of oxygen requirement ($r = 0.560$). This suggested that PCT might perhaps be useful as a novel parameter.

Discussion

Procalcitonin level has been shown to be a remarkable marker for the diagnosis of systemic/invasive bacterial infection, and superior to WBC count and CRP level in neonates.[9] It is especially difficult to determine the severity of bacterial infection based on WBC count alone because this decreases in severe infectious disease, and the reference value of WBC count varies between different age groups.

Maniaci *et al*. reported on the test performance of PCT level for identifying serious bacterial infection (SBI) without an identifiable bacterial source in febrile infants aged ≤90 days and an optimal cut-off value to identify infants at low risk for SBI.[10] They showed that the mean PCT level in infants with SBI was significantly higher than in infants without SBI. The AUC of the ROC curve was 0.76 for definite and possible SBI. For identifying definite and possible SBI, a cut-off value of 0.12 ng/mL had a sensitivity of 95.2% and a specificity of 25.5%.[10] Altunhan *et al*. showed that PCT level is a more sensitive marker of infection than CRP level in neonates.[11] PCT level at day 1 of life was more important than that at birth; PCT threshold for the diagnosis of sepsis was 0.59 ng/mL at birth (sensitivity, 48.7%; specificity, 68.6%) and 5.38 ng/mL at day 1 of life (sensitivity, 83.3%; specificity, 88.6%).[11]

In contrast, PCT alone cannot be used to accurately diagnose childhood bacterial infection because serum PCT increases in various diseases in children. Lapillonne *et al*. reported that serum PCT in premature infants was significantly higher in the infected group than in the non-infected group but that specificity for the diagnosis of bacterial infection was strikingly low (50%).[12] They emphasized that the lack of specificity was in part explained by significantly higher PCT in non-infected infants with RDS or hemodynamic failure than in other non-infected infants.[12]

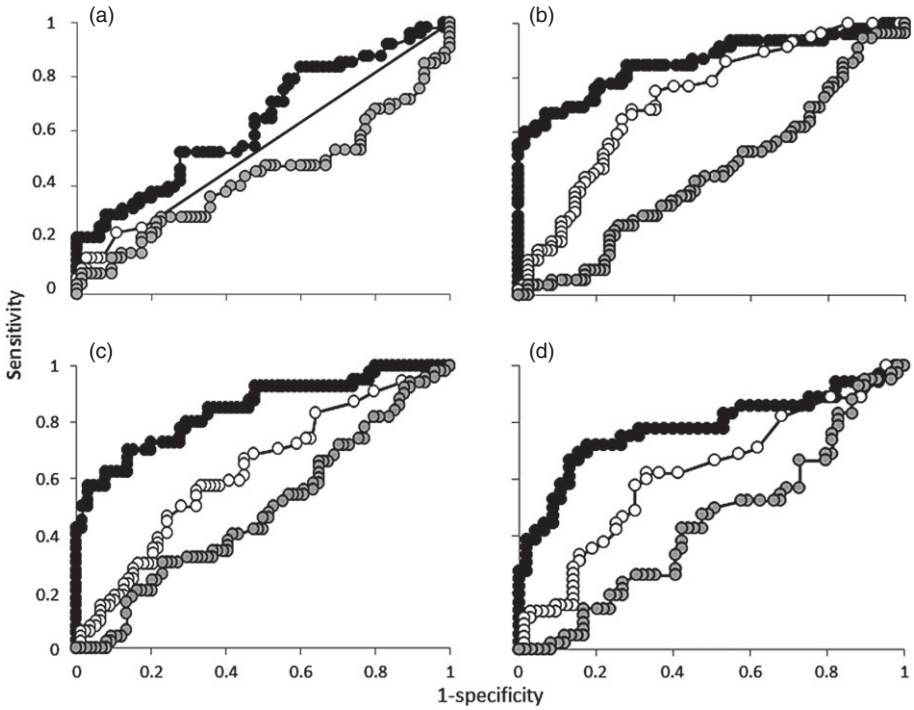

Fig. 2 Receiver operating characteristic (ROC) curves for (●) serum procalcitonin (PCT), (○) C-reactive protein (CRP), and (◍) white blood cell (WBC) count in neonates with and without respiratory disorder. (a) Birth; (b) day 1 of life; (c) day 2 of life; (d) day 3 of life.

Serum PCT increases in various non-infectious conditions in neonates, such as after surgery,[13] RDS,[12] hemodynamic failure,[12] or after birth in healthy newborns.[14] Bonac *et al*. reported that neonates with perinatal asphyxia, intracranial hemorrhage, pneumothorax, or who have been resuscitated have increased serum PCT similar to that of septic neonates up to 48 h after the onset of clinical signs of distress or infection.[15] Hypoxemia, which is common in neonatal distress, could be responsible for increased PCT concentration.[16,17] In particular, it is notable that PCT is increased significantly in various respiratory diseases,[12] as was noted in the present study.

Procalcitonin in healthy term newborns tends to be higher than in healthy preterm newborns.[18] The fact that the infants with respiratory failure were also preterm newborns, may explain the

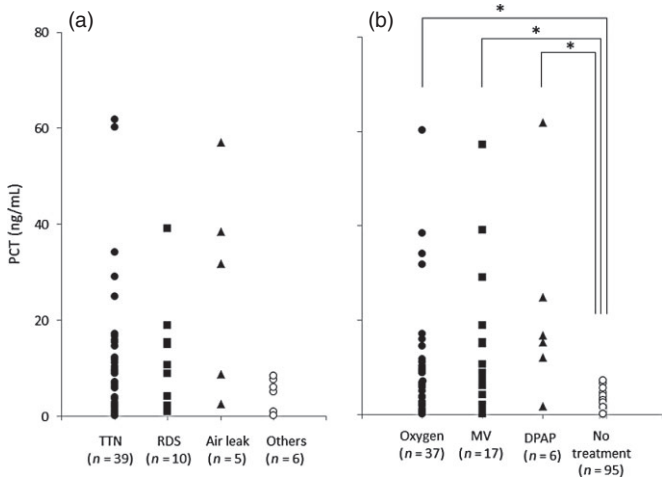

Fig. 3 Maximum procalcitonin (PCT) from birth to day 3 of life vs (a) respiratory disorder and (b) respiratory management. DPAP, directional positive airway pressure; MV, mechanical ventilation; RDS, respiratory distress syndrome; TTN, transient tachypnea of newborn. *$P < 0.001$.

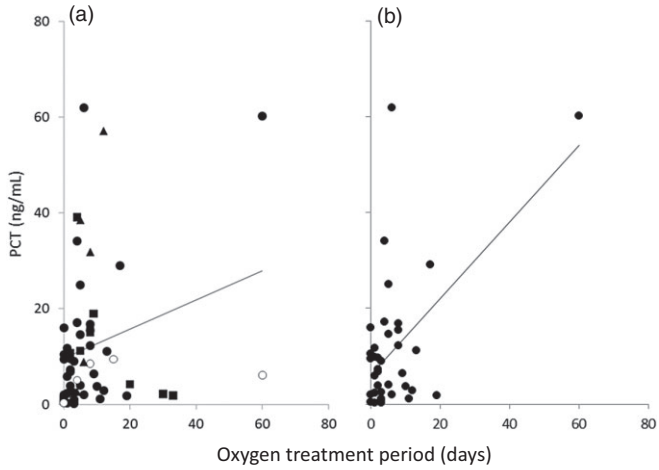

Fig. 4 Correlation of maximum procalcitonin (PCT) level from birth to day 3 of life with period of oxygen requirement in patients with (a) respiratory disorder (n = 60; ▲ air leak; ■ respiratory distress syndrome; ● transient tachypnea of newborn; ○ others), ——, regression line; $y = 0.303x + 9.72$, $r = 0.246$ and (b) transient tachypnea of newborn (n = 39), ——, regression line; $y = 0.798x + 6.12$, $r = 0.560$.

high PCT level. In the present study, there were no significant differences in PCT between term and preterm neonates with respiratory disorders ($P = 0.555$).

Although PCT is a useful marker for neonatal bacterial infection, an increase in PCT can also be observed in healthy newborns, and it peaks at 18–30 h of life.[6,9,16,19] Assumma *et al*. hypothesized that the postnatal increase in PCT indicates transplacental passage of maternal PCT.[7] PCT concentration, however, was higher in cord sera than in paired maternal samples at birth. They, therefore, concluded that the postnatal increase in PCT cannot be explained by transplacental passage. In this study, we found that serum PCT increased in neonates with various non-infectious respiratory disorders and that the increase in PCT in respiratory disorders was higher than the physiological increase in PCT from birth to day 3 of life.

Procalcitonin secretion begins within 4 h after stimulation and peaks at 8 h, while CRP secretion starts within 4–6 h after stimulation, peaking only after 36 h.[20–22] Furthermore, the half-life of PCT is 20–24 h, which is longer than that of CRP. We observed that serum PCT rapidly normalized after effective treatment. Thus, we suggest that PCT sampling helps to detect disease more quickly and is more sensitive than CRP level. In the present study, the change in PCT level was associated with general conditions, including neonate respiratory state.

Recently, serum PCT concentration guidance has substantially reduced antibiotic use in patients presenting to the emergency department or who are admitted to for lower respiratory tract infection.[23–26] Bouadma *et al*. showed that for patients with suspected infection, PCT-guided antibiotic treatment substantially lowered antibiotic exposure and had similar outcomes to standard care.[27] They were encouraged to discontinue antibiotics when PCT concentration was <80% of the peak concentration or an absolute concentration <0.5 μg/L was reached.[27] In neonates, it is difficult to determine requirement for antibiotics using PCT level alone. High PCT, however, is useful for distinguishing neonates with bacterial infection from those with respiratory disorder, and the time course of PCT induction may help determine the appropriate use of antibiotics and thus help to avoid unnecessary antibiotic use.

Conclusion

Procalcitonin is more susceptible as a diagnostic parameter of infection to the effect of respiratory disturbance than CRP and WBC, and may yield false-positive results in patients who also suffer from respiratory disturbance. When PCT remains high in the early neonatal period, accurate diagnosis, and prompt treatment of respiratory disorder are needed.

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