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Usefulness of estimation of blood procalcitonin concentration versus C-reactive protein concentration and white blood cell count for therapeutic monitoring of sepsis in neonates

Przydatność oznaczania stężenia prokalcytoniny w porównaniu ze stężeniem białka C-reaktywnego oraz ilością białych krwinek we krwi noworodków w monitorowaniu leczenia uogólnionych zakażeń szpitalnych

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Aim: This study was intended to assess the clinical usefulness of blood procalcitonin (PCT) concentrations for the diagnosis and therapeutic monitoring of nosocomial neonatal sepsis.

Material/Methods: The enrolment criterion was sepsis clinically manifesting after three days of life. PCT concentrations were measured in venous blood from 52 infected and 88 uninfected neonates. The results were interpreted against C-reactive protein (CRP) concentrations and white blood cell counts (WBC).

Results: Differences between the two groups in PCT and CRP concentrations were highly significant. No significant differences between the groups were noted for WBC. The threshold value on the receiver operator characteristic curve was 2.06 ng/mL for PCT (SE 75%; SP 80.68%; PPV 62.22%; NPV 88.75%; AUC 0.805), 5.0 mg/L for CRP (SE 67.44%; SP 73.68%; PPV 42.02%; NPV 88.89%; AUC 0.801), and 11.9 x109/L for WBC (SE 51.16%; SP 50.68%; PPV 23.16%; NPV 78.13%; AUC 0.484). Procalcitonin concentrations decreased 24 hours after initiation of antibiotic therapy and reverted to the control level after 5-7 days. C-reactive protein concentrations began to decline after two days of antibiotic therapy but were still higher than in the control group after 5-7 days of treatment. No significant changes in WBC during the treatment were observed.

Conclusions: Procalcitonin concentrations in blood appear to be of use for the diagnosis and therapeutic monitoring of nosocomial infections in neonates as this parameter demonstrates greater sensitivity and specificity than C-reactive protein. White blood cell counts appear to be of little diagnostic value in the early phase of infection or for therapeutic monitoring.

Keywords: **procalcitonin • therapeutic monitoring • neonatal sepsis • nosocomial infection**

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Introduction

Infections are the principal factor responsible for morbidity among term neonates and one of the causes of mortality among premature neonates. Concurrently with progress in perinatal care and with the introduction of improved, albeit more invasive, diagnostic and therapeutic procedures in pre-term neonates, the number of infants at risk of serious infections continues to grow. Early verification of latent asymptomatic infections is of great importance for defining the type and intensity of therapy. However, clinical symptoms as well as laboratory tests in use today are of low sensitivity and specificity for the diagnosis of infection in the premature neonate in particular and in the neonate in general [1,19,26].

Positive blood cultures remain the gold standard in the diagnosis of sepsis [18]. Unfortunately, cultures require a few days to perform and the result is often falsely negative [6,23]. Efforts continue in the search for a marker which could be useful for early detection of infection. Of no lesser importance is information on the effectiveness of therapy. The diagnostic method should be reliable, easily accessible, universal, and cheap. The fact that the concentration of procalcitonin (PCT) is increased in sepsis has aroused hope among clinicians that this parameter can be used for the diagnosis and therapeutic monitoring of infections in various groups of patients [4,5,8,15,21,22].

The present study was intended to assess the clinical usefulness of blood PCT concentration for the diagnosis and therapeutic monitoring of nosocomial infections in the neonate.

Material and methods

This clinical observational study was done at a third--degree reference center. The study protocol was approved by the local bioethics committee (BN-001/132/02). Written consent of parents was obtained in all cases.

The criterion for inclusion of a neonate in the study group (A, N=52) was clinically evidenced sepsis. Late--onset sepsis was diagnosed when symptoms appeared after three days of life. As all cases fulfilled the Centers for Disease Control and Prevention (CDC) criteria for nosocomial infection [10,25], the terms "late-onset" and "nosocomial" are used interchangeably.

The diagnosis of nosocomial neonatal sepsis required a few days of follow-up of the neonate and was based on physical examination and clinical findings noted during subsequent hours and days of life of the neonate, focusing on the dynamics of symptoms and results of routine laboratory tests.

Designation of infection status

Nosocomial neonatal sepsis was diagnosed based on the presence of three or more of the following five categories of clinical signs: 1. skin color (pallor, jaundice, cyanosis); 2. respiratory function (apnea, tachypnea >60/min, grunting, nasal flaring, intercostal or sternal retractions, need for high ventilator settings or oxygen); 3. cardiovascular function (brady/tachycardia, poor peripheral perfusion, hypotension); 4. neurologic findings (hypotonia, irritability, lethargy, seizures); 5. gastrointestinal function (abdominal distension, green or bloody residuals, vomiting, temperature instability) [27], and/or positive peripheral blood culture.

Laboratory tests routinely performed included C-reactive protein concentration (CRP values in venous blood > 5 mg/L were considered abnormal), white blood cell count with differential (WBC > 10 or < 5 $x10^9$/L was considered abnormal), platelet count (Plt < 100 $x10^9$/L was considered abnormal), and the immature to total neutrophil ratio (I:T ratio > 0.2 was considered abnormal) [11,20].

Other investigations were done when clinically indicated and included chest or abdominal radiographs, urine and spinal fluid microscopy and culture, tracheal aspirate culture, and cultures from superficial sites. In addition, standard laboratory tests (e.g. glucose, protein) and visual examinations were done.

Venous blood for cultures and laboratory tests (chiefly PCT, CRP, and WBC) was obtained at the onset of clinical symptoms of infection, prior to treatment, at the age of 17 ± 12 days (min. = 5, max. = 50). For therapeutic monitoring purposes, PCT, CRP, and WBC were determined after 24 h (A.1; N = 47), 48 h (A.2; N = 46), and 5-7 days of antimicrobial therapy (A.5-7; N = 50).

The criterion for inclusion in the control group (B; N = 88) was the absence of infection in the neonate. The usual

reason for hospitalization in this group was prematurity or non-infectious neonatal hyperbilirubinemia requiring phototherapy. Samples of venous blood from neonates without infection were obtained at the age of 14 ± 9 days (min. = 5, max. = 36).

Demographic and clinical characteristics of the study (A) and control (B) groups are shown in Table 1.

Laboratory examinations

Blood for PCT was centrifuged (10 min, 5000 RPM) within 30 minutes from collection and the serum was frozen (-30ºC). PCT concentrations were measured by quantitative immunoluminometry in 0.2 µl of serum in the LUMItest (BRAHMS Diagnostica GmbH, Berlin, Germany) on the LIA-MAT System 300 (BYK-Sangtec Diagnostica GmbH, Dietzenbach, Germany). The assay took approximately two hours. The borderline sensitivity of the test was 0.08 ng/mL. The concentration of PCT was determined from the calibration curve obtained using synthetic PCT. All measurements were performed in duplicate.

CRP concentrations were measured in serum 30 minutes after centrifugation of the blood sample using quantitative immunoturbidimetry on the Olympus AU 560 system (Olympus Diagnostica, Hamburg, Germany). Blood cell counts were performed with the Celldyn 1700 and Celldyn 3500 analyzers (Abbott Laboratories, IL, USA). The white blood cell profile was done manually by one of our experienced lab technicians.

Epidemiological investigations

All nosocomial infections were caused by multi-resistant strains of Gram-negative bacilli and staphylococci. Secondary fungal infections were not analyzed due to their scarcity. Infections caused by Gram-negative bacilli were fulminant, with rapidly deteriorating condition of the neonate, respiratory failure, and signs of septic shock. Staphylococcal infections often began with few or no symptoms and were associated with vascular cannulation.

Positive blood cultures were noted in 34 neonates (65.4%). Sepsis was caused by Gram-negative bacteria in 22 neonates (multi-resistant strains of *Klebsiella* spp. ESBL(+), *Pseudomonas aeruginosa* MBL, *Enterobacter* spp. AmpC, ESBL(+), *Serratia* spp., and *Citrobacter freundii*), Gram-positive bacteria in 8 neonates (coagulase-negative, methicillin-resistant (MR) staphylococci, *Staphylococcus aureus* MR), and *Candida* in 4 neonates. Details of the microbiological aspect of our findings have been published elsewhere [13].

Statistical analysis

The Shapiro-Wilk W test was used to check for normal distribution. Demographic and clinical characteristics of the groups were compared with Student's t-test, Mann-Whitney U test, and Chi^2 test, as appropriate. Equality of variances was studied with the Brown-Forsythe test. The Friedman test was applied to repeated measurements (changes of parameters over time). The Wilcoxon signed-rank test was used as a post hoc test. Due to inequality of variances and non-normal distribution, non-parametric methods were applied.

ROC (receiver operating characteristic) curves for PCT and CRP concentrations and WBC in venous blood were used to determine the cut-off points optimal for prediction of late-onset neonatal infection. Data are given as median and range. Exact 95% confidence intervals (CI) were calculated for sensitivity (SE%), specificity (SP%), and positive (PPV%) and negative (NPV%) predictive values. The value of p = 0.05 was taken as the significance level.

Table 1. Demographic and clinical features of neonates with nosocomial infection (A) and uninfected neonates (B)

Feature	Group A N = 52	Group B N = 88
Gestational age (week); X ± SD;(min.–max.)	29.7 ± 3.7 (22-38)	30.0 ± 5.1 (24-42)
Birth weight (g); X ± SD; (min.–max.)	1264 ± 574 (530-3320)	1502 ± 950 (600-4420)
Number of neonates ≤ 36 weeks; N (%)	51 (98)	76 (86)
Number of neonates ≤ 1500 g; N (%)	38 (73)	14 (16)
Number of cesarean sections; N (%)	42 (80)	59 (67)
Apgar score ≤ 5 at 5 min.; N (%)	18 (35)	7 (8)
Growth retardation; N (%)	18 (34,6)	9 (10)
Hospital stay in days; X ± SD, (min.–max.)	45 ± 23 (9-96)	45 ± 32 (5-103)
Death of neonate; N (%)	3 (6)	0 (0)

Legend: NS - not significant; X ± SD - mean ± standard deviation

Results

Three neonates in the study group died due to multiple organ dysfunction syndrome in the course of nosocomial sepsis caused by Gram-negative bacilli. Two deaths were due to pulmonary hemorrhage and one was due to renal failure in a premature neonate. These neonates demonstrated persistent high PCT concentrations (14.82 and 11.86 and 29.4 ng/mL) after 7 days of treatment.

Differences in PCT and CRP concentrations in venous blood between nosocomial neonatal infection at the onset of clinical symptoms of infection, prior to treatment, and control groups were highly significant. In other words, the concentration of PCT was 4.6 times higher and CRP was 7.5 times higher in infected than uninfected neonates. No significant differences were noted for WBC.

Cut-off points were next determined to assess the diagnostic usefulness of each parameter for the diagnosis of nosocomial neonatal infection. The area under the ROC curve (AUC) was similar for PCT and CRP, whereas the AUC for WBC indicated that this parameter is without importance for the diagnosis of nosocomial infections in the neonate (Table 3, Fig. 1).

Concentrations of PCT and CRP values in venous blood at the onset of infection and during subsequent days of treatment of neonates with nosocomial infection are presented in Figures 2 and 3. The level of significance is given only when the difference was statistically significant (Figures 2 and 3).

The concentration of PCT at the onset of infection was highest. It decreased significantly after the first day of treatment and was further reduced after two days and 5–7 days of therapy, reverting to the control group level (A.5-7: median 0.85 ng/mL, range 0.23-14.82 vs B: median 0.94 ng/mL, range 0.20-35.05; $p = 0.5$).

The concentration of CRP in venous blood of neonates with nosocomial infection increased during the first day of treatment almost to the level of significance (A vs A.1: $p = 0.05$) and began to decrease after two days of treatment, approaching the value at the onset of illness (A vs A.3: $p = 0.5$). CRP remained significantly above the control level after 5-7 days of treatment (A.5-7: median 7.60 mg/L, range 0.10-147.10 vs B: median 2.7 mg/L, range 0.10-57.0; $p < 0.001$).

WBC values in venous blood of neonates with nosocomial sepsis did not change significantly during treatment.

Discussion

The usefulness of diagnostic parameters is dependent on the accepted cut-off points. For example, Enguix et al. [7] demonstrated that PCT and CRP are equally useful for the diagnosis of infections in neonates older than three days (PCT: SE% 98.6, SP% 88.9 (cut-off point 8.1 ng/mL); CRP: SE% 95.8, SP% 83.6 (cut-off point 22.1 mg/L)). When we compared PCT with CRP in neonates with nosocomial infections, the sensitivity and specificity of PCT were higher than those of CRP (PCT SE% 75.68 vs CRP SE% 67.44; PCT SP% 80.68 vs CRP SP% 73.68) but at cut-off points differing from those of Enguix et al. [7] (2.06 ng/mL for PCT and 5.0 mg/L for CRP). Similar AUC values were obtained by us for PCT and CRP (0.805 vs 0.801). Blommendahl et al. [4] reported that the concentration of PCT equal to 1 ng/mL was more sensitive (SE% 77) but less specific (SP% 62) than CRP (SE% 58 and SP% 84 (cut-off point 1 mg/L)) for the diagnosis of sepsis in neonates. López Sastre et al. [14] suggested that the concentration of PCT is not a good individual marker of nosocomial sepsis in neonates but can be of value as an element of a comprehensive approach to the diagnosis of sepsis. The same authors found increased concentrations of PCT at 12-24 h and 36-48 h after the onset of infection. No mention was made of any antibiotic therapy, so these results cannot be compared with our study, which also focused on the monitoring of diagnostic efficacy. Chiesa et al. [5] reported that the sensitivity and specificity of PCT were 100% in a group of 23 neonates with serious symptoms of nosocomial infection and suggested that PCT concentrations can be useful for the early diagnosis of infections in neonates staying at an intensive care ward. There are many reports on the usefulness of PCT as an early marker of nosocomial infection in very low birth weight (VLBW) neonates. According to Vazzalvar et al. [28], PCT (0.5 ng/mL) is more sensitive than CRP for revealing nosocomial sepsis in VLBW. Auriti et al. [3] reported AUC for procalcitonin in nosocomial neonatal sepsis equal to 0.80 (95% CI 0.75 to 0.85), and

Table 2. PCT, CRP, and WBC values in venous blood of neonates with nosocomial infection prior to treatment (A), and uninfected neonates (B)

Parameter	Group A N = 52	group B N = 88	p
PCT (ng/mL)	4.30 (0.25-168.53)	0.94 (0.20-35.05)	< 0.05
CRP (mg/L)	20.30 (0.1-199.70)	2.7 (0.10-57.0)	< 0.05
WBC (x109/L)	11.60 (2.90-49.0)	10.0 (5.0-24.0)	0.2

median (min.–max.); (U Mann-Whitney test)

Table 3. Sensitivity (SE%), specificity (SP%), positive (PPV%) and negative (NPV%) predictive value, and area under curve (AUC) for PCT, CRP, and WBC in venous blood used to diagnose nosocomial neonatal infection

Parameter	Cut-off value	SE% [SE]	SP% [SE]	PPV% [SE]	NPV% [SE]	AUC [SE]
PCT (ng/mL)	> 2.06	75.68 [0.07]	80.68 [0.06]	62.22 [0.07]	88.75 [0.04]	0.805 [0.05]
CRP (mg/L)	> 5.0	67.44 [0.07]	73.68 [0.07]	42.03 [0.06]	88.89 [0.03]	0.801 [0.04]
WBC (x109/L)	> 11.9	51.16 [0.08]	50.68 [0.08]	23.16 [0.04]	78.13 [0.04]	0.484 [0.05]

[SE] – standard error
(U Mann-Whitney test, Wilcoxon signed-rank test)

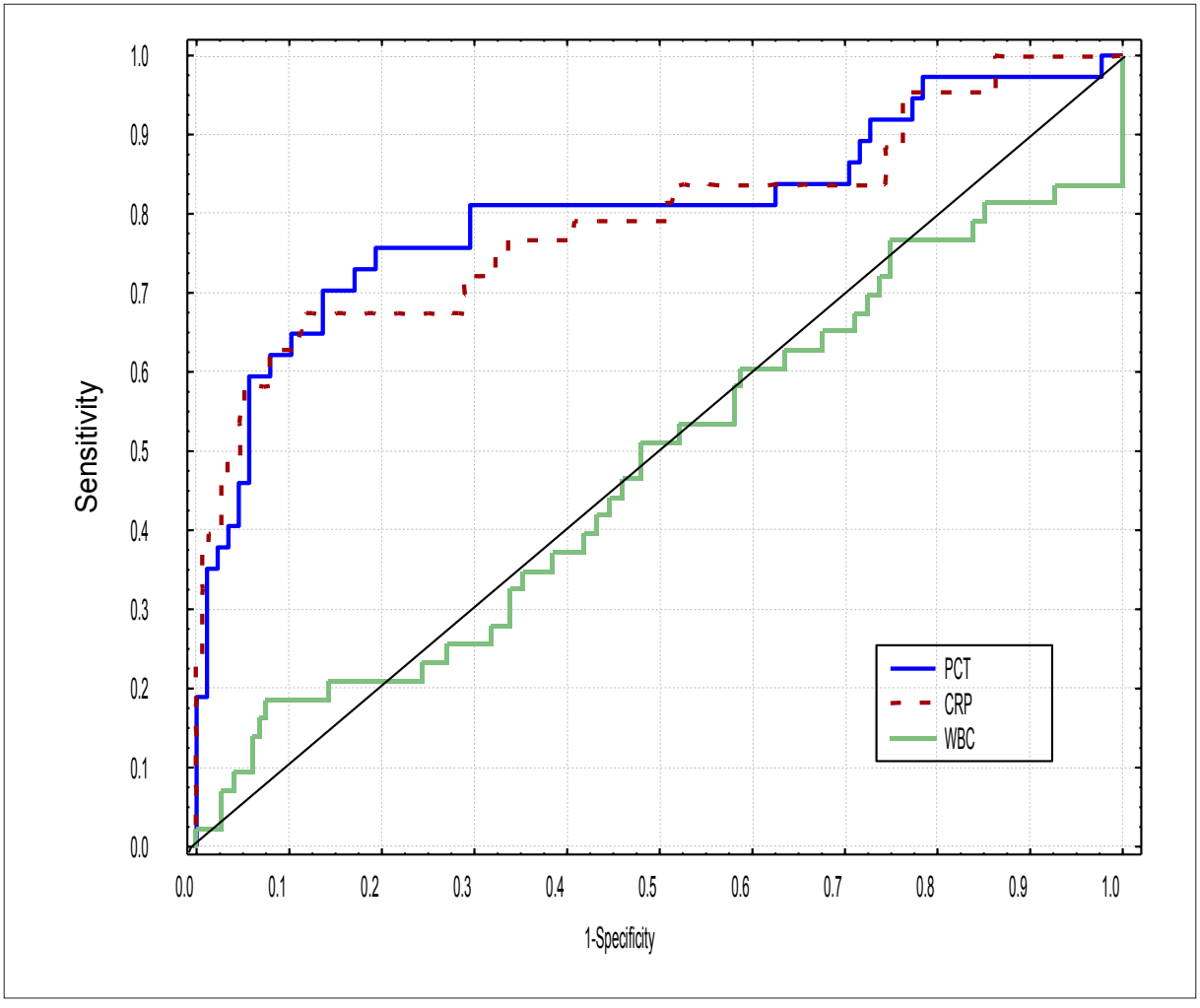

Fig. 1. ROC curve of PCT, CRP, and WBC in venous blood of neonates used for the diagnosis of nosocomial infections (group A)

varying from 0.79 (>1500 g) to 0.82 for VLBW infants, in agreement with our findings.

Evidence is accumulating that PCT is a useful marker for the early diagnosis of nosocomial neonatal sepsis. Yu et al. [29] in their meta-analysis of 22 reports found that PCT is more valuable than CRP for the diagnosis of late-onset rather than early-onset infections in neonates. According to Fendler and Piotrowski [9], diagnostic efficacy was highest for measurements made two or more hours after the onset of symptoms.

In our study group, PCT concentrations were highest at the onset of illness, prior to antibiotic therapy. A signifi-

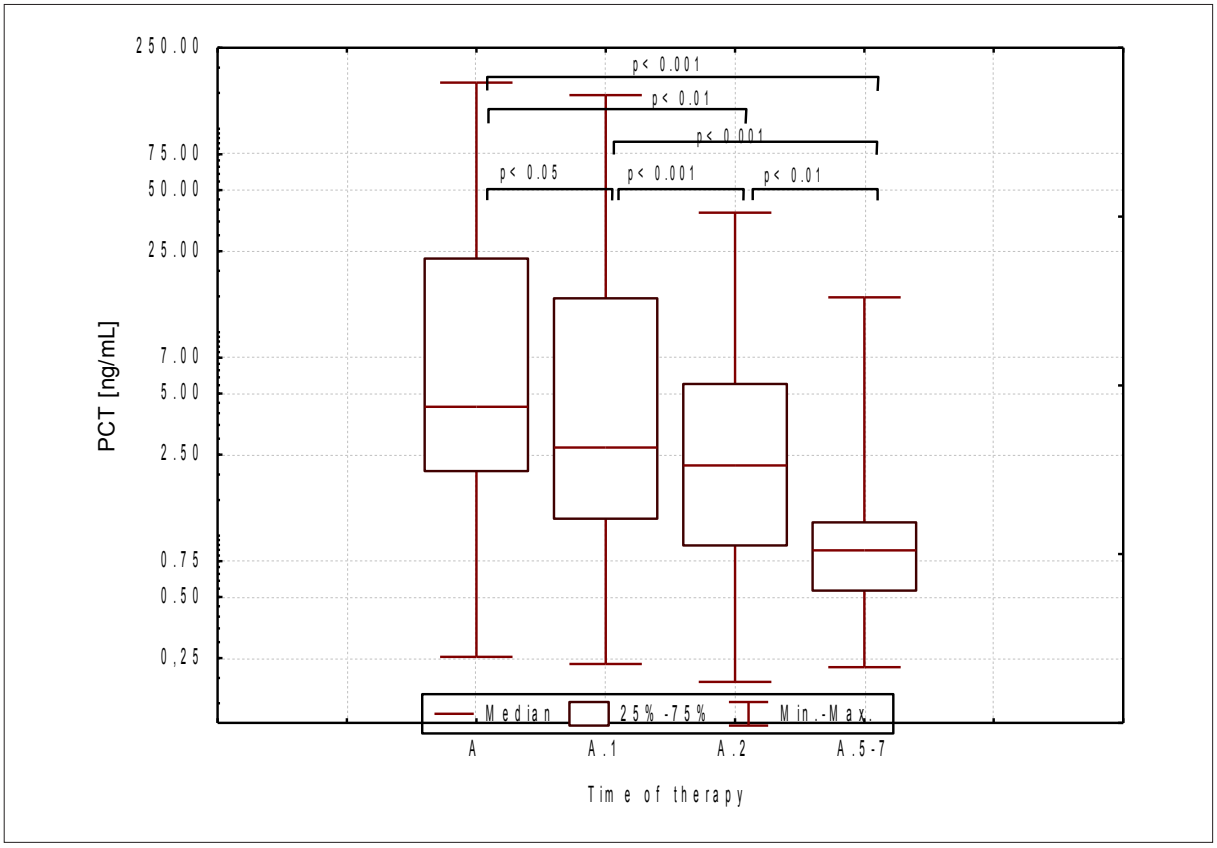

Fig. 2. PCT concentrations in venous blood of neonates with nosocomial infection at onset of symptoms (A) and after one day (A.1), two days (A.2), and 5–7 days (A.5–7) of therapy

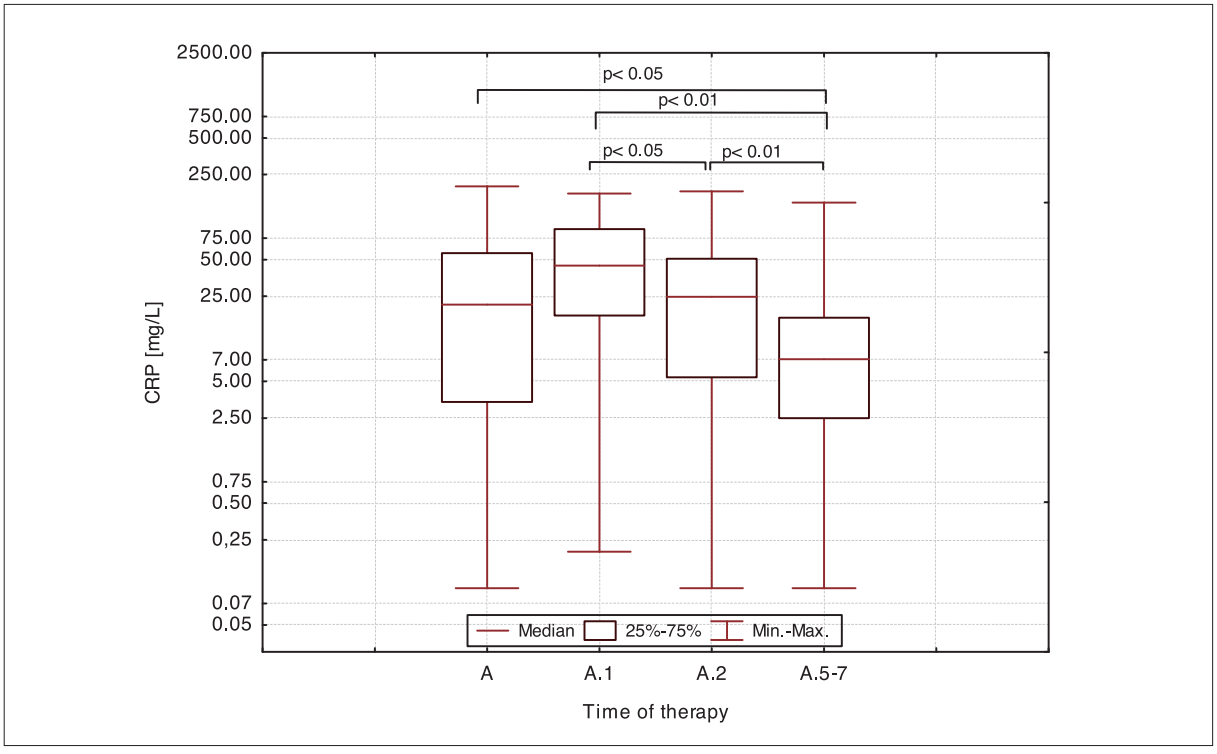

Fig. 3. CRP concentrations in venous blood of neonates with nosocomial infection at the onset of symptoms (A) and after one day (A.1), two days (A.2), and 5-7 days (A.5-7) of therapy

cant decrease in the concentration of PCT noted as early as 24 h after initiation of treatment and continuing until full normalization after 5-7 days of treatment is a finding which distinguishes PCT from CRP and corroborates its diagnostic usefulness. For clinical practice, it is important that the decrease in PCT confirming the right choice of antibiotic is noticed before the disappearance of symptoms of infection [12]. Chiesa et al. [5] reported normalization of PCT (< 1.0 ng/mL) 3-7 days after termination of antibiotic therapy. The response to antibiotic therapy is evidenced by PCT concentrations in a shorter time and with greater statistical significance than by CRP. Zahedpasha et al. [30] found dramatic declines in PCT concentrations in all types of neonatal sepses on the 5th day of therapy. Nylen et al. [17] found that PCT is one of the main markers of severity of systemic infection and mortality. According to these researchers, PCT is an integral part of inflammatory processes and exerts a direct effect on survival. High concentrations of PCT continuing despite treatment are a sign of poor prognosis. Our three neonates with sepsis caused by Gram-negative bacteria who died due to multiple organ dysfunction syndrome demonstrated high PCT concentrations (14.82 and 11.86 and 29.4 ng/mL) after 7 days of treatment.

Meisner et al. [16] believe that PCT is a better parameter for therapeutic monitoring than TNF-alpha, IL-6, or CRP: PCT decreased earlier in response to therapy. Ali et al. [2] concluded that the serum PCT concentration showed good diagnostic value for the early detection of neonatal sepsis of vertical transmission compared with other traditional markers of inflammation, facilitating early therapeutic intervention in those high-risk groups.

Any comparison of the results of studies in neonates is plagued by great difficulties due to the heterogeneity of the study and control groups. The immune response varies depending on the gestational age, i.e. maturity of the neonate. Other significant maternal factors operating during the fetal period include diseases, lifestyle, medication, and feeding habits. Some authors use control groups consisting of neonates without infection while others prefer neonates with negative blood cultures. All these discrepancies reappear later in the interpretation of the results. Clearly, multicenter studies with a uniform methodological approach are needed in a larger cohort of neonates. Stocker et al. [24] were able to reduce the duration of antibiotic therapy in suspected neonatal early-onset sepsis thanks to procalcitonin-guided decision-making. It appears that the same could be possible in late-onset neonatal infections.

Conclusions

The concentration of PCT in venous blood of neonates with nosocomial infection was higher than in uninfected neonates. Unlike CRP, the concentration of PCT decreased significantly after the first day of treatment and thus can serve to assess the efficacy of treatment. Moreover, the concentration of PCT (unlike CRP) reverted to the control value after 5-7 days of treatment. These findings indicate that the measurement of PCT concentrations in venous blood may be useful for the early diagnosis and therapeutic monitoring of nosocomial infections in neonates.

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