THE IMPORTANCE OF DETERMINING PROCALCITONIN AND C REACTIVE PROTEIN IN DIFFERENT STAGES OF SEPSIS

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Abstract

Rapid and early diagnosis of systemic infections is very important for acting on time with an adequate therapy.

The aim of this study is to determine the diagnostic importance of procalcitonin (PCT) and C-reactive protein (CRP) of bacterial infections in different stages of sepsis.

PCT and CRP have been determined in 45 newborns, 1-21 days of age, with different stages of sepsis, in the centre for prematurely born neonates. These parameters have also been determined for control group, in which there were 10 healthy newborns.

Procalcitonin values were significantly increased in neonates with septic shock (92,5 ng/mL; 6,06-200 ng/mL) compared to the systemic inflammatory response syndrome- SIRS (41 ng/mL; 0,28-200 ng/mL), neonatal sepsis (10,26 ng/mL; 1,08-111,3 ng/mL), neonatal sepsis and purulent meningitis (9,80 ng/mL; 4,3-18,9 ng/mL). The control group values were lower than 0,5 ng/mL. CRP is increased without statistical differences in all stages of sepsis in newborns with septic shock (93,2 mg/L; 6,0-196 mg/L) in cases with SIRS (45,64 mg/L; 6,0-147 mg/L), neonatal sepsis (70,02 mg/L; 6-177 mg/L), neonatal sepsis and purulent meningitis (61,98 mg/L; 24-192 mg/L). The average values for the control group were 4,7 mg/L. Procalcitonin is increased in all stages of sepsis with higher values in the septic shock. The increase of PCT levels is related to the severity, course of infection and prognosis of disease.

KEY WORDS: procalcitonin (PCT), C reactive protein (CRP), infection, sepsis, septic shock.

Introduction

Infections in newborns are the most often causes of morbidity and mortality. The early and rapid diagnosis of systemic infections is very important to start the right therapy on time. Infections at this age are accompanied by weak subclinical signs. So, they may not be diagnosed on time. As a result of a high activity of cytokines, procalcitonin and C-reactive protein (CRP) are released. C reactive protein is a sensitive and early indicator of systemic infection, but it can also increase at light and local bacterial infections as well as at viral infections (1). Procalcitonin (PCT) is an important parameter for bacterial infections. Procalcitonin is a protein which consists of 116 amino acids out of which 32 structure the calcitonin hormone (2, 3). The level of procalcitonin in serum increases during severe systemic bacterial infections, parasites and fungi with systemic manifestations (4, 5, 6). In severe viral infections or in inflammatory reactions with a non infective origin, the levels of procalcitonin don't increase, or there is a moderate increase (7). In the conditions of a normal metabolism, the active calcitonin hormone is produced and secreted in C cells of thyroid gland after the intracellular proteolitic process of procalcitonin prohormone. Specific proteases dissolve procalcitonin into calcitonin, katacalcine and in N-terminal residue (8). Procalcitonin increase can happen without infections in patients with carcinoma of thyroid gland C cells (9). Although new methods of treatments are being used (10), mortality in patients with sepsis remains high, often because of late diagnosis and treatment. Infections in newborns and young children in the region of Kosovo are frequent and frequently cause mortality. At these ages, early diagnosis of infections and the differential diagnosis between viral and bacterial infections, present different complications. This study's intention is to prove that the PCT and CRP concentration is different at various stages of sepsis development in newborns.

Material and Methods

Study Subjects

PCT and CRP have been determined in 45 neonates of 1-21 days of age with different stages of sepsis, who were patients in the Centre for Prematurely Born Babies, and in 10 healthy neonates. Patients have been classified into: patients with systemic inflammatory response syndrome (SIRS) (10 patients); with neonatal sepsis (23 patients); with neonatal sepsis and purulent meningitis (7 patients); and patients with septic shock (5 patients). There were 10 cases of healthy children.

Anamnesis

Some of the criteria to diagnose infections in newborns are hypothermia or hyperthermia, difficulties in diet, signs from the respiratory tract (cyanosis and apnoea), lethargy, jaundice, tachycardia, tachypnoea, changes in skin, hypotony, liver and spleen enlargement. Control group consists of 10 healthy newborns with normal weight and height, afebrile, normotonic, eupnoic and without evident changes for a disease.

Detailed analysis

The samples have been taken with monovettes of "Sarstedt" company. After serum separation, biochemical parameters were immediately determined. The determination of procalcitonin has been estabilished with the ELFA methods of producer B.R.A.H.M.S Diagnostica GmbH, Berlin, Germany. C reactive protein (CRP) has been determined with the standard turbidimetric methods (Synchron CX-7, Beckman Fullerton, CA).

Statistical analysis

The results of this research have been elaborated with the special statistical programme Instat 2, where the arithmetical average, median, standard deviation, minimal and maximal values as well as p value have been calculated. All these data have been presented in tables and graphics.

Results

In Table 1. newborns have been presented according to diseases. 23 cases or 51% of the examinees have suffered from neonatal sepsis, 10 cases or 22% have been with SIRS, 16% have been with neonatal sepsis and purulent meningitis and 11% with septic shock.

Diseases	Group		
	Newborns		Control
	N	%	
SIRS	10	22	
Neonatal sepsis	23	51	
Neonatal sepsis+ purulent meningitis	7	16	
Septic shock	5	11	
Healthy			10
Total	**45**	**100**	**10**

TABLE 1. The examinees according to groups and diseases

The average values of PCT and CRP in newborns with SIRS have been presented in Table 2. and Figure 1. It is noticed that there is an increase of both indicators with an increase rate of PCT, around 11 times more than CRP. There is a high statistical difference ($p<0,01$)

Compared analyses	Parameter	Newborns	Rate of increase*	χ^2-test of increase
PTC ng/mL	Number of examinees (N)	10,00	82,00	P<0,01
	Average value (Xb)	41,00		
	Standard deviation (SD)	73,90		
	Coefficient of variation (CV%)	180,25		
	Maximal value (X_{max})	200,00		
	Minimal value (X_{min})	0,28		
CRP mg/L	Number of examinees (N)	10,00	7,61	
	Average value (Xb)	45,64		
	Standard deviation(SD)	51,53		
	Coefficient of variation (CV%)	112,9		
	Maximal value (X_{max})	147,00		
	Minimal value (X_{min})	6,00		

*Rate of increase, the ratio between average values and reference values, how much it has increased in comparison to the normal value.

TABLE 2. The comparison between PTC and CRP values for newborns with SIRS

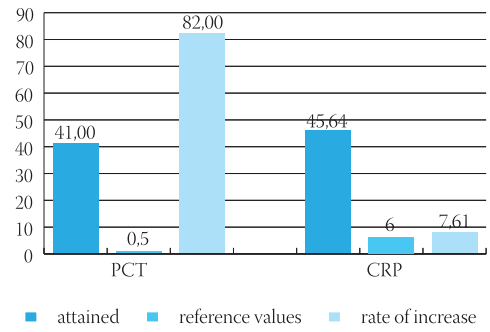

FIGURE 1. The comparison of values of PCT and CRP in neonates and the rate of increase towards reference values -**SIRS**

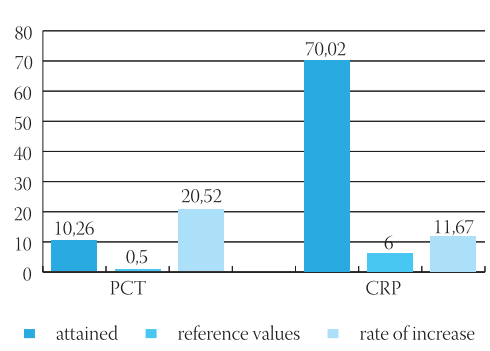

FIGURE 2. The comparison of value of PCT and CRP in newborns and the rate of increase towards reference values - **neonatal sepsis**

Compared analyses	Parameter	Newborns	Rate of increase*	χ^2-test of increase
PTC ng/mL	Number of examinees (N)	23	20,52	P<0,3886
	Average value (Xb)	10,26		
	Standard deviation (SD)	22,44		
	Coefficient of variation (CV%)	218,74		
	Maximal value (X_{max})	111,3		
	Minimal value (X_{min})	1,08		
CRP mg/L	Number of examinees (N)	23	11,67	
	Average value (Xb)	70,02		
	Standard deviation(SD)	54,59		
	Coefficient of variation (CV%)	77,97		
	Maximal value (X_{max})	177		
	Minimal value (X_{min})	6		

TABLE 3. The comparison between PTC and CRP values for newborns with neonatal sepsis

Values of PCT and CRP at newborns with neonatal sepsis are presented in Table 3. and Figure 2.. Although the rate of increase for PCT is almost two times higher than that of CRP, there is no statistical significance. In Table 4. and Figure 3. a comparison has been made between PCT and CRP in newborns with neonatal sepsis and with purulent meningitis. Both indicators of infection have resulted increased. The difference between the rates of increase has not been sufficient for a statistical significance.

The values of PCT and CRP in newborns with septic shock have been compared in Table 5. and Figure 4. It is seen that the rate of increase is much higher for PCT (around 184,96 times higher than reference values), while CRP is increased 15,53 times more than the reference values. This difference has a high statistical difference.

Compared analyses	Parameter	Newborns	Rate of increase*	χ^2-test of increase
PTC ng/mL	Number of examinees (N)	7	19,61	P<0,917
	Average value (Xb)	9,8		
	Standard deviation (SD)	4,91		
	Coefficient of variation (CV%)	50,09		
	Maximal value (X_{max})	18,9		
	Minimal value (X_{min})	4,3		
CRP mg/L	Number of examinees (N)	7	16,72	
	Average value (Xb)	100,3		
	Standard deviation(SD)	61,98		
	Coefficient of variation (CV%)	61,8		
	Maximal value (X_{max})	192		
	Minimal value (X_{min})	24		

TABLE 4. The comparison between PTC and CRP values for neonates with neonatal sepsis + purulent meningitis - statistical parameters

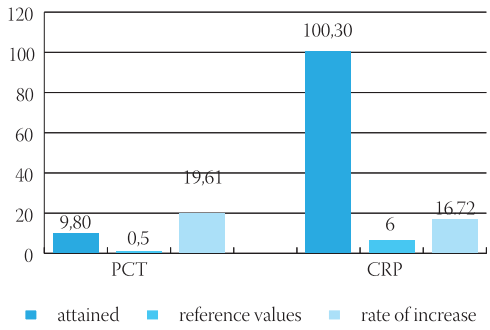

FIGURE 3. The comparison of PCT and CRP values in neonates and the rate of increase towards reference values – **neonatal sepsis + purulent meningitis**

Compared analyses	Parameter	Newborns	Rate of increase*	χ2-test of increase
PTC ng/mL	Number of examinees (N)	5,00	184,96	P<0,0001
	Average value (Xb)	92,48		
	Standard deviation (SD)	79,95		
	Coefficient of variation (CV%)	86,45		
	Maximal value (X_{max})	200,00		
	Minimal value (X_{min})	6,06		
CRP mg/L	Number of examinees (N)	5,00	15,53	
	Average value (Xb)	93,20		
	Standard deviation(SD)	93,23		
	Coefficient of variation (CV%)	100,03		
	Maximal value (X_{max})	196,00		
	Minimal value (X_{min})	6,00		

*Rate of increase, the ratio between average values and reference values, how much it has increased in comparison to the normal value.

TABLE 5. The comparison between PTC and CRP for newborns with septic shock

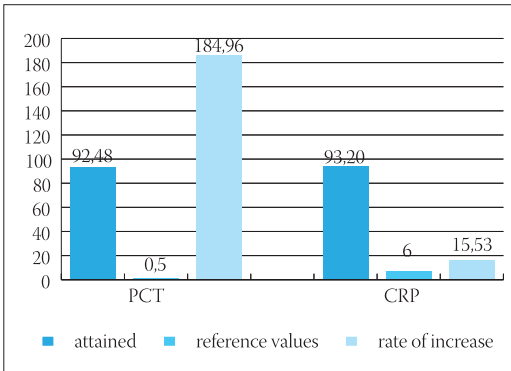

FIGURE 3. The comparison of PCT and CRP values in neonates and the rate of increase towards reference values - **septic shock**

Discussion

Sepsis is a catabolic acute state, which is caused by cytokines, the role of which can be synergic, by inducting or blocking, in which case the normal physiologic balance turns into a pathologic process, including a lot of organs (11). Untreated infection may end tragically, newborns with "suspected sepsis" are often subjected to a battery of extensive diagnostic procedures and unguided systemic antibiotic therapy pending further laboratory results (12). The clinical signs of the infection and the routine laboratory tests of sepsis, such as CRP and the number of leucocytes are not specific and sometimes even false. In cases of a severe infection, most proinflammatory cytokines such as TNF-α, IL-β, increase in a short period of time, or don't increase at all (13). In bacterial infections and in various forms of severe systemic inflammation, circulating levels of calcitonin precursors (CTpr), including the pro-hormone procalcitonin (ProCT), increase several –fold to several thousand –fold, and this increase often correlates with the severity of the condition and with mortality (7,14,15,16). Because the clinical diagnosis of sepsis is often subjective and uncertain, there's a difficult task to analyse the markers of infections. In this research, with the analysis of our results, we have reached some conclusions which are of a great value about early diagnosis and about giving the adequate therapy on time at newborns with bacterial infections. In our study the values of procalcitonin have resulted increased with a higher statistical significance in children with septic shock (median 92,5 ng/mL; range 6,06-200 ng/mL) in comparison to SIRS (median 41 ng/mL; range 0,28-200 ng/mL), neonatal sepsis (median 10,26 ng/mL; range 1,08-111,3 ng/mL), and neonatal sepsis + meningitis purulenta (median 9,80 ng/mL; range 4,3-18,9 ng/mL). In control group the values have been lower than 0,5 ng/mL. By many authors, a limit of 10 ng/ml PCT is considered to be a more reliable indicator of a severe infection with the symptoms of the systemic inflammation (17,18). CRP has increased in comparison to control group, but without significant statistical changes in all stages of sepsis (septic shock (median 93,2 mg/L; range 6,0 – 196 mg/L) in cases with SIRS (45,64 mg/L; range 6,0-147 mg/L), neonatal sepsis (median 70,02 mg/L; range 6-177 mg/L), and neonatal sepsis + purulent meningitis (median 61,98 mg/L; range 24-192 mg/L)). The average value for control group was 4,7 mg/L. CRP has been widely used clinically as a diagnostic tool for infection identification (26,27). The increase of CRP shows that it is a sensitive and classical marker of inflammation which cannot make the difference between a

bacterial infection and other infections (19). According to our results the values of PCT correlate with the severity of the disease (Table 5 and Figure 4). Early identification of patients with insidious septic illness allows early therapeutic intervention which may favourably influence the outcome (20). PCT was identified as a better discriminator than CRP in characterizing the degree of inflammation related to infection. PCT was more specific for sepsis-induced inflammation than CRP, (24) but no better than CRP at identifying infection uncomplicated by sepsis or organ failure (25). The course and follow up of PCT values is important for assessing both the clinical course of the disease and its prognosis in sepsis or systemic inflammation (21, 22, 23).

Conclusion

Based on our results, we concluded that procalcitonin is increased in all stages of sepsis, with higher values in the septic shock. The increase of PCT levels is related to the severity, course of infection and patient prognosis.

Acknowledgments

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