ORIGINAL RESEARCH ARTICLE

Is Procalcitonin a Marker of Neurologic Outcome or Early Infection in Patients Treated with Targeted Temperature Management?

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Abstract

Objectives: Although high procalcitonin (PCT) levels are associated with poor neurological outcomes and increased mortality rates in patients treated with targeted temperature management (TTM) in the postcardiac arrest (CA) period, there are limited data about the correlation between PCT levels and infection. The aim of our study was to assess the relationship of PCT levels in the first 48 hours with early period infections, late period neurological prognosis, and mortality in patients treated with TTM after CA.

Materials and methods: Serum PCT was measured on admission days 1 and 2. The early onset infection diagnosis before the seventh day in the intensive care unit (ICU) was made according to the criteria of infection centers for disease control and prevention. Mortality and neurologic outcomes were assessed 90 days after CA according to cerebral performance category (CPC) score.

Results: There was no statistically significant correlation between early period infection diagnosis and PCT levels at the time of admission, 24th, and 48th hours. Patients with poor neurologic outcomes on the 90th day had significantly high PCT levels at 24 ($p = 0.044$) and 48 hours ($p = 0.004$). There was no statistically significant correlation between admission PCT levels and neurological prognosis. While the correlation between mortality and PCT levels at 24 ($p = 0.049$) and 48 ($p = 0.004$) hours was significantly high, no statistically significant correlation was found between admission PCT levels and mortality.

Conclusion: In patients treated with TTM after CA, increased PCT levels were significantly correlated with poor neurologic outcomes and mortality. However, the elevated PCT levels were not significantly correlated with early period infections.

Keywords: Cardiac arrest, Patient outcome, Procalcitonin, Resuscitation, Targeted temperature management.

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Introduction

In patients with successful resuscitation and return of spontaneous circulation (ROSC) after cardiac arrest (CA), hypoxic brain damage related to severe neurological injuries and mortality rate is high in spite of innovations in intensive care treatment. Administration of targeted temperature management (TTM) to the patient group who are comatose after CA reduces the mortality rate and is known to improve neurological outcomes.[1] Additionally, one of the most important concerns during TTM is that the fever response to infection may be missed during this treatment in patients with increased risk of infection.[2] As a result, procalcitonin (PCT), being one of the biomarkers of infection, proves to be of great importance in this patient group.

The neurological outcome among the surviving CA patients comprises a broad range and it is difficult to determine the prognosis in the short-term. As a result, there is a need for prognostic markers. Studies with this aim are conducted based on clinical and laboratory data. Lack of extensor motor response on the third day after CA, the presence of status epilepticus in the first 24 hours,[3] S-100β, neuron-specific enolase (NSE), C-reactive protein (CRP), and PCT levels have been researched as prognostic markers.[4]

Procalcitonin is the calcitonin prohormone comprising 116 amino acids released by thyroid C cells and neuroendocrine cells in the lungs and intestines. Procalcitonin is released from all parenchymal tissues and differentiated cell types in the body, and its level increases in response to proinflammatory stimuli, especially bacterial infections.[5,6] Procalcitonin is a specific marker of bacterial infection in patients with sepsis and is an assessment tool guiding antibiotic treatment and an important indicator of sepsis-related mortality.[7]

During CA, the whole body is exposed to ischemia, and the reperfusion injury developing after ROSC activates the inflammatory system and causes a sepsis-like syndrome.[8,9] Procalcitonin levels that are clearly high after CA, especially in the first 72 hours, are associated with the severity of post-CA syndrome (PCAS), bad neurological outcomes, and increased mortality rates independent of sepsis or severe infections.[4,10,11]

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However, there are limited data about the PCT variation in patients treated with TTM in the period after CA or about the correlation between this variation and infection.

In our study, we investigated the correlation of early period infections, neurological outcomes, and mortality rates with PCT levels in the 24th and 48th hours in the patients treated with TTM post-CA.

Materials and Methods

Study Design

This prospective study was approved by the institutional review board and ethics committee of Faculty of Medicine Sciences (Nr:2016/3-1), and a written informed consent was obtained from the patient's next of kin.

This single-center, prospective observational study was performed on adult comatose patients who were treated with TTM in ICU from January 2017 to December 2018 with successful resuscitation and ROSC.

The study included 45 patients. Inclusion criteria for the study are patients treated with TTM above the age of 18 years with successful cardiopulmonary resuscitation (CPR), initial Glasgow coma scale (GCS) ≤8. Exclusion criteria are poor neurological status before CA, patients with intracerebral pathology or major hemorrhage, patients with infection or sepsis diagnosis causing CA, patients exiting within 7 days of admission to intensive care unit, and patients developing CA following trauma.

Data were collected prospectively and the following variables were recorded for each patient: demographic data, simplified acute physiology score (SAPS II), GCS, arrest location, time to ROSC, initial CPR rhythm, CPR duration, and hemodynamic/biochemical parameters of the first 7 days were recorded.

In the first 7 days after admission of the patients, the diagnosis of infection was recorded. At 6 months, neurological outcomes were assessed with the CPC score,[12] and mortality rates were recorded.

Postresuscitation Care/TTM Protocol

All patients had TTM treatment started within the first 12 hours using Artic Sun® hydrogel-coated water-circulating energy transfer pads (Medivance Corp., Louisville, KY, USA). For all patients, the targeted temperature was determined as 35°C for 24 hours. Temperature monitoring was performed with an esophageal temperature probe. During the hypothermia period, patients treated with TTM had sedation ensured with intravenous infusion of propofol (50 µg/kg/minute) and/or remifentanil (0.1 µg/kg/minute).

After completing the 24-hour TTM cooling period, heating began at a rate of 0.25°C/hour until 36.5°C was reached. Sedation and analgesia infusion were ended. Normothermia administration with TTM continued until the 5th day after CA. During the normothermia period, weaning was applied by assessing neurological score, respiratory, and hemodynamic parameters.

Serum PCT Measurement

Serum PCT levels were measured with the electrochemiluminescence immunoassay method with a Roche Cobas E411 device. The PCT levels for patients were recorded on the TTM reporting forms on admission to ICU and in 24 and 48 hours were also included in the assessment.

CPC Score

Neurological outcome was assessed with the CPC score at 6 months. Targeting analytic assessment, CPC scoring results were used to distinguish the two groups as the good and poor neurological outcomes. We defined those with CPC 1 and 2 as good neurological outcomes (group I) and those with CPC 3, 4, and 5 as poor neurological outcomes (group II).

Infection Diagnosis

Patients who proceeded to CA because of having an infection and diagnosed as sepsis were excluded from the study. The early onset infection diagnosis of the patients before the 7th day in the ICU was made according to the criteria of infection defined by the Centers for Disease Control and Prevention.

Statistical Analysis

Parametric analyses were applied to variables with normal distribution, while nonparametric analyses were applied to variables without normal distribution. Comparison of the two groups was done using the independent samples *t* test/Mann–Whitney *U* test. Chi-square analysis was used to compare the categorical data. Statistical significance was determined as $p < 0.05$.

Results

The study included 45 patients treated with TTM after CA in our ICU, from January 2017 to December 2018 and those selected based on the study inclusion criteria. Patients comprised 66.7% males ($n = 30$) and 33.3% females ($n = 15$) with a mean age of 49.09 (±14.90 SD) years. The baseline characteristics of patients are illustrated in Table 1.

Procalcitonin and Early Period Infections

Of the 45 patients, 19 (42.2%) were identified to have an early onset (in the first 7 days of ICU admission) infection. Of these infections, 13 were pneumonia (68.42%), 4 were infections related to the central catheter (21.0%), and 2 were urinary tract infections (10.52%). No statistically significant correlation between early period infection diagnosis and PCT levels ($p > 0.05$) at 24 and 48 hours (Table 2).

Patient Characteristics and the 90-day Neurological Outcome

Among the discharged patients, the 90-day CPC assessment found good neurological outcomes in 15 patients (35.6%) (CPC 1 or 2) and poor neurological outcomes in 30 patients (1 CPC 3 = severely disabled; 1 CPC 4 = vegetative state; and 28 CPC 5 = dead) (Table 3).

Table 1: Baseline characteristics of patients treated with targeted temperature management

Baseline characteristics of patients	*Values*
Patient number	45
Age, years, mean ± SD	49.09 ± 14.90
Gender, female/male, *n* (%)	15 (33.3%)/30 (66.7%)
SAPS II, mean ± SD	63.13 ± 15.29
Resuscitation location, *n* (%)	
Out of hospital	32 (71.1%)
In-hospital	13 (28.9%)
Time to ROSC, minute, mean ± SD	16.23 ± 12.20
Initial arrest rhythm	
Shockable, *n* (%)	25 (55.6%)
Nonshockable, *n* (%)	20 (44.4%)

ROSC, return of spontaneous circulation; SAPSII, simplified acute physiology score II; GCS, Glasgow coma scale

No statistically significant correlation was observed between the 90-day neurological outcomes of patients with gender, age, SAPS II, admission GCS, admission hemoglobin level, ROSC time, the location of resuscitation, and the initial rhythm (Table 3).

Procalcitonin and the 90-day Neurological Outcome

As shown in Table 3, patients with a good neurological outcome at 90 days had significantly lower serum PCT levels at 24 and 48 hours. No statistically significant correlation between admission PCT levels and neurological outcomes (Table 3).

Table 2: Procalcitonin levels and early period infection (within 7 days of ICU admission)

	Early period infection		
Variable	*İnfection (n = 19)*	*No infection (n = 26)*	*p*
Admission PCT (ng/mL), Med (Min, Max)	1.56 (0.14–10.74)	1.44 (0.01–43.30)	0.986
PCT 24th hour (ng/mL), Med (Min, Max)	4.64 (0.56–50.45)	3.78 (0.01–38.10)	0.483
PCT 48th hour (ng/mL), Med (Min, Max)	6.85 (0.55–48.96)	3.00 (0.19–29.77)	0.077

PCT, procalcitonin

Table 3: Association of patient characteristics and procalcitonin levels with the 90-day neurological outcome

Variable	*Good neurological outcome (CPC 1-2)*	*Poor neurological outcome (CPC 3-4-5)*	*p*
Patient number, *n* (%)	15 (33.3%)	30 (66.6%)	
Female/male, *n* (%)	4 (26.6%)/ 11 (36.7%)	11 (73.3%)/ 19 (63.3%)	0.502
Age, mean ± SD	45.33 ± 14.40	50.97 ± 15.03	0.236
SAPSII, Med (min–max)	57 (36–93)	64.5 (32–100)	0.476
GCS, Med (min–max)	5 (3–8)	3 (3–8)	0.062
Admission Hb, mean ± SD	13.40 ± 2.10	13.36 ± 2.74	0.961
Time to ROSC (in minutes), Med (min–max)	10 (2–30)	15 (3–60)	0.102
Resuscitation location			
In-hospital, *n* (%)	3 (23.1%)	10 (76.9%)	0.352
Out of hospital, *n* (%)	12 (37.5%)	20 (62.5%)	
Admission PCT, Med (min–max)	0.34 (0.01–17.70)	1.90 (0.01–43.30)	0.118
PCT 24th hour, Med (min–max)	2.45 (0.24–18.20)	6.20 (0.10–50.45)	**0.044***
PCT 48th hour, Med (min–max)	2.35 (0.28–12.10)	6.10 (0.19–48.96)	**0.004****

CPC, cerebral performance categories; SAPSII, simplified acute physiology score II; GCS, Glasgow coma scale; Hb, hemoglobin; ROSC, return of spontaneous circulation; PCT, procalcitonin
Statistical significance: $p < 0.05$ ** $p < 0.01$
Note: Values in boldface are statistically significant

Patient Characteristics and the 90-day Mortality

Not statistically significant correlation between the 90-day mortality of patients and gender, age, SAPS II, GCS, admission hemoglobin level, ROSC time and location of resuscitation (Table 4).

Patients with shockable initial CPR rhythm were found to have statistically significantly lower mortality rates compared to the group with nonshockable initial CPR rhythm (Table 4).

Procalcitonin and the 90-day Mortality

While the mortality rates were significantly high in patients with high serum PCT levels at 24 and 48 hours, and no statistically significant correlation between admission PCT levels and high mortality rates (Table 4).

Table 4: Association of patient characteristics and procalcitonin levels with mortality

Variable	*Survivors*	*Nonsurvivors*	*p*
Patient number, *n* (%)	17 (37.8%)	28 (62.2%)	
Female *n* (%)/ male, *n* (%)	5 (33.3%)/12 (40.0%)	10 (66.7%)/18 (60.0%)	0.752
Age, mean ± SD	45.12 ± 13.54	51.50 ± 15.40	0.172
SAPSII, Med (min–max)	60 (36–93)	64.5 (32–100)	0.579
Admission GCS, Med (min–max)	5 (3–8)	3 (3–8)	0.167
Admission Hb (g/dL), mean ± SD	13.21 ± 2.48	13.47 ± 2.48	0.742
Time to ROSC (minute), Med (min–max)	10 (2–30)	15 (3–60)	0.200
Resuscitation location			
In-hospital, *n* (%)	3 (23.1%)	10 (76.9%)	0.195
Out of hospital, *n* (%)	14 (43.8%)	18 (56.3%)	
Initial rhythm			
Shockable, *n* (%)	13 (52.0%)	12 (48.0%)	**0.035***
Nonshockable, *n* (%)	4 (20.0%)	16 (80.0%)	
Admission PCT (ng/mL), Med (min–max)	1.12 (0.01–17.70)	2.29 (0.01–43.30)	0.107
PCT 24th hour (ng/mL), Med (min–max)	3.21 (0.24–18.20)	5.40 (0.10–50.45)	**0.049***
PCT 48th hour (ng/mL), Med (min–max)	2.34 (0.28–12.10)	6.10 (0.19–8.96)	**0.004****

SAPSII, simplified acute physiology score II; GCS, Glasgow coma scale; Hb, hemoglobin; ROSC, return of spontaneous circulation; PCT, procalcitonin
Statistical significance: $p < 0.05$ ** $p < 0.01$
Note: Values in boldface are statistically significant

Discussion

According to this study, high serum PCT levels at 24 and 48 hours in patients treated with TTM after CA were significantly correlated with the 90-day bad neurological prognosis and mortality but not correlated with early period infections.

Procalcitonin is not useful as a marker of early infection in patients treated with hypothermia after CA.

Procalcitonin is a peptide released in response to proinflammatory stimuli, especially inflammatory mediators associated with bacteria.[13]

In studies, it was stated that PCT of critical patients may be used as a beneficial biomarker in addition to medical history, physical examination, and microbiological assessment for the early diagnosis of sepsis and also as a guide to reduce the duration and exposure to antibiotic treatment.[14]

Additionally, cytokine release and acute phase response stimulation may be triggered by noninfectious mechanisms such as severe trauma, operations, or cardiac shock.[11,15] These situations make identification of developing infectious complications more difficult.

Patients with successful resuscitation after CA may develop a severe inflammatory response called PCAS. The PCAS comprises three main processes: post-CA brain injury, post-CA myocardial dysfunction, and systemic ischemia/reperfusion injury. These processes cause symptoms similar to sepsis/systemic inflammatory response syndrome.[16]

These patients had high levels of cytokines in circulation and presence of endotoxin in plasma from a process similar to immunologic profile in sepsis patients.[8,9]

There are different results in literature about the predictor effect of serum PCT levels to monitor infection and for treatment after CA. Studies found that increasing PCT in the early period was associated with PCAS, rather than being a specific response to infection.

Oppert et al. found a correlation between PCT levels and ventilator-associated pneumonia (VAP) in patients after CPR. However, this study included a very low number of patients and patients with short CPR durations.[17] Another study evaluated the diagnostic value of PCT for early onset VAP during the TTM of post-CA patients as weak. They stated that PCAS may play a role in this lack of sensitivity and specificity of PCT.[18] Similarly, a study by Engel et al. reported that the increase in PCT levels was not associated with early period infections, similar to our study, but was related to the increased inflammatory response and mortality related to post-CA syndrome.[10] Another study found PCT and CRP were elevated in the patient group treated with TTM after CA independent of an underlying infection.[11] In accordance with literature, in our study, the infection diagnosis rate within the first 7 days of admission to ICU was 42.2% among patients treated with TTM after CA, while there was no correlation between PCT levels measured on admission, on the 24 and 48 hours with early period infections.

Patient Characteristics, Neurological Outcome, and Mortality

In our study, other predictive values of admission GCS and hemoglobin levels were investigated to aid prognostication.

In our study, no statistical correlation was found between admission GCS and ROSC durations with neurological prognosis and mortality. The small sample size may have caused the lack of difference between the prognosis groups.

In our study, we did not find a statistical correlation between admission hemoglobin levels and outcome. The inclusion of a patient group with high admission hemoglobin levels may have caused this lack of difference between prognosis groups.

Patients with shockable initial CPR rhythm had statistically significantly lower mortality rates than the patient group with nonshockable initial rhythm, in accordance with the literature[19,20] but no significant difference in terms of neurological prognosis.

Procalcitonin as a Marker of Neurological Outcome and Mortality

In the last decade, significant advances in care after resuscitation have significantly changed the coma prognosis after CA.[21] Addition of TTM treatment to current treatment protocols has made coma and mortality prognostication after CA a more complicated situation requiring a multimodal approach including clinical assessment, electrophysiological tests, and blood biomarkers.[22]

Currently, there is no specific diagnostic or prognostic test to determine the neurological prognosis and mortality of comatose patients treated with TTM after CA.

Current laboratory parameters studied as prognostic factors include NSE,[23] S-100B, glial fibrillary acidic protein (GFAP), and soluble 100-β 3,[24] though these biomarkers are not available in every organization or produce erroneous prognostic estimation rates when used alone.[22] Procalcitonin is a parameter that is more easily accessible and more common in clinical practice.

A few studies have found that serum PCT levels increased in the first 48 hours after ischemia for patients with CA and poor neurological outcomes and higher mortality rates.[10,11,25,26] Similarly, our study also showed that increased PCT at 24 and 48 hours is correlated with worse neurological prognosis and higher mortality rate.

Conclusion

An elevated PCT level at an early phase of PCAS is associated with poor neurological outcomes and high mortality rates. In contrast, elevated serum PCT level was not significantly correlated with early period infections. We believe that PCT levels may be included in a multimodal approach for outcome prognostication of patients treated with TTM after CA.

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